BASOLATERAL AMYGDALA DOPAMINE MODULATION OF MEDIAL PREFRONTAL CORTICAL AND NUCLEUS ACCUMBENS DOPAMINE FUNCTION

by

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ABSTRACT

Stress activates dopamine (DA) transmission in the basolateral amygdala (BLA), medial prefrontal cortex (mPFC) and nucleus accumbens (NAc), and DA transmission in these regions mediates different aspects of the behavioural response to stress. Evidence indicates that a functional interdependence exists between the DA projections to these areas. mPFC DA exerts an inhibitory influence on stress-induced NAc DA release. Similarly, BLA DA modulates mPFC and NAc DA function, although it is unknown if this is also the case in response to stress. Thus, we examined whether BLA DA modulates NAc and mPFC DA release in response to stress. We first determined the effects of BLA DA depletion on stress-induced NAc and mPFC DA release. BLA DA depletion potentiated the NAc and attenuated the mPFC DA responses to stress. We then examined the effects of intra-BLA D1 and D2/D3 receptor antagonists on the NAc and mPFC DA responses to stress. BLA D1, but not D2/D3, receptor antagonism potentiated and attenuated stress-induced NAc and mPFC DA release, respectively. Co-administration of D1 antagonist into BLA and DA agonists into mPFC abolished the potentiation of stress-induced NAc DA release, indicating that BLA D1 receptor modulation of the NAc DA stress response occurs indirectly by modulating stress-induced mPFC DA release. We then turned to examining the influence of BLA DA on behavioural measures of information processing which are themselves modulated by NAc and mPFC DA function. The effects of BLA D1 and D2/D3 receptor blockade on prepulse inhibition (PPI) and latent inhibition (LI) were examined. BLA D1 receptor antagonist enhanced and D2/D3 receptor antagonist reduced PPI. Conversely, neither BLA DA receptor antagonist had an effect on LI. Finally, we determined the effects of BLA D1 and D2/D3 receptor antagonists on acoustic startle habituation. Although BLA DA receptor antagonism had no effect on this measure, both D1 and D2/D3 receptor blockade reduced initial startle responsivity. These studies indicate that a functional interdependence exists between the various projections of the mesocorticolimbic DA system in response to stress. They also suggest that BLA DA may modulate certain forms of information processing independently of NAc and mPFC DA function.

RÉSUMÉ

Le stress induit la relâche de DA dans les régions de l'amygdale basolatérale (BLA), du cortex préfrontal médian (mPFC) et du noyau accumbens (NAc), et cette relâche contribue à différents aspects de la réponse comportementale liée au stress. Certaines évidences suggèrent une interdépendance fonctionnelle des projections dopaminergiques entre ces régions. Ainsi, la présence de DA dans le mPFC exerce une influence inhibitrice sur la relâche de DA induite par le stress dans le NAc. La relâche de DA au niveau du BLA module elle-même la fonction dopaminergique du mPFC et du NAc, toutefois, on ne sait pas encore si cette modulation peut advenir lors d'une réponse physiologique au stress. Afin de résoudre cette question, nous avons d'abord exploré les effets d'une déplétion de la DA de l'aire BLA sur la relâche de DA induite par le stress dans le mPFC et le NAc. Nous avons observé qu'une déplétion de la DA du BLA potentialisait la réponse dopaminergique liée au stress dans le NAc, tandis qu'elle atténuait cette réponse dans le mPFC. Nous avons également constaté que l'administration d'antagonistes des récepteurs D1 (mais pas D2/D3) au niveau du BLA reproduisait les effets d'une déplétion de DA sur la réponse dopaminergique liée au stress dans les aires mPFC et NAc. La co-administration d'antagoniste D1 dans le BLA et d'agonistes de DA dans le mPFC a abolit la potentialisation de la réponse dopaminergique du NAc, ce qui suggère que l'effet d'une modulation des récepteurs D1 de BLA sur la réponse au stress dans le NAc est produite indirectement par une modulation de la relâche de DA dans le mPFC. Nous avons ensuite voulu tester l'influence de la DA du BLA sur trois mesures comportementales du traitement de l'information qui sont elle-mêmes modulées par la DA au niveau du NAc et du mPFC. Les effets de bloqueurs D1 et D2/D3 sur l'inhibition prepulse (PPI) et sur l'inhibition latente (LI) ont d'abord été examiné. Les antagonistes D1 ont augmenté la PPI, tandis que les antagonistes D2/D3 produisaient l'effet inverse. Les antagonistes D1 et D2/D3 n'ont eut aucun effet sur la LI. Finalement, nous avons testé l'effet des bloqueurs (intra-BLA) sur l'habituation de la réponse aux stimuli sonores intenses. Les antagonistes D1 et D2/D3 sont restés sans effets sur l'habituation, mais tous deux ont réduit la réponse initiale. Nos résultats indiquent qu'une interdépendance fonctionnelle existe entre les

différentes projections dopaminergiques du système mésocorticolimbique impliqué dans la réponse au stress. Ils suggèrent aussi que la DA du BLA pourrait moduler certaines formes de traitement de l'information indépendamment du NAc et de mPFC.

CONTRIBUTIONS TO ORIGINAL KNOWLEDGE

Study 1. This study established that BLA DA depletion potentiates the NAc DA response to a physical stressor and a species-typical threat. BLA DA depletion was also shown to attenuate stress-induced mPFC DA release, although this was apparent only in response to the physical stressor and was lateralized to the right hemisphere. These experiments also raise the possibility that BLA DA may modulate stress-induced NAc DA release indirectly by modulating the mPFC DA stress response. This study shows that, during exposure to stress, a brain region involved in emotional regulation (BLA) can modulate neurotransmitter release in areas of the brain important in cognitive (mPFC) and motivational (NAc) function. It also adds to a growing body of evidence indicating a preferential role of right mPFC DA in mediating the behavioural response to at least certain types of stressful stimuli. Finally, this study also adds to previous evidence indicating that predator odours are effective in eliciting neurochemical responses in regions implicated in mediating physiological responses to stress.

Study 2. This study confirmed and extended the findings of the previous study, revealing that BLA DA modulation of stress-induced NAc and mPFC DA release occurs via activation of the D1 receptor subtype. This study also revealed that BLA D1 receptor activation modulates the NAc DA response to stress indirectly by modulating the mPFC DA stress response, adding to a large body of evidence indicating that mPFC DA transmission inhibits NAc DA function. Finally, this study proposes a neural circuitry model by which BLA DA modulates stress-induced mPFC and, in turn, NAc DA release.

Study 3. In this study, BLA DA was shown to modulate PPI but not LI. BLA D1 and D2/D3 receptor antagonists had the opposite effects on PPI, with D1 and D2/D3 receptor blockade enhancing and reducing PPI, respectively. This study confirmed and extended previous evidence implicating BLA function in the modulation of PPI. Furthermore, these results suggest that BLA DA modulation of PPI may occur independently of changes in NAc and mPFC DA function.

Study 4. This study revealed that while BLA DA receptor antagonism had no effect on habituation to acoustic startle, BLA D1 and D2/D3 receptor blockade both reduced

responsivity to the initial startle stimuli. This study adds to a growing body of evidence suggesting that BLA DA may be involved in the perception of the aversive nature of certain sensory stimuli.

CONTRIBUTION OF AUTHORS

Study 1. Dr. Ron M. Sullivan provided instruction on all aspects of the voltammetric technique, including construction and surgical implantation of electrodes, and provided instruction and assistance with behavioural testing, histology and statistical analysis. He also assisted in writing the manuscript. Dr. Alain Gratton supervised the project and assisted in writing the manuscript. The author of this thesis carried out the experiments, analyzed the data and wrote the manuscript.

Studies 2-4. Dr. Alain Gratton supervised each project and provided guidance in writing the manuscripts in their present form. The experiments, data analysis and writing of the manuscripts were conducted by the author of this thesis.

ABBREVIATIONS

6-OHDA	6-hydroxydopamine
AA	ascorbic acid
ACTH	adrenocorticotropic hormone
AMPH	*d*-amphetamine
ANOVA	analysis of variance
ASR	acoustic startle response
BLA	basolateral amygdala
CeA	central amygdaloid nucleus
CORT	corticosterone
CRF	corticotropin releasing factor
CS	conditioned stimulus
CTA	conditioned taste aversion
DA	dopamine
DAT	dopamine transporter
DOPAC	3,4dihydroxyphenylacetic acid
GABA	gamma-aminobutyric acid
GR	glucocorticoid receptors
HPA	hypothalamic-pituitary-adrenal
LI	latent inhibition
mPFC	medial prefrontal cortex

NAc	nucleus accumbens
NE	norepinephrine / noradrenaline
PFC	prefrontal cortex
PPI	prepulse inhibition
VTA	ventral tegmental area
UCS	unconditioned stimulus

1.0. GENERAL INTRODUCTION

1.1. Overview

Imagine yourself in the following situation: you are reading a newspaper in the park, sitting on a bench near a pond where a toddler and his mother are playing, although you are so engrossed in your reading that you barely notice them. After a while you hear a splash and look up to see that the young child has fallen head first into the water. Before you realize what you are doing, you find yourself out of your seat and running towards the child, unsure what to do when you reach him. Upon arriving at the pond you decide that the best course of action to take is to find the boy's mother. You quickly scan the area and soon see her running towards you both. A moment later the mother reaches the pond, picks her son up out of the water and cradles him in her arms. She looks up, sees the wild expression on your face and thanks you for your concern, explaining that her son will be fine. Relieved that the boy is unharmed, you turn away and head back to the bench where you were enjoying your newspaper, now strewn on the ground. You pick up the paper and start reading again, but after awhile you realize that you have been staring at the same page for quite some time without being able to remember a word of it. The noise of the local traffic, which you had not noticed before while reading, is now very distracting. You also find your whole body tensing at the slightest of sounds from all around you.

This scenario illustrates some of the overt responses to a stressful event and serves to raise some key issues regarding the effects of stress in general and the neural mechanisms involved in mediating such responses. For instance, how were you able to leave your seat and run towards the child in the pond automatically without thinking about what you were doing? A moment later, how were you then able to come up with a plan, locating the child's mother, to effectively cope with the stressful situation? Why were you able to read your newspaper before, but not after, the encounter with the little boy, given that the same distractions were present throughout? It turns out that stressful stimuli recruit several brain regions, each of which are thought to be involved in

mediating different aspects of the behavioural stress response. The complex brain circuitry that evolved to regulate our response to various environmental challenges comprises several key structures; the focus of the present research is on three of these: the amygdala, prefrontal cortex (PFC) and nucleus accumbens (NAc). Moreover, it is known that brain activity in these regions can modulate the function of one another during exposure to stressful stimuli.

Normally, cortical brain regions involved in mediating higher-order cognitive functions keep activity in areas involved in emotional and motivational regulation in check. The PFC is a brain region that has been implicated in cognitive functioning. Conversely, the initial response to stressful stimuli is inhibition of PFC function by the amygdala, a structure involved in emotional regulation. It is thought that stress-induced activation of the amygdala permits this structure to activate the NAc, a region involved in regulating motivation and modulating motor output. However, the immediate inhibition of PFC function caused by stressful stimuli is followed by recruitment of this brain region. Along with cognition, this brain region is also involved in so-called executive functioning, such as the planning of behaviourally relevant actions. Activation of the PFC allows for the initiation of coping responses to effectively deal with stressful stimuli that are executed, in turn, by the NAc.

Given the fact that stress can influence PFC, amygdala and NAc function, and that these structures have also been implicated in mediating various forms of complex sensory processing, suggests that stress has an impact on these types of information processing. Indeed, stress impairs certain forms of memory function via its effects on the PFC. Conversely, stress enhances other types of memory processes, including formation of "emotional" memories of the stressful event itself, a function that involves the amygdala. Moreover, certain forms of information processing are affected by activity in the amygdala, PFC and NAc.

The PFC, amygdala and NAc are inter-connected and, as previously mentioned, modulate the function of one another during behavioural stress responses. Furthermore, these three regions may also exert an influence on each other during particular types of sensory processing. Although studies suggest that

the PFC can modulate amygdala and NAc function, considerably less is known of a possible modulation of the PFC and NAc responsiveness to aversive stimuli by the amygdala. Moreover, few studies have studied the influence of the amygdala on automatic and learned forms of information processing mediated by the PFC and NAc.

One neurotransmitter system that has received much attention in this context comprises the population of dopamine (DA) neurons located in the ventral tegmental area (VTA) that innervates various cortical and limbic regions. One well known physiological response to stressful stimuli is an increase in the synaptic release of DA in these areas, including the amygdala, PFC and NAc. This neurotransmitter plays an important role in mediating the various functions of these areas during the behavioural stress response as well as in the processing of complex sensory stimuli. Furthermore, the DA projections to the amygdala, PFC and NAc appear to be functionally related. For example, PFC DA transmission exerts an inhibitory influence on NAc DA function in response to a variety of sensory stimuli, including stressors. Amygdala DA transmission also modulates PFC and NAc DA function, although the extent to which this occurs during the behavioural stress response remains unclear. Moreover, central DA transmission has also been implicated in mediating both reflexive and learned responses to sensory stimuli. Prior studies have focused on PFC and NAc DA function in this context but little is known of a possible role for amygdala dopamine in modulating these forms of sensory processing.

Thus, the present studies sought to determine how amygdala DA transmission modulates PFC and NAc DA function during a) the behavioural response to stress and b) certain types of information processing. The role of amygdala DA in modulating PFC and NAc DA function in response to stress and during information processing was determined by manipulating amygdala DA transmission and then examining stress-induced PFC and NAc DA release or measuring specific types of reflexive and learned forms of information processing, respectively, in the freely-behaving rat. The remainder of this introduction will expand upon the concepts introduced above and will review the

relevant literature concerning the involvement of the amygdala, PFC and NAc in both the behavioural stress response and the processing of aversive stimuli, with particular emphasis placed on the role of dopaminergic mechanisms. It should be noted at this point that, along with the behavioural response, stressors elicit a host of physiological responses, including the release of hormones and neurotransmitters involved in mediating neuroendocrine and autonomic responses to stress. Since the many physiological effects of stress can impact on the behavioural response to stressors, the present review will mention relevant aspects concerning these issues.

1.2. Central effects of stress

Even before the term "stress", as it is currently understood, came into use, Cannon (1929) observed that much in the manner in which organisms respond to their environment serves to preserve a steady physiological state or homeostasis. Selye (1936) borrowed the term stress from engineering to describe the physiological response of an organism to the demands placed on it by a "stressor", that is any stimulus or event that challenges homeostasis. He also introduced the concept of adaptation, which refers to the compensatory response of the organism in response to a stressor. Thus, stress has often been defined as a disruption of homeostasis, and a stressor as any stimulus, real or perceived, which elicits an adaptive response (Pacák and Palkovits, 2001). More recently, the term "allostasis" has been introduced to describe the physiological adaptation undertaken by the organism in response to a stressor (Sterling and Eyer, 1981; Schulkin et al., 1994). Allostasis refers both to the protective effects of compensatory responses in the short-term as well as to the potential detrimental effects of such responses in the long-term. These effects refer to the prolonged activation of physiological stress responses caused by chronic exposure to stressors and the ensuing emergence of maladaptive responses, including the inability to efficiently terminate the stress response.

Stressors and the responses that they elicit vary along several dimensions. The response to a single exposure to a given stressor differs from that elicited by

repeated or chronic exposure to the same stressor. Controllability is another important factor. Generally organisms fare better when they can actively diminish or terminate the impact of a stressor situation compared to when they have no control over a stressful situation. The nature of the stressor is also important. The central mechanisms mediating the stress response differ depending on whether the stressor is an overt physical insult (i.e. hemorrhage, exercise, hypoglycemia, immune challenge, tail pressure, etc.), a psychogenic challenge (restraint, social defeat, predator odour, etc.) or an otherwise innocuous stimulus closely associated with, and thus predictive of, a stressful situation (Pacák and Palkovits, 2001).

1.2.1. Neuroendocrine and autonomic stress responses

One of the best characterized physiological responses to stressors results from the activation of the hypothalamic-pituitary-adrenal (HPA) axis. Stressors elicit the release of corticotropin releasing factor (CRF) from the paraventricular nucleus of the hypothalamus and extra-hypothalamic sites such as the amygdala. The release of CRF into the median eminence elicits the release of adrenocorticotropic hormone (ACTH) from the pituitary. Once released into the bloodstream, this hormone acts on the adrenal gland, this serving the release of norepinephrine (NE) and epinephrine, as well as the glucocorticoid corticosterone (CORT) into the blood stream. This results in the mobilization and direction of energy resources to where they are needed in the body in order to effectively cope with the stressful stimulus. The HPA axis is tightly regulated by a negative feedback mechanism, such that circulating CORT eventually inhibits the further release of CRF and ACTH by binding to glucocorticoid receptors (GR) located in the pituitary, hypothalamus, and forebrain sites such as the hippocampus and PFC (Bohus et al., 1996; Buijs and van Eden, 2000; Pacák and Palkovits, 2001).

The amygdala plays an important role in modulating neuroendocrine and autonomic stress responses (Bohus et al, 1996; Buijis and van Eden, 2000). This heterogeneous brain region is comprised of several subnuclei that can be distinguished on the basis of differences in their extrinsic anatomical connections, chemoarchitecture and function. The basolateral amygdala (BLA) consists of the lateral, basal and accessory basal nuclei. This region of the amygdala receives

unprocessed and processed sensory input from the thalamus and the cerebral cortex, respectively (LeDoux et al., 1990; Turner and Herkenham, 1991; McDonald, 1998), which it transmits to the central amygdala (CeA) by way of both direct and indirect projections via the intercalated cell group (Davis et al., 1994b; Pitkänen et al., 1997; Paré et al., 2003). The CeA, in turn, projects to the hypothalamus, midbrain catecholamine nuclei and brain stem regions (periaqueductal gray, nucleus of the solitary tract, parabrachial nucleus) involved in mediating the neuroendocrine and autonomic responses to stressful stimuli (Figure 1; van der Kooy et al., 1984; Moga et al., 1990; Rizvi et al., 1991; Petrovich et al., 2001). Thus, CeA lesions attenuate stress-elicited ACTH and CORT release (Beaulieu et al., 1986; Roozendaal et al., 1990, 1991; Van der Kar et al., 1991). These lesions also diminish sympathetic activation, as measured by increased heart rate and blood pressure, and gastric ulcer formation induced by stressors (Henke, 1980; Sanders, 1994). The CeA can also directly mediate the physiological responses to stressors. For example, stressors induce both NE and CRF release in the CeA (Raber et al., 1995; Merali et al., 1998; Quirarte et al., 1998). The CeA is also involved in regulating HPA axis function, however this occurs in a feedforward manner, such that circulating CORT binds to amygdaloid GR and activates CRF-containing neurons (Gray and Bingaman, 1996).

The PFC is another brain region involved in regulating neuroendocrine and autonomic function (Buijis and van Eden, 1996; Sullivan and Gratton, 2002a). This area is comprised of anatomically and functionally distinct subregions, including the medial prefrontal, anterior cingulate, agranular and orbitofrontal cortical areas. The medial PFC (mPFC) integrates sensory inputs from several brain regions and, in turn, sends descending projections to sites involved in modulating neuroendocrine and autonomic function (Sesack et al., 1989; Terreberry and Neafsey, 1987; Jodo et al., 1998). Activation of GR by CORT in the mPFC contributes to the feedback regulation of HPA axis function (Ostrander et al., 2003). Moreover, it appears that the dorsal and ventral subregions of the mPFC play different roles in modulating neuroendocrine function. For example, lesions to the dorsal and ventral subregions of the mPFC

have different effects, such that dorsal (anterior cingulate and prelimbic cortices) lesions enhance stressor-induced CORT release (Diorio et al., 1993) and sympathetic activation (Powell et al., 1994), while ventral mPFC (infralimbic cortex) lesions have the same effect as lesions to the CeA, inhibiting CORT release (Sullivan and Gratton, 1999) as well as various indices of autonomic function (Frysztak and Neafsey, 1991, 1994; Powell et al., 1994) in response to stressors. As will be discussed in greater detail below, mPFC modulation of physiological stress responses occurs in an asymmetrical manner, such that right, but not left, lesions to the ventral mPFC attenuate both the neuroendocrine and autonomic responses to stress (Sullivan and Gratton, 1999).

1.2.2. Behavioural stress responses

Behavioural responses to stressors can be classified into two broad categories according to the coping strategy used by the organism. Active coping implies just that, actively engaging in behaviours that allow the organism to reduce, or eliminate altogether, the consequences of being exposed to a stressor. For example, animals will learn to avoid stressors by escaping to an adjacent chamber or by pressing on a lever to prevent the onset of a stressor (Carlson et al., 1993). Animals may also display adjunctive or so-called displacement behaviours in response to various stressors. Such behaviours differ from active coping responses in that they do not contribute to the termination of the stressful situation; however, they do serve to attenuate various physiological stress responses. One example of such displacement behaviour is chewing, which is often observed in rodents exposed to a stressor and will result in a diminished response of the HPA axis (Antelman et al., 1975; Hennessy and Foy, 1987; Berridge and Dunn, 1989). In some instances, simply doing nothing is often the best option when faced with a threat. Passive coping strategies refer to reactions, rather than actions, elicited by stressors. The prototypical passive coping response to a number of stressors in the rat (e.g. novelty, predator odour, unconditioned and conditioned footshock) is "freezing", or immobility (Pacák and Palkovits, 2001). Immobility presumably evolved as a successful coping strategy

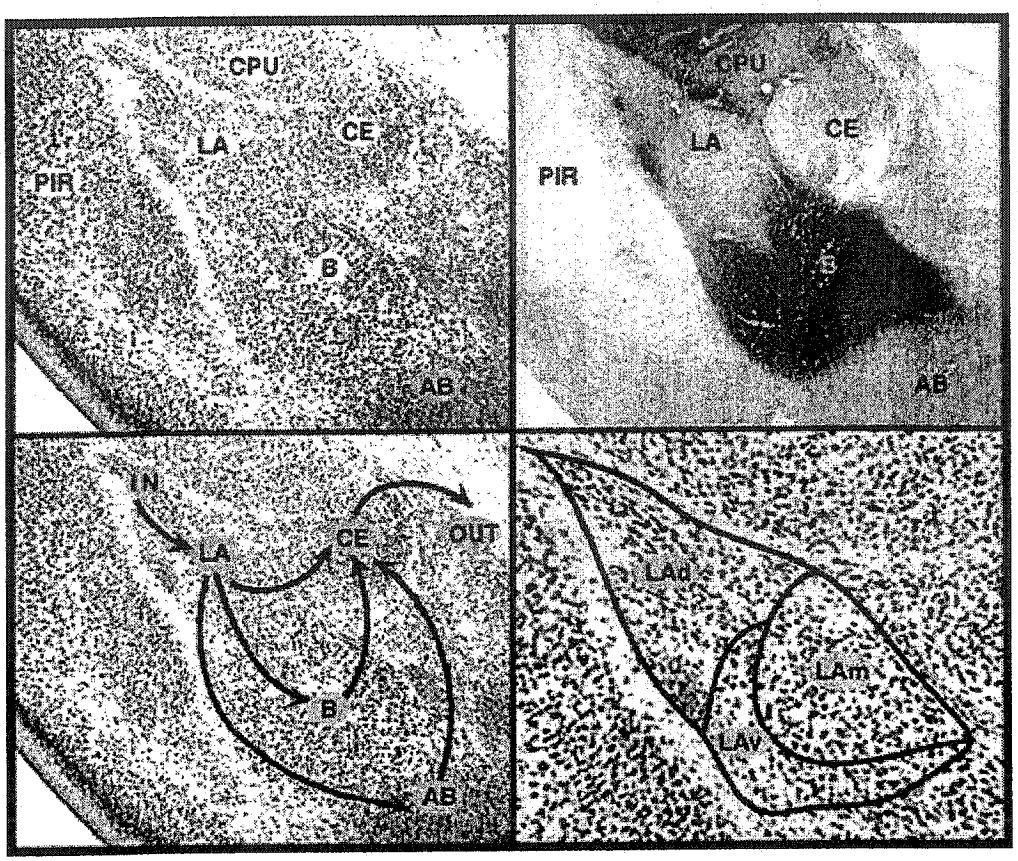

Figure 1. Sensory information from the thalamus and cortex access the amygdala via projections to the lateral nucleus (LA) of the BLA. The LA, basal (B) and accessory basal (AB) nuclei in turn project to the central amygdala (CE). The CE then projects to hypothalamic and brain stem structures involved in neuroendocrine and autonomic regulation (Le Doux, 2000; Reprinted, with permission, from the *Annual Review of Neuroscience*, Volume 23 © 2000 by Annual Reviews).

because in certain circumstances, such as an encounter with a predator, this coping strategy is often the most effective (Engel, 1977).

The amygdala and mPFC are also involved in mediating the behavioural responses to stressors. The amygdala is probably best known for its involvement in Pavlovian fear conditioning (Davis, 1992; LeDoux, 2000). In this form of aversive learning, an innocuous sensory stimulus, typically an auditory or visual cue, is presented together with an aversive unconditioned stimulus, typically a mild footshock. After as little as one pairing, the neutral or conditioned stimulus (CS) acquires the aversive properties of the unconditioned stimulus (UCS), such that presentation of the CS alone elicits neuroendocrine, autonomic and behavioural (i.e. freezing) responses to stress. Lesion studies have demonstrated that the amygdala plays a critical role in mediating both the acquisition and expression of Pavlovian fear conditioning. Lesions to the BLA prevent the acquisition of fear conditioning, whereas CeA lesions interfere with the expression of physiological and behavioural responses to a CS (Hitchcock and Davis, 1986; LeDoux et al, 1990; Van de Kar et al., 1991; Campeau and Davis, 1995). Animals returned to the environment in which conditioning originally took place also exhibit fear responses. This phenomenon is referred to as contextual fear conditioning and is mediated by both the BLA and hippocampus, as damage to either of these regions disrupts this process (Phillips and LeDoux, 1992; Maren et al., 1997). Evidence also indicates that the CeA is involved in mediating passive, but not active, coping responses. This is best observed in the defensive burying paradigm, where an electrified prod is placed in the rat's home cage. In this situation the rat can select an active coping response, by burying the prod with bedding, or a passive response, by freezing or avoiding the prod altogether. CeA lesions diminish freezing behaviour but have no effect on defensive burying in this paradigm (Roozendaal et al., 1991).

Lesions to the mPFC also result in changes in freezing behaviour. Dorsal mPFC lesions enhance freezing behaviour in response to a conditioned fear stimulus (Morgan and LeDoux, 1995), whereas more ventral lesions have the opposite effect (Frysztak and Neafsey, 1991). Similarly, rats with lesions to the

ventral mPFC spend significantly more time exploring the open arms of an elevated plus maze than do sham-lesioned controls (Lacroix et al., 2000b; Sullivan and Gratton, 2002b). However, in contrast to the CeA, the mPFC likely mediates active coping responses as well. As will be discussed below, displacement behaviours such as chewing can modulate mPFC DA transmission (Berridge et al., 1999). As is the case with physiological stress responses, mPFC modulation of behavioural responses to stressors also occurs in a lateralized manner, as, again, right, but not left, lesions to the ventral mPFC appear to be anxiolytic, resulting in increased time exploring the open arms of an elevated plus maze (Sullivan and Gratton, 2002b). Furthermore, the stressor-elicited displacement behaviours, such as chewing, appear to be selectively modulated by a DA-sensitive mechanism in the right mPFC (Berridge et al., 1999).

The NAc is another structure that has been implicated in the regulation of behavioural stress responses. The NAc is probably best known for its role in behaviours motivated by rewards such as feeding, copulation and drug self-administration (Schultz, 1998; Horvitz, 2002; Salamone and Correa, 2002). However, the fact that stressors also activate the NAc suggests that this structure mediates the behavioural responses to any biologically significant stimulus (Horvitz, 2000, 2002; Salamone and Correa; 2002). Current understanding posits that the NAc integrates input from the environment with information concerning internal affective states and contextual cues, then relays it via direct and indirect projections to brain stem motor structures (Groenewegen et al., 1996). Thus, the NAc can be thought of as an interface between sensory, limbic and motor systems (Mogenson et al., 1980).

The NAc receives processed and unprocessed sensory input via projections from the mPFC and thalamus, respectively (Carter, 1982; Berendse and Groenewegen, 1990; Berendse et al., 1992; Sesack and Pickel, 1992; Ding et al., 2001). The NAc also receives contextual information from the hippocampus and emotion-related information from the BLA (Krettek and Price, 1977; Kelley et al., 1982; Groenewegen et al., 1987; McDonald, 1991). Moreover, anatomical and electrophysiological evidence indicates that inputs originating in the mPFC,

thalamus and BLA converge on the same NAc neurons (Finch, 1996; Groenewegen et al., 1996). The NAc sends projections, in turn, to brain stem regions mediating motor activity, directly and indirectly via the substantia nigra pars reticulata and ventral pallidum (Mogensen and Nielsen, 1983; Garcia-Rill, 1986; Swerdlow and Koob, 1987; Deniau et al, 1994). Thus, the NAc is capable of modulating behavioural stress responses by virtue of its anatomical connections with, among other brain regions, the BLA and mPFC.

The NAc is comprised of two main subregions, the dorsolaterally located "core" and the more ventromedial "shell". These two subterritories can be distinguished in part by their differences in chemoarchitecture, connectivity and function (Zahm and Brog, 1992; Brog et al., 1993; Groenewegen et al., 1996; Zahm, 1999, 2000). It is thought that the core represents a ventral extension of the dorsal striatum, whereas the shell is viewed as a part of the extended amygdala. For example, although the core and shell receive afferent input from many of the same regions, the shell afferentation appears to be more widespread to include brain areas involved in mediating the physiological responses to stress (i.e. hypothalamus, brainstem, CeA; Zahm and Brog, 1992; Groenewegen et al., 1996; Zahm, 1999, 2000). The core and shell have been reported to receive topographical afferent input from the dorsal and ventral mPFC, respectively (Sesack et al., 1989; Hurley et al., 1991), although more recent evidence suggests that the core and shell may receive both dorsal and ventral mPFC afferents (Ding et al., 2001). The efferent projections of each NAc subregion also differ, such that the core projects preferentially to brainstem motor regions via the dorsal ventral pallidum, whereas the shell sends projections to the mPFC by way of the medial ventral pallidum and thalamus. It should be noted that the core also receives a relatively dense projection from the shell. Thus, the core and shell can be viewed as being more involved in mediating the motor and motivational aspects of behaviour, respectively (Zahm and Brog, 1992; Groenewegen et al., 1996; Zahm, 1999, 2000).

1.2.3. Effects of stressors on information processing

Successful adaptation to environmental challenges requires the assimilation of large amounts of information, originating from external and internal sources alike. Evidence indicates that, whereas stressors enhance some forms of complex information processing, other types of sensory processing are actually disrupted by aversive stimuli. For example, the ability to selectively attend to relevant environmental stimuli is crucial in mounting active coping responses. However, evidence indicates that one of the initial effects of acute stress is to disrupt selective attention. Ignoring irrelevant stimuli is another means of managing overwhelming sensory stimulation. Again, one of the initial effects of acute stress, however, is the disruption of this important function. As mentioned above, previous experience with sensory stimuli in general, and with stressors in particular, guides future behavioural responses to similar aversive stimuli. For example, fear conditioning is enhanced by stress. Given the functions of the amygdala, mPFC and NAc, it is not surprising, therefore, that these regions are involved in mediating these forms of information processing.

The mPFC is now known to play a central role in so-called executive functioning. For example, working memory, the ability to transiently hold sensory representations "on-line", allows this structure to mediate selective attention, behavioural flexibility and the planning of actions (Robbins, 2000; Aultman and Moghaddam, 2001). However, a certain amount of stimulus processing also occurs reflexively or automatically, and this form of perception may guide selective attention to potentially relevant environmental stimuli. Moreover, automatic attentional processing may be mediated by various subcortical structures (Dolan and Vuilleumier, 2003). This behavioural process can be quantified experimentally in both animals and humans by measuring selective aspects of the acoustic startle response (ASR), the coordinated contraction of the skeletal musculature that occurs in response to a loud sound (Davis, 1980). The ASR results in the cessation of ongoing behaviour and may allow for protection against injury and preparation of behavioural stress responses (Koch, 1999). The ASR also exhibits plasticity, as evidenced by prepulse

inhibition (PPI), the reduction in the ASR observed when the startling stimulus is immediately preceded by a weaker, non-startling tone (Geyer et al, 1990; Koch, 1999). This behaviour is thought to reflect sensorimotor gating and to model a form of subconscious or "automatic" selective attention, as the (50 msec) interval between the prepulse and the startle stimulus is too short to allow for extensive cortical processing.

Several neural substrates mediate PPI. The NAc, with its postulated role as a sensorimotor interface, has been the subject of the most study. As will be discussed below, pharmacological manipulations of NAc DA transmission have been shown to modulate PPI (Geyer et al., 2001; see also section 1.4.2. below). Lesions to the NAc impair PPI (Kodsi and Swerdlow, 1994, 1997), as do combined lesions of the BLA and CeA, as well as selective lesions of the BLA (Decker et al., 1995; Wan and Swerdlow, 1997; Shoemaker et al., 2003); it is unknown, however, what effect specific lesions to the CeA may have on PPI. Finally, although not as extensively studied, a role for the mPFC in modulating PPI has also been demonstrated, as lesions to this region disrupt PPI (Lacroix et al., 2000c; Yee, 2000).

As mentioned above, ignoring irrelevant stimuli is another mechanism by which only relevant information concerning the environment is processed. This process can also be quantified experimentally in animals and humans. Latent inhibition (LI) refers to the attenuation in stimulus conditioning that occurs with repeated, non-reinforced exposure to that stimulus prior to conditioning. This type of sensory processing has been characterized to study the central mechanisms that mediate the process of ignoring irrelevant stimuli. Tests for LI typically involve examining the effects of non-reinforced preexposure to an innocuous stimulus prior to it being paired with an aversive stimulus in either a conditioned avoidance, conditioned emotional response or, more recently, fear-potentiated startle and conditioned taste aversion (CTA) paradigm (Ellenbroek et al., 1997; Schauz and Koch, 2000; Russig et al., 2003; Weiner, 2003). Studies in animals have revealed that the NAc plays a crucial role in mediating LI (Weiner, 2003). Moreover, the NAc core and shell appear to mediate different aspects of LI, as

lesions to the shell disrupt LI and core lesions result in persistent LI under conditions in which LI is normally disrupted (Tai et al., 1995; Weiner et al., 1996a, 1999; Jongen-Relo et al., 2002). The BLA may also modulate LI (Sotty et al., 1996; Radulovic et al., 1998), however its precise role remains unclear given that BLA lesions have been reported to attenuate, potentiate or have no effect on LI (Weiner et al., 1996b; Coutureau et al., 2001; Weiner, 2003). The mPFC, however, has yet to be implicated as a neural substrate involved in mediating LI, as lesions to this region fail to affect this behavioural measure (Joel et al., 1997; Lacroix et al., 1998, 2000c).

Habituation to sensory stimuli is another process by which once potentially relevant stimuli become irrelevant and are thus ignored. Habituation is usually observed as a gradual decrement in a physiological or behavioural response to repeated stimulus presentation. Habituation is a non-associative learning process in that the decrement in responding depends solely on presentation of the stimulus itself and its gradual loss of behavioural significance (Koch, 1999). Studies in animals and humans show that the amygdala and PFC form part of a neural circuit involved in the habituation to various auditory, olfactory, visual and nociceptive stimuli (Ben-Ari and La Gal La Salle, 1974; Breiter et al., 1996; Poellinger et al., 2001; Wright et al., 2001; Rosenkranz and Grace, 2002b; Fischer et al, 2003; Luan Phan, 2003). Habituation of the ASR is characterized by a decrease in the magnitude of the startle response that occurs with repeated presentation of the startling stimulus (Geyer and Braff, 1987). While there is a paucity of evidence implicating the mPFC in habituation of ASR, the amygdala is thought to play an important role in mediating this process. Infusion of the GABA receptor agonist diazepam into the BLA accelerates habituation of the ASR, whereas intra-CeA infusion of trans-ACPD, a metabotropic glutamate receptor agonist, has the opposite effect (Young et al., 1991; Koch, 1993).

The effects of stress on information processing are likely due, in part, to functional changes in the amygdala, NAc and mPFC in response to stress. Given that both stress and mPFC lesions can disrupt measures of working memory and

selective attention, it is tempting to speculate that stress-induced impairment of working memory reflects a disruption in mPFC function (Granon et al., 1994; Delatour and Gisquet-Verrier, 1996; Muir et al., 1996; Arnsten and Goldman-Rakic, 1998; Aultman and Moghaddam, 2001). Although not traditionally associated with working memory function, recent studies indicate that the BLA (Peinado-Manzano, 1990; Ohno et al., 1993; Ingles et al., 1993; Barros et al., 2002; Addy et al., 2003; May-Simera and Levin, 2003) and NAc (Mair et al., 2002; Jongen-Relo et al., 2003) may also contribute to this function. Chronic noise stress impairs LI in rats (Hellman et al., 1983; McDonald et al., 2003) and psychological stress has the same effect in humans (Braunstein-Bercovitz et al., 2001). Studies show that acute stressors can also affect PPI; cold swim stress, for example, will disrupt PPI (Leitner, 1989), as does intra-cerebroventricular infusion of CRF (Conti et al., 2002). Moreover, transgenic mice that over-express brain CRF are impaired on tests of PPI and display slower habituation of the ASR (Dirks et al., 2002). Moreover, three days (two hours/day) of uncontrollable stress has been reported to retard habituation of the ASR four days after the last stress day (Beck et al., 2002). Finally, fear conditioning is enhanced by intra-BLA infusion of CORT or NE, suggesting that stressors can facilitate aversive learning (McGaugh et al., 2000).

1.2.4. Functional interactions between the amygdala, prefrontal cortex and nucleus accumbens

The BLA, mPFC and NAc are activated in response to stressful stimuli and are each involved in mediating different aspects of the behavioural stress response (Figure 2). The mPFC is positioned to regulate both amygdala and NAc function. Glutamatergic pyramidal (projection) cells of the mPFC innervate neurons in several amygdaloid nuclei, including those located in the BLA, intercalated cell group and CeA (Ottersen, 1982; Room et al., 1985; Cassell and Wright, 1986; McDonald, 1987, 1991b, 1996; Cassell et al., 1989; Sesack et al., 1989; Hurley et al., 1991; Takagishi and Chiba, 1991; Pinto and Sesack, 2000; Vertes, 2004). Input from mPFC projection neurons to the BLA terminates preferentially on local pyramidal cells (Brinley-Reed et al., 1995). However,

electrical stimulation of the mPFC *reduces* the firing rate of BLA projection neurons, presumably as a result of indirect activation of local GABA interneurons or recurrent collaterals of inhibitory intercalated cells (Matsuda and Fujimura, 1996; Smith et al., 2000; Rosenkranz and Grace, 2001, 2002a; Paré et al., 2003). Moreover, mPFC stimulation dampens the activity of BLA projection neurons in response to stimulation of sensory cortical areas (Rosenkranz and Grace, 2001, 2002a) and reduces the responsiveness of CeA neurons to stimulation of the BLA (Quirk et al., 2003). Stimulation of the mPFC also suppresses BLA neuronal activity in response to unconditioned and conditioned stimuli, and blocks neuronal plasticity in the BLA normally induced by fear conditioning (Rosenkranz et al., 2003). The anatomical and electrophysiological evidence is supported by behavioural studies indicating that mPFC stimulation reduces the sympathetic and motor components of the behavioural response to unconditioned and conditioned stress (al Maskati and Zbrozyna, 1989; Zbrozyna and Westwood, 1991) which may be mediated, at least in part, by the amygdala (Quirk et al., 2003). Functional imaging studies in humans appear to be in agreement with studies conducted in animals. Threatening stimuli such as angry or fearful facial expressions elicit activation of the amygdala; however, cognitive appraisal of these faces by the viewer results in a concomitant activation of the mPFC and inhibition of amygdala activity (Hariri et al., 2000, 2002). Moreover, the attenuation in amygdala activity was correlated with mPFC activation and was also associated with a diminished autonomic response (Hariri et al., 2002).

The mPFC also sends a glutamatergic projection to the NAc (Carter, 1982; Christie et al., 1987; Takagishi and Chiba, 1991; Berendse et al., 1992; Sesack and Pickel, 1992; Brog et al., 1993; Wright and Groenewegen, 1995; Montaron et al., 1996; Gorelova and Yang, 1997; Pinto and Sesack, 2000; Ding et al., 2001; French and Totterdell, 2002; Vertes, 2004). Electrical stimulation of the mPFC increases both glutamate release (You et al., 1998) and neuronal activity in the NAc (O'Donnell and Grace, 1995; Finch, 1996; Grace and Moore, 1998; Goto and O'Donnell, 2002; Pistis et al., 2002). Moreover, in a recent study examining cortical modulation of limbic input to the NAc, it was found that the effect of

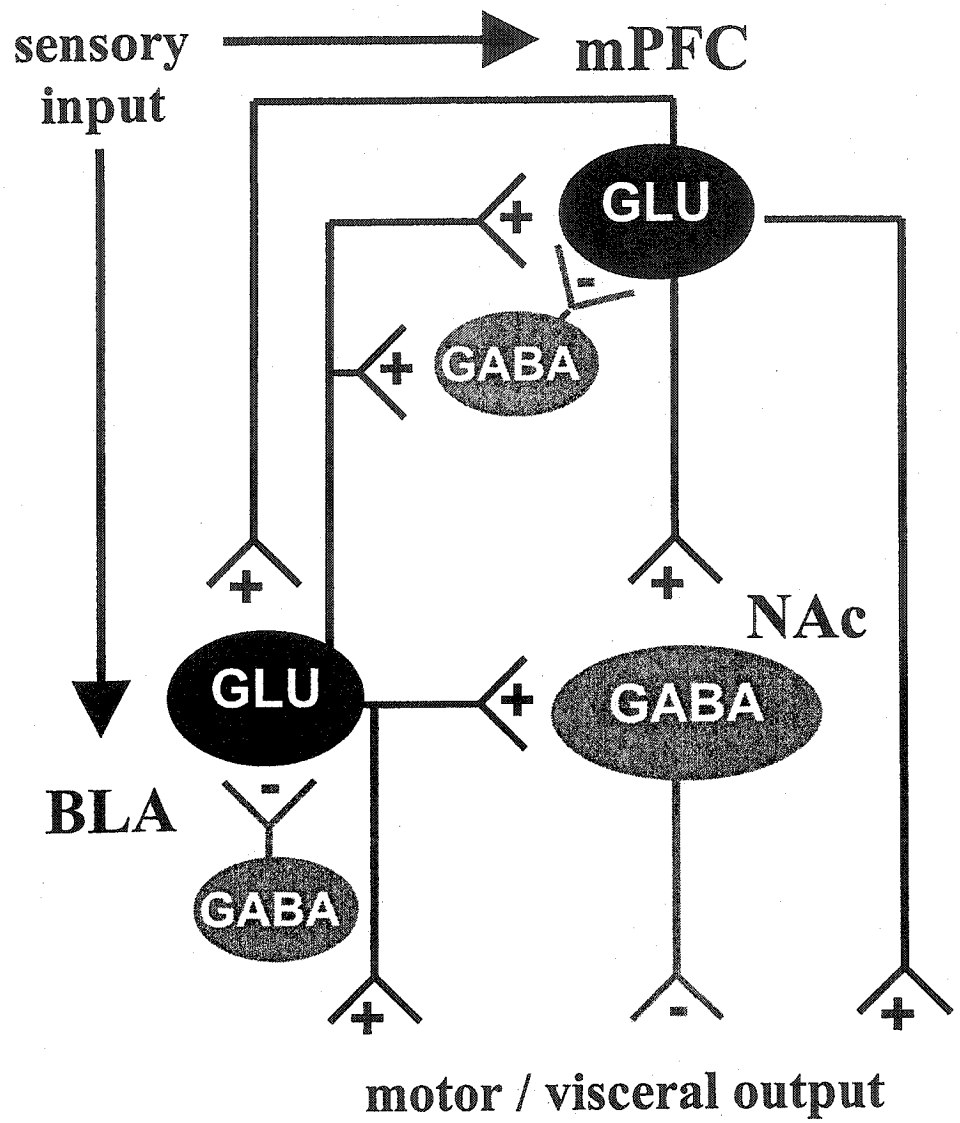

Figure 2. The BLA and mPFC receive unprocessed (thalamic) and processed (cortical) sensory input. These two regions share reciprocal connections, allowing them to modulate each other's function. The BLA and mPFC also project to the NAc, allowing these two areas to modulate NAc function. Finally, the BLA, mPFC and NAc each project both indirectly and directly to motor and visceral output regions.

BLA stimulation on neuronal activity in the NAc is dampened by prior stimulation of the mPFC (Goto and O'Donnell, 2002). From this, it appears that regulation of amygdala and NAc function allows the mPFC to control behaviour in an appropriate and context-dependent manner (Jackson and Moghaddam, 2001).

It remains, however, that the initial response to stressful stimuli is activation of the amygdala (Campeau et al., 1991; Beck and Fibiger, 1995; Smith et al., 1997) and, as a consequence, an inhibition of PFC function. Functional imaging studies in humans suggest that potentially threatening stimuli can be processed automatically by the amygdala, independently of cortical structures (including the PFC) that are closely involved in the initiation of appropriate coping behaviours (Morris et al., 1998, 1999, 2001; Whalen et al., 1998; Vuilleumier et al., 2001a, b, 2002; Anderson et al., 2003). This so-called automaticity of processing by the amygdala may allow for the interruption of ongoing activity and redirect attention towards relevant stimuli in the surrounding environment (Dolan and Vuilleumier, 2003).

Several lines of evidence indicate that the BLA receives unprocessed sensory input via the thalamus prior to receiving processed information from the cortex, allowing the amygdala access to a rapid but less refined representation of the surrounding environment (LeDoux et al., 1990; Turner and Herkenham, 1991; Anderson et al., 2003). Glutamatergic pyramidal cells in the BLA send excitatory projections to both inhibitory GABA interneurons and glutamatergic projection neurons of the mPFC (Krettek and Price, 1977; Sarter and Markowitsch, 1983, 1984; McDonald, 1987, 1991b, 1996; Granato et al., 1991; Shinonaga et al., 1994; Bacon et al., 1996; Petrovich et al., 1996; Ishikawa and Nakamura, 2003). Furthermore, electrophysiological and behavioural studies indicate that this anatomical arrangement is behaviourally relevant. Electrical stimulation of the BLA results in decreased activity of projection neuron activity in the mPFC, presumably as a consequence of increased activity in local GABA interneurons (Canedo, 1982; Pérez-Jaranay and Vives, 1991). Mice subjected to fear conditioning show reduced mPFC neuronal activity in response to CS

presentation that is correlated with the expression of freezing behaviour. Moreover, post-training lesions to the BLA abolished both the reduction in CS-induced mPFC unit activity and the freezing behaviour in response to CS presentation, suggesting that fear-induced changes in mPFC activity are mediated indirectly by the BLA (Garcia et al., 1999). Finally, a single exposure to an unconditioned stressor blocks long-term potentiation, a model of learning thought to represent certain aspects of memory formation processes, in the BLA-mPFC pathway, suggesting that BLA activation can inhibit mPFC function as a consequence of fear conditioning (Maroun and Richter-Levin, 2003).

Thus, it appears that stressor-induced activation of the BLA can override mPFC function, enabling the BLA to directly modulate the execution of goal-directed behaviour, presumably via the direct glutamatergic projection it sends to the NAc (Kelley et al., 1982; McDonald, 1991a, b, 1996; Shinonaga et al., 1994; Petrovich et al., 1996; Wright and Groenewegen, 1996; French and Totterdell, 2003). Electrical stimulation of the BLA activates NAc neurons (Yim and Mogenson, 1982, 1986, 1988; Callaway et al., 1991; Mulder et al., 1998; Floresco et al., 2001a, b; Pistis et al., 2002) and induces glutamate release in the NAc (Jackson and Moghaddam, 2001). Moreover, pharmacological activation of the BLA with the glutamate receptor agonist NMDA suppresses locomotor activity. This effect can be blocked by infusing an NMDA receptor antagonist into the NAc, suggesting that BLA modulation of motor output is mediated, at least in part, by the NAc (Yim and Mogenson, 1989). Thus, it appears that the BLA may influence behaviour by directly modulating NAc function in response to stressors.

As mentioned above, the mPFC is involved in action planning, a process which requires stimulus attention and evaluation, as well as selection of appropriate behavioural responses to cope with a given stressor (Frysztak and Neafsey, 1991; Morgan and LeDoux, 1995; Berridge et al., 1999; Lacroix et al., 2000b; Sullivan and Gratton, 2002a,b). It is likely that the mPFC mediates coping responses to stressors by modulating NAc function, allowing the mPFC to control the execution of goal-directed behaviour in response to stress. Moreover, it appears that mPFC modulation of NAc function occurs in concert with the

amygdala, allowing information on internal affective states to guide behavioural output. The NAc receives excitatory projections from the BLA and mPFC and electrophysiological evidence indicates that this input converges on individual neurons in the NAc and increases the probability of neuronal activation (Finch et al., 1996). Moreover, prior BLA stimulation facilitates NAc neuronal activation induced by stimulation of the mPFC, suggesting that emotionally charged stimuli can gate mPFC modulation of NAc function (Grace and Moore, 1998; Goto and O'Donnell, 2002).

Given the connectivity that exists between the BLA, mPFC and NAc, and the involvement of these structures in mediating various forms information processing, it is possible that the effects of stressors on information processing are due to the activation of these functional pathways. For example, threatening stimuli disrupt working memory while activating the BLA at the expense of mPFC activation, suggesting the possibility that the BLA may modulate working memory indirectly via the mPFC. Indeed, recent evidence suggests that working memory may be modulated by BLA function in certain paradigms (Peinado-Manzano, 1990; Ohno et al., 1993; Ingles et al., 1993; Barros et al., 2002; Addy et al., 2003; May-Simera and Levin, 2003). Similarly, disinhibition of BLA (Fendt et al., 2000) or mPFC (Japha and Koch, 1999) function, induced by the local infusion of a $GABA_A$ receptor antagonist, results in disrupted PPI. Repeated electrical stimulation, or kindling, of the BLA also disrupts PPI (Koch and Ebert, 1998). Thus, it is possible that increased activity in the BLA or mPFC disrupts PPI indirectly via actions on the NAc.

1.3. Characteristics of central DA transmission

The neurotransmitter DA plays a key role in mediating all aspects of the behavioural response to stress by modulating amygdala, mPFC and NAc function and, consequently, various aspects of behaviour mediated by these regions. Stressors elicit DA release in each of these regions and, importantly, a functional inter-dependence appears to exist between the dopaminergic projections to the BLA, mPFC and NAc. Moreover, the involvement of DA neurotransmission in

mediating the types of learned and reflexive sensory processing described above is essential.

1.3.1. Anatomy of mesocorticolimbic DA systems

The amygdala receives a relatively dense, heterogeneous input from mesolimbic DA neurons located predominantly in the VTA (Fallon et al., 1978). This projection is most dense in the CeA and the basal nucleus of the BLA, although the intercalated cell group also receives a substantial DA input (Asan, 1997; Fuxe et al., 2003). Both excitatory glutamatergic projection neurons and inhibitory GABAergic interneurons within the BLA receive input from DA afferents (Asan, 1997; Brinley-Reed and McDonald, 1999). A subpopulation of mesocortical DA neurons sends projections to the mPFC (Loughlin and Fallon, 1984) where they terminate on glutamatergic pyramidal cells and local GABAergic interneurons (Cowan et al., 1994; Sesack et al., 1995). Compared to the BLA and mPFC, the NAc receives a much denser DA projection that terminates on GABAergic medium spiny projection neurons and cholinergic aspiny interneurons (Fallon and Moore, 1978).

1.3.2. Properties of VTA neurons

Mesocorticolimbic DA neurons have distinctly longer duration action potentials and slower, irregular firing patterns than VTA GABA neurons (Deniau et al., 1980; German et al., 1980; Wang, 1981). Moreover, VTA DA neurons exhibit a burst-firing pattern *in vivo*, but not *in vitro* (i.e. in slices), indicating that afferents play a predominant role in regulating the activity of these cells (Freeman and Bunney, 1987; Grace and Onn, 1989). Burst firing occurs *in vivo* under specific behavioural contexts, resulting in a disproportionately larger quantal DA release from the synaptic terminal compared to irregular single-spike firing (Miller et al., 1981; White, 1996). Thus, this pattern of activity in VTA DA neurons is particularly important in mediating behaviourally relevant DA release (see below). Evidence indicates that subgroups of VTA DA neurons may have different electrophysiological characteristics, such that mesocortical DA cells exhibit faster basal firing rates and more bursting activity compared to mesolimbic DA neurons (Chiodo et al., 1984; White and Wang, 1984).

1.3.3. Mesocorticolimbic DA receptor signalling

DA transmission occurs via activation of synaptic DA receptors. There are at least five distinct DA receptor subtypes that are classified into two major groups, the so-called D1-like (D1 and D5) and D2-like (D2, D3 and D4) receptors, based on similarities in structure and function, such as second messenger signalling mechanisms. Thus, activation of D1- and D2-like receptors stimulates and inhibits activation of adenylyl cyclase, respectively, via activation of different G proteins, leading to changes in cAMP levels in the brain (Missale et al., 1998).

The main DA receptor subtypes of the amygdala are the D1 receptor, which is located predominantly in the BLA, and the D2 receptor, found in the CeA, although the D3 and D4 receptor subtypes are also observed in this structure (Scibilia et al., 1992; Levey et al., 1993; Missale et al., 1998). The cellular distribution of DA receptor subtypes within the amygdala has yet to be characterized. Conversely, it is thought that D1 receptors in the mPFC are located preferentially on pyramidal (projection) neurons whereas D2 receptors are found on both pyramidal cells and non-pyramidal interneurons. Moreover, both D1 and D2 receptors are colocalized in a subgroup of local circuit interneurons (Vincent et al., 1993, 1995). More recently, the D4 receptor subtype has also been reported to be located on pyramidal and non-pyramidal neurons (Defagot et al., 1997). Similar to the mPFC, D1, D2 and, to a lesser extent, D4 receptors are located in medium spiny neurons and interneurons of the NAc (Ariano et al., 1989; Svingos et al., 1997). The NAc shell in particular also has an abundance of D3 receptors, again located on both neuronal subtypes (Stanwood et al., 2000).

1.3.4. Termination of DA neurotransmission

Along with causing synaptic DA release in terminal areas, VTA DA neuronal firing results in the local dendritic release of DA (Beart et al., 1979; Kalivas et al., 1989). This local DA release activates somatodendritic D2-like autoreceptors, resulting in decreased firing of DA neurons (Aghajanian and Bunney, 1977; Johnson and North, 1992; Sesack et al., 1994). Thus, somatodendritic autoreceptor activation and the subsequent decrease in the firing

rate of VTA DA neurons is an important mechanism by which neurotransmission is regulated (White, 1996). The expression of impulse-regulating DA autoreceptors in the VTA appears to be heterogeneous, as evidence indicates that a subpopulation of mesocortical DA neurons lacks functional autoreceptors (Chiodo et al., 1984; White and Wang, 1984). Therefore somatodendritic autoreceptor regulation of DA neuron activity may not be as critical in modulating the firing of mesocortical DA neurons.

Dopaminergic transmission is also regulated by terminal autoreceptors that regulate the release or synthesis of DA (Starke et al., 1989; Wolf and Roth, 1990). As is the case of somatodendritic autoreceptors, terminal autoreceptors are expressed heterogeneously on DA neurons projecting to different brain regions. Release- and synthesis-modulating autoreceptors are found on DA terminals in the NAc (Anden et al., 1983; Cragg and Greenfield, 1997). Conversely, release regulating, but not synthesis-modulating, terminal autoreceptors are found on meso-amygdaloid (Kilts et al., 1987; Bull et al., 1991) and meso-PFC DA neurons (Anden et al., 1983; Wolf et al., 1986; Wolf and Roth, 1987; Gariano et al., 1989; Doherty and Gratton, 1999).

Clearance of extracellular DA from the synapse by the DA transporter (DAT) is the primary means by which DA signalling is terminated in the brain. This protein is located presynaptically on DA terminals and is responsible for transmitter reuptake into the terminal (Horn, 1990). Moreover, the heterogeneity of DAT localization and function in different regions contributes greatly to the different characteristics of DA transmission seen in various areas of the brain. The DAT is found on the soma and dendrites of VTA DA neurons, presumably serving as an uptake site for somatodendritically-released DA. High affinity DAT sites are also located on DA terminals in the NAc to terminate DA transmission in this region (Freed et al., 1995; Shimada et al., 1992). Compared to the NAc, DA reuptake occurs at a lower rate in the mPFC. This may reflect the lower density of DAT in the mPFC compared to the NAc or differences in post-translational modification of DAT between these two regions (Garris and Wightman, 1993, 1994a; Sesack et al., 1998). Although recent studies suggest a preferential role for

the norepinephrine (NE) transporter over the DAT in mPFC DA reuptake (Yamamoto and Novotney, 1998; Morón et al., 2002), pharmacological evidence does support a role for DAT-mediated reuptake of DA in this region (Doherty and Gratton, 1996, 1999). DA reuptake in the BLA occurs at an even lower rate than in the mPFC, which may, again, be attributable to the relatively lower number of DAT sites in this region or to differences in glycosylation of the DAT protein (Garris and Wightman, 1994a, b, 1995; Jones et al., 1995; Revay et al., 1996).

In summary, the heterogeneity of terminal autoreceptor and DAT localization and function seen in these regions, as well as differences in VTA DA neuronal activity and somatodendritic autoreceptor function, may account for the differences in DA transmission seen in these regions (Garris and Wightman, 1994a). As mentioned above, NAc DA transmission is tightly regulated primarily by DA reuptake but also by negative feedback inhibition of synthesis, release and firing. In contrast, BLA DA release is under less stringent control by terminal autoreceptors and the sparse density of DAT would cause a greater extra-synaptic accumulation of DA in this area, compared to the NAc. Similarly, the greater firing rate of meso-PFC DA neurons along with the paucity of autoreceptor inhibition and DA reuptake would, as in the case of the BLA, also result in prolonged synaptic DA accumulation. The importance of this will be examined in more detail below.

1.4. Functional significance of central DA transmission

Certain aspects of the electrophysiological effects of DA release on BLA, mPFC and NAc function are addressed below. The behavioural relevance of DA release in these regions will then be examined, with an emphasis placed on the role of DA in mediating various aspects of information processing and the behavioural response to stress.

1.4.1. Electrophysiology

DA has complex effects on neuronal activity in the BLA, mPFC and NAc that are mediated by different DA receptor subtypes in these regions. Early studies examining the effects of BLA DA receptor activation on local neuronal

activity yielded mixed results (Wepsic and Austin, 1971; Ben-Ari and Kelly, 1976; Bashore et al., 1978; Spehlman and Norcross, 1984). More recent electrophysiological studies by Rosenkranz and Grace (1999, 2002a) have examined the effects of differences in DA-mediated effects on neuronal activity based on the segregation of the two main subtypes of neurons present in this region. The authors found that DA receptor activation had opposite effects on BLA pyramidal cell and interneuron activity, with DA receptor activation decreasing spontaneous firing in the former and increasing firing rate in the latter (Rosenkranz and Grace, 1999). In a more recent study, Rosenkranz and Grace (2002a) further characterized the effects of D1 and D2 receptor activation on the activity of BLA projection neurons and found that D1 receptor activation resulted in a suppression of spontaneous firing. However, D2 receptor activation enhanced the excitability of these neurons (Figure 3). These seemingly counterbalancing effects of DA receptor activation are hypothesized to allow BLA DA to suppress weaker inputs to this region, via D1 receptor activation, and enhance stronger input to the BLA, by activating local D2 receptors (Rosenkranz and Grace, 2002a).

The effects of DA receptor activation on neuronal activity in the mPFC have received considerably more attention. Traditionally, DA has been thought of as having an inhibitory influence on neuronal activity in this region. Evidence indicates that activation of D1 or D2 receptors on mPFC neurons decreases spontaneous excitability of local pyramidal cells, possibly by indirectly activating local GABA interneurons (Pirot et al., 1992; Geijo-Barrientos and Pastore, 1995; Gulledge and Jaffe, 1998, 2001; Zhou and Hablitz, 1999; Gonzalez-Islas and Hablitz, 2001; Gorelova et al., 2002). However, studies have also shown that D1 receptor activation can increase neuronal excitability in mPFC neurons (Penit-Soria et al., 1987; Yang and Seamans, 1996; Shi et al., 1997; Gulledge and Jaffe, 2001; Gonzalez-Islas and Hablitz, 2003). Thus, DA modulation of mPFC neuronal activity appears to occur in a complex manner. A likely explanation for these seemingly opposing effects is that DA modulates mPFC pyramidal cell activity in a state-dependent manner. Pyramidal neurons in the mPFC exhibit a

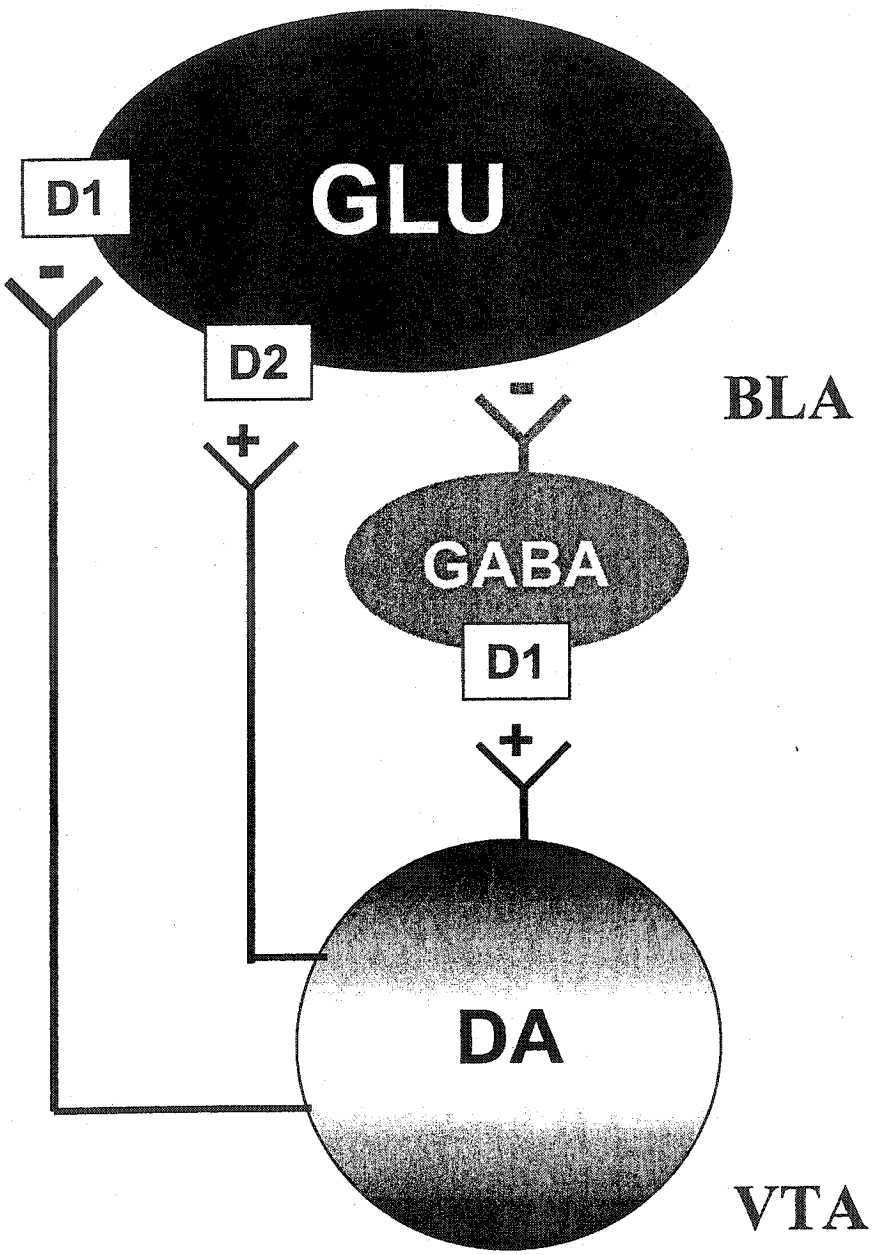

Figure 3. Intra-BLA infusion of DA or D1 receptor agonist increases GABA interneuron and decreases glutamatergic projection neuron activity (Rosenkranz and Grace, 1999). Additionally, BLA D1 receptor activation suppresses spontaneous activity, while activation of D2 receptors increases the excitability, of BLA projection neurons (Rosenkranz and Grace, 2002a).

bistable state characterized by fluctuating depolarized ("up") and hyperpolarized ("down") membrane potential states (Branchereau et al., 1996; Lewis and O'Donnell, 2000). Recent studies examining the effects of DA-induced changes in mPFC neuronal activity have shown that D1 receptor activation only increases excitability when the pyramidal cell is in the "up" state (Lewis and O'Donnell, 2000; Lavin and Grace, 2001). Low doses of DA potentiate the enhancement of cellular excitability caused by NMDA receptor activation, via D1 receptor activation (Zheng et al., 1999; Seamans et al., 2001; Wang and O'Donnell, 2001; Gonzalez-Islas and Hablitz, 2003). Conversely, higher doses of dopamine, acting at D2 receptors, have the opposite effect on the potentiation of neuronal excitability induced by NMDA receptor activation (Law-Tho et al., 1994; Zheng et al., 1999).

As is the case with the mPFC, numerous studies have also revealed that DA regulates NAc neuronal activity in a complex manner. Medium spiny GABAergic neurons of the NAc also exhibit bistable resting membrane potential states. These cells are normally found in their "down" state, however afferent input can bring them to their "up" state, at which they can fire action potentials if they receive further excitatory input (O'Donnell and Grace, 1995, 1998). Again, DA has different effects on cellular excitability depending on the state of the neuron. D1 receptor activation during the "down" state results in a further decrease in spontaneous activity, whereas in the "up" state DA potentiates glutamate-evoked activity via activation of the same receptor subtype (Kiyatkin and Rebec, 1996, 1999; Levine et al., 1996; Gonon, 1997). On the other hand, activation of D2 receptors may suppress spontaneous activity regardless of the bistable state of the neuron (West and Grace, 2002; O'Donnell, 2003)

Therefore central DA does not act as a rapid inhibitory or excitatory neurotransmitter but rather acts as a slow neuromodulator. DA is thought to increase the "signal-to-noise" ratio of excitatory signalling to a region, allowing for the selective suppression of weaker inputs and enhancement of coordinated afferent signalling. Thus, DA modulation of neuronal activity depends on the timing and strength of excitatory inputs received by the BLA, mPFC and NAc

(O'Donnell and Grace, 1999; Yang et al., 1999; Nicola et al., 2000; Rosenkranz and Grace 2002a; O'Donnell, 2003).

1.4.2. Behaviour

Given the ability of DA to modulate cortical and subcortical function it should come as no surprise that this neurotransmitter is intimately involved in mediating a vast array of behaviours. DA is probably best known for its involvement in mediating the reinforcing properties of natural (i.e. food, sex, etc.) and drug rewards (Berridge and Robinson, 1998; Schultz, 1998; Kelley and Berridge, 2002), as unconditioned and conditioned appetitive stimuli induce firing in VTA DA neurons (Schultz, 1998) and DA release in the amygdala (Hori et al., 1993; Hajnal and Lenard, 1997; Harmer and Phillips, 1999), mPFC (Richardson and Gratton, 1998; Feenstra et al., 1999) and NAc (Richardson and Gratton, 1996; Bassareo and Di Chiara, 1999; Datla et al., 2002; Cheng et al., 2003).

However, unconditioned aversive stimuli can also activate VTA DA neurons and local GABA interneurons (Kiyatkin et al., 1988; Kiyatkin and Zhukov, 1988). Moreover, this is also the case with conditioned stimuli, suggesting that neuronal activation in response to stressors is likely due to the negative affective component associated with the stimulus, and not to novelty or other non-specific sensory properties of the stimulus (Trulson and Preussler, 1984; Guarraci and Kapp, 1999). This electrophysiological evidence is supported by studies indicating that various stressful stimuli induce genomic activation in VTA DA cells (Deutch et al., 1991; Redmond et al., 2002). Again, the fact that both unconditioned physical (tail shock) and emotional (restraint, predator odour) stressors, as well as conditioned aversive stimuli, elicit genomic activation in VTA DA cells suggests that this occurs due to the motivational properties of the stressor.

Various stressors elicit increased DA transmission when administered acutely, as measured indirectly by changes in DA metabolism or directly by examining DA release, in several brain regions including the BLA (Herman et al., 1982; Coco et al., 1992; Young and Rees, 1998; Inglis and Moghaddam, 1999; Morrow et al., 2000b; Funada and Hara, 2001), mPFC (Thierry et al., 1976;

Abercrombie et al., 1989; Imperato et al., 1989; Sullivan and Gratton, 1998; Brake et al., 2000; Morrow et al., 2000a, b, c; Del Arco and Mora, 2001) and NAc (Thierry et al., 1976; Dunn and File, 1984; Claustre et al., 1986; Imperato et al., 1989; Doherty and Gratton, 1992, 1996; Brake et al., 1997). Stressors of varying intensity have different effects on the DA projections to each of these regions. For example, evidence suggests that mild stressors selectively increase mPFC DA transmission (Deutch et al., 1985; Abercrombie et al., 1989; Kaneyuki et al., 1991; Inoue et al., 1994; Morrow et al., 2000b), whereas more intense stressors recruit the DA projection to the NAc (Abercrombie et al., 1989; Inoue et al., 1994). However, studies examining the effects of different stressors on DA release in the BLA indicate that the DA projection to this region is as reactive to stressful stimuli, if not more so, than the meso-PFC DA projection (Herman et al., 1982; Inglis and Moghaddam, 1999). In contrast to the response elicited by acute stressors, chronic (i.e. once daily stress for 2-3 weeks) stressors appear to result in a complex adaptation of the responsivity of mPFC and NAc DA to subsequent stressors (Imperato et al., 1993; Cabib and Puglisi-Allegra, 1996; Cuadra et al., 1999, 2001; Mangiavacchi et al., 2001; Scheggi et al., 2002), possibly as a result of changes in the activity patterns of VTA DA neurons themselves (Moore et al., 2001). Thus, the fact that both appetitive and aversive stimuli activate central DA transmission has been taken to suggest that DA neurons are activated in response to salient or arousing stimuli in general, regardless of their affective valence (Ikemoto and Panksepp, 1999; Horvitz, 2000; Salamone and Corea, 2002). As we shall see below, stressor-induced DA release in the BLA, mPFC and NAc mediate different aspects of the behavioural stress response, including various types of information processing.

Amygdaloid DA is involved in modulating neuroendocrine and autonomic function in response to stressors. CeA DA exerts an inhibitory influence on stressor-induced neuroendocrine function (Beaulieu et al., 1987). Infusion of DA or DA receptor agonists into the BLA or CeA also attenuates the stressor-induced formation of gastric ulcers (Ray et al., 1987, 1988; Ray and Henke, 1991). BLA DA release is also important in the stressor-induced activation of this structure

and, consequently, inhibition of mPFC function. Stimulation of the mPFC decreases BLA function indirectly, possibly by increasing activity in local GABA interneurons (Rosenkranz and Grace, 1999, 2002a). Moreover, mPFC stimulation also attenuates sensory cortical input to the BLA (Rosenkranz and Grace; 2001, 2002a). However, BLA DA activates local projection neuron activity, presumably via D2 receptor activation (Rosenkranz and Grace, 2002a). Furthermore, DA receptor activation in the BLA attenuates mPFC input to this structure while enhancing sensory cortical input to this region (Rosenkranz and Grace, 1999, 2001, 2002a). Thus, stressor-induced DA release in the BLA may activate this structure, resulting in the selective filtering of cortical information in favour of sensory inputs and at the expense of input from mPFC.

Recent evidence indicates that BLA DA also plays a key role in attributing affective significance to sensory stimuli. For example, intra-BLA infusion of the indirect DA receptor agonist d-amphetamine (AMPH) or a D3-preferring agonist facilitates appetitive conditioning (Hitchcott et al., 1997a, b, c; Hitchcott and Phillips 1998a, b), whereas infusion of a specific D3 receptor antagonist into the BLA impairs this form of learning (Phillips et al., 2002). Similarly, D1 or D2/D3 receptor antagonism within the BLA impairs fear conditioning in several different learning paradigms (Ashford and Jones, 1976; Lamont and Kokkinidis, 1998; Nader and LeDoux, 1999; Guarraci et al., 1999, 2000; Greba and Kokkinidis, 2000; Greba et al., 2001; Rosenkranz and Grace, 2002b). Thus, DA transmission in the BLA may be necessary for both appetitive and aversive learning.

DA transmission in the mPFC plays an integral role in the cognitive aspects of the behavioural response to stress. Selective attention is mediated to a great extent by mPFC DA. Accuracy in completing a working memory task is related to mPFC DA release (Phillips et al., 2004) and perturbations in mPFC DA tone impair working memory function. Acute stress disrupts working memory function, presumably by increasing mPFC DA transmission (Murphy et al., 1996a, b). However, it appears that mechanisms mediating selective attention require an optimal level of dopaminergic tone in the mPFC, as both D1 receptor agonists (Murphy et al., 1996a, b; Zahrt et al., 1997) and antagonists (Aultman

and Moghaddam, 2001) infused into the mPFC impair performance on working memory tasks. Moreover, low doses of AMPH improve while higher doses impair working memory function (Aultman and Moghaddam, 2001). Dopaminergic tone in the mPFC also plays a crucial role in mediating the executive functions necessary to mount a successful coping response to stressful stimuli (Horger and Roth, 1996). For example, mPFC DA is critical in mediating appropriate response selection, as intra-mPFC infusion of D1 receptor agonists improves performance in certain behavioural tasks (Granon et al., 2000; Passetti et al., 2003). Although DA transmission in the mPFC does not seem to be involved in the acquisition of fear conditioning, the expression of behaviour (i.e. freezing) in response to conditioned aversive stimuli is mediated by mPFC DA (Morrow et al., 1999; Pezze et al., 2003). Studies in the mouse and rat have provided convincing evidence linking adaptive coping behaviour and mPFC DA function. In studies examining the differences in behavioural responding to stressors it has been demonstrated that animals utilizing active coping strategies show increased DA transmission compared to those using passive or avoidance coping responses (D'Angio et al., 1988; Giorgi et al., 2003). Similarly, studies examining the effects of stressor controllability have shown that inescapable, but not escapable, stress elicits increased DA tone in the mPFC (Carlson et al., 1993; Bland et al., 2003), possibly reflecting ongoing cognitive assessment of the situation.

A growing body of evidence indicates that mesocortical DA regulation of physiological stress responses is lateralized to the right hemisphere (Sullivan and Gratton, 2002a). For example, mPFC DA depletion bilaterally or of the right, but not left, hemisphere exacerbates gastric ulcer formation induced by cold restraint stress (Sullivan and Szechtman, 1995). In one study, right, but not left, mPFC DA release induced by predator odour stress was positively correlated with circulating levels of CORT (Sullivan and Gratton, 1998). Similarly, infusion of a non-selective DA receptor antagonist bilaterally or into the right, but not the left, hemisphere potentiates restraint stress-induced activation of ACTH (Sullivan and Dufresne, 2002). The fact that the mPFC DA response to stress occurs

asymmetrically also appears to be relevant for successful coping. In one study examining the effects of an uncontrollable stressor, right mPFC DA transmission was correlated with successful coping in response to subsequent exposure to a stressor (Carlson et al., 1993). In another study examining the relationship between behaviour in an open field and central DA transmission it was found that greater right mPFC DA metabolism was associated with a lower anxiety profile (Thiel and Schwarting, 2001). In animals subjected to a stressful environment (brightly lit open field), chewing on a wooden block present in the environment decreased mPFC DA metabolism selectively in the right hemisphere (Berridge et al., 1999). It has been suggested that this lateralized reduction in mPFC DA tone reflects a reduction in the aversive nature of the stressful situation (Sullivan and Gratton, 2002a).

In contrast to the BLA and mPFC, the DA innervation of the NAc has been implicated in attributing incentive salience to environmental stimuli (Berridge and Robinson, 1998; Ikemoto and Panksepp, 1999; Horvitz, 2000; Salamone and Correa, 2002). In other words, NAc DA confers motivational properties on significant sensory stimuli that are relevant for survival. It is thought that activation of NAc DA transmission in response to both natural rewards, such as food (Richardson and Gratton, 1996; Bassareo and Di Chiara, 1999; Datla et al., 2002; Cheng et al., 2003) and sex (Mitchell and Gratton, 1991a, b; Damsma et al., 1992; Pfaus et al., 1995), and aversive stimuli (Thierry et al., 1976; Dunn and File, 1984; Claustre et al., 1986; Imperato et al., 1989; Doherty and Gratton, 1992, 1996; Brake et al., 1997) has evolutionary value. NAc DA is also involved in mediating the execution of goal-directed behaviour. In a process known as instrumental conditioning, animals can be trained to perform arbitrary responses (i.e. lever pressing, moving within a compartment, etc.) in order to obtain positive reinforcers such as receiving a food reward or avoiding a footshock. The performance of this action-outcome behaviour can be modulated in several paradigms by changes in NAc DA transmission. For example, intra-NAc DA depletion (McCullough et al., 1993), non-selective DA receptor antagonist infusion (Ikemoto and Panksepp, 1996) or D2 receptor antagonist

infusion (Wadenberg et al., 1990) disrupts the behavioural expression (i.e. approach) of instrumental conditioning. Thus, NAc DA plays a crucial role in sensorimotor integration, functioning to "tag" sensory stimuli with salience and at the same time allows for the implementation of relevant behavioural output (Ikemoto and Panksepp, 1999).

The core and shell subregions of the NAc differ in several aspects of their respective DA innervations. The core exhibits greater basal levels of DA and more DAT than does the shell. Electrical stimulation of DA fibres also induces greater DA release in the core compared to the shell (Deutch and Cameron, 1992; Kalivas and Duffy, 1995; Jones et al., 1996; King et al., 1997). Several studies have shown that stressors selectively or preferentially activate DA transmission in the NAc shell (Deutch and Cameron, 1992; Kalivas and Duffy, 1995; King and Finlay, 1997; King et al., 1997; Barrot et al. 1999; Wu et al., 1999). However, others have demonstrated that stress exerts robust increases in DA metabolism (Morrow et al., 1997; Berridge et al., 1999) or release (Doherty and Gratton, 1992, 1996, 1997, 1999; Brake et al., 1997, 1999, 2000b) in the core of the NAc. In one study directly comparing DA release in these two subregions in response to repeated stress it was found that stressor-induced DA release was greater in the core in response to the first acute exposure of the stressor. However, DA release in the shell, but not the core, increased with subsequent stressor exposures (i.e. sensitized), such that there was no difference in the magnitude of DA release between the core and shell during the fifth stressor exposure (Chretien and Gratton, 1998).

Various forms of information processing are modulated by central DA transmission, although somewhat less is known about the contribution of different DA projections in these measures. As stated previously, mPFC DA is important in mediating cognitive and executive function; however, it is unknown what, if any, role DA function in the BLA or NAc plays in working memory function. A large body of evidence indicates that PPI of the ASR is modulated by central DA transmission. Intra-amygdala DA infusion impairs both PPI and ASR magnitude (Swerdlow et al., 1992), although which amygdaloid nucleus and DA receptor

subtypes involved in mediating these effects have yet to be established. Similarly, mPFC DA depletion (Bubser and Koch, 1994; Koch and Bubser, 1994) and DA receptor agonist (Broersen et al., 1999; Lacroix et al., 2000a) or antagonist (Ellenbroek et al., 1996; Crain et al., 2003) infusion into the mPFC result in disrupted PPI, therefore the exact nature of the involvement of mPFC DA in this type of sensory processing remains unclear. Considerably more is known about NAc DA modulation of PPI. Systemic administration of indirect and direct DA receptor agonists impairs PPI and this effect can be reversed by prior NAc DA depletion (Swerdlow et al., 1990b). The effects of systemic DA receptor agonist treatment can also be partially ameliorated by infusing D2 receptor antagonist in to the NAc (Hart et al., 1998). Moreover direct infusion of DA (Swerdlow et al., 1990a, 1992) or D2 receptor agonist (Wan and Swerdlow, 1993; Wan et al., 1994) into the NAc impairs PPI.

The involvement of NAc DA transmission in LI has also been well characterized. As is the case with PPI, systemic administration of the indirect DA receptor agonist AMPH during the pre-exposure and conditioning phases disrupts LI, an effect that is reversed by infusion of D2 receptor antagonist into the NAc (Joseph et al., 2000). NAc DA depletion and intra-NAc D2 receptor infusion potentiate LI (Joseph et al., 2000) and AMPH infusion into the NAc during both training phases has the opposite effect (Solomon and Staton, 1982). A direct role of NAc DA in LI has been demonstrated by examining NAc DA release during LI testing. Tone-shock pairing results in NAc DA release in response to subsequent presentations of the tone and this effect can be blocked by previous presentations of the tone alone prior to conditioning (Young et al., 1993). DA transmission in both the NAc core (Jeanblanc et al., 2002) and shell (Murphy et al., 2000) has been implicated in LI. In contrast, a role for BLA or mPFC DA has yet to be demonstrated in LI (Ellenbroek et al., 1996; Broersen et al., 1999; Weiner, 2003).

Although previous pharmacological characterization studies have failed to demonstrate that central DA systems are involved in modulating habituation of the ASR (Davis and Aghajanian, 1976; Geyer et al., 1978; Davis, 1980; Geyer and Braff, 1987), a recent study examining the effects of startle habituation on

NAc and mPFC DA release suggest that DA transmission in these regions may be relevant in mediating this form of information processing. Compared to NAc DA release during initial exposure to the startling stimuli, DA release in this region was diminished after re-exposure to the same stimuli one day later. Interestingly, mPFC DA release was increased on the second day of exposure to the startling stimulus compared to the first day (Storozheva et al, 2003). No studies conducted to date have examined the role of BLA DA in modulation of startle habituation.

1.4.3. Central DA system interactions

Not only do the BLA, mPFC and NAc play fundamental roles in mediating the behavioural stress response and information processing, these regions can also modulate DA function in other inter-connected areas of the brain in a behaviourally-relevant manner (Figure 4). For example, chemical or electrical stimulation of the mPFC increases NAc DA transmission (Murase et al., 1993; Taber and Fibiger, 1995; Karreman and Moghaddam, 1996; You et al., 1998), although more recent evidence suggests that mPFC stimulation at physiologically relevant frequencies in the freely behaving animal has the opposite effect on DA release in the NAc (Jackson et al., 2001). Similarly, BLA stimulation elicits DA release in the mPFC (Jackson and Moghaddam, 2001) and NAc (Floresco et al., 1998; Howland et al., 2002). BLA kindling has also been shown to affect DA transmission in these two regions (Rada and Hernandez, 1990). Amygdala regulation of mPFC DA transmission appears to be behaviourally relevant, as CeA lesions attenuate stress-induced activation of the mPFC DA projection (Davis et al., 1994a; Goldstein et al., 1996).

Moreover, the DA projections to these areas are capable of exerting a functionally relevant influence over each other. The DA projection to the mPFC exerts an inhibitory influence on NAc DA function, as mPFC DA depletion (Pycock et al., 1980; Fernandez Espejo, 2003) or intra-mPFC infusion of DA receptor antagonists (Louilot et al., 1989) enhances NAc DA transmission. Importantly, these effects are also seen in response to stressful stimuli (Deutch et al., 1990; Doherty and Gratton, 1996; King and Finlay, 1997; King et al., 1997). DA transmission in the mPFC and NAc is also modulated by a DA-dependent

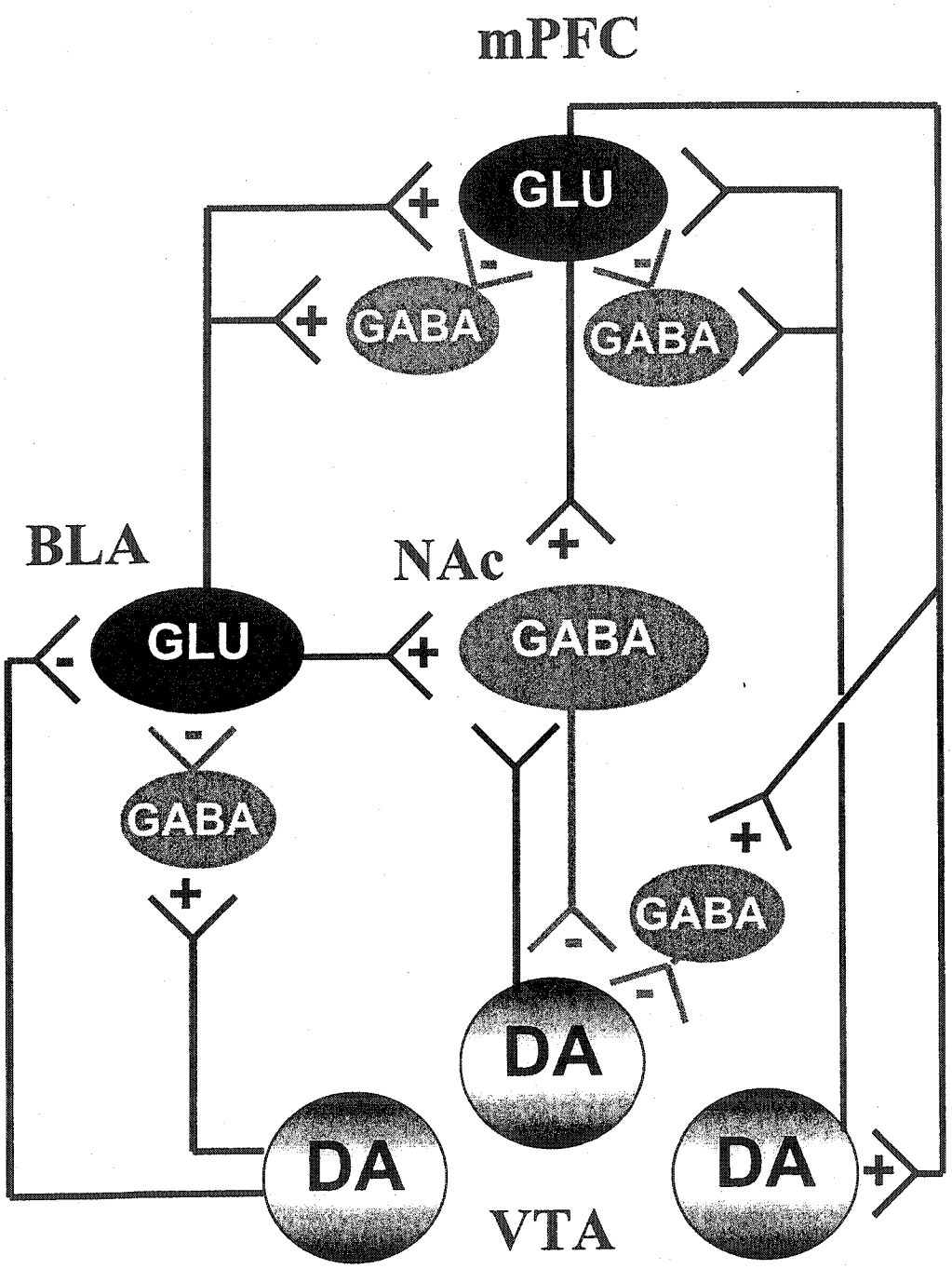

Figure 4. DA cell bodies located in the VTA innervate the BLA, mPFC and NAc. The mPFC and NAc, in turn, project back to both VTA DA neurons and GABA interneurons, allowing these regions to modulate central DA function (adapted from Stevenson and Gratton, 2003; reprinted with permission from Blackwell Publishing, UK).

mechanism in the BLA. Furthermore, BLA DA modulates mPFC and NAc DA function in an opposite manner, such that BLA DA exerts an excitatory influence on mPFC and an inhibitory influence on NAc DA transmission. Under basal conditions, BLA DA depletion or intra-BLA DA receptor antagonism attenuates mPFC and potentiates NAc DA function (Louilot et al., 1985; McGregor et al., 1994; Simon et al., 1988). A similar modulation occurs under conditions of increased central DA transmission, as BLA DA depletion potentiates locomotor activation induced by systemic AMPH administration (Deminière et al., 1988; Simon et al., 1988). BLA D1 receptor blockade also facilitates cocaine self-administration while concomitantly potentiating NAc DA release (Hurd et al., 1997).

1.5. Rationale and Objectives

It seems clear from the present review that the DA innervation of the BLA, mPFC and NAc plays an integral role in mounting an appropriate behavioural stress response as well as in mediating reflexive and learned forms of sensory processing. Moreover, these regions exert a behaviourally relevant influence over one another via their respective DA projections, although the functional interdependence of central DA systems related to the behavioural stress response and information processing has been less well characterized. For example, it is currently unknown what, if any, influence BLA DA has on mPFC and NAc DA transmission in response to stressors. It is also unclear how or even if BLA DA modulates certain types of information processing. Thus, the present research was undertaken to elucidate the role of BLA DA in modulating mPFC and NAc DA function during a) the behavioural stress response and b) various forms of sensory processing that are mediated in part by central DA transmission and are affected by stressors.

In vivo voltammetry was used to examine the effects of BLA DA depletion and intra-BLA infusion of specific D1 and D2/D3 receptor antagonists on stressor-induced DA release in the mPFC and NAc. It was hypothesized that BLA DA depletion and BLA DA receptor blockade would have opposite effects

on the mPFC and NAc DA stress responses, attenuating the former and potentiating the latter. Moreover, given the influence of mPFC DA on NAc DA function, it was also hypothesized that the potentiation of stressor-induced NAc DA release would occur indirectly as a result of attenuated mPFC DA release in response to stress.

The effects of stressor-induced DA release in both hemispheres of the mPFC were determined in one study to assess any possible lateralized effects on the mPFC DA stress response, given the presumed asymmetrical role of mPFC DA transmission in mediating the physiological and behavioural responses to stress (Sullivan and Gratton, 2000a). Stressor-elicited DA release was determined in the infralimbic subregion of the mPFC. Previous studies indicate that the DA stress response in this area is more robust compared to that of the prelimbic cortex (Deutch, 1991; Doherty and Gratton, 1996). The core subregion of the NAc was chosen as the site to determine stressor-induced DA release because previous studies conducted in our laboratory have characterized the effects of tail pinch stress on NAc DA release in this area (Doherty and Gratton, 1992; Brake et al., 1997; Chretien and Gratton, 1998). It was found that the magnitude of DA release elicited by tail pinch stress in the NAc core remains stable over five consecutive once-daily stress sessions. The effects of another stressor, predator odour (fox urine), on NAc and mPFC DA release were assessed in one experiment in order to compare the DA responses to a well-characterized stressor and a potentially more relevant species typical threat. For example, the odours of various rodent predators (cat, fox, weasel, etc.) have been shown to elicit behavioural (Blanchard et. al., 1990; Zangrossi and File, 1992; Hogg and File, 1994; Wallace and Rosen, 2000, 2001), neuroendocrine (File et al., 1993; Perrot-Sinal et al., 1999; Morrow et al., 2000b, c) and neurochemical indices of stress, including increased mPFC (Sullivan and Gratton, 1998; Morrow et al., 2000b, c) and NAc (Bassareo et al., 2002) DA transmission.

It is possible that BLA DA can influence certain types of information processing either directly or indirectly by modulating mPFC and NAc DA function. For example, the exact nature of the modulatory influence of BLA DA

on PPI has yet to be detailed (Swerdlow et al., 1992). Moreover, no studies examining the possibility that BLA DA modulates LI or habituation of the ASR have been conducted to date. Thus, the effects of intra-BLA infusion of specific DA receptor antagonists on PPI, LI and habituation of the ASR were examined in the last two studies. It was hypothesized that BLA DA receptor blockade would impair PPI and habituation of the ASR indirectly as a consequence of diminished mPFC and enhanced NAc DA transmission. It was also hypothesized that this manipulation would result in disrupted LI by potentiating NAc DA function.

2.0. STUDY #1

EFFECTS OF BASOLATERAL AMYGDALA DOPAMINE DEPLETION ON THE NUCLEUS ACCUMBENS AND MEDIAL PREFRONTAL CORTICAL DOPAMINE RESPONSES TO STRESS

Carl W. Stevenson, Ronald M. Sullivan and A. Gratton

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2.1. PREFACE

The first study examined whether BLA DA modulates NAc and mPFC DA release in response to stressful stimuli. A physical stressor and a species-typical threat were used to elicit DA release in the NAc and mPFC of rats that had previously received DA-depleting lesions of the BLA. Previous evidence suggests that BLA DA can modulate NAc and mPFC DA function, although these studies did not address this issue in the context of the behavioural response to stress. This study also examined the possibility that BLA DA modulates the mPFC DA stress response in a lateralized manner, given that evidence indicates that right, but not left, mPFC DA transmission plays a specialized role in mediating the behavioural response to stress.

2.2. ABSTRACT

In vivo voltammetry was used to study the effects of basolateral amygdala dopamine depletion on stress-induced dopamine release in the nucleus accumbens and medial prefrontal cortex. Male Long–Evans rats received bilateral microinjections of 6-hydroxydopamine or vehicle into the basolateral amygdala. Changes in dopamine signal were monitored in the nucleus accumbens and in the right and left hemispheres of medial prefrontal cortex, in lesioned animals and shams. Animals were subjected to a physical stressor (tail pinch) and a species-typical threat (fox odour); each stressor was presented twice over four consecutive daily sessions. The results indicate that the nucleus accumbens dopamine responses to both stressors are significantly potentiated by dopamine-depleting lesions to basolateral amygdala. In contrast, while the dopamine stress response in the left medial prefrontal cortex did not differ between lesioned animals and shams, the right medial prefrontal cortical dopamine response to tail pinch, but not fox odour stress, was significantly attenuated in lesioned animals. Therefore, basolateral amygdala dopamine depletion had opposite effects on the nucleus accumbens and medial prefrontal cortical dopamine responses to stress, although the effect on the latter is lateralized to the right hemisphere in a stressor-specific manner.

These data indicate that stress-induced activation of meso-amygdaloid dopamine exerts an inhibitory influence on the nucleus accumbens dopamine response to stress. They also suggest the possibility that meso-amygdaloid dopamine influences the nucleus accumbens dopamine response to stress indirectly by modulating stress-induced dopamine release in medial prefrontal cortex. These findings add to a growing body of evidence of a preferential involvement of right medial prefrontal cortical dopamine in a wide range of physiological responses to stress.

2.3. INTRODUCTION

The amygdala is a limbic structure that is thought to attribute affective significance to environmental stimuli by forming a link between brain regions that process sensory information and areas involved in the production of emotional responses (Aggleton, 1993). The basolateral amygdaloid complex (BLA; lateral, basal, and accessory basal nuclei) relays sensory information from the cortex to the central amygdaloid nucleus (CeA), which in turn conveys information to the hypothalamus, midbrain, and brainstem (Davis et al., 1994b). A large body of evidence now indicates that the amygdala plays a significant role in mediating the behavioural, autonomic, and neuroendocrine responses to stressful stimuli (for reviews, see Davis, 1992; Henke, 1996; Gray and Bingaman, 1996; LeDoux, 1996).

The dopamine (DA) projections from the ventral tegmental area (VTA) to the nucleus accumbens (NAc) and medial prefrontal cortex (mPFC) have long been known to be activated by stress (Thierry et al., 1976; Herman et al., 1982; Dunn et al., 1984; Claustre et al., 1986; Abercrombie et al., 1989; Imperato et al., 1989; Doherty and Gratton, 1992, 1996; Sullivan and Gratton, 1998; Brake et al., 2000). Several studies now indicate that the VTA also sends a stress-responsive DA projection to the amygdala (Fallon et al., 1978; Herman et al., 1982; Coco et al., 1992; Young and Rees, 1998; Inglis and Moghaddam, 1999; Morrow et al., 2000a, Funada and Hara, 2001). Neuroanatomical and electrophysiological evidence suggests that the amygdala forms connections with several brain regions innervated by mesocorticolimbic DA neurons, notably the NAc, which is innervated by glutamate pyramidal neurons and where electrical stimulation of BLA evokes increases in neuronal activity (Kelley et al., 1982; Mogenson, 1988; McDonald, 1991). BLA also shares reciprocal glutamatergic connections with the mPFC (Krettek and Price, 1977; McDonald, 1991; McDonald et al., 1996), where BLA stimulation evokes complex changes in neuronal activity (Pérez-Jaranay and Vives, 1991). Finally, the amygdala projects to the VTA, and electrical stimulation of BLA also increases neuronal activity in this area (Maeda and

Mogenson, 1981; Gonzales and Chesselet, 1990; Wallace et al., 1992). Given its involvement in modulating responses to stress and its interconnections with the NAc, mPFC, and VTA, the amygdala would therefore be expected to influence stress-induced changes in mesocorticolimbic DA function.

Indeed, data from previous studies indicate that meso-amygdaloid DA neurons exert an inhibitory influence on NAc DA transmission. For example, injections of DA D2 receptor antagonists into BLA are reported to enhance NAc DA function, whereas similar injections of amphetamine attenuate these levels (Louilot et al., 1985). Intra-BLA administration of the D1 receptor antagonist SCH 23390 also appears to have a facilitatory affect on NAc DA release, accompanied by an increased rate of cocaine self-administration (Hurd et al., 1997). Similarly, DA-depleting lesions to BLA have been previously reported to enhance the locomotor response to amphetamine, as well as facilitate amphetamine self-adminstration (Simon et al., 1988). It appears also that a DA-sensitive mechanism in amygdala modulates mPFC DA function. The enhancement of NAc DA function resulting from 6-hydroxydopamine (6-OHDA) lesions to BLA is accompanied by attenuated mPFC DA transmission (Simon et al., 1988). Similarly, amygdaloid kindling has been shown to have opposite effects on NAc and mPFC DA release (Rada and Hernandez, 1990). Finally, amygdala lesions appear to attenuate the increase in mPFC DA metabolism elicited by unconditioned (Davis et al., 1994a) and conditioned stress (Goldstein et al., 1996).

In the present study we examined the possibility that BLA DA is involved in modulating the NAc and mPFC DA responses to stress in the freely behaving rat. Animals received either 6-OHDA or sham BLA lesions, and in vivo voltammetry was used to monitor changes in NAc or mPFC DA release elicited by exposure to a physical stressor (tail pinch) and a species-typical threat (fox odour). Finally, several lines of evidence indicate that the DA projection to mPFC is asymmetrically activated in response to stress (Sullivan and Gratton, 1998; Brake et al., 2000), suggesting that cortical regulation of physiological

responses to stress is lateralized (Carlson et al., 1993, 1996; Sullivan and Szchectman, 1995; Berridge et al., 1999). Therefore we examined the mesocortical DA stress response in the left and right hemispheres to determine if BLA 6-OHDA lesions affect the mPFC DA response to stress asymmetrically.

2.4. EXPERIMENTAL PROCEDURES

2.3.1. Animals

Male Long–Evans rats (Charles River, St. Constant, Québec, Canada) weighing 350–400 g at the time of surgery were used. The animals were housed singly on a 12-h light/dark reverse cycle (lights off at 0700 h) with free access to food and water. All procedures in the present study conformed to the guidelines of the Canadian Council on Animal Care. Unless indicated otherwise, all chemicals were obtained from Sigma (St. Louis, MO, USA).

2.4.2. Surgery

2.4.2.1. Lesions

Animals were randomly assigned to a sham- or a 6-OHDA-lesioned group. Animals were injected with atropine sulphate (0.1 mg/kg, i.p.) and anaesthetised with sodium pentobarbital (60 mg/kg, i.p.). Animals were placed in a stereotaxic apparatus and, with the incisor bar adjusted to maintain the skull horizontal, an injection cannula was inserted into the BLA 2.8 mm anterior to bregma, 4.0 mm lateral to the midline (angled 5° off of the vertical plane), and 8.0 mm ventral to the surface of the brain (Paxinos and Watson, 1982). Animals received bilateral microinjections of 6-OHDA (4 ug/0.5 ul in 0.1% ascorbic acid; AA) or vehicle (0.1% AA) over 2 min, and the cannula was left in place for an additional 4 min to allow for diffusion of 6-OHDA away from the cannula tip. Animals receiving 6-OHDA injections were pretreated with the norepinephrine (NE) uptake inhibitor desipramine (25 mg/kg, i.p.) 30 min prior to 6-OHDA infusion.

2.4.2.2. Electrode implantation

Three to four weeks after the lesioning procedure, animals were injected with atropine sulphate (0.1 mg/kg, i.p.), anaesthetised with sodium pentobarbital (60 mg/kg, i.p.), and placed in a stereotaxic apparatus. In the first experiment, animals were implanted with a voltammetric recording electrode into the right NAc core. The flat skull coordinates of the electrode implants were 1.6 mm anterior to bregma, 1.6 mm lateral to the midline, and 7.4 mm ventral to the surface of the brain. In the second experiment, animals were implanted with a voltammetric probe aimed at either the left or right mPFC. The flat skull coordinates of the electrode implants were 3.5 mm anterior to bregma, 0.8 mm lateral to the midline, and 4.7 mm ventral to the surface of the brain. In addition, animals were each implanted with a Ag/AgCl reference electrode and a stainless steel ground wire in the contralateral and ipsilateral parietal cortices, respectively. Miniature pin connectors soldered to the voltammetric and reference electrodes, and ground wire, were inserted into a plastic strip connector. The assembly was then secured with acrylic dental cement to three or four stainless steel screws threaded into the cranium. Testing began 3–4 days after implantation.

2.4.3. In vivo electrochemistry

2.4.3.1. Electrochemical probes

Voltammetric electrodes each consisted of three 30-m-diameter carbon fibres (Textron Systems, Wilmington, MA, USA) that extended 50–100 m beyond the sealed tip of a pulled glass capillary (outside diameter (o.d.) = 0.5 mm). The exposed fibres were repeatedly coated with a 5% solution of Nafion (Aldrich, Milwaukee, WI, USA), a perfluorinated ionomer. This treatment promotes the exchange of cations such as DA, while impeding the exchange of interfering anionic species such as AA and DOPAC. Each electrode was calibrated prior to implantation to determine its sensitivity to DA and its selectivity for DA against

AA. Calibrations were performed in 0.1 M phosphate-buffered saline (pH 7.4). Only electrodes with a highly linear response (r0.997) to increasing concentrations of DA and a DA-to-AA selectivity ratio greater than 1000:1 were used.

2.4.3.2. Chronoamperometric recordings

Electrochemical recordings were performed using a computer-controlled, high-speed chronoamperometric apparatus (Quanteon, Lexington, KY, USA). An oxidation potential of +0.55 mV (with respect to the reference electrode) was applied to the electrode for 100 ms at a rate of 5 Hz. The oxidation current was digitally integrated during the last 80 ms of each pulse. The sums of every 10 digitized oxidative cycles of the chronoamperometric waveform were automatically converted into equivalent values of DA concentration using the in vitro calibration factor. Values were displayed graphically on a video monitor at 2-s intervals. Extensive discussions concerning the interpretation of chronoamperometric data have been published previously (Mitchell and Gratton, 1991, 1992; Doherty and Gratton, 1992, 1996; Kiyatkin et al., 1993; Gratton and Wise, 1994; Noël and Gratton, 1995).

2.4.3.3. Testing procedure

Electrochemical recordings began 3-4 days after surgery. Immediately before a recording session, the in vitro calibration factor (the slope of the function relating increases in oxidation current to increases in DA concentration) for the animal's electrode was entered in the data acquisition software. This allowed on-line conversion of an increase in oxidation current to a value equivalent to the change in DA concentration that was required to produce an equal change in signal in vitro. Each animal was placed in a recording chamber and connected to the chronoamperometric instrument via a shielded cable and a low impedance multi-channel commutator (Airflyte, Bayonne, NJ, USA). Electrical interference was minimised by connecting a pre-amplifier configured as a current-to-voltage converter (gain=$1\times\ 10^{8}$) directly into each animal's head assembly. An

experiment began only after obtaining 60 min of stable baseline recordings. Animals received either 15 min of tail pinch or fox odour stress on four consecutive daily sessions; animals were subjected to each stressor twice, in counterbalanced order. Tail pinch stress consisted of placing a wooden clothespin on the animal's tail approximately 1-2 cm from its base, whereas fox odour stress consisted of placing a cotton swab tip dipped in fox urine (Buck Expert, Québec, Qc., Canada) in the recording chamber. Recordings were obtained during the stress period, and for 30–45 min after removal of the stressor (recovery period).

2.4.3.4. Electrochemical data format

Because of the inherent differences in sensitivity between Nafion-coated electrodes, in vivo changes in oxidation current recorded with different electrodes (i.e. in different animals) cannot be assumed to be equivalent. Thus, valid comparisons are possible only if the sensitivity of each electrode is calibrated against a standard and the electrochemical data are expressed as standard equivalent values. Because DA was used as the standard to calibrate electrode sensitivity, in vivo changes in oxidation current are expressed as molar equivalent values of DA concentration. Data are presented as changes in electrochemical signal (M DA equivalent) relative to the signal level immediately prior to the onset of stress (Time 0). Because the recording at Time 0 was the point of comparison for changes in electrochemical signal that followed, it was arbitrarily given a value of 0 M. Therefore, a value of 0 M is not meant to correspond to the concentration of extracellular DA; electrochemical data represent relative changes in extracellular DA levels elicited by a stimulus such as stress.

2.4.4. Histology and neurochemical analysis

At the conclusion of testing, animals were decapitated and the brains were rapidly removed and placed on ice. The brains were placed in a brain mould and transected coronally 1.0–1.5 mm posterior to the electrode tract. The sections of each brain containing the NAc or mPFC were kept for later histological verification of electrode placements; sections were placed in a 10% formalin

solution and then cryo-protected in a 30% sucrose solution. The sections were then sliced into 30-m coronal slices and stained with formal-thionin to confirm the position of the electrode tips. Brain sections containing the amygdala were transected coronally into 1-mm-thick slices, from which bilateral tissue punches of the basolateral and centromedial subregions were made. The tissue was frozen on dry ice and then stored at -80°C for subsequent determination of DA and NE content using high-performance liquid chromatography (HPLC) and electrochemical detection.

Left and right amygdala tissue sections were weighed and homogenised separately in a 0.1 M perchloric acid solution, containing 2.7 mM disodium EDTA and 3.3 mM glutathione (pH 5.0). Samples were centrifuged (14,000 r.p.m. for 15 min, at 4°C) and the homogenate supernatants were then filtered through 0.2-m nylon filters by centrifugation (14,000 r.p.m. for 15 min, at 4°C). Filtered supernatant was combined with 3,4-dihydroxybenzylamine (internal standard) and injected with an HPLC pump (Model L-7100, Hitachi, Tokyo, Japan) onto a reversed-phase silica/C18 column (CSC-Hypersil, 4.6×150 mm, 5-m particle size, Chromatography Sciences Corporation, Montréal, Qc., Canada). Mobile phase consisted of 58 mM monobasic sodium phosphate, 0.54 mM octyl sodium sulphate, and 0.21 mM disodium EDTA, and 10% v/v methanol solution (pH 3.5, adjusted with 10 N hydrochloric acid). The mobile phase was circulated through the HPLC system at a flow rate of 1.0 ml/min. Electrochemical detection was performed using amperometric detection (EG and G Model 400, Princeton Applied Research, Princeton, NJ, USA) at a glassy carbon dual working electrode (EG and G). The applied potential was set at +650 mV relative to a Ag/AgCl reference electrode, with a sensitivity setting of 0.5 nA/V. The limits of detection were approximately 90 pg/20 l and 20 pg/20 l for DA and NE, respectively. Acquisition of chromatograms was performed by computer using the Peak Simple Chromatography Data System (SRI Instruments, Torrance, CA, USA). Concentrations of DA and NE were determined by comparing the oxidation peaks produced by the samples to those produced by standards of known concentrations.

2.4.5. Statistical analysis

A mixed-measures analysis of variance (ANOVA), with lesion group and subregion as factors, was used to individually analyse amygdaloid DA and NE content. A mixed-measures ANOVA, with lesion group and time as factors, was also used to individually analyse DA signal increases in response to each stressor, in each brain region examined (NAc, left and right mPFC). Comparisons were based on differences in the amplitude of electrochemical signal increases taken at 5-min intervals from the onset of stress. When indicated, post-hoc comparisons were performed using Tukey's Honestly Significant Difference test. The level of significance for all comparisons was $P < 0.05$.

2.5. RESULTS

2.5.1. Effect of 6-OHDA lesions on amygdaloid dopamine and norepinephrine content

Amygdaloid tissue levels of DA and NE did not differ in the left and right hemispheres, of either lesioned animals or shams (data not shown), therefore the means of the left and right hemispheres of each brain were used in the statistical analysis of DA and NE content (Table 1). In the BLA of lesioned animals there was a significant decrease in DA content (45.5%) compared with shams ($F_{1, 96} = 10.54$, $P < 0.01$), as a well as a smaller but significant decrease (27.7%) in NE content ($F_{1, 96} = 6.25$, $P < 0.05$). Importantly, there was no difference in DA ($F_{1, 96} = 0.46$, $P > 0.05$) or NE ($F_{1, 96} = 1.56$, $P > 0.05$) content between lesioned animals and shams in the centromedial amygdala.

2.5.2. In vivo electrochemistry

2.5.2.1. Electrode placement verification

The location of the electrode tips within the NAc or mPFC is presented in Fig. 1. Only animals with histologically confirmed electrode placements in the NAc core or infralimbic mPFC were included in the data analysis.

2.5.2.2. Nucleus accumbens dopamine stress response

There were no differences, in any of the regions examined, between the amplitude of DA signals in response to the first or second exposure to either stressor (data not shown). Therefore, for each animal, the means of the first and second exposures (to the same stressor) were used in the statistical analysis of stress-induced DA signal increases. The mean increases in NAc DA signal, in response to tail pinch and fox odour stress, are presented in Fig. 2. In general, the DA responses to both stressors were greater in lesioned animals compared with shams. This was confirmed by the statistical analysis, which revealed a significant lesion group x time interaction ($F_{8, 120} = 2.18$, $P < 0.05$) in the DA response to tail pinch; post-hoc comparisons indicated a significantly greater increase in DA signal ($P < 0.05$) at all but the 5- and 45-min time intervals in lesioned animals. Similarly, there was a significant lesion group × time interaction ($F_{8, 120} = 2.33$, $P < 0.05$) in the DA response to fox odour and post-hoc comparisons indicated a significantly greater increase in DA signal ($P < 0.05$) at all but the 5- and 10-min intervals in 6-OHDA-lesioned animals.

2.5.2.3. Medial prefrontal cortical dopamine stress response

The mean increases in the left and right mPFC DA signals, elicited by both stressors, are presented in Fig. 3. In general, 6-OHDA lesions had no effect on DA signal increases in the left mPFC, in response to tail pinch ($F_{1, 16} = 0.31$, $P > 0.05$) or fox odour ($F_{1, 16} = 1.19$, $P > 0.05$). In the right mPFC however, the DA response to tail pinch in lesioned animals was significantly smaller than that of shams ($F_{11, 143} = 1.95$, $P < 0.05$); post-hoc comparisons revealed that this decrease was significant at the 15-, 20-, and 25-min time intervals ($P < 0.05$). There was no such group difference in the right mPFC DA response to fox odour ($F_{1, 13} = 1.21$, $P > 0.05$).

2.6. DISCUSSION

2.6.1. Mesocorticolimbic dopamine responses to stress

One of the main findings of the present study is that stress-induced NAc DA release is enhanced in animals that have received DA-depleting lesions of BLA; this potentiation was seen in response to a physical stressor as well as a species-typical threat. In rats, exposure to predator odour elicits a number of stress-related physiological responses, such as increased freezing and avoidance behaviours (Blanchard et. al., 1990; Zangrossi and File, 1992; Hogg and File, 1994; Wallace and Rosen, 2000, 2001). Predator odour has been shown to elicit a neuroendocrine stress response (File et al., 1993; Perrot-Sinal et al., 1999; Morrow et al., 2000a, b) as well as increases in mPFC DA transmission (Sullivan and Gratton, 1998; Morrow et al., 2000a, b; Bassareo et al., 2002). In agreement with the present results, a recent report indicates that fox odour also evokes DA release in the NAc (Bassareo et al., 2002). This finding is at odds with the study of Morrow et al. (2000a), who failed to observe any effect of 2,5-dihydro-2,4,5-trimethylthiazoline (TMT), an odour derived from fox feces, on NAc DA metabolism. Whereas the present study and that of Bassareo et al. (2002) used in vivo measures to quantify DA release, Morrow et al. (2000a) measured NAc DA metabolism using post-mortem methods. Furthermore, the present study and that of Bassareo et al. (2002) used fox urine as predator odour, while Morrow et al. (2000a) used TMT. Thus, differences in methodological approach may explain this discrepancy. The present findings are in agreement with other evidence of increased NAc DA transmission as a result of impaired BLA DA function (Louilot et al., 1985; Simon et al., 1988; Hurd et al., 1997). Taken together with the present study, it would appear that meso-amygdaloid DA exerts an inhibitory influence on stress-induced DA function in the NAc, for both types of stress examined.

Previous studies have shown that perturbations in amygdala function result in opposite changes in NAc and mPFC DA transmission (Simon et al., 1988; and

Rada and Hernandez, 1990). Similarly, we report that the increased stress-induced release of NAc DA was accompanied by decreased release of mPFC DA, albeit the latter effect was lateralized and stressor-specific. DA release in NAc is known to be inhibited by a DA-sensitive mechanism in mPFC. Injections of DA antagonists into the mPFC increase extracellular levels of DOPAC in NAc, whereas similar injections of the indirect DA agonist amphetamine (AMPH) decrease NAc DOPAC levels (Louilot et al., 1989). Similarly, injections of D1 receptor antagonists into the mPFC enhance stress-induced increases in NAc DA levels (Doherty and Gratton, 1996). Finally, DA-depleting lesions of mPFC enhance NAc DA transmission in response to pharmacological and environmental stimuli (Deutch et al., 1990; Mitchell and Gratton, 1992; Thompson and Moss, 1995). It is thus tempting to speculate that in response to at least some stressors, meso-amygdaloid DA can influence the NAc DA release indirectly by modulating the mPFC DA stress response.

2.6.2. Mesocortical DA asymmetry, stress and coping

We presently report that DA-depleting lesions to BLA attenuate the right mPFC DA response to tail pinch stress and not fox odour. While the reason for this selective effect is not obvious, one likely explanation involves the nature of the coping responses elicited by the different types of stress. During tail pinch stress, animals typically chew vigorously on the clothes pin for much of the session. In contrast, fox odour exposure typically causes rats to retreat to a corner of the testing chamber where they remain passively. It is known that rats exposed to novelty stress show increased mPFC DA turnover, particularly in the right mPFC, and that this right-sided increase is selectively reduced by allowing the animal to chew on an inedible object as a displacement behaviour or active coping response (Berridge et al., 1999). The right mPFC, in conjunction with the amygdala, may be especially important in mediating such responses. The amygdala is well known to stimulate chewing movements (Takeuchi et al., 1988), as seen with subthreshold kindling stimulation. If this activity were disinhibited by amygdala DA depletion, this behaviour could be facilitated in the appropriate

situation, effectively enhancing the active coping response and reducing stressfulness, as reflected in an attenuated right mPFC DA stress response. The present lateralized finding in mPFC is yet another example of stress-related asymmetries in mesocortical DA function (e.g. Berridge et al., 1999; Brake et al., 2000; Carlson et al., 1991, 1993, 1996; Sullivan and Gratton 1998), and the right mPFC DA system appears especially important in coping with stress (Sullivan and Szechtman, 1995). While amygdala-mPFC connectivity and functional interactions are well documented (see below), the asymmetrical nature of such interactions is virtually unstudied. It is known, however, that left vs. right mPFC DA depletion has distinct effects on subcortical DA function (Carlson et al., 1996), including that in amygdala (Sullivan and Szechtman, 1995). The present findings suggest that amygdala DA depletion is also capable of producing asymmetrical effects in mPFC.

2.6.3. Circuitry mediating amygdala modulation of mesocorticolimbic dopamine stress responses

Within the BLA, DA has been shown to increase the firing rate of local GABA interneurons, and decrease the activity of glutamatergic pyramidal neurons, resulting in an attenuation of BLA projection neuron activity (Rosenkranz and Grace, 1999). A decrease in BLA DA tone would therefore be expected to disinhibit projection neurons, resulting in potentiated glutamate release in regions that receive BLA input.

There are several possible anatomical circuits by which meso-amygdaloid DA could influence stress-induced DA release in the NAc and mPFC. One such possibility is activation of the amygdalo-fugal pathway. BLA pyramidal neurons project to GABAergic neurons of the CeA (Davis et al., 1994b), and evidence suggests that CeA neurons send a direct projection to VTA GABA interneurons (Maeda and Mogenson, 1981; Wallace et al., 1992; Esclapez et al., 1993; Sun and Cassell, 1993). These interneurons exert an inhibitory influence on VTA DA neurons (Johnson and North, 1992); therefore, BLA DA depletion, resulting in

disinhibition of BLA projection neuron activity, could have an indirect effect on the activity of VTA DA neurons and, consequently, NAc and mPFC DA release.

Another possibility is that BLA DA may modulate VTA neuronal activity indirectly via the NAc. BLA pyramidal neurons are known to project to the NAc, presumably terminating on GABA neurons (Krettek and Price, 1978; Kelley et al., 1982; McDonald, 1991), which, in turn, project to DA and GABA neurons in the VTA (Walaas and Fonnum, 1980; Kalivas et al., 1993). Thus it is entirely possible that disinhibition of BLA output may also influence the NAc DA response to stress via a direct amygdalo-accumbens projection. The fact that electrical stimulation of the BLA elicits DA release in NAc (Floresco et al., 1998; Howland et al., 2002) is in general agreement with the present findings.

The DA projection to the BLA might also modulate the NAc DA response to stress indirectly by altering the mPFC DA stress response. BLA pyramidal cells send a glutamatergic projection to GABA interneurons and glutamatergic projection neurons in the mPFC (McDonald, 1991; Bacon et al., 1996), and anatomical evidence indicates that meso-accumbens DA transmission is regulated by the mPFC, via glutamatergic inputs to both the NAc and VTA (Walaas and Fonnum, 1980; Carter, 1982; Christie et al., 1985; Sesack and Pickel, 1992; Kalivas et al., 1993; Carr and Sesack, 2000; Ding et al., 2001). In the present study, BLA DA depletion resulted in an attenuation of mPFC DA release in response to tail pinch stress. Stress is also known to evoke glutamate release in mPFC (Moghaddam, 2002), a source of which may originate in the BLA. Although the effects of mPFC glutamate on the local DA stress response are complex (Takahata and Moghaddam, 1998; Feenstra et al., 1998; Del Arco and Mora, 2001), a recent report indicates that glutamate receptor activation in the mPFC can attenuate local DA release in response to stress (Del Arco and Mora, 2001). Therefore disinhibition of the glutamatergic projection from the BLA to the mPFC, as a result of BLA DA depletion, may result in a potentiation of stress-induced glutamate release in the mPFC and, consequently, an attenuated mPFC DA stress response. Diminished mPFC DA release in response to stress would

then be expected to result in a potentiated NAc DA stress response (Deutch et al., 1990; Doherty and Gratton, 1996).

2.6.4. Conclusions

DA-depleting lesions to BLA resulted in a potentiation of the NAc DA response to a physical stressor and a species-typical threat, suggesting that meso-amygdaloid DA exerts an inhibitory influence on the NAc DA response to stress. DA depletion in BLA also attenuated the right mPFC DA response to a physical stress, raising the possibility that meso-amygdaloid DA can influence the NAc DA stress response indirectly via a DA-sensitive mechanism in mPFC. Finally, these data add to a growing body of evidence indicating that stress-induced DA activity in the right mPFC is especially sensitive to a variety of manipulations, including BLA DA depletion.

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REFERENCES

Abercrombie ED, Keefe KA, DiFrischia DS and Zigmond MJ (1989) Differential effect of stress on *in vivo* dopamine release in striatum, nucleus accumbens, and medial frontal cortex. J Neurochem 52:1655-1658.

Aggleton JP (1993) The contribution of the amygdala to normal and abnormal emotional states. Trends Neurosci 16:328-333.

Bacon SJ, Headlam AJN, Gabbott PLA and Smith AD (1996) Amygdala input to medial prefrontal cortex (mPFC) in the rat: a light and electron microscope study. Brain Res 720:211-219.

Bassareo V, De Luca MA and Di Chiara G (2002) Differential expression of motivational stimulus properties by dopamine in nucleus accumbens shell versus core and prefrontal cortex. J Neurosci 22:4709-19.

Berridge CW, Mitton E, Clark W and Roth RH (1999) Engagement in a non-escape (displacement) behavior elicits a selective and lateralized suppression of frontal cortical dopaminergic utilization in stress. Synapse 32:187-197.

Blanchard RJ, Blanchard DC, Rodgers J and Weiss SM (1990) The characterization and modelling of anti-predator defensive behavior. Neurosci Biobehav Rev 14:463-472.

Blanchard DC (1997) Stimulus, environmental, and pharmacological control of defensive behaviors. In: Bouton ME and Fanselow MS (Eds), Learning, Motivation, and Cognition: The Functional Behaviorism of Robert C. Bolles. Washington, DC: American Psychological Association, pp. 283-303.

Brake WG, Sullivan RM and Gratton A (2000) Perinatal distress leads to lateralized medial prefrontal cortical dopamine hypofunction in adult rats. J Neurosci 20:5538-5543.

Carlson JN, Fitzgerald LW, Keller RW and Glick SD (1991) Side and region dependent changes in dopamine activation with various durations of restraint stress. Brain Res 550:313-318.

Carlson JN, Fitzgerald LW, Keller RW and Glick SD (1993) Lateralized changes in prefrontal cortical dopamine activity induced by controllable and uncontrollable stress in the rat. Brain Res 630:178-187.

Carlson JN, Visker KE, Keller RW and Glick SD (1996) Left and right 6-hydroxydopamine lesions of the medial prefrontal cortex differentially alter subcortical dopamine utilization and the behavioral response to stress. Brain Res 711:1-9.

Carr DB and Sesack SR (2000) Projections from the rat prefrontal cortex to the ventral tegmental area: target specificity in the synaptic associations with mesocortical and mesoaccumbens neurons. J Neurosci 20:3864-73.

Carter CJ (1982) Topographical distribution of possible glutamatergic pathways from the frontal cortex in the striatum and substantia nigra in rats. Neuropharmacology 21:383-393.

Christie MJ, Bridge S, James LB and Beart PM (1985) Excitotoxic lesions suggest an aspartatergic projection from rat medial prefrontal cortex to ventral tegmental area. Brain Res 333:169-172.

Claustre Y, Rivy JP, Dennis T, and Scatton B (1986) Pharmacological studies on stress-induced increase in frontal cortical dopamine metabolism in the rat. J Pharmacol Exp Ther 238:693-700.

Coco ML, Kuhn CM, Ely TD and Kilts CD (1992) Selective activation of mesoamygdaloid dopamine neurons by conditioned stress: attenuation by diazepam. Brain Res 590:39-47.

Davis M (1992) The role of the amygdala in conditioned fear. In: Aggleton JP (Ed), The Amygdala. Neurobiological Aspects of Emotion, Memory, and Mental Dysfunction, Wiley-Liss, New York, pp. 255-305.

Davis M, Hitchcock JM, Bowers MB, Berridge CW, Melia KR and Roth RH (1994a) Stress-induced activation of prefrontal cortex dopamine turnover: blockade by lesions of the amygdala. Brain Res 664:207-210.

Davis M, Rainnie D and Cassell M (1994b) Neurotransmission in the rat amygdala related to fear and anxiety. Trends Neurosci 17:208-214.

Del Arco A and Mora F (2001) Dopamine release in the prefrontal cortex during stress is reduced by the local activation of glutamate receptors. Brain Res Bull 56:125-130.

Ding DC, Gabbott PL and Totterdell S (2001) Differences in the laminar origin of projections from the medial prefrontal cortex to the nucleus accumbens shell and core regions in the rat. Brain Res 917:81-89.

Deutch AY, Clark WA and Roth RH (1990) Prefrontal cortical dopamine depletion enhances the responsiveness of mesolimbic dopamine neurons to stress. Brain Res 521:311-315.

Doherty MD and Gratton A (1996) Medial prefrontal cortical D1 receptor modulation of the meso-accumbens dopamine response to stress: an electrochemical study in freely-behaving rats. Brain Res 715:86-97.

Doherty MD and Gratton A (1992) High-speed chronoamperometric measurements of mesolimbic and nigrostriatal dopamine release associated with repeated daily stress. Brain Res 586:295-302.

Dunn AJ and File SE (1984) Cold restraint alters dopamine metabolism in frontal cortex, nucleus accumbens and neostriatum. Physiol Behav 31:511-513.

Esclapez M, Tillakaratne NJ, Tobin AJ and Houser CR (1993) Comparative localization of mRNAs encoding two forms of glutamic acid decarboxylase with nonradioactive in situ hybridization methods. J Comp Neurol 331:339-362.

Fallon JH, Koziell DA and Moore RY (1978) Catecholamine innervation of the basal forebrain II. Amygdala, suprarhinal cortex and entorhinal cortex. J Comp Neurol 180:509-531.

File SE, Zangrossi H, Sanders FL and Mabbutt PS (1993) Dissociation between behavioural and corticosterone responses on repeated exposures to cat odor. Physiol Behav 54:1109-1111.

Floresco SB, Yang CR, Phillips AG and Blaha CD (1998) Basolateral amygdala stimulation evokes glutamate receptor-dependent dopamine efflux in the nucleus accumbens of the anaesthetized rat. Eur J Neurosci 10:1241-1251.

Feenstra MGP, Botterblom MHA and Van Uum JHM (1998) Local activation of metabotropic glutamate receptors inhibits the handling-induced increased release of dopamine in the nucleus accumbens but not that of dopamine or noradrenaline in the prefrontal cortex: comparison with inhibition of ionotropic receptors. J Neurochem 70:1104-1113.

Funada M and Hara C (2001) Differential effects of psychological stress on activation of the 5-hydroxytryptamine- and dopamine-containing neurons in the brain of freely moving rats. Brain Res 901:247-251.

Goldstein LE, Rasmusson AM, Bunney BS and Roth RH (1996) Role of the amygdala in the coordination of behavioral, neuroendocrine, and prefrontal cortical monoamine responses to psychological stress in the rat. J Neurosci 16:4787-4798.

Gonzales C and Chesselet MF (1990) Amygdalonigral pathway: an anterograde study in the rat with phaseolus vulgaris leucoagglutinin (PHA-L). J Comp Neurol 297:182-200.

Gratton A and Wise RA (1994) Drug- and behavior-associated changes in dopamine-related electrochemical signals during intravenous cocaine self-administration in rats. J Neurosci 14:4130-4146.

Gray TS and Bingaman EW (1996) The amygdala: corticotropin-releasing factor, steroids, and stress. Crit Rev Neurobiol 10:155-168.

Henke PG (1992) Stomach pathology and the amygdala. In: Aggleton JP (Ed), The Amygdala. Neurobiological Aspects of Emotion, Memory, and Mental Dysfunction, Wiley-Liss, New York, pp. 323-338.

Herman JP, Guillonneau D, Dantzer R, Scatton B, Semerdjian-Rouqier L and Le Moal M (1982) Differential effects of inescapable footshocks and of stimuli previously paired with inescapable footshocks on dopamine turnover in cortical and limbic areas of the rat. Life Sci 30:2207-2214.

Hogg S and File SE (1994) Responders and nonresponders to cat odor do not differ in other tests of anxiety. Pharmacol Biochem Behav 49:219-222.

Howland JG, Taepavarapruk P and Phillips AG (2002) Glutamate receptor-dependent modulation of dopamine efflux in the nucleus accumbens by basolateral, but not central, nucleus of the amygdala in rats. J Neurosci 22:1137-1145.

Hurd RL, McGregor A and Pontén M (1997) *In vivo* amygdala dopamine levels modulate cocaine self-administration behaviour in the rat: D1 dopamine receptor involvement. Eu. J Neurosci 9:2541-2548.

Imperato A, Puglisi-Allegra S, Casolini P, Zocchi A and Angelucci L (1989) Stress-induced enhancement of dopamine and acetylcholine release in limbic structures: role of corticosterone. Eur J Pharmacol 165:337-338.

Inglis FM and Moghaddam B (1999) Dopaminergic innervation of the amygdala is highly responsive to stress. J Neurochem 72:1088-1094.

Johnson SW and North RA (1992) Two types of neurones in the rat ventral tegmental area and their synaptic inputs. J Physiol (Lond) 450:455-468.

Kalivas PW, Churchill L and Klitenick MA (1993) GABA and enkephalin projection from the nucleus accumbens and ventral pallidum to the ventral tegmental area. Neuroscience 57:1047-1060.

Kelley AE, Domesick VB and Nauta WJH (1982) The amygdalostriatal projection in the rat - an anatomical study by anterograde and retrograde tracing methods. Neuroscience 7:615-630.

Kiyatkin EA, Wise RA and Gratton A (1993) Drug- and behavior-associated changes in dopamine-related electrochemical signals during intravenous heroin self-administration in rats. Synapse 14:60-72.

Krettek JE and Price JL (1977) Projections from the amygdaloid complex to the cerebral cortex and thalamus in the rat and cat. J Comp Neurol 172:687-722.

LeDoux JE (1996) Emotion networks and motor control: a fearful view. Prog Brain Res 107:437-446.

Louilot A, Le Moal M and Simon H (1989) Opposite influences of dopaminergic pathways to the prefrontal cortex or the septum on dopaminergic transmission in the nucleus accumbens: an *in vivo* voltammetric study. Neuroscience 29:45-56.

Louilot A, Simon H, Taghzouti K and Le Moal M (1985) Modulation of dopaminergic activity in the nucleus accumbens following facilitation or blockade of the dopaminergic transmission in the amygdala: a study by *in vivo* differential pulse voltammetry. Brain Res 346:141-145.

Maeda H and Mogenson GJ (1981) Electrophysiological responses of the ventral tegmental area to electrical stimulation of amygdala and septum. Neuroscience 6:367-376.

McDonald AJ, Mascagni F and Guo L (1996) Projections of the medial and lateral prefrontal cortices to the amygdala: a phaseolus vulgaris leucoagglutin study in the rat. Neuroscience 71:55-75.

McDonald AJ (1991) Organization of amygdaloid projections to the prefrontal cortex and associated striatum in the rat. Neuroscience 44:1-14.

Mitchell JB and Gratton A (1992) Partial dopamine depletion of the prefrontal cortex leads to enhanced mesolimbic dopamine release elicited by repeated exposure to naturally reinforcing stimuli. J Neurosci 12:3609-3618.

Mitchell JB and Gratton A (1991) Opioid modulation and sensitization of dopamine release elicited by sexually relevant stimuli: a high-speed chronoamperometric study in freely-behaving rats. Brain Res 551:20-27.

Mogenson GJ, Yang CR and Yim CY (1988) Influence of dopamine on limbic inputs to the nucleus accumbens. Ann NY Acad Sci 537:173-187.

Moghaddam B (2002) Stress activation of glutamate neurotransmission in the prefrontal cortex: implications for dopamine-associated psychiatric disorders. Biol Psychiatry 51:775-787.

Morrow BA, Redmond AJ, Roth RH and Elsworth JD (2000a) The predator odor, TMT, displays a unique, stress-like pattern of dopaminergic and endocrinological activation in the rat. Brain Res 864:146-151.

Morrow BA, Roth RH and Elsworth JD (2000b) TMT, a predator odor, elevates mesoprefrontal dopamine metabolic activity and disrupts short-term working memory in the rat. Brain Res Bull 52:519-523.

Noël MB and Gratton A (1995) Electrochemical evidence of increased dopamine transmission in prefrontal cortex and nucleus accumbens elicited by ventral tegmental F-opioid receptor activation in freely-behaving rats. Synapse 21:110-122.

Paxinos G and Watson C (1982) The rat brain in stereotaxic coordinates, Academic, New York.

Pérez-Jaranay JM and Vives F (1991) Electrophysiological study of the response of medial prefrontal cortex neurons to stimulation of the basolateral nucleus of the amygdala in the rat. Brain Res 564:97-101.

Perrot-Sinal TS, Ossenkopp K-P and Kavaliers M (1999) Brief predator odour exposure activates the HPA axis independent of locomotor changes. NeuroReport 10:775-780.

Rada P and Hernandez L (1990) Opposite changes of dopamine turnover in prefrontal cortex and nucleus accumbens after amygdaloid kindling. Neurosci Lett 117:144-148.

Rosenkranz JA and Grace AA (1999) Modulation of basolateral amygdala neuronal firing and afferent drive by dopamine receptor activation *in vivo*. J Neurosci 19:11027-11039.

Sesack SR and Pickel VM (1992) Prefrontal cortical efferents in the rat synapse on unlabeled neuronal targets of catecholamine terminal in the nucleus accumbens septi and on dopamine neurons in the ventral tegmental area. J Comp Neurol 320:145-160.

Simon H, Taghzouti K, Gozlan H, Studler JM, Louilot A, Herve D, Glowinski J, Tassin JP and Le Moal M (1988) Lesion of dopaminergic terminals in the amygdala produces enhanced locomotor response to D-amphetamine and opposite changes in dopaminergic activity in prefrontal cortex and nucleus accumbens. Brain Res 447:335-340.

Sullivan RM and Gratton A (1998) Relationships between stress-induced increases in medial prefrontal cortical dopamine and plasma corticosterone levels in rats: role of cerebral laterality. Neuroscience 83:81-91.

Sullivan RM and Szechtman H (1995) Asymmetrical influence of mesocortical dopamine depletion on stress ulcer development and subcortical dopamine systems in rats: implications for psychopathology. Neuroscience 65:757-766.

Sun N and Cassell MD (1993) Intrinsic GABAergic neurons in the rat central extended amygdala. J Comp Neurol 330:381-404.

Takahata R and Moghaddam B (1998) Glutamatergic regulation of basal and stimulus-activated dopamine release in the prefrontal cortex. J Neurochem 71:1443-1449.

Takeuchi Y, Satoda T and Matsushima R (1988) Amygdaloid projections to commissural interneurons for masticatory motoneurons. Brain Res Bull 21:123-127.

Thierry AM, Tassin JP, Blanc G and Glowinski J (1976) Selective activation of the mesocortical dopamine system by stress. Nature 263:242-244.

Thompson TL and Moss RL (1995) *In vivo* stimulated dopamine release in the nucleus accumbens: modulation by the prefrontal cortex. Brain Res 686:93-98.

Walaas I and Fonnum F (1980) Biochemical evidence for gamma-aminobutyrate containing fibers from the nucleus accumbens to the substantia nigra and ventral tegmental area in the rat. Neuroscience 5:325-336.

Wallace DM, Magnuson DJ and Gray TS (1992) Organization of amygdaloid projections to brainstem dopaminergic, noradrenergic, and adrenergic cell groups in the rat. Brain Res Bull 28:447-454.

Wallace KJ and Rosen JB (2001) Neurotoxic lesions of the lateral nucleus of the amygdala decrease conditioned fear but not unconditioned fear of a predator odor: comparison with electrolytic lesions. J Neurosci 21:3619-3627.

Wallace KJ and Rosen JB (2000) Predator odor as an unconditioned fear stimulus in rats: elicitation of freezing by trimethylthiazoline, a component of fox feces. Behav Neurosci 114:912-922.

Young AMJ and Rees KR (1998) Dopamine release in the amygdaloid complex of the rat, studied by brain microdialysis. Neurosci Lett 249:49-52.

Zangrossi H and File SE (1992) Behavioural consequences in animal tests of anxiety and exploration of exposure to cat odour. Brain Res Bull 29:381-388.

Table 1. Dopamine and norepinephrine content in basolateral and centromedial amygdala of sham- and 6-hydroxydopamine-lesioned animals.

	BLA		CM	
	DA	NE	DA	NE
Sham (n=25)	339 ± 44.7	93.1 ± 5.5	259 ± 27.0	87.2 ± 4.4
Lesion (n=25)	185 ± 22.5[a]	67.3 ± 6.4[b]	226 ± 35.9	100 ± 11.1

DA and NE content are expressed as pg/mg wet tissue. Values are expressed as means ± S.E.M.

[a] Significantly different from DA content in BLA of shams ($P < 0.01$).

[b] Significantly different from NE content in BLA of shams ($P < 0.05$).

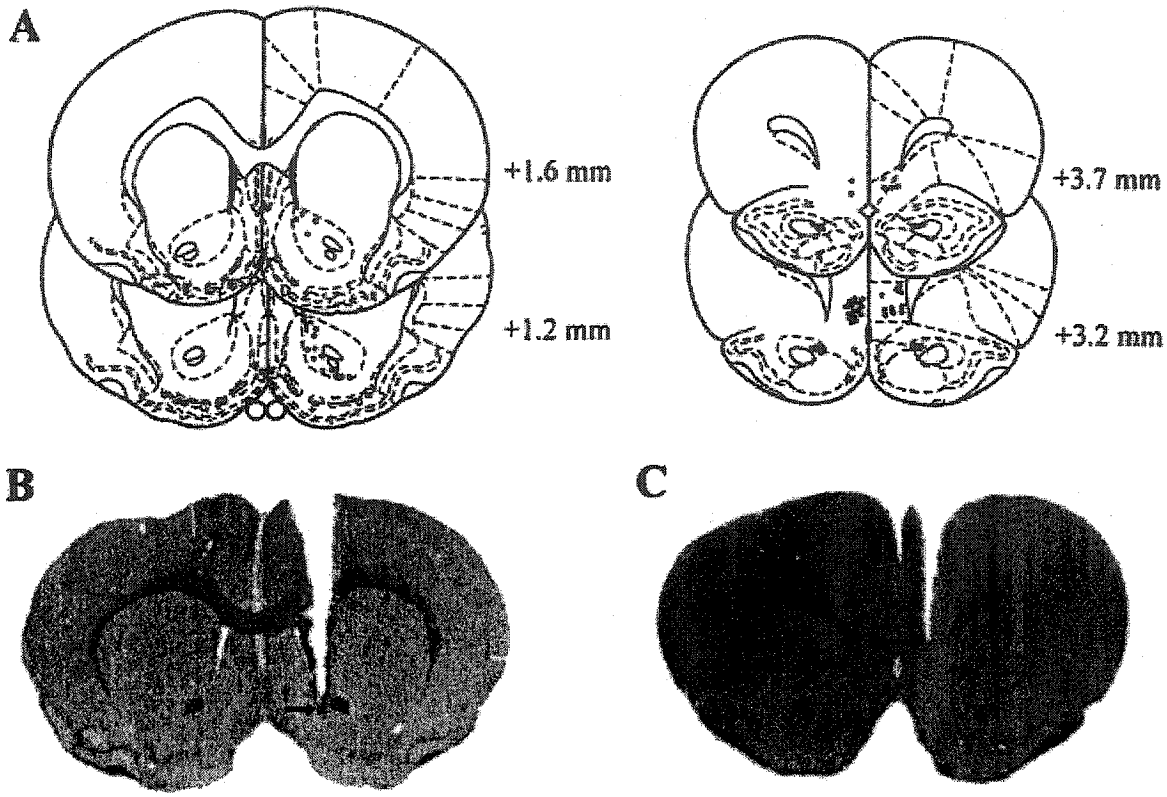


Fig. 1. Histological verification of electrode tip placements. (A) Schematic illustration of the location of electrode tip placements within the NAc and mPFC. Photomicrographs of representative histological sections showing electrode tip placements within the (B) NAc and (C) mPFC (arrows indicate the most ventral extent of the electrode tip). (Reprinted with permission from Elsevier © 2003).

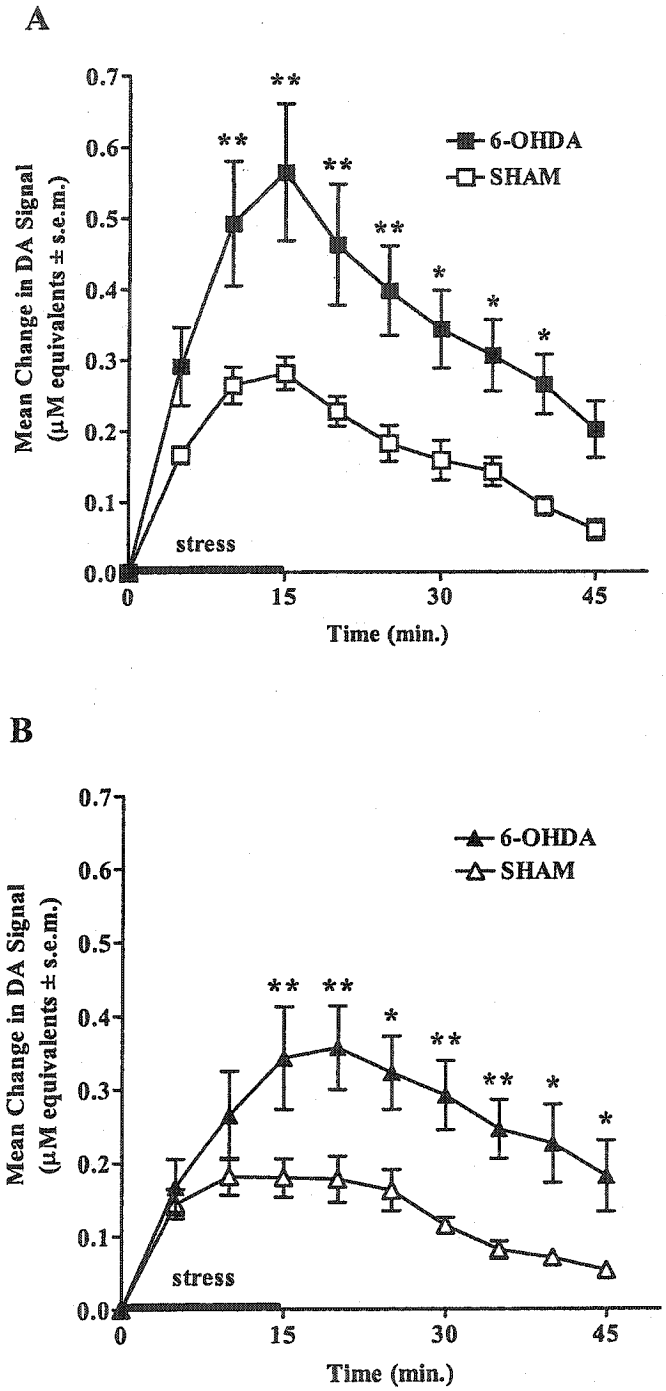
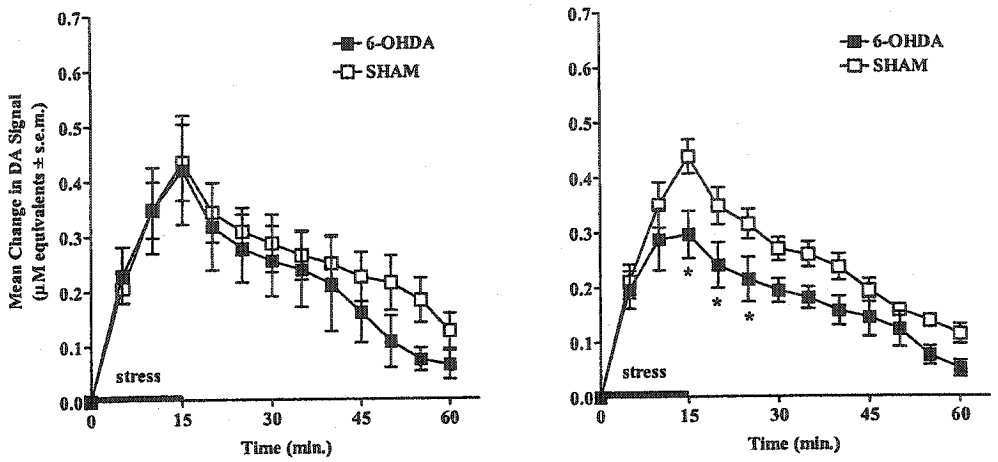


Fig. 2. NAc DA responses to (A) tail pinch and (B) fox odour stress. 6-OHDA-lesioned animals (n=9) had significantly enhanced DA signals compared with shams (n=8), in response to both stressors (* $P < 0.05$, ** $P < 0.01$; Tukey's HSD). (Reprinted with permission from Elsevier © 2003).

A



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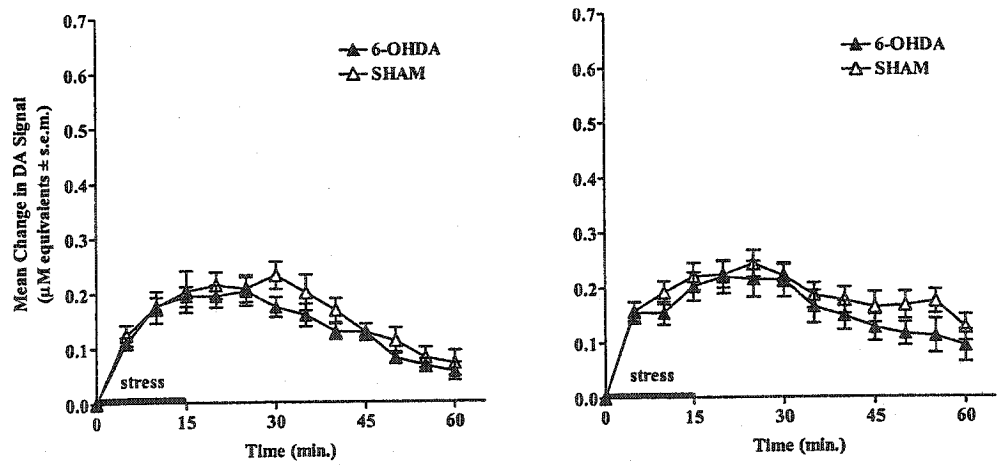

Fig. 3. mPFC DA responses to (A) tail pinch and (B) fox odour stress. In left mPFC, there were no significant differences between the DA signals of 6-OHDA- (n=9) and sham-lesioned (n=9) animals, in response to either stressor. In right mPFC, 6-OHDA-lesioned animals (n=7) had significantly attenuated DA signals compared with shams (n=8), in response to (A) tail pinch but not (B) fox odour stress (* $P < 0.05$; Tukey's HSD). (Reprinted with permission from Elsevier © 2003).

3.0. STUDY #2

BASOLATERAL AMYGDALA MODULATION OF THE NUCLEUS ACCUMBENS DOPAMINE RESPONSE TO STRESS: ROLE OF THE MEDIAL PREFRONTAL CORTEX

C. W. Stevenson and A. Gratton

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3.1. PREFACE

The previous study revealed that basolateral amygdala dopamine depletion resulted in a potentiation of the NAc DA response to stress. This study also suggested the possibility that the potentiation of the NAc DA stress response caused by BLA DA depletion may be due, at least in part, to the attenuation of the mPFC DA response to stress. However, one caveat of the previous study is that 6-OHDA lesions to the BLA resulted in significant depletions of both DA and, to a lesser extent, NE. Therefore it is possible that the effects on the NAc and mPFC DA stress responses were due to BLA NE, and not DA, depletion. Furthermore, if the effects seen in the previous study are due to BLA DA, and not NE, depletion, it is unknown which BLA DA receptor subtype(s) is involved in mediating the effects on stress-induced NAc and mPFC DA release. Thus, the present study examined the effects of intra-BLA infusion of specific DA D1 and D2/D3 receptor antagonists on the NAc and mPFC DA responses to stress. Moreover, the hypothesis that BLA DA modulates the NAc DA stress response indirectly by modulating stress-induced mPFC DA release was directly tested in the present study.

3.2. ABSTRACT

The basolateral amygdala (BLA) is involved in modulating affective responses to stress and, along with the nucleus accumbens (NAc) and medial prefrontal cortex (mPFC), receives a stress-responsive dopamine (DA) projection from the ventral tegmental area. The present study was undertaken to characterize the role of BLA DA D1 and D2/D3 receptor subtypes in modulating the NAc and mPFC DA responses to stress. Voltammetry was used to monitor, in freely behaving rats, stress-induced DA release in NAc or mPFC after injection of D1 (SCH 23390) or D2/D3 (raclopride) receptor antagonist into BLA. Intra-BLA SCH 23390 injection potentiated stress-induced NAc DA release but attenuated the mPFC DA stress response; raclopride had no effect on either the NAc or mPFC DA responses to stress. Based on these results, we also examined the possibility that BLA can indirectly modulate the NAc DA stress response via its projection to mPFC. To do so we studied the effects of intra-mPFC co-administration of D1 (SKF 38393) and D2/D3 (quinpirole) receptor agonists on the potentiated NAc DA stress response resulting from intra-BLA SCH 23390 injection. Alone, mPFC D1 and D2/D3 receptor co-activation had no effect on stress-induced NAc DA release, but did prevent the potentiated NAc DA stress response produced by BLA D1 receptor blockade. These findings indicate that BLA DA modulates the NAc and mPFC DA stress responses via activation of the D1 receptor subtype. They also suggest that BLA DA modulates stress-induced NAc DA release indirectly by modulating the mPFC DA response to stress.

3.3. INTRODUCTION

Central dopamine (DA) dysfunction is thought to play a key role in the pathophysiology of a number of psychiatric diseases, including schizophrenia, drug addiction, and affective disorders (Weinberger, 1987; Wilner et al., 1991; Brown and Gershon, 1993; Grace, 1993, 2000), and stress can exacerbate the symptomatology and even precipitate the onset of these diseases (Gispen-de Wied, 2000; Sinha, 2001; Moghaddam, 2002). These effects may be mediated in part by DA projections from the ventral tegmental area (VTA) to the nucleus accumbens (NAc) and medial prefrontal cortex (mPFC), which are known to be activated in response to a variety of different stressors (Thierry et al., 1976; Herman et al., 1982; Abercrombie et al., 1989; Doherty and Gratton, 1992, 1996; Finlay and Zigmond, 1997).

Psychopathologies such as schizophrenia, drug addiction, and depression have also been associated with abnormalities in amygdala morphology and function (Reynolds, 1992; Grant et al., 1996; Lawrie and Abukmeil, 1998; Childress et al., 1999; Drevets, 2000). This structure plays a key role in mediating the behavioural, autonomic, and neuroendocrine responses to stress (Davis, 1992; Henke, 1992; Gray and Bingaman, 1996). The basolateral amygdala (BLA; lateral, basal, and accessory basal nuclei) relays sensory information to the central amygdaloid nucleus, which in turn projects to regions involved in autonomic and neuroendocrine output, allowing the amygdala to attribute affective significance to environmental stimuli (Aggleton, 1993; Davis et al., 1994). A number of recent studies suggest that DA is implicated in this aspect of amygdaloid function. The BLA receives a stress-responsive DA projection from the VTA, which a growing body of evidence indicates is involved in forming associations between neutral and aversive stimuli (Fallon et al., 1978; Herman et al., 1982; Coco et al., 1992; Lamont and Kokkinidis, 1998; Guarraci et al., 1999; Inglis and Moghaddam, 1999; Greba and Kokkinidis, 2000; Greba et al., 2001; Rosenkranz and Grace, 2002b).

Converging lines of evidence also suggest that the meso-amygdaloid DA projection to BLA modulates NAc and mPFC DA transmission. Electrophysiological and anatomical data indicate that the BLA sends direct glutamatergic projections to the NAc and mPFC (Mogenson et al., 1988; Pérez-Jaranay and Vives, 1991; McDonald, 1996; Petrovich et al., 1996). Furthermore, in keeping with previous reports (Louilot et al., 1985; Simon et al., 1988; Hurd et al., 1997), we have recently shown that BLA DA depletion, while potentiating the NAc DA response to stress, will attenuate the DA stress response in the mPFC (Stevenson et al., 2003). This suggests that increased BLA DA transmission has opposite effects on the NAc and mPFC DA responses to stress, dampening the response in the former and facilitating it in the latter. In an attempt to elucidate the interaction between these three structures, we investigated the role of BLA D1 and D2/D3 receptors in modulating the NAc and mPFC DA responses to stress. Another objective of this study was to test the hypothesis that BLA modulation of the NAc DA stress response occurs indirectly as a consequence of its influence on the mPFC DA response to stress.

3.4. MATERIAL AND METHODS

3.4.1. Animals and surgery

All procedures in the present study conformed to the guidelines of the Canadian Council on Animal Care. Male Long-Evans rats (Charles River, St. Constant, Qc., Canada) weighing 300-400 g at the time of surgery were used. The animals were housed singly on a 12 h light -12 h dark reverse cycle (lights off at 07.00 h) with free access to food and water. Animals were pretreated with atropine sulphate (0.1 mg/kg, i.p.), anaesthetized with sodium pentobarbital (60 mg/kg, i.p.), and placed in a stereotaxic apparatus. The incisor bar was adjusted so that the cranium was horizontal (flat skull coordinate system). In the first experiment, animals were each implanted with a voltammetric recording electrode into the right NAc core (AP, +1.6 mm anterior to bregma; L, 1.6 mm lateral to bregma; DV, 7.4 mm below the cortical surface; Paxinos and Watson, 1982) and with a 22-gauge guide cannula (Plastics One, Roanoke, VA) aimed at a

point 1 mm above the injection site within the right BLA (AP, 2.8 mm; L, 4.8 mm; DV, 6.8 mm; Paxinos and Watson, 1982); stainless steel obturators were inserted to a depth of 1 mm beyond the tip of the guide cannula. Electrochemical recordings were performed in the core subregion of the NAc because our previous studies indicated that repeated, once daily tail-pinch stress elicits robust and reliable increases in DA signal from this region (Doherty and Gratton, 1992, 1996, 1997; Stevenson et al., 2003). For the second experiment, animals were each implanted with a voltammetric electrode into the right infralimbic mPFC (AP, +3.5 mm; L, 0.8 mm; DV, 4.5 mm; Paxinos and Watson, 1982) and with a guide cannula into the right BLA (see above for coordinates). We have recently reported that bilateral BLA DA depletion will attenuate the right, but not the left, mPFC DA response to tail pinch stress (Stevenson et al., 2003), therefore only the right mPFC DA response to stress was examined in the present study. For the third experiment, animals were each implanted with a voltammetric electrode into the right NAc core and with guide cannulae into the right BLA and infralimbic mPFC (see above for coordinates). Animals were also each implanted with a Ag/AgCl reference electrode and a stainless steel ground-wire in the contralateral and ipsilateral parietal cortices, respectively. Miniature pin connectors soldered to the voltammetric and reference electrodes, and ground wire, were inserted into a Carleton connector (Ginder Scientific, Ottawa, ON, Canada). The assembly was then secured with acrylic dental cement to four stainless steel screws threaded into the cranium.

3.4.2. In vivo electrochemistry

Voltammetric electrodes each consisted of a bundle of three 30 μm diameter carbon fibres (Textron Systems, Wilmington, MA) that extended 50-100 μm beyond the sealed tip of a pulled glass capillary (o.d. = 0.5 mm). The exposed fibres were repeatedly coated with a 5% solution of Nafion (Aldrich, Milwaukee, WI, USA), a perfluorinated ionomer which promotes the exchange of cations such as DA, while impeding the exchange of interfering anionic species such as ascorbic acid (AA) and 3,4-dihydroxyphenylacetic acid (DOPAC). Each

electrode was calibrated prior to implantation to determine its sensitivity to DA and its selectivity for DA compared to AA. Calibrations were performed in 0.1 M phosphate-buffered saline (pH 7.4) that contained 250 μM AA to mimic brain extracellular conditions. Only electrodes with a highly linear response ($r = 0.997$) to increasing concentrations of DA and a DA-to-AA selectivity ratio of at least 1000:1 were used. Electrodes used in the present study had a mean (± SEM) DA-to-AA selectivity ratio of 3376:1 (± 483:1). In addition, we have shown previously that these Nafion-coated carbon fibre electrodes will retain their sensitivity for DA and their selectivity for DA vs. AA (and DOPAC) for several days following implantation (Doherty and Gratton, 1997).

Electrochemical recordings were performed using a computer-controlled, high-speed chronoamperometric apparatus (Quanteon, Lexington, KY, USA). An oxidation potential of +0.55 mV (with respect to the reference electrode) was applied to the electrode for 100 ms at a rate of 5 Hz. The oxidation current was digitally integrated during the last 80 ms of each pulse. The sums of every 10 digitized oxidative cycles of the chronoamperometric waveform were automatically converted into equivalent values of DA concentration using the *in vitro* calibration factor. Values were displayed graphically on a video monitor at 2 s intervals. The reduction current generated when the potential was returned to resting level (0.0 V for 100 ms) was digitized and summed in the same manner and served as an index to identify the main electroactive species contributing to the stress-induced increases in electrochemical signals. With Nafion-coated electrodes and a sampling rate of 5 Hz, the magnitude of the increase in reduction current elicited by an elevation in DA concentration is typically 60-80% of the corresponding increase in oxidation current, i.e. the reduction-to-oxidation ratio (red:ox) = 0.6-0.8 (Doherty and Gratton, 1992; Gerhardt et al., 1988, 1989; Gratton et al., 1989; Mitchell and Gratton, 1991, 1992; Pentney and Gratton, 1991). Previous work also indicates that the oxidation of AA is virtually irreversible (red:ox = 0-0.1), whereas that of DOPAC is almost entirely reversible (red:ox = 1.0); the reduction to oxidation ratios for norepinephrine (NE) and serotonin (5-HT) are 0.4-0.5 and 0.1-0.3, respectively.

3.4.3. Electrochemical recordings

Electrochemical recordings began 3-4 days after surgery. Immediately before a recording session, the *in vitro* calibration factor (the slope of the function relating increases in oxidation current to increases in DA concentration) for each animal's electrode was entered in the data acquisition software. This allowed on-line conversion of an increase in oxidation current to a value equivalent to the change in DA concentration that was required to produce an equal change in signal *in vitro*. Each animal was placed in a recording chamber and connected to the chronoamperometric instrument via a shielded cable and a low impedance multichannel commutator (Airflyte, Bayonne, NJ, USA). Electrical interference was minimized by connecting a preamplifier configured as a current-to-voltage converter (gain = 1 10^8) directly into the animal's head assembly. An experiment began only after obtaining 60 min of stable baseline recordings.

3.4.4. Central drug injections

Raclopride HCl, quinpirole HCl, SCH 23390 HCl and SKF 38393 HCl were obtained from Sigma-Aldrich (St. Louis, MO, USA). The drugs were dissolved in saline and injected in a volume of 0.5 µL over 1 min via a 30-gauge stainless steel cannula that was connected to a Hamilton microsyringe by a length of polyethylene tubing. The injection cannula was left in place for an additional 1-2 min following infusion to allow diffusion of the drug before it was removed and the obturator replaced; the stressor was applied 4-5 min following the drug treatment.

3.4.5. Testing procedure

In the first and second experiments, separate groups of animals with electrodes either in the NAc (first experiment) or the mPFC (second experiment) received intra-BLA injections of either SCH 23390 or raclopride prior to receiving 15 min of tail pinch stress. On each of four consecutive daily sessions animals received, in counter-balanced order, one of four treatments (vehicle, or drug at either 0.1, 1.0, or 10 nmol). Intra-BLA SCH 23390 and raclopride

administration, within the range of doses used in the present study, has previously been shown to affect Pavlovian fear conditioning behaviour (Lamont and Kokkinidis, 1998; Guarraci et al., 1999; Greba and Kokkinidis, 2000; Greba et al., 2001). Tail pinch stress consisted of placing a wooden clothes pin 1-2 cm from the base of the animal's tail. In response to this stressor, animals typically alternate between remaining immobile and making repeated attempts to remove the clothes pin (i.e. chewing). Changes in electrochemical signal were monitored during the stress period and for 45 min thereafter. In the third experiment, animals with electrodes in the NAc received intra-mPFC injections of vehicle or SKF 38393 and quinpirole (3.0 nmol each), and intra-BLA injections of vehicle or SCH 23390 (10 nmol). On each of four consecutive daily sessions animals received, in counter-balanced order, one of four treatment combinations (intra-BLA vehicle/intra-mPFC vehicle; intra-BLA SCH 23390/intra-mPFC vehicle; intra-BLA vehicle/intra-mPFC SKF 38393 + quinpirole; and intra-BLA SCH 23390/intra-mPFC SKF 38393 + quinpirole). Changes in electrochemical signal were again monitored during the stress period and for 45 min thereafter.

3.4.6. Electrochemical data format

Because of the inherent differences in sensitivity between Nafion-coated electrodes, *in vivo* changes in oxidation current recorded with different electrodes (i.e. in different animals) cannot be assumed to be equivalent. Thus, valid comparisons are possible only if the sensitivity of each electrode is calibrated against a standard and the electrochemical data are expressed as standard equivalent values. Because DA was used as the standard to calibrate electrode sensitivity, *in vivo* changes in oxidation current are expressed as μM equivalent values of DA concentration. Data are presented as changes in electrochemical signal (μM DA equivalents) relative to the signal level recorded immediately prior to the onset of stress (Time 0). Because the recording at Time 0 was the point of comparison for changes in electrochemical signal that followed, it was arbitrarily given a value of 0 μM. Therefore, a value of 0 μM is not meant to correspond to

the concentration of extracellular DA; electrochemical data represent relative changes in extracellular DA levels elicited by a stimulus such as stress.

3.4.7. Histology

At the end of each experiment, all animals were deeply anaesthetized with chloral hydrate (400 mg/kg, i.p.) and transcardially perfused with saline followed by 10% formalin. The brains were removed, placed in 10% formalin, and later cryo-protected with 30% sucrose. The brains were then sliced into 30 μm sections and stained with formal thionin (NAc and mPFC sections) or acetylcholinesterase (BLA sections) for verification of electrode and cannula tip placements.

3.4.8. Statistical analysis

In the first and second experiments, a two-factor analysis of variance (ANOVA), with dose and time as within-subject factors, was used to assess the magnitude of drug effects on stress-induced signal increases recorded in the NAc or mPFC. In the third experiment, a two-factor ANOVA, with drug and time as within-subject factors, was used to assess the magnitude of treatment effects on signal increases elicited in the NAc. Comparisons were based on differences in the amplitude of electrochemical signal increases taken at 5 min intervals from the onset of stress. When indicated, *post hoc* comparisons were performed using Tukey's Honestly Significant Difference test. The alpha level for all comparisons was set at 0.05.

3.5. RESULTS

3.5.1. Histology

Only data from animals with histologically-confirmed electrode tip placements within the NAc or mPFC, and injection cannulae tip placements within the BLA or mPFC, were included in the statistical analysis (Fig. 1).

Animals were also excluded from the study when (i) tail pinch stress failed to elicit a robust, short-latency increase in electrochemical signal, and (ii) stress-induced increases in electrochemical signal had red:ox ratios of less than 0.5. A total of 46 animals met the above criteria (Exp. 1, $n = 20$; Exp. 2, $n = 17$; Exp. 3, $n = 9$). Reliable increases in electrochemical signals were recorded in both NAc and mPFC within 2-3 min. of onset of tail-pinch stress. Signals would continue to rise steadily, typically reaching peak amplitude during the latter half of the 15 min. stress period. Signals would generally remain elevated until the clothes pin was removed from the animals' tail after which signals would start to decline gradually towards pre-stress levels (see Fig. 4 for representative recordings). The mean (± SEM) of the red:ox ratios at peak amplitude of the NAc and mPFC electrochemical responses to stress were 0.88 (± 0.006) and 0.88 (± 0.012), respectively. Red:ox ratios in this range are typical of an increase in DA concentration; they also rule out AA as a significant contributor to the stress-induced signal increases recorded in NAc and mPFC.

3.5.2. Effects of intra-BLA DA receptor antagonists on the NAc DA stress response

Intra-BLA injections of the D1 receptor antagonist, SCH 23390, resulted in a dose-dependent potentiation of the NAc electrochemical response to stress (dose-time interaction, $F_{30,\ 270} = 1.76$, $P < 0.05$; Fig. 2A). A significant enhancement of stress-induced signal increases in the NAc was seen after injection of the 1.0 and 10 nmol doses of SCH 23390, and was most evident at the end of the stress period and for up to 20 min after removal of the stressor ($P < 0.05$). Intra-BLA injection of the D2/D3 receptor antagonist raclopride had no significant effect on stress-induced increases in NAc signals, compared to saline injection (Fig. 2B; $F_{3,27} = 0.52$, $P > 0.05$).

3.5.3. Effects of intra-BLA DA receptor antagonists on the mPFC DA stress response

In contrast to the enhancement seen in NAc, intra-BLA injection of SCH 23390 produced a significant dose-dependent attenuation of the mPFC electrochemical response to stress (main effect of dose, $F_{3,24} = 8.47$, $P < 0.01$; 1.0 and 10 nmol vs. saline, $P < 0.01$; Fig. 3A). Again, intra-BLA injections of raclopride had no effect on stress-induced signal increases in mPFC, compared to saline injection (Fig. 3B; $F_{3,21} = 0.85$, $P > 0.05$).

3.5.4. Effects of intra-mPFC DA agonists and intra-BLA SCH 23390 on the NAc DA stress response

The results of the first two experiments raised the possibility that the potentiation of the NAc electrochemical response to stress, resulting from BLA D1 receptor blockade (Fig. 4), is a consequence of attenuated stress-induced activation of mPFC DA transmission. In order to test this possibility, we examined whether the facilitatory effect of intra-BLA SCH 23390 administration on the NAc electrochemical response to stress could be prevented by intra-mPFC injection of D1 and D2/D3 receptor agonists. The results show that intra-mPFC co-administration of SKF 38393 and quinpirole (D1 and D2/D3 receptor agonists, respectively) blocked the enhancement of stress-induced signal increases seen in NAc following intra-BLA SCH 23390 administration (Fig. 5). Statistical analysis revealed a significant drug-time interaction ($F_{30,240} = 1.80$, $P < 0.01$). As was found in the first experiment, intra-BLA injection of SCH 23390 (10 nmol) significantly potentiated the NAc electrochemical response to stress ($P < 0.05$), when compared to saline injection. However, this effect of intra-BLA SCH 23390 was completely abolished by intra-mPFC co-administration of SKF 38393 and quinpirole (3.0 nmol each; $P > 0.05$). As previously reported, intra-mPFC SKF 38393 and quinpirole administration had no effect of its own on the NAc electrochemical response to stress (Doherty and Gratton, 1996).

3.6. DISCUSSION

In the present study, we used voltammetry and central injections of D1 and D2/D3 receptor selective drugs to investigate the role of BLA in modulating the NAc and mPFC DA responses to stress. One potential limitation of this approach is that voltammetry does not provide sufficient information to unequivocally identify the electroactive species responsible for the recorded changes in oxidation current. Thus, the possibility that increased levels of an oxidizable compound other than DA is responsible for the stress-elicited signal increases reported here has to be examined carefully. The most problematic species is AA, as its basal extracellular concentration is higher than that of DA and because stress has been reported to elevate striatal levels of AA (Miele et al., 1994). Repeatedly coating the electrode surface with Nafion is one of several procedures that has been shown to substantially reduce contributions by AA and other anionic species, including the DA metabolite DOPAC (Gerhardt et al., 1984; Nagy et al., 1985; Brazell et al., 1987; Capella et al., 1990; Crespi and Mobius, 1992). The electrodes used in the present study had a mean (± SEM) DA:AA selectivity ratio of 3376:1 (± 483:1). Thus, the Nafion treatment would significantly reduce a potential contribution of AA to the increases in signal reported here.

Information on the identity of the predominant electroactive species can be derived by comparing the magnitude of the increase in reduction current to that of the increase in oxidation current. In the present study, stress-induced increases in reduction current were found to be 88% of the corresponding increases in oxidation current. At the sampling rate used (5 Hz), such high levels of reduction current rule out increases in levels of AA (red:ox = 0.0-0.1) as the cause for the stress-induced signal increases reported here. However, the oxidation of DOPAC, like that of DA, is a highly reversible reaction; the current generated during the reduction of DOPAC is close to 100% of the current generated during its oxidation. Thus, the red:ox ratios of DA and DOPAC are sufficiently similar as to preclude a clear dissociation based on this criterion alone.

The high red:ox ratios observed in the present study would rule out, however, an increase in 5-HT or of its metabolite, 5-hydroxyindoleacetic acid, as the cause for the stress-induced increases in signal as the red:ox ratios of both compounds (0.1-0.2) are considerably lower than that of DA. While the reduced form of NE is more readily detected (red:ox = 0.4-0.5), the relatively lower sensitivity of this type of electrode for NE and the sparse NE innervation of NAc relative to that of DA would make NE an unlikely contributor to the stress-induced signal increases. The potential for a NE contribution to the signal would be greater in mPFC where the densities of DA and NE terminals are relatively similar.

Thus, of the known species that are oxidized at the potential used in the present study, it appears that DA and DOPAC could have contributed significantly to the stress-elicited increases in signal recorded in mPFC and NAc. If there was a significant contribution of DOPAC to the increases in signal though, it is unlikely to have occurred at any time soon after onset of the stress episode; increases in extracellular levels of metabolites, such as DOPAC, occur more gradually and are delayed relative to increases in DA levels. In the present study, electrochemical signals typically increased within 2-3 min following onset of stress and these continued to rise steadily to peak approximately 10 min later; signals would start to decline gradually at or close to the end of the 15 min stress period. Had DOPAC, rather than DA, been the predominant species detected by the electrode, increases in electrochemical signal would have been expected to peak later and would have remained elevated considerably longer following stress (see for example Venator et al., 1999). Thus, it seems unlikely that the relatively rapid increases in signal seen in response to stress can be ascribed to the slow extracellular accumulation of DOPAC that follows from increased DA efflux. Studies using microdialysis and high performance liquid chromatography are planned to confirm the present results.

Insofar as the increases in electrochemical signals recorded in the present study are due mainly to increases in extracellular DA, the present results provide

evidence that the mPFC and NAc DA responses to stress are modulated by a DA-sensitive mechanism in BLA. A large body of evidence indicates that a variety of different stressors activate DA transmission in mPFC and NAc (Thierry et al., 1976; Abercrombie et al., 1989), and studies have shown that mPFC DA exerts an inhibitory influence on stress-induced NAc DA release (Deutch et al., 1990; Doherty and Gratton, 1996). Evidence also indicates that a number of stressors strongly activate the DA projection to the BLA (Herman et al., 1982; Coco et al., 1992; Inglis and Moghaddam, 1999; Morrow et al., 2000). The present study provides evidence that the mPFC and NAc DA stress responses are modulated by BLA DA, but in an opposite manner. Specifically, D1, but not D2/D3, receptor blockade in BLA potentiated stress-induced NAc DA release while it attenuated the DA stress response in mPFC. This finding is in agreement with other evidence of increased NAc, and decreased mPFC, DA transmission as a result of impaired BLA DA function (Louilot et al., 1985; Simon et al., 1988; Hurd et al., 1997). It also complements data from our previous study showing that BLA DA depletion results in potentiated NAc, and attenuated mPFC, stress-induced DA release (Stevenson et al., 2003). It is unclear why BLA D1, but not D2/D3, receptor blockade was shown to modulate stress-induced NAc and mPFC DA release in the present study, given that local D1 and D2 receptor blockade appear to have opposite effects on the activity of BLA projection neurons (Rosenkranz and Grace, 2002a). However, autoradiographical and immunohistochemical studies indicate that the D1 receptor is the predominant DA receptor subtype in BLA (Scibilia et al., 1992; Levey et al., 1993).

We also report in the present study that D1 and D2/D3 receptor coactivation in mPFC prevents the potentiated NAc DA stress response resulting from BLA D1 receptor blockade, suggesting that BLA DA can indirectly modulate the NAc DA stress response via a DA-sensitive mechanism in mPFC. In agreement with a previous report (Doherty and Gratton, 1996), D1 and D2/D3 receptor activation in mPFC was found in the present study to have no effect on the NAc DA stress response. Given that mPFC DA exerts an inhibitory influence on stress-induced NAc DA release, mPFC DA receptor activation could be

expected to dampen the NAc DA stress response. However, it should be remembered that, during stress, intra-mPFC SKF 38393 and quinpirole would most likely exert their actions on the same DA receptor population that is activated by the endogenous ligand. As a result of this, the effects of mPFC D1 and D2/D3 receptor activation on the NAc DA stress response would not be expected to supercede those produced by the concomitant increase in mPFC DA release. As the D1 and D2/D3 receptor agonists were co-administered, it is not known which mPFC DA receptor subtype(s) is involved in the BLA DA modulation of the NAc DA stress response. Therefore, additional experimentation will be necessary to clarify this issue.

3.6.1. BLA modulation of stress-induced mesocorticolimbic DA release

Given that local D1 receptor activation appears to have a net inhibitory effect on the activity of BLA projection neurons (Rosenkranz and Grace, 1999, 2002a), it is reasonable to assume that local BLA D1 receptor blockade would disinhibit the activity of BLA output neurons. These output neurons send a glutamatergic projection to mPFC that terminates on local gamma-aminobutyric acid (GABA) interneurons and cortico-fugal glutamatergic neurons (Bacon et al., 1996; McDonald, 1996). In addition to stimulating DA release, stress also evokes glutamate release in mPFC (Moghaddam, 2002), a source of which may originate in BLA. Thus, it is entirely conceivable that BLA D1 receptor blockade disinhibits the glutamatergic projection from BLA to mPFC, resulting in greater mPFC glutamate release during stress. Increased glutamate tone in mPFC has been shown to increase local GABA release (Del Arco and Mora, 1999, 2002), presumably by activating local GABA interneurons, which in turn would inhibit the activity of mPFC glutamatergic projection neurons. Such a possibility is supported by the fact that electrical stimulation of the BLA inhibits the activity of mPFC pyramidal neurons indirectly by activating local GABA interneurons (Pérez-Jaranay and Vives, 1991).

Exactly how BLA-induced modulation of mPFC output influences NAc DA transmission is open to speculation. However, one possibility is suggested by

anatomical evidence that DA and GABA neurons in the VTA receive different patterns of glutamatergic input from the mPFC (Carr and Sesack, 2000). Specifically, whereas mPFC pyramidal neurons project to VTA DA cells that innervate the mPFC, VTA DA neurons that project to NAc appear to be indirectly modulated by an mPFC input to mesencephalic GABA interneurons. This arrangement could conceivably allow the mPFC projection to VTA to exert opposite effects on mPFC and NAc DA transmission, such that inhibition of mPFC output neurons projecting to the VTA would attenuate stress-induced mPFC DA release while potentiating the NAc DA stress response. Such a possibility would be consistent with the fact that activation of glutamate receptors in mPFC will increase local GABA release (Yonezawa et al., 1998; Del Arco and Mora, 1999, 2002) while attenuating the local DA response to stress (Del Arco and Mora, 2001). Furthermore, increased mPFC GABA tone results in diminished local DA transmission (Santiago et al., 1993). It remains, however, that future studies examining the effect of BLA modulation of stress-induced glutamate and GABA release in mPFC will be necessary to confirm this hypothesis (see Fig. 6 for circuit diagram).

Recent evidence indicates that electrical stimulation of the BLA elicits NAc DA release independently of changes in VTA DA neuronal activity (Floresco et al., 1998; Howland et al., 2002). Similarly, NAc DA release is elicited by electrical and chemical stimulation of the mPFC (Murase et al., 1993; Taber and Fibiger, 1995; Karreman and Moghaddam, 1996; You et al., 1998), suggesting the possibility that BLA D1 receptor modulation of stress-induced NAc DA release may occur indirectly via increased, and not decreased, mPFC output. However, in their study, Howland et al., (2002) showed that pharmacological inactivation of the mPFC has no effect on NAc DA release elicited by BLA stimulation. Furthermore, a recent study suggests that electrical stimulation of the mPFC at physiologically relevant frequencies results in decreased NAc DA efflux (Jackson et al., 2001). Finally, given the specificity of the anatomical projections from the mPFC to VTA (see above), it is unlikely that

increased mPFC output is responsible for affecting the BLA D1 receptor modulation of stress-induced NAc DA release.

3.6.2. Functional implications

The present results indicate that one consequence of BLA D1 receptor blockade might be to disinhibit the activity of BLA projection neurons. It is suggested that this results in an attenuated mPFC DA stress response and consequently, a potentiated NAc DA response to stress. How then might disinhibition of BLA output impact on the coordination of the stress response? The mPFC is generally acknowledged to play a pivotal role in such cognitive processes as working memory and sustained attention. For its part, the NAc appears to be critical in attributing incentive salience to environmental stimuli and executing goal-directed behaviour. DA is a crucial component of the circuitries mediating both mPFC and NAc DA function (Ikemoto and Panksepp, 1999; Horvitz, 2000; Robbins, 2000). Similarly, it appears that BLA DA plays an important role in amygdaloid-mediated functions (Rosenkranz and Grace, 2002b), including that of ascribing emotional valence to sensory stimuli (Aggleton, 1993; Davis et al., 1994). Increasingly, it appears that, under basal conditions, the mPFC can modulate both amygdaloid activity and NAc function. Specifically, recent evidence suggests that the mPFC can influence behaviours elicited by environmental stimuli by inhibiting BLA-mediated affective responses (Rosenkranz and Grace, 2001, 2002a) as well as by modulating NAc DA transmission (Jackson and Moghaddam, 2001).

During exposure to stressful stimuli, activation of DA projections to the mPFC and NAc are thought to subserve different functions in the coordination of the stress response. Although there is evidence that stress can impair working memory performance (Murphy et al., 1996), increased mPFC DA transmission is thought to be important during performance of attentional tasks, suggesting that stress-induced mPFC DA release would allow animals to attend more readily to behaviourally relevant stimuli (Robbins, 2000). Thus, mPFC DA appears to play an important role in mediating the adaptive coping response to stress, involving

stimulus evaluation and appropriate response selection (Horger and Roth, 1996; Sullivan and Gratton, 2002). Stress-induced NAc DA release may impart salience on the stressful stimulus, mediating behavioural responsivity to the stimulus and allowing for the execution of goal-directed behaviour (Ikemoto and Panksepp, 1999; Horvitz, 2000). Aversive stimuli have also been shown to activate the BLA (Campeau et al., 1991). Thus, increased activation of the BLA may, as a result of facilitating the mPFC input to NAc, promote appropriate response selection to threatening stimuli and execution of goal-directed behaviour (Grace and Moore, 1998), presumably as a consequence of increased NAc DA release (Jackson and Moghaddam, 2001).

Impaired BLA DA function therefore would be expected to alter affective responses to environmental stimuli, particularly to threatening or stressful events. As a consequence of this, attenuation of the mPFC DA response to stress may diminish cognitive function, sustained attention, and adaptive responding to stressful stimuli (Horger and Roth, 1996; Robbins, 2000; Sullivan and Gratton, 2002). Dysregulated inhibition of BLA output to mPFC might also result in an abnormal decrease in stress-induced activation of mPFC projection neurons (Pérez-Jaranay and Vives, 1991). These conditions could conceivably lead to behavioural disinhibition and the expression of inappropriate behaviours (Morgan et al., 1993; Jentsch and Taylor, 1999; Morrow et al., 1999).

3.6.3. Conclusions

The results of the present study indicate that BLA DA, acting at D1 receptors, modulates the NAc DA response to stress indirectly via a DA-sensitive mechanism in mPFC. Taken together with previous findings, the present results indicate that, during exposure to stressful stimuli, there is a functional interdependence between the DA projections to the BLA, mPFC, and NAc. They also suggest a mechanism by which dysregulation of BLA DA transmission might contribute to maladaptive prefrontal cortical responses to stressful stimuli and the emergence of inappropriate subcortically-mediated behaviours.

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REFERENCES

Abercrombie ED, Keefe KA, DiFrischia DS and Zigmond MJ (1989) Differential effect of stress on in vivo dopamine release in striatum, nucleus accumbens, and medial frontal cortex. J Neurochem 52:1655-1658.

Aggleton JP (1993) The contribution of the amygdala to normal and abnormal emotional states. Trends Neurosci 16:328-333.

Bacon SJ, Headlam AJN, Gabbott PLA and Smith AD (1996) Amygdala input to the medial prefrontal cortex (mPFC) in the rat: a light and electron microscopy study. Brain Res 720:211-219.

Brazell MP, Feng J, Kasser RJ, Moghaddam B and Adams RN (1987) An improved method for Nafion coating carbon fiber electrodes for in vivo electrochemistry. J Neurosci Meth 22:167-172.

Brown AS and Gershon S (1993) Dopamine and depression. J Neural Transm 91:75-109.

Campeau S, Hayward MD, Hope BT, Rosen JB, Nestler EJ and Davis M (1991) Induction of the c-fos proto-oncogene in rat amygdala during unconditioned and conditioned fear. Brain Res 565:349-352.

Capella P, Ghasemzadeh B, Mitchell K and Adams RN (1990) Nafion-coated carbon fiber electrodes for neurochemical studies in brain tissue. Electroanalysis 2:175-182.

Carr DB and Sesack SR (2000) Projections from the rat prefrontal cortex to the ventral tegmental area: target specificity in the synaptic associations with mesocortical and mesoaccumbens neurons. J Neurosci 20:3864-73.

Childress AR, Mozley PD, McElgin W, Fitzgerald J and O'Brien CP (1999) Limbic activation during cue-induced cocaine craving. Am J Psychiatry 156:11-18.

Coco ML, Kuhn CM, Ely TD and Kilts CD (1992) Selective activation of mesoamygdaloid dopamine neurons by conditioned stress: attenuation by diazepam. Brain Res 590:39-47.

Crespi F and Mobius C (1992) In vivo selective monitoring of basal levels of cerebral dopamine using voltammetry with Nafion modified (NA-CRO) carbon fibre micro-electrodes. J Neurosci Meth 42:149-161.

Davis M (1992) The role of the amygdala in conditioned fear. In Aggleton JP (ed), The amygdala. neurobiological aspects of emotion, memory, and mental dysfunction. Wiley-Liss, New York, pp. 255-305.

Davis M, Rainnie D and Cassell M (1994) Neurotransmission in the rat amygdala related to fear and anxiety. Trends Neurosci 17:208-214.

Del Arco A and Mora F (1999) Effects of endogenous glutamate on extracellular concentrations of GABA, dopamine and dopamine metabolites in the prefrontal of the freely moving rat: involvement of NMDA and AMPA/kainate receptors. Neurochem Res 24:1027-1035.

Del Arco A and Mora F (2001) Dopamine release in the prefrontal cortex during stress is reduced by the local activation of glutamate receptors. Brain Res Bull 56:125-130.

Del Arco A and Mora F (2002) NMDA and AMPA/kainate glutamatergic agonists increase the extracellular concentrations of GABA in the prefrontal cortex of the freely moving rat: modulation by endogenous dopamine. Brain Res Bull 57:623-630.

Deutch A. Y., Clark W. A. and Roth R. H. (1990) Prefrontal cortical dopamine depletion enhances the responsiveness of mesolimbic dopamine neurons to stress. Brain Res 521:311-315.

Doherty MD and Gratton A (1992) High-speed chronoamperometric measurements of mesolimbic and nigrostriatal dopamine release associated with repeated daily stress. Brain Res 586:295-302.

Doherty MD and Gratton A (1996) Medial prefrontal cortical D1 receptor modulation of the meso-accumbens dopamine response to stress: an electrochemical study in freely-behaving rats. Brain Res 715:86-97.

Doherty MD and Gratton A (1997) NMDA receptors in nucleus accumbens modulate stress-induced dopamine release in nucleus accumbens and ventral tegmental area. Synapse 26:225-234.

Drevets WC (2000) Functional anatomical abnormalities in limbic and prefrontal cortical structures in major depression. Prog Brain Res 126:413-431.

Fallon JH, Koziell DA and Moore RY (1978) Catecholamine innervation of the basal forebrain II. Amygdala, suprarhinal cortex and entorhinal cortex. J Comp Neurol 180:509-531.

Finlay JM and Zigmond MJ (1997) The effects of stress on central dopaminergic neurons: possible clinical implications. Neurochem Res 22:1387-1394.

Floresco SB, Yang CR, Phillips AG and Blaha CD (1998) Basolateral amygdala stimulation evokes glutamate receptor-dependent dopamine efflux in the nucleus accumbens of the anesthetized rat. Eur J Neurosci 10:1241-1251.

Gerhardt G, Oke AF, Nagy G, Moghaddam and Adams RN (1984) Nafion-coated electrodes with high selectivity for CNS electrochemistry. Brain Res 290:390-395.

Gerhardt GA, Gratton A and Rose GM (1988) In vivo electrochemical studies of the effects of cocaine on dopamine nerve terminals in the rat neostriatum. Physiologia Bohemoslovaca 37:249-257.

Gerhardt GA, Friedman M, Brodie MS, Vickroy TW, Gratton A, Hoffer BJ and Rose GM (1989) The effects of cholecystokinin (CCK-8) on dopamine-containing nerve terminals in the caudate nucleus and nucleus accumbens of the anesthetized rat: an in vivo electrochemical study. Brain Res 499:157-163.

Gispen-de Wied CC (2000) Stress in schizophrenia: an integrative view. Eur J Pharmacol 405:375-384.

Grace AA (1993) Cortical regulation of subcortical dopamine systems and its possible relevance to schizophrenia. J Neural Transm 91:111-134.

Grace AA and Moore H (1998) Regulation of information flow in the nucleus accumbens: a model for the pathophysiology of schizophrenia. In Lenzenweger MF and Dworkin RH (eds) Origins and development of schizophrenia: advances in experimental psychopathology. American Psychological Association, Washington, pp. 123-157.

Grace AA (2000) The tonic/phasic model of dopamine system regulation and its implications for understanding alcohol and psychostimulant craving. Addiction 95(Suppl 2):S199-S128.

Grant S, London ED, Newlin DB, Villemagne VL, Liu X, Contoreggi C, Phillips RL, Kimes AS and Margolin A (1996) Activation of memory circuits during cue-elicited cocaine craving. Proc Natl Acad Sci USA 93:12040-12045.

Gratton A, Hoffer BJ and Gerhardt GA (1989) In vivo electrochemical determination of monoamine release in the medial prefrontal cortex of the rat. Neuroscience 29:57-64.

Gratton A and Wise RA (1994) Drug- and behaviour-associated changes in dopamine-related electrochemical signals during intravenous cocaine self-administration in rats. J Neurosci 14:4130-4146.

Gray TS and Bingaman EW (1996) The amygdala: corticotropin-releasing factor, steroids, and stress. Crit Rev Neurobiol 10:155-168.

Greba Q and Kokkinidis L (2000) Peripheral and intraamygdalar administration of the dopamine D1 receptor antagonist SCH 23390 blocks fear-potentiated startle but not shock reactivity or the shock sensitization of acoustic startle. Behav Neurosci 114:262-272.

Greba Q, Gifkins A and Kokkinidis L (2001) Inhibition of amygdaloid dopamine D2 receptors impairs emotional learning measured with fear-potentiated startle. Brain Res 899:218-226.

Guarraci FA, Frohardt RJ and Kapp BS (1999) Amygdaloid D1 dopamine receptor involvement in Pavlovian fear conditioning. Brain Res 827:28-40.

Henke PG (1992) Stomach pathology and the amygdala. In Aggleton JP (ed), The amygdala. neurobiological aspects of emotion, memory, and mental dysfunction. Wiley-Liss, New York, pp. 323-338.

Herman JP, Guillonneau D, Dantzer R, Scatton B, Semerdjian-Rouqier L and Le Moal M (1982) Differential effects of inescapable footshocks and of stimuli previously paired with inescapable footshocks on dopamine turnover in cortical and limbic areas of the rat. Life Sci 30:2207-2214.

Horger BA and Roth RH (1996) The role of mesoprefrontal dopamine neurons in stress. Crit Rev Neurobiol 10:395-418.

Horvitz JC (2000) Mesolimbocortical and nigrostriatal dopamine responses to salient non-reward events. Neuroscience 96:651-656.

Howland JG, Taepavarapruk P and Phillips AG (2002) Glutamate receptor-dependent modulation of dopamine efflux in the nucleus accumbens by basolateral, but not central, nucleus of the amygdale in rats. J Neurosci 22:1137-1145.

Hurd RL, McGregor A and Pontén M (1997) In vivo amygdala dopamine levels modulate cocaine self-administration behaviour in the rat: D1 dopamine receptor involvement. Eur J Neurosci 9:2541-2548.

Ikemoto S and Panksepp J (1999) The role of nucleus accumbens dopamine in motivated behaviour: a unifying interpretation with special reference to reward-seeking. Brain Res Rev 31:6-41.

Inglis FM and Moghaddam B (1999) Dopaminergic innervation of the amygdala is highly responsive to stress. J Neurochem 72:1088-94.

Jackson ME, Frost AS and Moghaddam B (2001) Stimulation of prefrontal cortex at physiologically relevant frequencies inhibits dopamine release in the nucleus accumbens. J Neurochem 78:920-923.

Jackson ME and Moghaddam B (2001) Amygdala regulation of nucleus accumbens dopamine output is governed by the prefrontal cortex. J Neurosci 21:676-681.

Jentsch JD and Taylor JR (1999) Impulsivity resulting from frontostriatal dysfunction in drug abuse: implications for the control of behaviour by reward-related stimuli. Psychopharmacology 146:373-390.

Karreman M and Moghaddam B (1996) The prefrontal cortex regulates the basal release of dopamine in the limbic striatum: an effect mediated by ventral tegmental area. J Neurochem 66:589-598.

Kiyatkin EA, Wise RA and Gratton A (1993) Drug- and behaviour-associated changes in dopamine-related electrochemical signals during intravenous heroin self-administration in rats. Synapse 14:60-72.

Lamont EW and Kokkinidis L (1998) Infusion of the dopamine D1 receptor antagonist SCH 23390 into the amygdala blocks fear expression in a potentiated startle paradigm. Brain Res 795:128-136.

Lawrie SM and Abukmeil SS (1998) Brain abnormality in schizophrenia. A systematic and quantitative review of volumetric magnetic resonance imaging studies. Br J Psychiatry 172:110-120.

Levey AI, Hersch SM, Rye DB, Sunahara RK, Niznik HB, Kitt CA, Price DL, Maggio R, Brann MR and Ciliax BJ (1993) Localization of D1 and D2 dopamine receptors in brain with subtype-specific antibodies. Proc Natl Acad Sci USA 90:8861-8865.

Louilot A, Simon H, Taghzouti K and Le Moal M (1985) Modulation of dopaminergic activity in the nucleus accumbens following facilitation or blockade of the dopaminergic transmission in the amygdala: a study by in vivo differential pulse voltammetry. Brain Res 346:141-145.

McDonald AJ (1996) Glutamate and aspartate immunoreactive neurons of the rat basolateral amygdala: colocalization of excitatory amino acids and projections to the limbic circuit. J Comp Neurol 365:367-379.

Miele M, Boutelle MG and Fillenz M (1994) The physiologically induced release of ascorbate in rat brain is dependent on impulse traffic, calcium influx and glutamate uptake. Neuroscience 62:87-91.

Mitchell JB and Gratton A (1991) Opioid modulation and sensitization of dopamine release elicited by sexually relevant stimuli: a high-speed chronoamperometric study in freely-behaving rats. Brain Res 551:20-27.

Mitchell JB and Gratton A (1992) Partial dopamine depletion of the prefrontal cortex leads to enhanced mesolimbic dopamine release elicited by repeated exposure to naturally reinforcing stimuli. J Neurosci 12:3609-3618.

Mogenson GJ, Yang CR and Yim CY (1988) Influence of dopamine on limbic inputs to the nucleus accumbens. Ann N Y Acad Sci 537:173-187.

Moghaddam B. (2002) Stress activation of glutamate neurotransmission in the prefrontal cortex: implications for dopamine-associated psychiatric disorders. Biol Psychiatry 51:775-787.

Morgan ME, Romanski LM and LeDoux JE (1993) Extinction of emotional learning: contribution of medial prefrontal cortex. Neurosci Lett 163:109-113.

Morrow BA, Elsworth JD, Rasmusson AM and Roth RH (1999) The role of mesoprefrontal dopamine neurons in the acquisition and expression of conditioned fear in the rat. Neuroscience 92:553-564.

Morrow BA, Redmond AJ, Roth RH and Elsworth JD (2000) The predator odor, TMT, displays a unique, stress-like pattern of dopaminergic and endocrinological activation in the rat. Brain Res 864:146-151.

Murase S, Grenhoff J, Chouvet G, Gonon FG and Svensson TH (1993) Prefrontal cortex regulates burst firing and transmitter release in rat mesolimbic dopamine neurons studied in vivo. Neurosci Lett 157:53-56.

Murphy BL, Arnsten AF, Goldman-Rakic PS and Roth RH (1996) Increased dopamine turnover in the prefrontal cortex impairs spatial working memory performance in rats and monkeys. Proc Natl Acad Sci USA 93:1325-1329.

Nagy G, Gerhardt GA, Oke AF, Rice ME, Adams RN, Moore RB, Szentirmay MN and Martin CR (1985) Ion exchange and transport of neurotransmitters in Nafion films on conventional and microelectrode surfaces. J Electroanalytical Chem 188:85-94.

Noel MB and Gratton A (1995) Electrochemical evidence of increased dopamine transmission in prefrontal cortex and nucleus accumbens elicited by ventral tegmental F-opioid receptor activation in freely-behaving rats. Synapse 21:110-122.

Paxinos G and Watson C (1982) The rat brain in stereotaxic coordinates. Academic, New York.

Pentney RJW and Gratton A (1991) Effects of local delta and mu opioid receptor activation on basal and stimulated dopamine release in striatum and nucleus accumbens of rat: An in vivo electrochemical study. Neuroscience 45:95-102.

Pérez-Jaranay JM and Vives F (1991) Electrophysiological study of the response of medial prefrontal cortex neurons to stimulation of the basolateral nucleus of the amygdala in the rat. Brain Res 564:97-101.

Petrovich GD, Risold PY and Swanson LW (1996) Organization of projections from the basomedial nucleus of the amygdala: a PHAL study in the rat. J Comp Neurol 374:387-420.

Reynolds GP (1992) The amygdala and the neurochemistry of schizophrenia. In Aggleton JP (ed), The amygdala. neurobiological aspects of emotion, memory, and mental dysfunction. Wiley-Liss, New York, pp. 561-574.

Robbins T (2000) From arousal to cognition the integrative position of the prefrontal cortex. Prog Brain Res 126:469-483.

Rosenkranz JA and Grace AA (1999) Modulation of basolateral amygdala neuronal firing and different drive by dopamine receptor activation in vivo. J Neurosci 19:11027-39.

Rosenkranz JA and Grace AA (2001) Dopamine attenuates prefrontal cortical suppression of sensory inputs to the basolateral amygdala of rats. J Neurosci 21:4090-103.

Rosenkranz JA and Grace AA (2002a) Cellular mechanisms of infralimbic and prelimbic prefrontal cortical inhibition and dopaminergic modulation of basolateral amygdala neurons in vivo. J Neurosci 22:324-337.

Rosenkranz JA and Grace AA (2002b) Dopamine-mediated modulation of odour-evoked amygdala potentials during Pavlovian conditioning. Nature 417:282-287.

Santiago M, Machado A and Cano J (1993) Regulation of the prefrontal cortical dopamine release by $GABA_A$ and $GABA_B$ receptor agonists and antagonists. Brain Res 630:28-31.

Scibilia RJ, Lachowicz JE and Kilts CD (1992) Topographic nonoverlapping distribution of D1 and D2 dopamine receptors in the amygdaloid nuclear complex of the rat brain. Synapse 11:146-154.

Simon H, Taghzouti K, Gozlan H, Studler JM, Louilot A, Herve D, Glowinski J, Tassin JP and Le Moal M (1988) Lesion of dopaminergic terminals in the amygdala produces enhanced locomotor response to D-amphetamine and opposite changes in dopaminergic activity in prefrontal cortex and nucleus accumbens. Brain Res 447:335-340.

Sinha R (2001) How does stress increase risk of drug abuse and relapse? Psychopharmacology 158:343-359.

Stevenson CW, Sullivan RM and Gratton A (2003) Effects of basolateral amygdala dopamine depletion on the nucleus accumbens and medial prefrontal cortical dopamine responses to stress. Neuroscience 116:285-293.

Sullivan RM and Gratton A (2002) Prefrontal cortical regulation of hypothalamic-pituitary-adrenal function in the rat and implications for psychopathology: side matters. Psychoneuroendocrinology 27:99-114.

Taber MT and Fibiger HC (1995) Electrical stimulation of the prefrontal cortex increases dopamine release in the nucleus accumbens of the rat: modulation by metabotropic glutamate receptors. J Neurosci 15:3896-3904.

Thierry AM, Tassin JP, Blanc G and Glowinski J (1976) Selective activation of the mesocortical dopamine system by stress. Nature 263:242-244.

Venator DK, Lewis DA and Finlay JM (1999) Effects of partial dopamine loss in the medial prefrontal cortex on local baseline and stress-evoked extracellular dopamine concentrations. Neuroscience 93:497-505.

Weinberger DR (1987) Implications of normal brain development for the pathogenesis of schizophrenia. Arch Gen Psychiatry 44:660-669.

Wilner P, Muscat R, Papp M and Sampson D (1991) Dopamine, depression and anti-depressant drugs. In Willner P and Scheel-Krüger J (eds), The mesolimbic dopamine system: from motivation to action. Wiley-Liss, New York, pp. 387-410.

Yonezawa Y, Kuroki T, Kawahara T, Tashiro N and Ucimura H (1998) Involvement of γ-aminobutyric acid neurotransmission in phencyclidine-induced dopamine release in the medial prefrontal cortex. Eur J Pharmacol 341:45-56.

You ZB, Tzschentke TM, Brodin E and Wise RA (1998) Electrical stimulation of the prefrontal cortex increases cholecystokinin, glutamate, and dopamine release in the nucleus accumbens: an in vivo microdialysis study in freely moving rats. J Neurosci 18:6492-6500.

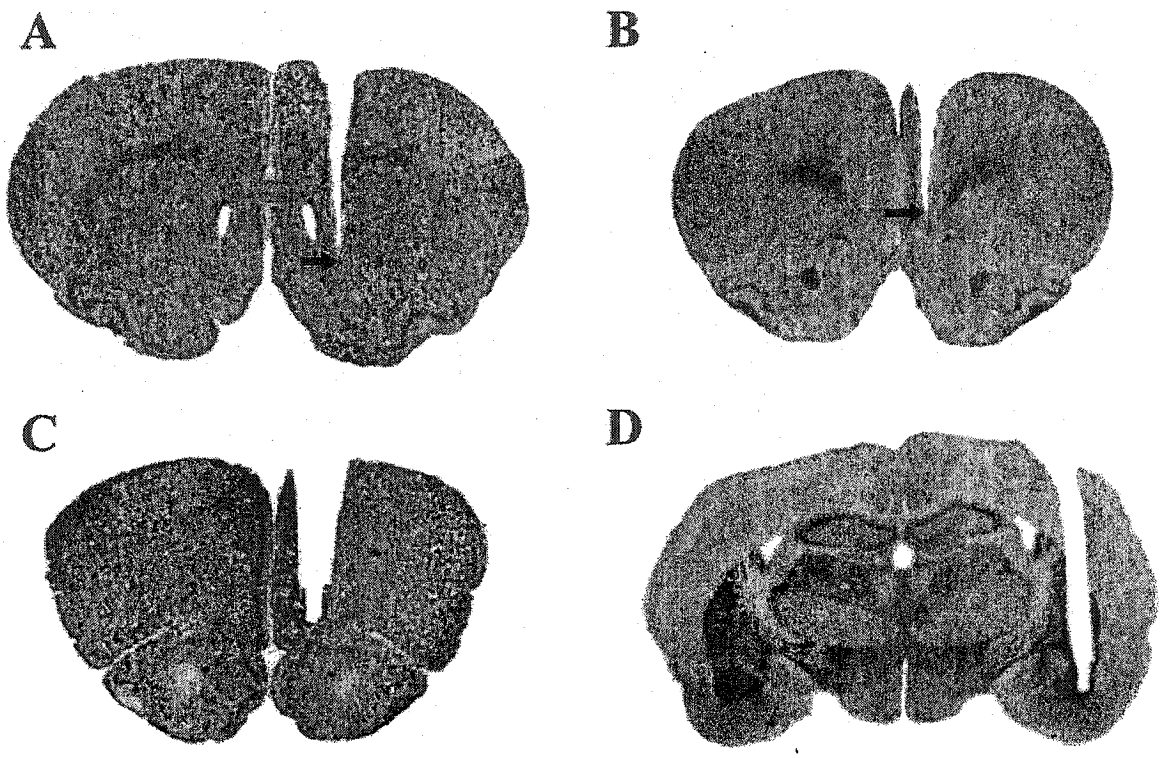

Fig. 1. Photomicrographs of (A) NAc and (B) mPFC electrode tip placements, and (C) mPFC and (D) BLA cannulae placements. The arrows indicate the most ventral extent of the electrode tips (Reprinted with permission from Blackwell Publishing, UK).

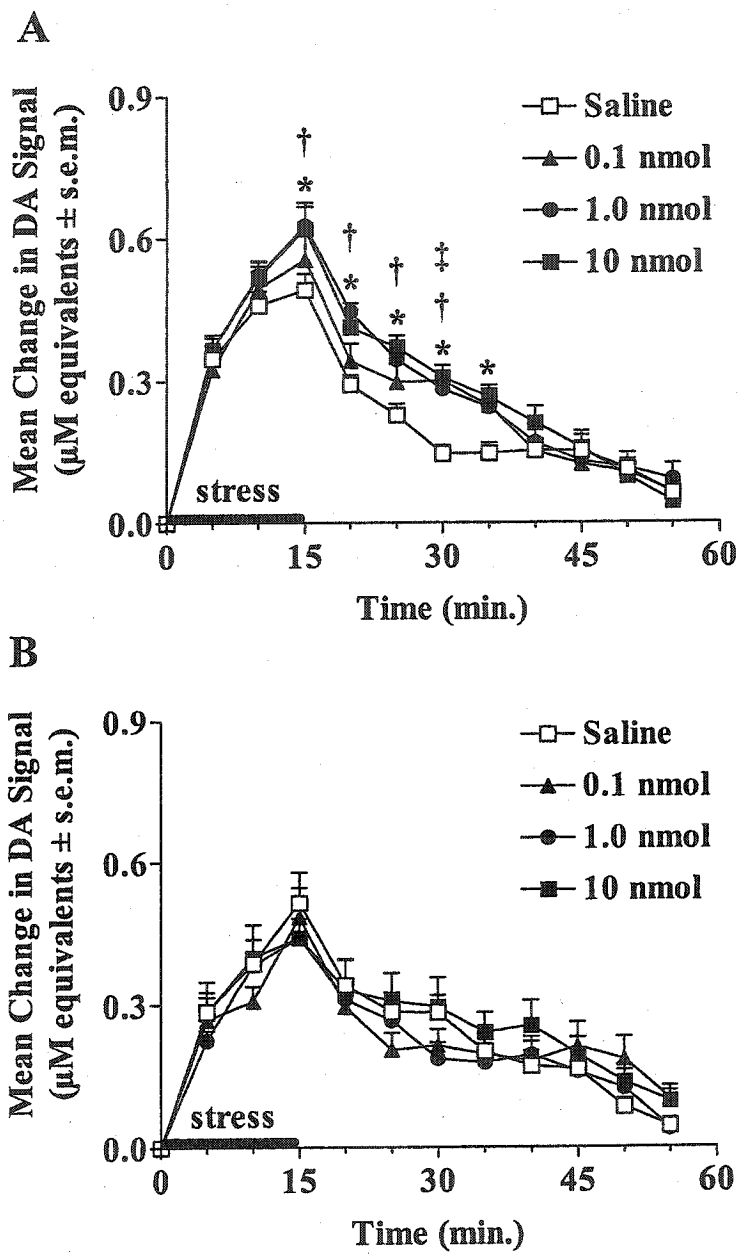

Fig. 2. Effects of intra-BLA injection of DA receptor antagonists on the NAc electrochemical response to stress. A) The D1 receptor antagonist SCH 23390 produced a significant dose-dependent potentiation of stress-induced increases in NAc DA signals (‡ 0.1 mol vs. saline, $P < 0.05$; † 1.0 nmol vs. saline, $P < 0.05$; * 10 nmol vs. saline, $P < 0.05$; n=10). B) The D2/D3 receptor antagonist raclopride had no effect on the NAc electrochemical response to stress (n=10) (Reprinted with permission from Blackwell Publishing, UK).

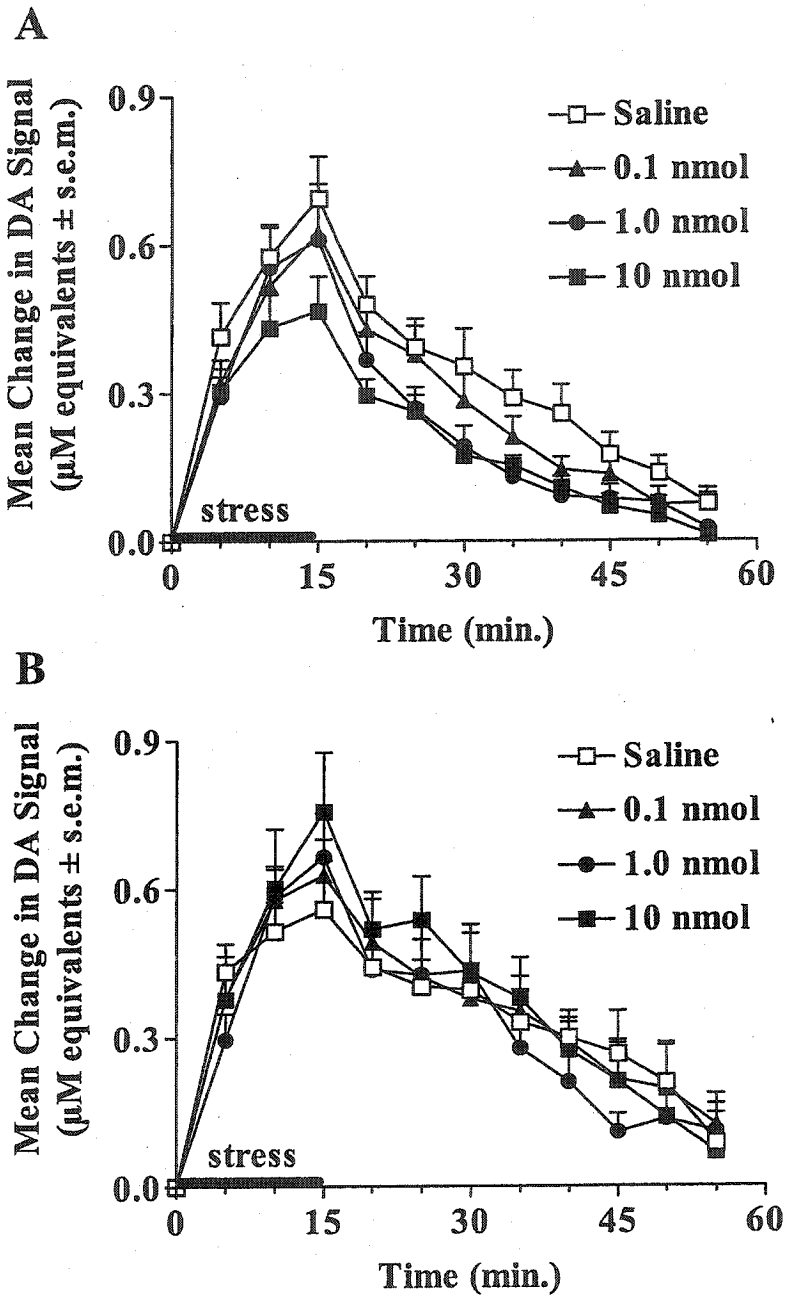

Fig. 3. Effects of intra-BLA injection of DA receptor antagonists on the mPFC electrochemical response to stress. A) The D1 receptor antagonist SCH 23390 resulted in a significant dose-dependent attenuation of stress-induced increases in mPFC DA signals (1.0 and 10 nmol vs. saline: Tukey's HSD, $P < 0.01$; n=9). B) The D2/D3 receptor antagonist raclopride had no effect on the mPFC response to stress (n=8) (Reprinted with permission from Blackwell Publishing, UK).

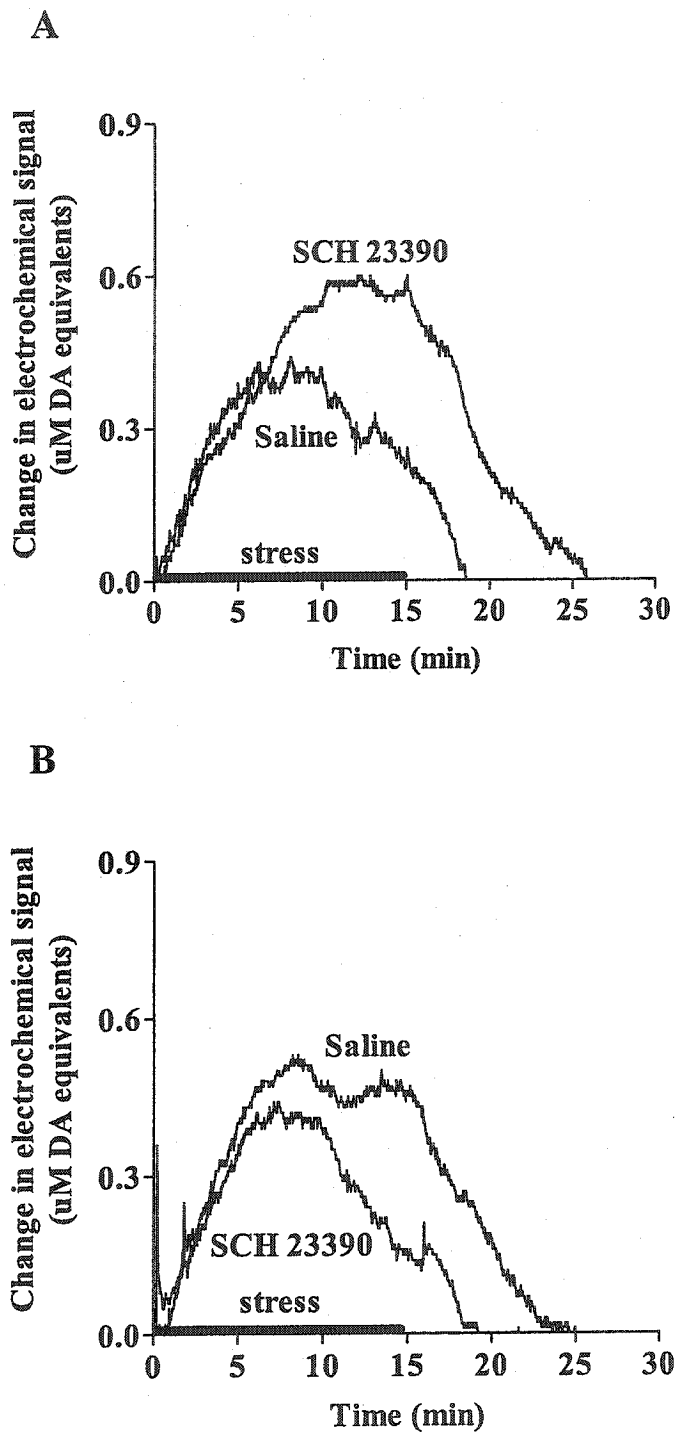

Fig. 4. Examples of the effect of intra-BLA SCH 23390 (10 nmol) on stress-induced DA signal increases in A) NAc and B) mPFC. (Reprinted with permission from Blackwell Publishing, UK).

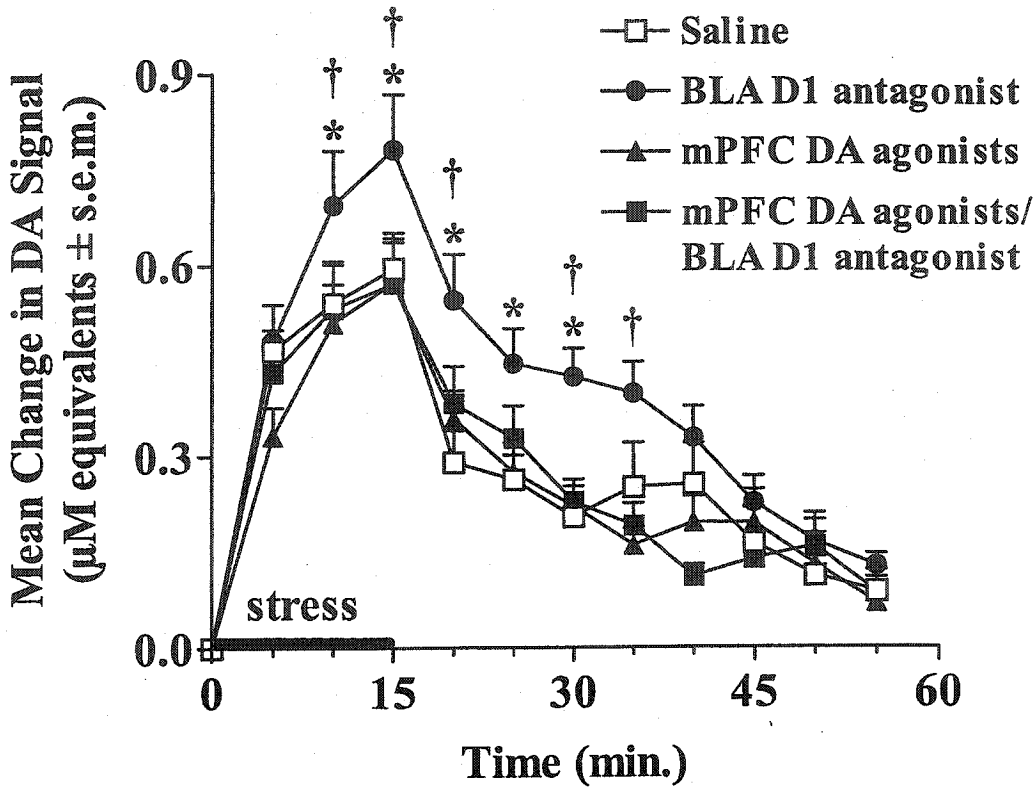

Fig. 5. Effects of simultaneous injections of D1 receptor antagonist into BLA and D1 and D2/D3 receptor agonists into mPFC on the NAc electrochemical response to stress. Intra-BLA injection of the D1 receptor antagonist SCH 23390 resulted in a significant potentiation of stress-induced DA signal increases in NAc (* BLA D1 antagonist vs. saline, $P < 0.05$). Intra-mPFC injection of the D1 agonist SKF 38393 and the D2/D3 agonist quinpirole had no effect on the NAc DA response to stress. Intra-mPFC injection of D1 and D2/D3 receptor agonists blocked the potentiation of stress-induced increases in NAc DA signals caused by injection of D1 receptor antagonist into BLA († BLA D1 antagonist vs. mPFC DA agonist/BLA D1 antagonist, $P < 0.05$; n=9). (Reprinted with permission from Blackwell Publishing, UK).

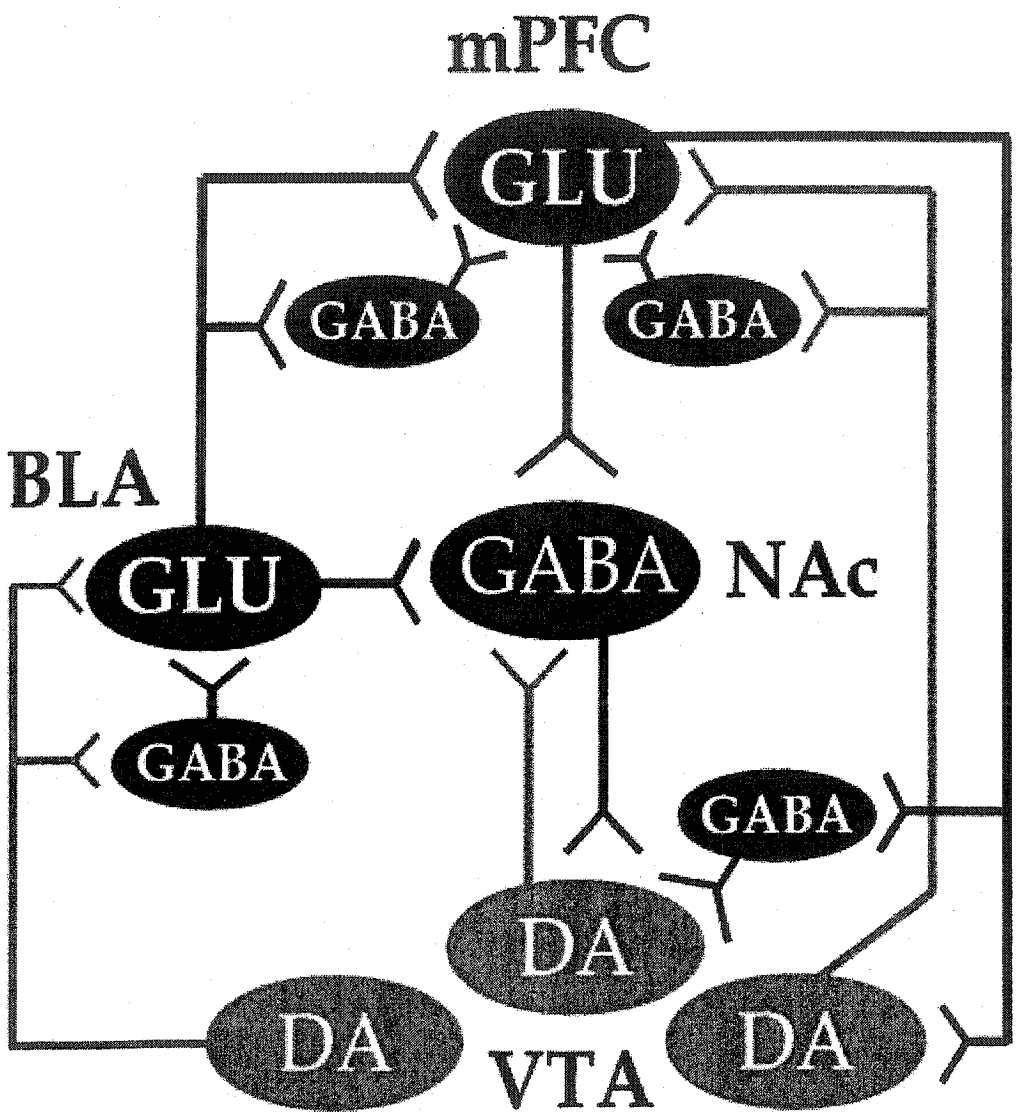

Fig. 6. Circuit diagram of stress-responsive DA projections to and glutamate- and GABA-containing interconnections between NAc, mPFC and BLA. Disinhibition of BLA projection neurons results in an attenuated mPFC DA response to stress and, consequently, in a potentiated NAc DA stress response. Abbreviations: BLA - basolateral amygdala; DA - dopamine; GLU - glutamate; mPFC - medial prefrontal cortex; NAc - nucleus accumbens; VTA - ventral tegmental area. (Reprinted with permission from Blackwell Publishing, UK).

4.0. STUDY #3

ROLE OF BASOLATERAL AMYGDALA DOPAMINE IN MODULATING PREPULSE INHIBITION AND LATENT INHIBITION IN THE RAT

Carl W. Stevenson and A. Gratton

(*Psychopharmacology,* in press)

4.1. PREFACE

The previous study revealed that BLA DA modulates the NAc DA response to stress indirectly by modulating stress-induced mPFC DA release, via activation of the DA D1 receptor subtype. The present study examined whether BLA DA modulation of mPFC and NAc DA function also occurs in a behaviourally-relevant manner during the processing of other sensory stimuli, particularly during certain types of information processing that are themselves modulated by NAc and mPFC DA function. Converging lines of evidence indicate that both BLA function and NAc and mPFC DA transmission are implicated in the modulation of PPI and LI. Thus, the present study investigated the effects of intra-BLA infusion of D1 and D2/D3 receptor antagonists on PPI and LI.

4.2. ABSTRACT

Rationale: The dopamine (DA) projection to the basolateral amygdala (BLA) modulates nucleus accumbens (NAc) and medial prefrontal cortex (mPFC) DA transmission. Given the involvement of the BLA, and of NAc and mPFC DA, in select forms of information processing, we sought to determine the role of BLA DA in modulating prepulse inhibition (PPI) and latent inhibition (LI). *Objective:* The effects of BLA D1 (SCH 23390) and D2/D3 (raclopride) receptor blockade on PPI and LI were examined. *Methods:* Separate groups of male Long Evans rats received bilateral intra-BLA infusions of SCH 23390 (3.2 or 6.4 μg/0.5 μL/side), raclopride (2.5 or 5.0 μg/0.5 μL/side) or saline prior to testing. In two experiments, the effects of BLA DA receptor antagonism on PPI of the acoustic startle response (ASR) and LI of conditioned taste aversion were determined. A control group received bilateral intra-striatal infusions of SCH 23390 or raclopride prior to PPI testing. *Results:* Intra-BLA SCH 23390 or raclopride had no effect on the ASR. Intra-BLA SCH 23390 enhanced and raclopride disrupted PPI, both in a dose-related manner. Intra-striatal SCH 23390 or raclopride had no effect on PPI or ASR magnitude. Finally, BLA DA receptor blockade had no effect on LI. *Conclusions:* These results indicate that PPI is modulated by BLA DA and suggest that this modulation occurs independently of changes in NAc and/or mPFC DA transmission. They also suggest that BLA DA is not involved in modulating LI and add to evidence indicating that PPI and LI are mediated by different neural substrates.

4.3. INTRODUCTION

The basolateral amygdala (BLA; lateral, basal and accessory basal nuclei) plays a key role in assigning emotional significance to exteroceptive stimuli (Aggleton, 2000). The BLA has been implicated in both aversive (Davis, 1992; LeDoux, 1996) and appetitive (Gallagher and Holland, 1994; Everitt et al., 1999) conditioning and recent evidence indicates that the dopamine (DA) projection to BLA is involved in mediating some aspect of associative learning (Lamont and Kokkinidis, 1998; Guarraci et al., 1999, 2000; Greba et al., 2001; Rosenkranz and Grace, 2002a).

The BLA has also been implicated in other forms of information processing, including prepulse inhibition (PPI) of the acoustic startle response (ASR) and latent inhibition (LI). The ASR is a coordinated contraction of the skeletal musculature elicited in response to a loud sound, while PPI refers to the attenuated ASR that is observed when the startling sound is immediately preceded by a weaker, non-startling acoustic stimulus (Geyer et al. 1990). Latent inhibition (LI) refers to an attenuated conditioned response that occurs with repeated, non-reinforced pre-exposure to the to-be-conditioned stimulus (Weiner, 2003). Lesions to the BLA (Wan and Swerdlow, 1997; Shoemaker et al., 2003) as well as intra-BLA injections of glutamate receptor antagonists (Bakshi and Geyer, 1998; Fendt et al., 2000) have been reported to disrupt PPI. The BLA may also modulate LI, however its precise role remains unclear, given that lesions to this area have been reported to potentiate (Weiner, 2003), attenuate (Coutureau et al., 2001), or have no effect (Weiner et al., 1996) on LI.

The DA projections to the nucleus accumbens (NAc; Swerdlow et al., 1990a, 1990b, 1992; Zhang et al., 2000) and medial prefrontal cortex (mPFC; Bubser and Koch, 1994; Koch and Bubser, 1994; Ellenbroek et al., 1996) also appear to be important in mediating PPI. Although a role for mPFC DA in the modulation of LI has yet to be established (Ellenbroek et al., 1996), NAc DA has been implicated in the modulation of this form of learning (Young et al., 1993; Warburton et al., 1996; Joseph et al., 2000).

The BLA sends direct glutamatergic projections to both the NAc and mPFC (McDonald, 1991) and functional evidence indicates that DA transmission in these two brain areas is modulated by a DA-dependent mechanism in the BLA (Simon et al., 1988; Hurd et al., 1997). We have previously reported evidence that BLA DA depletion and local BLA D1 receptor blockade will facilitate and inhibit DA transmission in NAc and mPFC, respectively (Stevenson et al., 2003; Stevenson and Gratton, 2003). In contrast, DA transmission in mPFC and NAc was found to be unaffected by local BLA D2/D3 receptor blockade. Taken together with evidence implicating mPFC and/or NAc DA in PPI and LI, these findings raise the possibility that BLA DA might modulate these two behaviours as a consequence of the indirect influence it exerts on mPFC and/or NAc DA transmission. In an initial attempt to address this question, we examined the effects of local BLA D1 or D2/D3 receptor blockade on PPI and LI.

4.4. MATERIALS AND METHODS

4.4.1. Animals

Male Long Evans rats (Charles River, St. Constant, Québec) weighing 300-350 g at the time of surgery were used in each of the experiments. Animals were housed singly on a 12-hour light/dark reverse cycle (lights off at 0800 h) with free access to food and water. Behavioural testing occurred during the animals' dark cycle. The experiments were conducted in separate groups of experimentally- and drug-naïve animals. All procedures in the present study conformed to the guidelines of the Canadian Council on Animal Care.

4.4.2. Surgery

Animals were pretreated with atropine sulfate (0.1 mg/kg, i.p.), anesthetized with sodium pentobarbital (60 mg/kg, i.p.), and placed in a stereotaxic apparatus. Animals were each implanted bilaterally with 22-gauge guide cannulae aimed at a point 1 mm above the injection site within the BLA (AP -2.8 mm, L 4.9 mm, DV 6.6 mm) and 28-gauge stainless steel obturators were inserted to a depth of 1 mm beyond the tip of the guide cannula prior to implantation. In order to rule out possible effects due to drug diffusion to distal

sites, a group of dorsal control animals were implanted with guide cannulae aimed at the caudal striatum (AP -2.8, L 4.9, DV 4.6 mm). Animals were allowed to recover from surgery for 1 week prior to testing.

4.4.3. Central drug injections

SCH 23390 HCl and raclopride HCl were obtained from Sigma (St Louis, MO). Both drugs were dissolved in saline and injected in a volume of 0.5 μL. Separate groups of animals received intra-BLA injections of either vehicle (saline) or SCH 23390 at a dose of either 3.2 or 6.4 μg/0.5 μL/side or raclopride at a dose of 2.5, or 5.0 μg/0.5 μL/side. Intra-BLA infusion of SCH 23390 and raclopride, at these dose ranges, have previously been shown to have behaviorally relevant effects (Greba et al., 2001; Stevenson and Gratton, 2003). Doses were calculated as the salt of the drug. The dorsal control animals each received, in counter-balanced order, infusions of vehicle (saline), SCH 23390 (6.4 μg/0.5 μL/side), and raclopride (5.0 μg/0.5 μL/side).

Animals were hand-held while solutions were infused over 30 sec. via a 28-gauge stainless steel cannula connected to a 1 μL syringe by a length of polyethylene tubing. Following drug administration the injector was left in place for 30 sec. before it was removed and the obturator replaced. Testing began immediately following injection.

4.4.4. Acoustic startle response and prepulse inhibition

Tests were conducted using a commercially available system (SR-LAB, San Diego Instruments, San Diego, U.S.A.) that comprised two sound-attenuating chambers each equipped with a cylindrical Plexiglas animal enclosure (length=16 cm; inner diameter=8.2 cm). Ventilation was provided by a small electric fan that also generated a 70 dB background noise. Tone pulses were presented by a speaker positioned 24 cm directly above the animal enclosure. A piezoelectric accelerometer affixed to the animal enclosure frame was used to detect and transduce motion resulting from the animals' response. Tone pulse parameters were controlled by a microcomputer using a commercial software package (SR-

LAB) and interface assembly that also digitized (0-4095), rectified, and recorded stabilimeter readings.

Measures of both ASR and PPI were obtained in a single session from separate groups of drug-naïve animals. After receiving the intra-BLA treatment, animals were placed in the Plexiglas enclosure and allowed to acclimatize to the environment for 5 min before being tested during 37 discrete trials. On the first two trials, the magnitude of the ASR to a 50 ms duration 120 dB tone was measured. These first two startle tones were presented in order to habituate the animals to the testing procedure; therefore the ASR magnitude of these two trials was omitted from the statistical analysis of the mean ASR amplitude. On the subsequent 35 trials, the startle tone was either presented alone or 100 ms after presentation of a 30 ms duration prepulse. Prepulse intensity ranged from 3 to 15 dB above background noise and was varied randomly between trials in 3 dB steps. Measures were taken at each of the five prepulse intensities on five trials; animals were randomly presented with the startle tone alone during the other 10 trials. The same stimulus condition was never presented on more than two consecutive trials. The interval between each trial was programmed to a variable time schedule with an average duration of 15 sec. (range 5 to 30 sec.). A measure of startle response amplitude was derived from the mean of 100 digitized data points collected from stimulus onset at a rate of 1 kHz. Prepulse effectiveness in suppressing the startle response was expressed as a percentage based on the mean amplitude of responses to the startle tone alone (n=10) relative to those recorded under the five prepulse conditions (n=5/condition):

% PPI = 100 – (startle preceded by prepulse / startle alone) x 100%

4.4.5. Latent inhibition

Measures of LI were obtained using a conditioned taste aversion (CTA) paradigm which has been described in detail elsewhere (Ellenbroek et al., 1997). The involvement of central DA systems in the modulation of LI employing the CTA paradigm has been shown to be similar to that previously observed with other LI paradigms (Ellenbroek et al., 1997; Russig et al., 2003). Briefly, the LI

procedure consisted of three days of pre-exposure, one day of conditioning, and one day of testing, each of which occurred in the animals' home cages. Animals were water-deprived 24 h before the onset of the experiment. On days 1-3, separate groups of animals received intra-BLA injections of either vehicle, SCH23390 or raclopride and then, 5 min post-injection, were given free access to either 5% sucrose (pre-exposed; PE) or water (non-pre-exposed; NPE) for 30 min. On day 4 (conditioning), after receiving their respective central drug treatment, all animals were given access to a 5% sucrose solution for 30 min., immediately followed by an injection of lithium chloride (LiCl; 75 mg/kg dissolved in 10 ml saline, i.p.). Although studies indicate that DA plays a critical role in LI during conditioning (Peters and Joseph, 1993; Weiner et al., 1997; Joseph et al., 2000), recent evidence suggests that the BLA may be involved in modulating LI during pre-exposure (Schauz and Koch, 2000). Thus, intra-BLA infusions of DA receptor antagonists were given prior to both pre-exposure and conditioning phases of the experiment. On day 5 (testing), all animals were given access to both 5% sucrose and water for 30 min. The amount of 5% sucrose and water consumed was determined by weighing the two bottles prior to and after the 30 min presentation. Comparisons between conditions (PE vs. NPE) and drug pre-treatments were based on the amount of 5% sucrose consumed relative to total fluid consumption during the day 5 test session where:

$$\textbf{LI} = \textbf{sucrose consumed} / (\textbf{sucrose consumed} + \textbf{water consumed}) \times \textbf{100\%}$$

For intact LI, the percent consumption of sucrose would be expected to be greater in PE animals that in the NPE counterparts.

4.4.6. Histology

All animals were deeply anesthetized with chloral hydrate (500 mg/kg, i.p.) and decapitated. The brains were removed and immediately frozen in isopentane kept on dry ice. The brains were then sliced into 30 μm sections and stained for acetylcholinesterase to determine cannula tip placements within the BLA or striatum.

4.4.7. Statistical analysis

The effects of intra-BLA infusion of each DA receptor antagonist on ASR and PPI were analyzed separately. A one-factor analysis of variance (ANOVA), with drug dose as the between-subject factor, was used to assess the magnitude of drug effects on the ASR. A two-factor repeated-measures ANOVA, with drug dose as the between-subject factor and prepulse intensity as the within-subject factor, was used to assess the magnitude of drug effects on PPI. The PPI data obtained from the dorsal control animals were analysed separately using a two-factor repeated-measures ANOVA, with drug and prepulse intensity as within-subject factors. In the LI experiment, total fluid consumption (sucrose + water) and the relative sucrose consumption (% sucrose) on the test day were analyzed separately. A two-factor ANOVA, with drug dose and condition (PE vs. NPE) as the between-subject variables, was used to assess the effects of intra-BLA infusion of DA receptor antagonist on total fluid consumption. A two-factor ANOVA, with drug dose and condition as between-subject variables, was used to assess the effects of BLA DA receptor blockade on relative sucrose consumption. When indicated, post-hoc comparisons were performed using Tukey's Honestly Significant Difference test.

4.5. RESULTS

4.5.1. Histology

Only data from animals with histologically confirmed bilateral cannulae tip placements within the BLA were included in the statistical analysis (Figure 1). In general, BLA cannulae tips were located caudally and ventrally within the basal amygdaloid nucleus, although some were also visualized in the accessory basal and lateral nuclei of the amygdala. A total of 139 animals (PPI experiment: n=53; LI experiment: n=86) met this inclusion criterion. Data were also obtained from 11 dorsal control animals; the cannulae placements in these animals were all found to lie within the striatum (Figure 1b).

4.5.2. Acoustic startle response

The effects of intra-BLA SCH 23390 and raclopride (n=10-11/group) on the mean ASR magnitude are presented in Figure 2. A one-factor ANOVA revealed no significant effect of intra-BLA SCH 23390 or raclopride infusion on mean ASR magnitude, at either of the doses tested.

4.5.3. Prepulse inhibition

The effects of intra-BLA SCH 23390 and raclopride PPI are presented in Figure 3. A two-factor ANOVA revealed a significant dose x prepulse intensity interaction ($F_{(8, 116)} = 2.56$, $P = 0.013$) in animals that received intra-BLA SCH 23390. Analysis of simple effects tests followed by post-hoc tests revealed that intra-BLA SCH 23390 resulted in a significant enhancement of PPI at the lowest and highest prepulse intensities tested ($P < 0.05$). In contrast, intra-BLA raclopride produced a significant dose-dependent attenuation of PPI ($F_{(2, 29)} = 3.74$, $P = 0.036$); post-hoc analysis revealed significantly reduced PPI at the higher dose tested (saline vs. 5.0 μg, $P < 0.05$). In the dorsal control animals, neither SCH23390 nor raclopride affected PPI when injected into striatum at doses that were effective when injected into BLA; there was no significant drug effect or a drug x prepulse intensity interaction.

4.5.4. Latent Inhibition

The effects of intra-BLA SCH 23390 and raclopride (n=7-10/group) on relative 5% sucrose consumption on the test day (day 5) are presented in Figure 4. A two-factor ANOVA revealed a significant main effect of exposure in animals given intra-BLA SCH 23390 ($F_{(1, 46)} = 17.95$, $P = 0.0001$), indicating that the PE animals drank significantly more 5% sucrose than water on the test day. However, there was no main effect of dose or an exposure x dose interaction, indicating that intra-BLA SCH 23390 infusion prior to pre-exposure and conditioning had no effect on LI. Similarly, in animals that received intra-BLA raclopride, a two-factor ANOVA revealed a significant main effect of exposure ($F_{(1, 46)} = 35.61$, $P < 0.0001$), again indicating that PE animals drank significantly more 5% sucrose than water on the test day. Moreover, no main effect of dose or

exposure x dose interaction was found, indicating that intra-BLA raclopride infusion had no effect on LI.

The effects of intra-BLA SCH 23390 and raclopride on total fluid consumption are presented in Figure 5. In animals treated with intra-BLA SCH 23390, a two-factor ANOVA revealed a significant main effect of exposure ($F_{(1, 46)} = 7.16$, $P = 0.010$), indicating that total fluid consumption (5% sucrose + water) among PE animals was significantly reduced compared to NPE animals. The statistical analysis also revealed a non-significant trend towards a main effect of dose ($F_{(2, 46)} = 2.94$, $P = 0.063$); intra-BLA SCH 23390 tended to decrease total fluid consumption on the test day. No such trend was apparent in animals given intra-BLA raclopride as there was no significant main effect of exposure or dose, or an exposure x dose interaction.

4.6. DISCUSSION

In the present study, we examined the effects of intra-BLA injections of DA receptor antagonists on PPI and LI. At the doses tested here, neither BLA D1 nor D2/D3 receptor blockade had any effect on the magnitude of the ASR. In contrast, local BLA D1 and D2/D3 receptor antagonism produced opposite effects on PPI. Whereas PPI was enhanced by BLA D1 blockade, it was attenuated following local D2/D3 receptor blockade. These effects appear to be specific to the BLA as PPI was unaffected by either drug when injected in the striatum at doses that were effective when applied to the BLA. We also report in the present study that local BLA D1 or D2/D3 receptor blockade had no effect on LI in a CTA paradigm.

The present finding that the ASR is unaffected by intra-BLA DA receptor blockade is in general agreement with a previous report (Lamont and Kokkinidis, 1998) but appears to be at odds with a study by Swerdlow et al. (1992), who reported a decrease in ASR magnitude following locally applied DA. In that study, however, DA was infused into both the BLA and the central amygdaloid nucleus (CeA); thus it is possible that the effect of DA infusion into the amygdala was mediated by the CeA rather than the BLA (Swerdlow et al., 1992). A

preferential role of the CeA in modulating the ASR is also suggested by the fact that electrical stimulation of the BLA is relatively ineffective at enhancing ASR magnitude, whereas CeA stimulation at low current intensities enhances the ASR (Rosen and Davis, 1988).

The present findings are also generally consistent with those of a previous study suggesting that amygdaloid DA may modulate PPI (Swerdlow et al., 1992). Thus, the present data suggest that DA neurons that project to BLA can influence PPI in different directions by actions at D1 and D2/D3 receptors. Additional studies examining the effects of intra-BLA infusion of selective D1 and D2/D3 receptor agonists would be useful to confirm the present findings. It is unlikely that the results of the present study are attributable to the spread of drug from the BLA to other potential sites of action. For example, when injected dorsally to the BLA (i.e. striatum), neither SCH23390 nor raclopride had any effect on PPI. The site-specificity of the present drug effects on PPI is also supported by previous evidence showing that [^{3}H] SCH 23390 infused into the BLA does not diffuse into the NAc, even 60 min. post-treatment (Hurd et al., 1997). Moreover, intra-NAc infusion of haloperidol, a D2/D3 receptor antagonist, partially ameliorates the PPI-disrupting effects of systemic amphetamine (AMPH) administration (Hart et al., 1998), whereas intra-BLA raclopride infusion disrupted PPI in the present study, suggesting that D2/D3 receptor antagonist infusion into the NAc and BLA have different effects.

Recent electrophysiological evidence indicates that BLA D1 and D2/D3 receptor activation have different effects on local neuronal activity; BLA D1 receptor activation has a net inhibitory effect on local pyramidal cell activity, whereas BLA D2/D3 receptor activation has a net excitatory effect (Rosenkranz and Grace, 2002b). Thus, although the underlying mechanism remains to be elucidated, the opposite effects of BLA D1 and D2/D3 receptor blockade on PPI reported in the present study would be congruent with the known differential effects of D1 and D2/D3 receptor activation on BLA cell activity.

While previous studies indicate that systemic administration of the D2/D3 receptor antagonist raclopride enhances PPI (Johansson et al., 1995; Zhang et al.,

2000), in the present study, intra-BLA raclopride had the opposite effect on PPI. Although the different routes of administration preclude direct comparisons between the present study and those of Johansson et al. (1995) and Zhang et al. (2000), it would appear that D2/D3 receptors at sites other than BLA play a key role in mediating the effects of systemic raclopride administration on PPI.

The BLA projects to the NAc and mPFC (McDonald, 1991) and recent evidence indicates that local BLA D1 receptor blockade potentiates and attenuates DA function in NAc and mPFC, respectively. For example, intra-BLA SCH 23390 results in a concomitant enhancement of cocaine self-administration and NAc DA release (Hurd et al., 1997). BLA infusion of SCH 23390 also enhances stress-induced NAc DA release but will attenuate the DA stress response in mPFC (Stevenson and Gratton, 2003). Enhanced NAc (Swerdlow et al., 1990a, b, 1992; Zhang et al., 2000) and diminished mPFC (Bubser and Koch, 1994; Ellenbroek et al., 1996) DA transmission disrupt PPI. If BLA DA modulated PPI indirectly by enhancing NAc and/or decreasing mPFC DA function, then local BLA D1 receptor blockade would be expected to *reduce* PPI. However, this was clearly not the case in the present study. It would appear, therefore, that BLA DA may modulate PPI independently of changes in NAc and/or mPFC DA transmission.

In contrast to the effects of BLA DA receptor blockade on PPI, intra-BLA infusion of DA receptor antagonists had no effect on LI in a CTA paradigm. Nevertheless, a role for the BLA in modulating LI has been demonstrated using both appetitive (Coutureau et al., 2001) and aversive (Schauz and Koch, 2000; Coutureau et al., 2001; Weiner, 2003) conditioning paradigms. One possible explanation for this apparent discrepancy is that BLA DA modulation of LI may only occur under conditions of increased DA transmission such as would occur, for example, following AMPH administration. Indeed, BLA DA depletion facilitates AMPH self-administration and potentiates both AMPH-induced locomotor activity (Simon et al., 1988) and stress-induced NAc DA release (Stevenson et al., 2003). Similarly, BLA D1 receptor blockade facilitates cocaine self-administration and potentiates cocaine- and stress-induced NAc DA release (Hurd et al., 1997; Stevenson and Gratton, 2003). Evidence suggests that

disruption of LI by AMPH is best observed following repeated administration of the drug, suggesting that sensitization of central DA projections may be a necessary condition for this effect to occur (Weiner et al., 1988; Warburton et al., 1996). The fact that meso-amygdaloid DA neurons will sensitize to the effects of AMPH would be supportive of such a notion (Harmer et al., 1997). Thus, future studies examining the effects of BLA DA modulation of AMPH-induced disruption of LI may also help to clarify this issue.

4.6.1. Conclusions

The results of the present study indicate that sensorimotor gating, as measured by PPI, is modulated by a DA-sensitive mechanism in BLA. They also suggest, in agreement with other lines of evidence, that BLA D1 and D2/D3 receptor activation have opposing effects of PPI. However, based on the currently available evidence, it would appear that BLA DA modulation of PPI occurs independently of changes in NAc and mPFC DA transmission. Finally, the present study also indicates that LI in a CTA paradigm is insensitive to pharmacological manipulations of D1 and D2/D3 receptors in the BLA.

ACKNOWLEDGEMENTS

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REFERENCES

Aggleton JP (2000) The amygdala. A functional analysis. Oxford University Press, Oxford.

Bakshi VP and Geyer MA (1998) Multiple limbic regions mediate the disruption of prepulse inhibition produced in rats by the noncompetitive NMDA antagonist dizocilpine. J Neurosci 18:8394-8401.

Bubser M and Koch M (1994) Prepulse inhibition of the acoustic startle response of rats is reduced by 6-hydroxydopamine lesions of the medial prefrontal cortex. Psychopharmacology 113:487-492.

Coutureau E, Blundell PJ and Killcross S (2001) Basolateral amygdala lesions disrupt latent inhibition in rats. Brain Res Bull 56:49-53.

Davis M (1992) The role of the amygdala in fear and anxiety. Annu Rev Neurosci 15:353-375.

Ellenbroek BA, Budde S and Cools AR (1996) Prepulse inhibition and latent inhibition: the role of dopamine in the medial prefrontal cortex. Neuroscience 75:535-542.

Ellenbroek BA, Knobbout DA and Cools AR (1997) The role of mesolimbic and nigrostriatal dopamine in latent inhibition as measured with the conditioned taste aversion paradigm. Psychopharmacology 129:112-20.

Everitt BJ, Parkinson JA, Olmstead MC, Arroyo M, Robledo P and Robbins TW (1999) Associative processes in addiction and reward: the role of the amygdala-ventral striatal subsystems. Ann N Y Acad Sci 877:412-438.

Fendt M, Schwienbacher I and Koch M (2000) Amygdaloid N-methyl-D-aspartate and gamma-aminobutyric acid(A) receptors regulate sensorimotor gating in a dopamine-dependent way in rats. Neuroscience 98:55-60.

Gallagher M and Holland PC (1994) The amygdala complex: multiple roles in associative learning and attention. Proc Natl Acad Sci USA 91:11771-11776.

Geyer MA, Swerdlow NR, Mansbach RS and Braff DL (1990) Startle response models of sensorimotor gating and habituation deficits in schizophrenia. Brain Res Bull 25:485-498.

Greba Q, Gifkins A and Kokkinidis L (2001) Inhibition of amygdaloid dopamine D2 receptors impairs emotional learning measured with fear-potentiated startle. Brain Res 899:218-226.

Guarraci FA, Frohardt RJ, Falls WA and Kapp BS (2000) The effects of intra-amygdaloid infusions of a D_2 dopamine receptor antagonist on Pavlovian fear conditioning. Behav Neurosci 114:647-651.

Guarraci FA, Frohardt RJ and Kapp BS (1999) Amygdaloid D_1 dopamine receptor involvement in Pavlovian fear conditioning. Brain Res 827:28-40.

Harmer CJ, Hitchcott PK, Morutto SL and Phillips GD (1997) Repeated d-amphetamine enhances stimulated mesoamygdaloid dopamine transmission. Psychopharmacology 132:247-254.

Hart S, Zreik M, Carper R and Swerdlow NR (1998) Localizing haloperidol effects on sensorimotor gating in a predictive model of antipsychotic potency. Pharmacol Biochem Behav 61:113-119.

Hurd RL, McGregor A and Ponten M (1997) *In vivo* amygdala dopamine levels modulate cocaine self-administration behavior in the rat: D1 dopamine receptor involvement. Eur J Neurosci 9:2541-2548.

Johansson C, Jackson DM, Zhang J and Svensson L (1995) Prepulse inhibition of acoustic startle, a measure of sensorimotor gating: effects of antipsychotics and other agents in rats. Pharmacol Biochem Behav 52:649-654.

Joseph MH, Peters SL, Moran PM, Grigoryan GA, Young AMJ and Gray JA (2000) Modulation of latent inhibition in the rat by altered dopamine transmission in the nucleus accumbens at the time of conditioning. Neuroscience 101:921-930.

Koch M and Bubser M (1994) Deficient sensorimotor gating after 6-hydroxydopamine lesion of the rat medial prefrontal cortex is reversed by haloperidol. Eur J Neurosci 6:1837-1845.

Lamont EW and Kokkinidis L (1998) Infusion of the dopamine D_1 receptor antagonist SCH 23390 into the amygdala blocks fear expression in a potentiated startle paradigm. Brain Res 795:128-136.

LeDoux JE (1996) The emotional brain. Simon and Schuster, New York.

McDonald AJ (1991) Organization of amygdaloid projections to the prefrontal cortex and associated striatum in the rat. Neuroscience 44:1-14.

Peters SL and Joseph MH (1993) Haloperidol potentiation of latent inhibition in rats: evidence for a critical role at conditioning rather than pre-exposure. Behav Pharmacol 4:183-186.

Rosen JB and Davis M (1988) Enhancement of acoustic startle by electrical stimulation of the amygdala. Behav Neurosci 102:195-202.

Rosenkranz JA and Grace AA (2002a) Dopamine-mediated modulation of odour-evoked amygdala potentials during Pavlovian conditioning. Nature 417:282-287.

Rosenkranz JA and Grace AA (2002b) Cellular mechanisms of infralimbic and prelimbic prefrontal cortical inhibition and dopaminergic modulation of basolateral amygdala neurons *in vivo*. J Neurosci 22:324-337.

Russig H, Kovacevic A, Murphy CA and Feldon J (2003) Haloperidol and clozapine antagonise amphetamine-induced disruption of latent inhibition of conditioned taste aversion. Psychopharmacology 170:263-270.

Schauz C and Koch M (2000) Blockade of NMDA receptors in the amygdala prevents latent inhibition of fear-conditioning. Learn Mem 7:393-399.

Shoemaker JM, Pitcher L, Noh HR and Swerdlow NR (2003) Quetiapine produces a prolonged reversal of the sensorimotor gating-disruptive effects of basolateral amygdala lesions in rats. Behav Neurosci 117:136-143.

Simon H, Taghzouti K, Gozlan H, Studler JM, Louilot A, Herve D, Glowinski J, Tassin JP and Le Moal M (1988) Lesion of dopaminergic terminals in the amygdala produces enhanced locomotor response to D-amphetamine and opposite changes in dopaminergic activity in prefrontal cortex and nucleus accumbens. Brain Res 447:335-340.

Stevenson CW and Gratton A (2003) Basolateral amygdala modulation of the nucleus accumbens dopamine response to stress: role of the medial prefrontal cortex. Eur J Neurosci 17:1287-1295.

Stevenson CW, Sullivan RM and Gratton RM (2003) Effects of basolateral amygdala dopamine depletion on the nucleus accumbens and medial prefrontal cortical dopamine responses to stress. Neuroscience 161:285-293.

Swerdlow NR, Braff DL, Masten VL and Geyer MA (1990a) Schizophrenic-like sensorimotor gating abnormalities in rats following dopamine infusion into the nucleus accumbens. Psychopharmacology 101:414-420.

Swerdlow NR, Mansbach RS, Geyer MA, Pulvirenti L, Koob GF and Braff DL (1990b) Amphetamine disruption of prepulse inhibition of acoustic startle is reversed by depletion of mesolimbic dopamine. Psychopharmacology 100:413-416.

Swerdlow NR, Caine SB and Geyer MA (1992) Regionally selective effects of intracerebral dopamine infusion on sensorimotor gating of the startle reflex in rats. Psychopharmacology 108:189-195.

Swerdlow NR, Geyer MA and Braff DL (2001) Neural circuit regulation of prepulse inhibition of startle in the rat: current knowledge and future challenges. Psychopharmacology 156:194-215.

Swerdlow NR, Mansbach RS, Geyer MA, Pulvirenti L, Koob GF and Braff DL (1990b) Amphetamine disruption of prepulse inhibition of acoustic startle is reversed by depletion of mesolimbic dopamine. Psychopharmacology. 100:413-416.

Wan FJ and Swerdlow NR (1997) The basolateral amygdala regulates sensorimotor gating of acoustic startle in the rat. Neuroscience 76:715-724.

Warburton EC, Mitchell SN and Joseph MH (1996) Calcium dependence of sensitised dopamine release in rat nucleus accumbens following amphetamine challenge: implications for the disruption of latent inhibition. Behav Pharmacol 7:119-129.

Weiner I, Lubow RE and Feldon J (1988) Disruption of latent inhibition by acute administration of low doses of amphetamine. Pharmacol Biochem Behav 30:871-878.

Weiner I, Shadach E, Barkai R and Feldon J (1997) Haloperidol- and clozapine-induced enhancement of latent inhibition with extended conditioning: implications for the mechanism of action of neuroleptic drugs. Neuropsychopharmacology 16:42-50.

Weiner I, Tarrasch R and Feldon J (1996) Basolateral amygdala lesions do not disrupt latent inhibition. Behav Brain Res 72:73-81.

Weiner I (2003) The "two-headed" latent inhibition model of schizophrenia: modeling positive and negative symptoms and their treatment. Psychopharmacology 169:257-297.

Young AM, Joseph MH and Gray JA (1993) Latent inhibition of conditioned dopamine release in rat nucleus accumbens. Neuroscience 54:5-9.

Zhang J, Forkstam C, Engel JA and Svensson L (2000) Role of dopamine in prepulse inhibition of acoustic startle. Psychopharmacology 149:181-188.

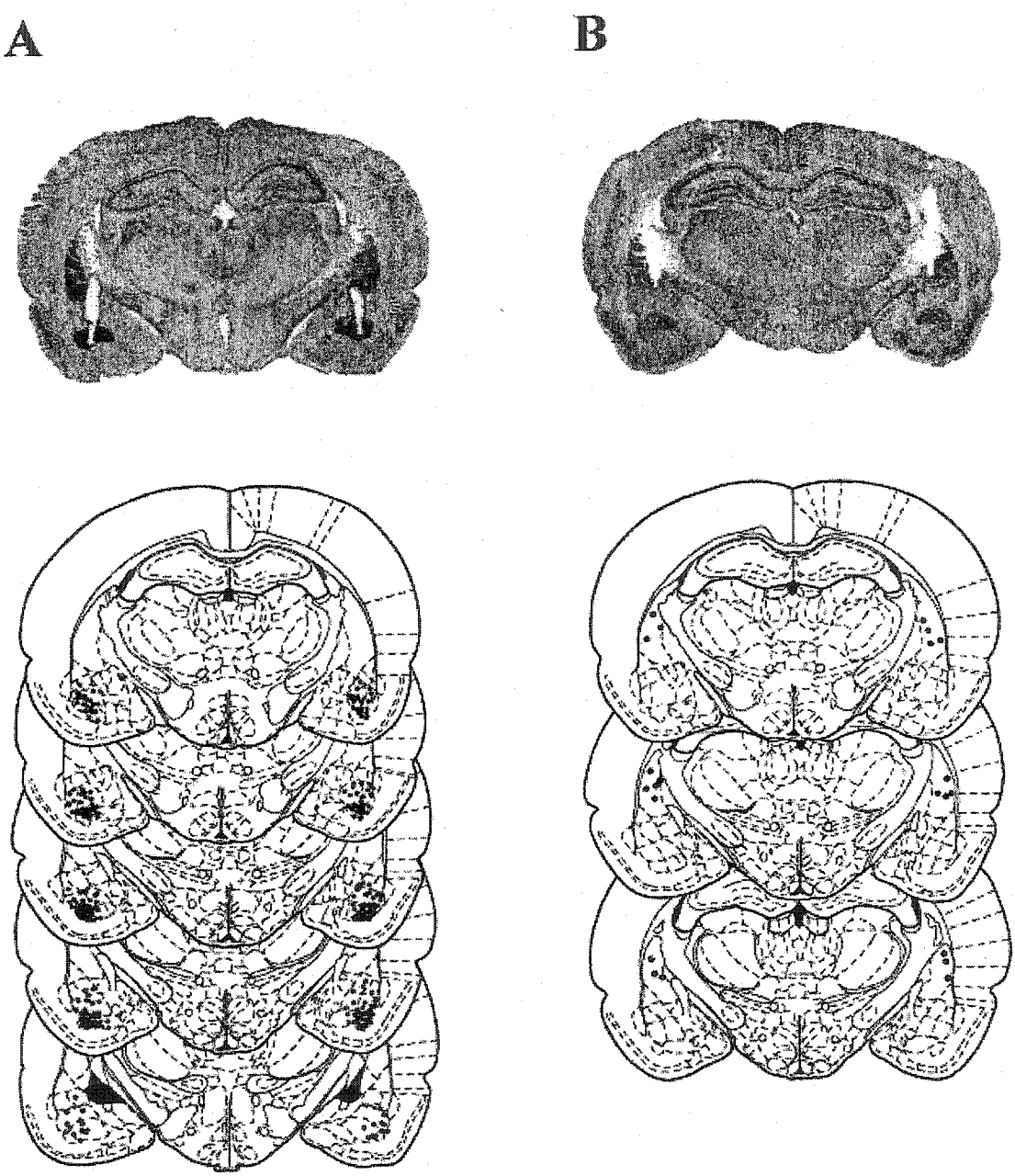

Figure 1. Photomicrographs of representative histological sections and schematics of cannulae tip placements within the A) BLA and B) striatum (dorsal control animals) (Reprinted with permission from Springer-Verlag).

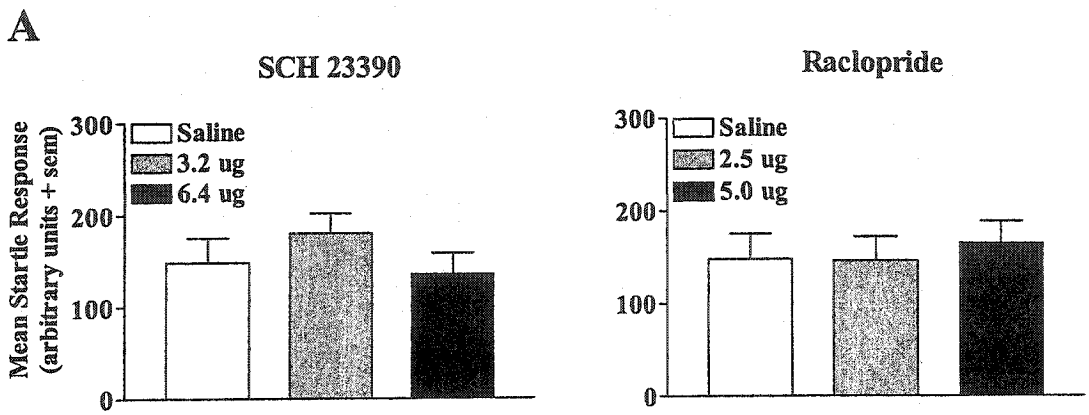

Figure 2. Effects of intra-BLA D1 and D2/D3 receptor antagonists on the ASR. Intra-BLA SCH 23390 and raclopride (n=10-11/group) had no effects on the mean ASR magnitude (Reprinted with permission from Springer-Verlag).

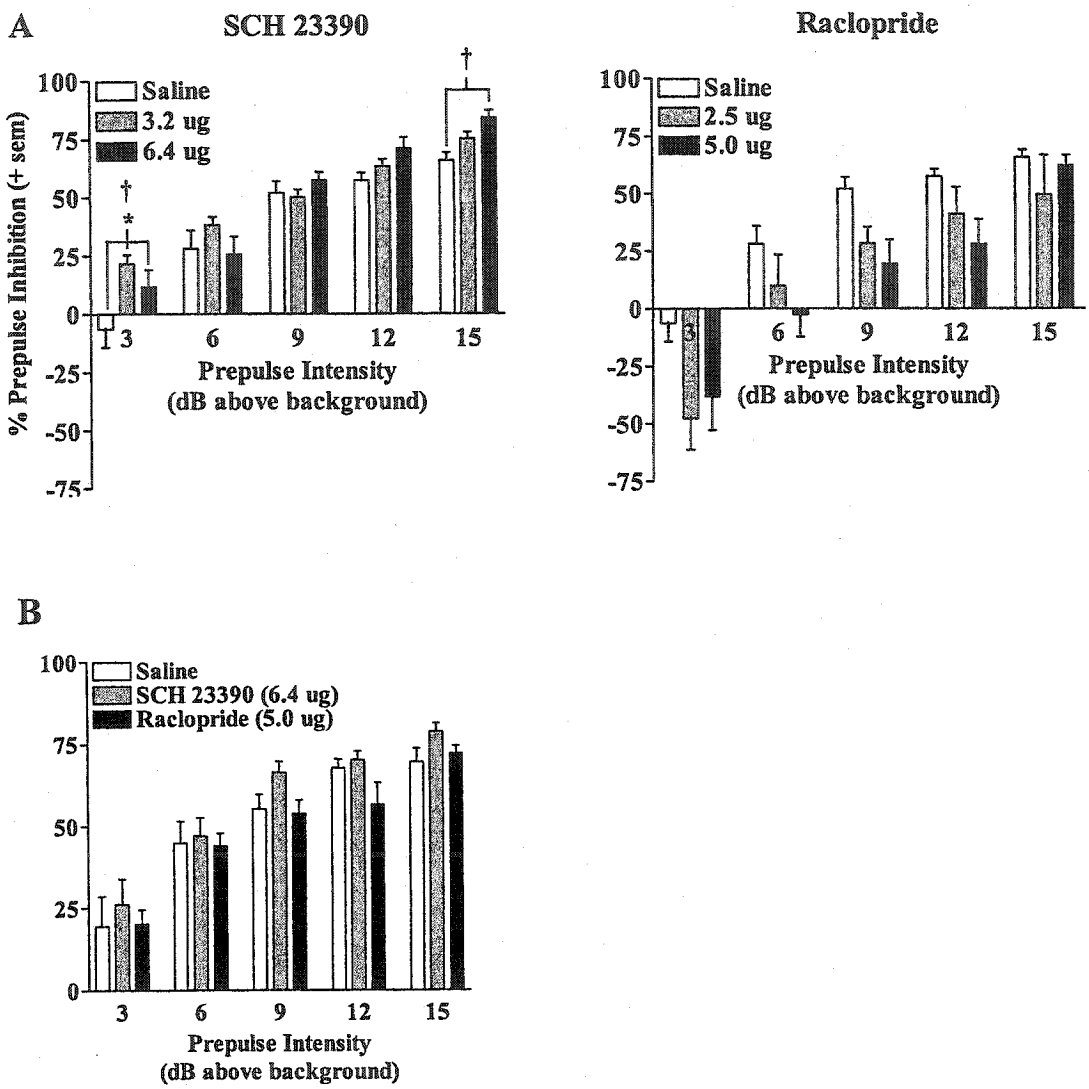

Figure 3. A) Effects of local BLA D1 and D2/D3 receptor blockade on PPI. Intra-BLA SCH 23390 dose-dependently enhanced PPI (* saline vs. 3.2 μg, † saline vs. 6.4 μg; $P < 0.05$). Conversely, intra-BLA raclopride dose-dependently reduced PPI, with this effect reaching significance at the higher (5.0 μg) dose tested ($P < 0.05$). B) In dorsal control animals, intra-striatal infusions of either DA receptor antagonist had no effect on PPI (Reprinted with permission from Springer-Verlag).

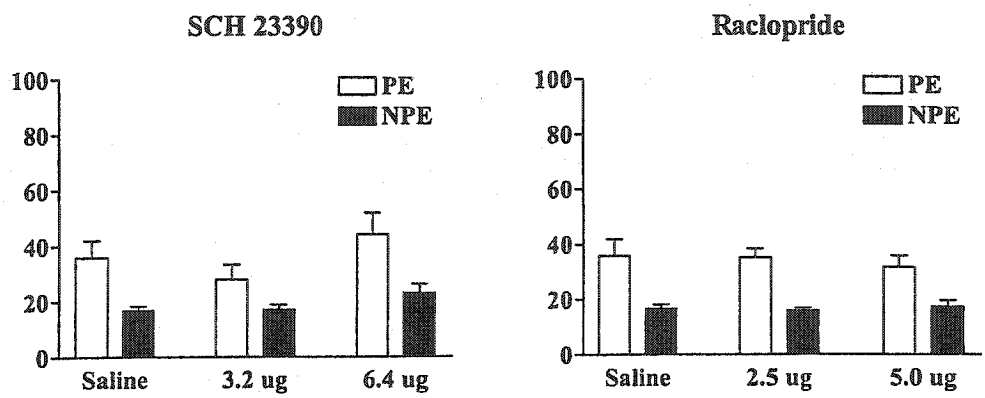

Figure 4. Effects of local BLA D1 and D2/D3 receptor blockade on LI (n=7-10/group). Animals preexposed (PE) to 5% sucrose consumed a greater percentage of sucrose on the test day, compared to non-preexposed (NPE) animals (SCH 23390, $P < 0.001$; raclopride, $P < 0.0001$). However, PE and NPE animals given intra-BLA SCH 23390 or raclopride did not show differences in the percentage of sucrose consumed on the test day, compared to intra-BLA saline controls, at either of the doses tested (Reprinted with permission from Springer-Verlag).

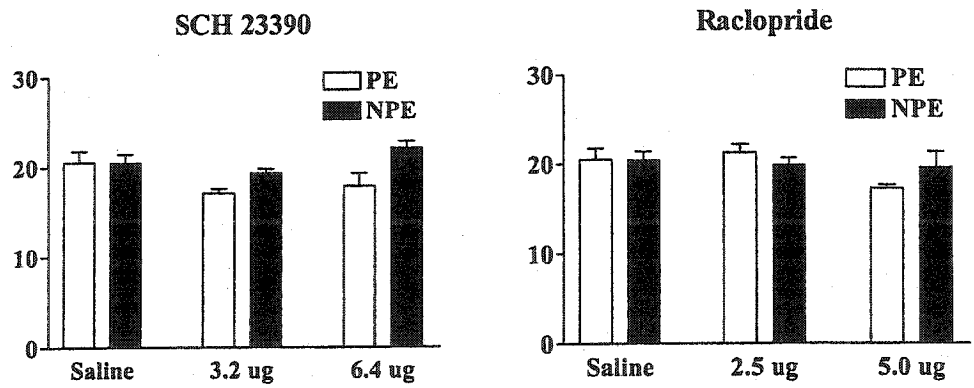

Figure 5. Effects of local BLA D1 and D2/D3 receptor blockade on total fluid consumption. Intra-BLA SCH 23390 decreased total fluid consumption in PE animals compared to NPE animals ($P < 0.05$). There were no group differences in total fluid consumption following intra-BLA raclopride (Reprinted with permission from Springer-Verlag).

5.0. STUDY #4

BASOLATERAL AMYGDALA DOPAMINE RECEPTOR ANTAGONISM MODULATES INITIAL REACTIVITY TO BUT NOT HABITUATION OF THE ACOUSTIC STARTLE RESPONSE

Carl W. Stevenson and A. Gratton

(*Behav Brain Res*, in press)

5.1. PREFACE

The first two studies indicated that BLA DA modulates stress-induced NAc and mPFC DA release. The third study indicated that BLA DA also modulates PPI, a form of acoustic startle plasticity, presumably independently of changes in NAc and/or mPFC DA transmission. Habituation is another form of startle plasticity in which NAc and mPFC DA function may be involved. Thus, the present study investigated the effects of intra-BLA infusion of D1 and D2/D3 receptor antagonists on habituation of the acoustic startle response.

5.2. ABSTRACT

Although the basolateral amygdala (BLA) plays a role in the habituation to sensory stimuli, the receptor mechanisms mediating this process remain unclear. In the present study, we investigated the role of BLA dopamine (DA) in the habituation of the acoustic startle response (ASR) with intra-BLA infusions of DA receptor antagonists. Male Long Evans rats were subjected to startle pulses over two consecutive once-daily sessions. Prior to testing on Day 1, separate groups of animals received bilateral intra-BLA infusions of a D1 (SCH 23390: 0, 3.2, 6.4 μg/side) or a D2/D3 (raclopride: 0, 2.5, 5.0 μg/side) receptor antagonist. Animals were retested 24 hrs later (Day 2) without prior drug infusion in order to assess possible treatment effects on within- and between-session habituation of the ASR. As expected, within- and between-session habituation was observed in vehicle-treated controls. Within-session habituation was also seen in SCH 23390- and raclopride-treated animals both on Day 1 as well as 24 hours later (Day 2). Evidence of between-session habituation was observed in SCH 23390-treated animals. However, compared to vehicle, intra-BLA SCH 23390 or raclopride attenuated the initial startle response on Day 1, but not Day 2. No evidence of between-session habituation was found in raclopride-treated animals, although this probably reflected the attenuated initial response to the startling stimulus on Day 1 rather than a reduced rate of habituation on Day 2. The present study suggests that while BLA DA is not involved in habituation of the ASR, it may mediate the perceived aversive nature of the initially startling stimuli.

5.3. INTRODUCTION

The basolateral amygdala (BLA) is generally thought to play an integral role in aversive conditioning (Davis, 1992; LeDoux, 1986) and evidence indicates that the dopamine (DA) projection to this region is involved in mediating this type of learning (Lamont and Kokkinidis, 1998; Nader and LeDoux, 1999; Guarracci et al, 1999, 2000; Greba and Kokkinidis, 2001; Greba et al, 2001). Habituation of the acoustic startle response (ASR) is a form of learning characterized by a gradual decrease in the magnitude of the startle response that occurs with repeated presentation of the startling stimulus (Geyer and Braff, 1987). While there is evidence implicating the BLA in habituation to various stimuli (Ben-Ari and Le Gal La Salle, 1974; Rosenkranz and Grace, 2002), including an intense auditory stimulus (Young et al, 1991), there is relatively little information on the role of DA in this process.

In fact, early studies examining the effects of systemic administration of indirect and direct DA agonists on the ASR provided little support for DA in mediating habituation of the ASR (Davis and Aghajanian, 1976; Geyer et al., 1978; Davis, 1980; Geyer and Braff, 1987). However, in one recent study the ASR was reported to be associated with an increase in nucleus accumbens (NAc) DA release that was significantly reduced 24 hours after initial exposure to the startling stimuli. Interestingly, the opposite pattern was seen in the medial prefrontal cortex (mPFC); there the increase in DA levels that accompanied the ASR was greater 24 after initial startle stimuli presentation (Storozheva et al, 2003). This finding is congruent with other lines of evidence indicating that NAc DA transmission in response to a variety of stimuli, including an aversive stimulus, is under the inhibitory influence of a DA-sensitive mechanism in the mPFC, such that increased mPFC DA tone serves to dampen the responsivity of meso-accumbens DA neurons (Deutch et al, 1996; Doherty and Gratton, 1996).

We have previously reported evidence that DA transmission in the NAc and mPFC is similarly modulated by the DA projection to the BLA. Specifically, we showed that DA depletion or local DA receptor blockade in this region enhances stress-induced DA release in NAc while attenuating the DA stress

response in mPFC (Stevenson et al, 2003; Stevenson and Gratton, 2003). Taken together with the findings of Storozheva et al (2003), our data raise the possibility that the opposing changes in NAc and mPFC DA transmission associated with the ASR may in fact be modulated indirectly by a DA-dependent mechanism in the BLA. Thus, in the present study, we sought to determine if habituation of the ASR is also modulated by the DA projection to BLA and, if so, whether this process is mediated by the D1 or D2/D3 receptor subtype, or both.

5.4. MATERIALS AND METHODS

5.4.1. Animals

Male Long Evans rats (Charles River, St. Constant, Québec) weighing 300-350 g at the time of surgery were used in each of the experiments. Animals were housed singly on a 12-hour light/dark reverse cycle (lights off at 0800 h) with free access to food and water. Animals were tested during their dark cycle. All procedures in the present study conformed to the guidelines of the Canadian Council on Animal Care.

5.4.2. Surgery

Animals were pretreated with atropine sulfate (0.1 mg/kg, i.p.), anesthetized with sodium pentobarbital (60 mg/kg, i.p.), and placed in a stereotaxic apparatus. Animals were each implanted bilaterally with 22-gauge guide cannulae aimed at a point 1 mm above the injection site within the BLA (AP -2.8 mm, L 4.8 mm, DV 6.6 mm); 28-gauge stainless steel obturators were inserted to a depth of 1 mm beyond the tip of the guide cannula prior to implantation. Animals were allowed one week to recover from surgery prior to behavioural testing.

5.4.3. Drugs

SCH 23390 HCl and raclopride HCl were obtained from Sigma (St Louis, MO). Both drugs were dissolved in saline and injected in a volume of 0.5 µL. SCH 23390 was infused at doses of 0, 3.2 (10 nmol) and 6.4 (20 nmol) µg/side whereas raclopride was given at doses of 0, 2.5 (5 nmol), and 5.0 (10 nmol) µg/side. The effects of each treatment were tested in separate groups of 11-13

animals. Intra-BLA infusion of SCH 23390 and raclopride, at these dose ranges, have previously been shown to have behaviourally-relevant effects (Caine et al, 1995; Nader and LeDoux, 1999; Greba and Kokkinidis, 2001; Greba et al, 2001; Stevenson et al, 2002, 2003; Stevenson and Gratton, 2003). Each dose used was calculated as the salt of the drug.

5.4.4. Central drug infusions

Drug solutions (SCH 23390, raclopride, or saline) were infused over 30 sec. via a 28-gauge stainless steel cannula that extended 1 mm beyond the tip of the guide cannula and was connected to a 1 μL syringe by a length of polyethylene tubing. Following drug administration the injector was left in place for 30 sec. before it was removed and the obturator replaced. Behavioural testing began 5 min. after central drug infusion (see below).

5.4.5. Testing apparatus

Habituation of the ASR was measured using a commercially available system (SR-LAB, San Diego Instruments, San Diego, U.S.A.) that comprised two sound-attenuating chambers each equipped with a cylindrical Plexiglas animal enclosure (length=16 cm; inner diameter=8.2 cm). Ventilation was provided by a small electric fan that also generated a 70 dB background noise. Tone pulses were presented by a speaker positioned 24 cm directly above the animal enclosure. A piezoelectric accelerometer affixed to the animal enclosure frame was used to detect and transduce motion resulting from the animals' response. Tone pulse parameters were controlled by a microcomputer using a commercial software package (SR-LAB) and interface assembly (0-4095) that also digitized, rectified, and recorded stabilimeter readings.

5.4.6. Acoustic Startle Habituation

The animals' startle responses to a tone pulse (120 dB, 50 ms duration) presented every 15 sec. was measured during two consecutive once-daily sessions. Animals were placed in the Plexiglass enclosure and allowed to acclimatize to the environment for 5 min before being tested during 81 discrete trials. A measure of startle response magnitude was derived from the mean of 100 digitized data points

collected from stimulus onset at a rate of 1 kHz. Prior to the first session (Day 1), separate groups of animals received intra-BLA infusions of SCH 23390, raclopride or saline. Animals were then retested 24 hours later (Day 2) without receiving any drug treatment. This experimental design was used to examine the effects of drug treatment on both within- and between-session habituation of ASR.

5.4.7. Histology

At the end of each experiment, all animals were deeply anesthetized with chloral hydrate (500 mg/kg, i.p.) and decapitated. The brains were removed and immediately frozen in an isopentane bath kept on dry ice. The brains were then sliced into 30 μm sections and stained for acetylcholinesterase to confirm the cannulae placements within the BLA.

5.4.8. Statistical analysis

The data were analyzed as trial blocks, with each block representing the mean startle response magnitude to three consecutive tone presentations. A three-factor repeated-measures analysis of variance (ANOVA), with drug dose as the between-factor variable and trial block and test day as the within-subject factors, was used to assess the effects of intra-BLA infusion of SCH 23390 or raclopride (two separate analyses) on ASR magnitude. These analyses allowed for the determination of within- and between-session habituation to the ASR.

5.5. RESULTS

5.5.1. Histology

Only data from animals with confirmed cannulae placements within the BLA were included in the statistical analysis (Figure 1). A total of 59 animals met the criteria for inclusion in the data analysis. In the few remaining animals, cannulae placements were located either medial or lateral to the BLA; no consistent effects of locally-applied raclopride or SCH 23390 were observed in these animals (data not shown).

5.5.2. Startle Habituation

The effects of intra-BLA infusion of SCH 23390 at the two doses tested (n=11-13/group) on acoustic startle habituation are presented in Figure 2. A three-factor ANOVA revealed a significant dose x trial block x day interaction ($F_{(52, 858)} = 2.10$, $P < 0.0001$). Simple main effects and post-hoc analysis revealed that the magnitude of the ASR in vehicle- and SCH 23390-treated animals were, on both Day 1 and Day 2, significantly lower on the last block of trials when compared to the first trial block ($P < 0.01$), indicating that intra-BLA SCH 23390 had no effect on within-session habituation. Similarly, the ASR of both vehicle- and SCH 23390-treated animals were significantly lower on Day 2 than on Day 1, indicating that between-session habituation of the ASR was also unaffected by intra-BLA SCH 23390. However, the statistical analysis did reveal differences in the startle response of vehicle- and SCH 23390-treated animals to the first few tone pulse presentations of the sessions. Simple main effects and post-hoc analysis confirmed that, when compared to vehicle-treated animals, SCH 23390-treated animals had attenuated ASR magnitudes on the first two trial blocks of Day 1, but not on Day 2 ($P < 0.01$).

The effects of intra-BLA infusion of raclopride (n=11-13/group) on habituation of the ASR are presented in Figure 3. Again, a three-factor ANOVA revealed a significant dose x trial block x day interaction for intra-BLA raclopride ($F_{(52, 858)} = 1.85$, $P < 0.001$). As seen with intra-BLA SCH 23390, saline- and raclopride-treated animals had smaller ASR during the last block of trials compared to the first trial block of the session ($P < 0.01$), indicating that intra-BLA raclopride also had no effect on within-session habituation. When compared to saline-treated animals, the ASR of raclopride-treated animals was also significantly attenuated during the first three trial blocks of Day 1 but not on Day 2. Conversely, whereas vehicle-treated controls had an attenuated ASR on Day 2 compared to day 1, the ASR of raclopride-treated animals recorded on Days 1 and 2 did not differ.

5.6. DISCUSSION

In the present study, we investigated the acute effects of local BLA D1 and D2/D3 receptor blockade on habituation of the ASR. Using a test-retest design, habituation of the ASR was examined both immediately after drug treatment as well as 24 hours later. One of the findings reported here is that on Day 1, when the animals were naïve to the experimental conditions, local D1 and D2/D3 receptor blockade in the BLA both attenuated the magnitude of the ASR. The lower dose of both drugs tested appeared to have a maximal effect on acoustic startle responding, as no further decrease in the ASR magnitude was seen by doubling the dose of each drug.

At first glance, it may appear that the acute effect of intra-BLA SCH 23390 and raclopride was to accelerate the rate of habituation of the ASR. Closer examination of the data, however, suggests otherwise. Our results indicate that D1 or D2/D3 receptor blockade attenuated the ASR elicited by the initial tone pulses, but that the responses to the subsequent tone pulse presentations of the session decreased gradually to levels comparable to those seen in vehicle-treated controls. Therefore, it seems that the main effect of BLA D1 and D2/D3 receptor antagonism was to diminish the animals' initial reactivity to the startling stimuli rather than to accelerate the rate at which they habituated to the stimuli. Had the drug treatments affected habituation, the initial ASR of the session would have been expected to be comparable to that of vehicle-treated controls, followed by a more rapid decline in the magnitude of the ASR to subsequent tone pulse presentations. This was clearly not the case here. Thus, although BLA D1 and D2/D3 receptor blockade attenuated initial responsivity to the startling stimuli, these drug treatments had no apparent effect on within-session habituation of the ASR.

Since vehicle- and SCH 23390-treated animals both showed between-session habituation, the present findings indicate that BLA D1 receptors are not involved in the between-session habituation of the ASR. It appears also that raclopride-treated animals did not exhibit between-session habituation. Upon closer scrutiny, however, this apparent lack of between-session habituation among

raclopride-treated animals is more likely due to the fact that the ASR was significantly attenuated at the very onset of test Day 1, and not due to a slower rate of habituation of the ASR on Day 2. Thus, it appears that BLA D2 receptors are not involved in habituation of the ASR either.

Based on the present findings, it would seem unlikely that BLA DA is involved in modulating the changes in NAc and PFC DA transmission that were recently reported to accompany the ASR (Storozheva et al, 2003). However, such a conclusion should perhaps be viewed as tentative until the effects of intra-BLA infusion of selective DA receptor agonists on habituation of the ASR are examined as well. Swerdlow et al (1992) have previously shown that intra-amygdaloid DA infusion also decreases ASR magnitude. However, in that study, DA was infused into both the BLA and the central amygdaloid nucleus (CeA), suggesting the possibility that the CeA mediates amygdaloid DA modulation of the ASR (Swerdlow et al, 1992). A preferential role of the CeA in modulating the ASR is also suggested by the fact that BLA lesions have no effect on the ASR (Wan and Swerdlow, 1997) and that electrical stimulation of the BLA is relatively ineffective at enhancing the ASR, whereas CeA stimulation at low current intensities enhances ASR magnitude (Rosen and Davis, 1988).

Evidence that the ASR was relatively unaffected by BLA DA receptor antagonism has been reported previously (Lamont and Kokkinidis, 1998; Stevenson et al, 2002). However, in these studies, measures of habituation of the ASR were taken either after significant habituation had already occurred prior to drug infusion (Lamont and Kokkinidis, 1998), or during tests for prepulse inhibition (PPI) where the majority of startling pulse presentations were immediately preceded by a low intensity non-startling pulse (Stevenson and Gratton, in press). In the present study, BLA DA receptor antagonism diminished the ASR selectively over the first several trials on the first test day, suggesting that BLA DA modulates initial startle reactivity. Thus, the present results add to previous evidence indicating a role for BLA DA (Lamont and Kokkinidis, 1998; Nader and LeDoux, 1999; Guarracci et al, 1999, 2000; Greba and Kokkinidis, 2001; Greba et al, 2001) in modulating the perceived aversive nature of sensory

stimuli (Borszcz et al, 1989; Leaton and Cranney, 1990; Plappert et al, 1993, 1999).

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REFERENCES

Ben-Ari Y and Le Gal La Salle G (1974) Lateral amygdala unit activity: II. Habituating and non-habituating neurons. Electroencephalogr Clin Neurophysiol 37:463-472.

Borszcz GS, Cranney J and Leaton RN (1989) Influence of long-term sensitization on long-term habituation of the acoustic startle response in rats: central gray lesions, preexposure, and extinction. J Exp Psychol Animal Behav Processes 15:54-64.

Caine SB, Heinrichs SC, Coffin VL and Koob GF (1995) Effects of the dopamine D_1 antagonist SCH 23390 microinjected into the accumbens, amygdala or striatum on cocaine self-administration in the rat. Brain Res 692:47-56.

Davis M (1980) Neurochemical modulation of sensory-motor reactivity: acoustic and tactile startle reflexes. Neurosci Biobehav Rev 4:241-263.

Davis M (1992) The role of the amygdala in fear and anxiety. Annu Rev Neurosci 15:353-375.

Davis M and Aghajanian GK (1976) Effects of apomorphine and haloperidol in the acoustic startle response in rats. Psychopharmacology 47:217-233.

Deutch AY, Clark WA and Roth RH (1990) Prefrontal cortical dopamine depletion enhances the responsiveness of mesolimbic dopamine neurons to stress. Brain Res 521:311-315.

Doherty MD and Gratton A (1996) Medial prefrontal cortical D1 receptor modulation of the meso-accumbens dopamine response to stress: an electrochemical study in freely-behaving rats. Brain Res 715:86-97.

Geyer MA and Braff DL (1987) Startle habituation and sensorimotor gating in schizophrenia and related animal models. Schizophrenia Bull 13:643-668.

Geyer MA, Petersen LR, Rose GJ, Horwitt DD, Light RK, Adams LM, Zook JA, Hawkind RL and Mandell AJ (1978) The effects of LSD and mescaline-derived hallucinogens on sensory-integrative function: tactile startle. J Pharmacol Exp Ther 207:837-847.

Greba Q, Gifkins A and Kokkinidis L (2001) Inhibition of amygdaloid dopamine D2 receptors impairs emotional learning measured with fear-potentiated startle. Brain Res 899:218-226.

Greba Q and Kokkinidis L (2001) Peripheral and intraamygdalar administration of the dopamine D_1 receptor antagonist SCH 23390 blocks fear-potentiated startle but not shock reactivity or the shock sensitization of acoustic startle. Behav Neurosci 114:262-272.

Guarraci FA, Frohardt RJ, Falls WA and Kapp BS (2000) The effects of intra-amygdaloid infusions of a D_2 dopamine receptor antagonist on Pavlovian fear conditioning. Behav Neurosci, 2000; 114:647-651.

Guarraci FA, Frohardt RJ and Kapp BS (1999) Amygdaloid D_1 dopamine receptor involvement in Pavlovian fear conditioning. Brain Res 827:28-40.

Lamont EW and Kokkinidis L (1998) Infusion of the dopamine D_1 receptor antagonist SCH 23390 into the amygdala blocks fear expression in a potentiated startle paradigm. Brain Res 795:128-136.

Leaton RN and Cranney J (1990) Potentiation of the acoustic startle response by a conditioned stimulus paired with acoustic startle stimulus in rats. J Exp Psychol Animal Behav Processes 16:279-287.

LeDoux JE (1996) The emotional brain. New York: Simon and Schuster.

Nader K and LeDoux JE (1999) Inhibition of the mesoamygdala dopaminergic pathway impairs the retrieval of conditioned fear associations. Behav Neurosci 113:891-901.

Plappert CF, Pilz PKD and Schnitzler H-U (1999) Interaction between acoustic and electric sensitization of the acoustic startle response in rats. Behav Brain Res 103:195-201.

Plappert CF, Pilz PKD and Schnitzler H-U (1993) Acoustic startle response and habituation in freezing and nonfreezing rats. Behav Neurosci 107:981-987.

Rosen JB and Davis M (1988) Enhancement of acoustic startle by electrical stimulation of the amygdala. Behav Neurosci 102:195-202.

Rosenkranz JA and Grace AA (2002) Dopamine-mediated modulation of odour-evoked amygdala potentials during Pavlovian conditioning. Nature 417:282-287.

See RE, Kruzich PJ and Grimm JW (2001) Dopamine, but not glutamate, receptor blockade in the basolateral amygdala attenuates conditioned reward in a rat model of relapse to cocaine-seeking behavior. Psychopharmacology 154:301-310.

Stevenson CW and Gratton A. Role of basolateral amygdala dopamine in modulating prepulse inhibition and latent inhibition in the rat. Psychopharmacology, in press.

Stevenson CW and Gratton A (2003) Basolateral amygdala modulation of the nucleus accumbens dopamine response to stress: role of the medial prefrontal cortex. Eur J Neurosci 17:1287-1295.

Stevenson CW, Sullivan RM and Gratton A (2003) Effects of basolateral amygdala dopamine depletion on the nucleus accumbens and medial prefrontal cortical dopamine responses to stress. Neuroscience 161:285-293.

Storozheva ZI, Afanas'ev II, Proshin AT and Kudrin VS (2003) Dynamics if intracellular dopamine contents in the rat brain during the formation of conditioned contextual fear and extinction of an acoustic startle reaction. Neurosci Behav Physiol 33:307-312.

Swerdlow NR, Caine SB and Geyer MA (1992) Regionally selective effects of intracerebral dopamine infusion on sensorimotor gating of the startle reflex in rats. Psychopharmacology 108:189-195.

Wan F-J and Swerdlow NR (1997) The basolateral amygdala regulates sensorimotor gating of acoustic startle in the rat. Neuroscience 76:715-724.

Young BJ, Helmstetter FJ, Rabchenuk SA and Leaton RN (1991) Effects of systemic and intra-amygdaloid diazepam on long-term habituation of acoustic startle in rats. Pharmacol Biochem Behav 39:903-909.

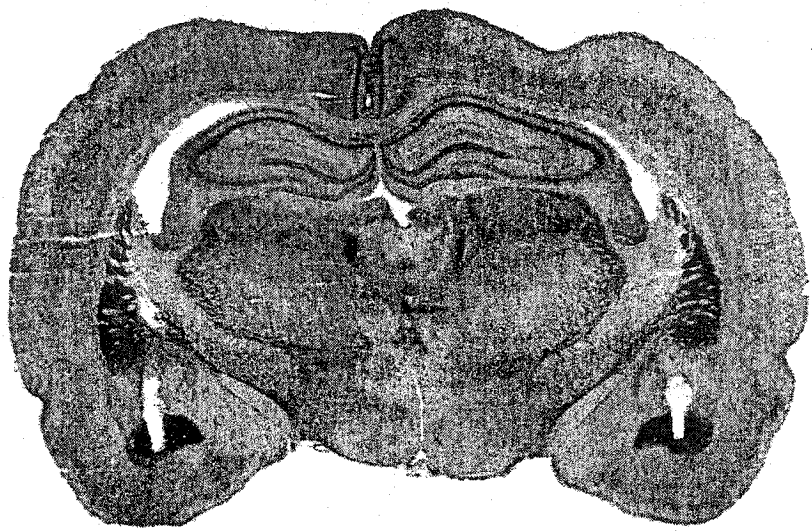

Figure 1. Photomicrograph of a representative histological section showing cannula tip placements within the BLA. (Reprinted with permission from Elsevier © 2003).

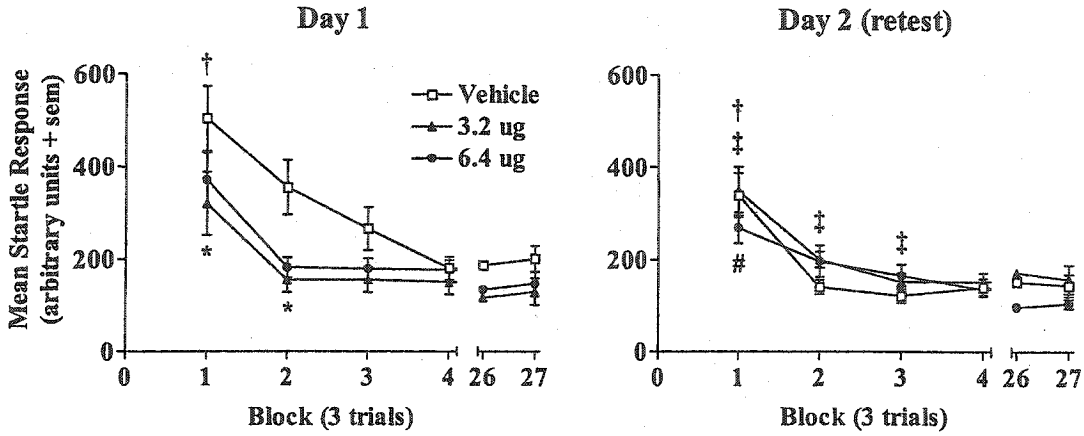

Figure 2. Effects of intra-BLA infusion of SCH 23390 on habituation of the ASR (n=11-13/group). Habituation of the ASR was examined immediately after intra-BLA drug infusion (Day 1) as well as 24 hours later (Day 2 - retest). Vehicle- and SCH 23390-treated animals showed within-session habituation of the ASR during both test (Day 1) and retest (Day 2) sessions († Block 1 > Block 27, $P < 0.01$). Similarly, both vehicle- and SCH 23390-treated animals showed between-session habituation (‡ saline: Blocks 1-3, Day 1 > Day 2, $P < 0.01$; # SCH 23390: Block 1, Day 1 > Day 2, $P < 0.01$). On Day 1, intra-BLA SCH 23390 attenuated the ASR during trial blocks 1-2, compared to intra-BLA saline (* $P < 0.01$). (Reprinted with permission from Elsevier © 2003).

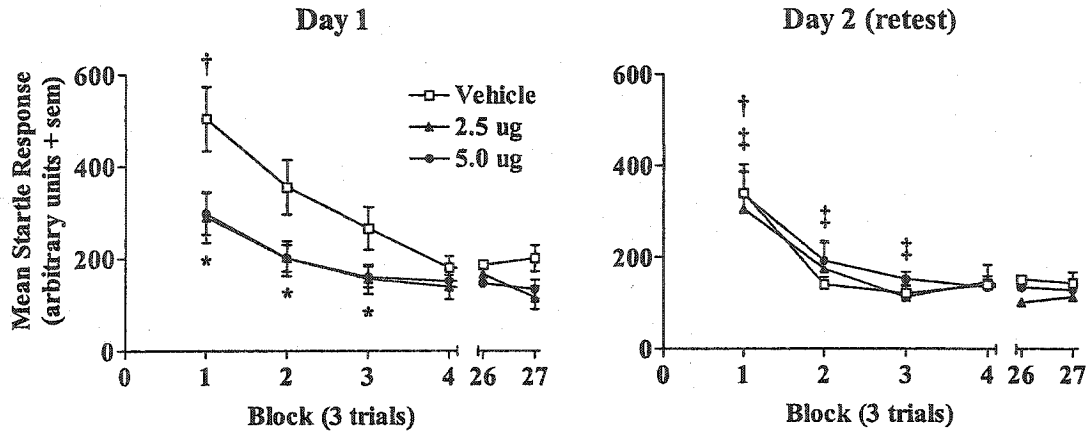

Figure 3. Effects of intra-BLA infusion of raclopride on habituation of the ASR (n=11-13/group). As was the case with SCH 23390, vehicle- and raclopride-treated animals showed within-session habituation, over both days of testing († Block 1 > Block 27, $P < 0.01$). Similarly, intra-BLA raclopride attenuated the ASR on trial blocks 1-3, compared to intra-BLA vehicle (* $P < 0.05$), on Day 1. Conversely, vehicle-treated, but not raclopride-treated, animals showed between session habituation (‡ Blocks 1-3, Day 1 > Day 2; $P < 0.01$). (Reprinted with permission from Elsevier © 2003).

6.0. GENERAL DISCUSSION

6.1. Summary of findings

The results of studies 1 and 2 provide evidence of a role for the VTA DA projection to the BLA in modulating the NAc and mPFC DA responses to stressors. In study 1, DA-depleting lesions to the BLA were found to produce opposite effects on stressor-induced DA release in the NAc and mPFC, enhancing the DA response in the NAc but attenuating it in the mPFC. Study 1 also revealed that, whereas BLA DA depletion potentiates the NAc DA response to both a physical stressor (tail pinch) and a species-typical threat (fox odour), mPFC DA release was attenuated in response to tail pinch, but not fox odour, stress. Moreover, although BLA DA was depleted bilaterally, the resulting attenuation of the mPFC DA stress response was found to be lateralized to the right hemisphere in a stressor-specific manner.

Based on the results of study 1, we then examined the pharmacological properties of these BLA DA-mediated effects on the mPFC and NAc DA stress responses. The results of this second study showed that, as was the case with BLA DA depletion, BLA D1, but not D2/D3, receptor antagonism resulted in enhanced NAc and dampened mPFC DA release in response to tail pinch stress. We then examined the possibility that BLA D1 receptor blockade could potentiate the NAc DA response to stress indirectly by attenuating DA release in the mPFC. Our results confirmed this hypothesis, as co-infusion of D1 and D2/D3 receptor agonists into mPFC abolished the potentiation of stressor-induced NAc DA release caused by local BLA D1 receptor blockade.

The results of studies 3 and 4 provide evidence that BLA DA mediates only some types of sensory processing which have been previously linked to DA-sensitive mechanisms in the NAc and mPFC. BLA D1 and D2/D3 receptor blockade resulted in opposite effects on PPI, with BLA D1 receptor antagonism enhancing and BLA D2/D3 receptor blockade reducing prepulse effectiveness in attenuating the ASR. In contrast, neither of these treatments had any effect on LI in a CTA paradigm. Finally, although BLA DA receptor blockade had no effect

on habituation of the ASR, both D1 and D2/D3 receptor blockade reduced initial startle responsivity.

6.2. Implications

6.2.1. Central dopamine involvement in the behavioural stress response

In agreement with other lines of evidence (Louilot et al., 1985; Simon et al., 1988; Hurd et al., 1997), the present studies indicate that the DA projections to the BLA, mPFC and NAc share a functional relationship in mediating the behavioural response to stressors. In general the present findings suggest that BLA DA exerts an inhibitory influence on stressor-induced NAc DA release. However, it appears that the mechanisms mediating this inhibitory influence are stressor-specific. The data indicate that BLA DA can act directly to modulate the NAc DA response to predator odour but that, in the case of a physical stressor, this modulation occurs indirectly by facilitating the mPFC DA stress response selectively in the right hemisphere. Furthermore, our data indicate that BLA DA modulation of both the mPFC and NAc DA responses to a physical stressor is mediated by D1 receptors.

Converging lines of evidence suggest that stressor-induced DA release in the BLA, mPFC and NAc is involved in mediating distinct aspects of the behavioural stress response. For the most part, the evidence points to a central role of BLA DA in ascribing emotional significance to stressful stimuli, whereas the initiation and execution of appropriate coping responses to stressors are functions subserved predominantly by the DA inputs to the mPFC and NAc, respectively. The results of the present studies add to evidence suggesting that, although the organization of these behavioural processes occurs in parallel, there is a sequential activation of the DA projections to the BLA, mPFC and NAc when the organism is confronted with a stressor. It also appears that the nature of such temporal processing is functionally relevant to the organization and execution of an appropriate behavioural stress response. It has been proposed that, in response to stressors, DA release in the BLA serves to selectively filter information in

favour of inputs from the sensory association cortex, at the expense of the executive control inputs provided by the mPFC (Rosenkranz and Grace, 1999, 2001, 2002a). As a result of this input filtering, increased DA transmission in the BLA may serve to "tag" threatening stimuli with emotional significance (Ashford and Jones, 1976; Lamont and Kokkinidis, 1998; Nader and LeDoux, 1999; Guarracci et al, 1999, 2000; Greba and Kokkinidis, 2001; Greba et al, 2001). The results of the present studies are in general agreement with this working hypothesis, suggesting that stressor-induced BLA DA release serves to enhance mPFC DA transmission and, as a consequence, facilitates the organization of appropriate coping responses (D'Angio et al., 1988; Carlson et al., 1993; Horger and Roth, 1996; Sullivan and Gratton, 1998; Berridge et al., 1999; Thiel and Schwarting, 2001; Bland et al., 2003; Giorgi et al., 2003). Our data also suggest that stressor-induced activation of BLA DA transmission may contribute to the execution of coping responses by modulating the concurrent activation of NAc DA release, either via a direct glutamatergic input or indirectly via a DA-sensitive mechanism in the mPFC (Wadenberg et al., 1990; McCullough et al., 1993; Ikemoto and Panksepp, 1996, 1999). The finding that the NAc DA stress response is under inhibitory control by meso-amygdaloid and meso-PFC DA neurons reinforces the general view that NAc-mediated attribution of incentive salience to stimuli, such as stressors, is influenced by processed information concerning the affective value of stimuli and the available coping responses arriving from the BLA and mPFC, respectively (Berridge and Robinson, 1998; Ikemoto and Panksepp, 1999; Horvitz, 2000; Salamone and Correa, 2002). For example, animals typically freeze, or remain immobile, in response to threatening stimuli (e.g. in the presence of a predator), presumably because such responses ensure the greatest rate of survival in that particular situation. The fact that increased BLA and mPFC DA transmission act to dampen NAc DA responsiveness to stressors may prevent the animal from engaging in maladaptive and potentially fatal behaviours (i.e. escape).

For all of its intuitive appeal, and despite the accumulation of indirect evidence, the fact remains that there is no direct evidence in support of such a

sequential activation by stressors of these central DA projections. Although different responses to tail pinch (chewing) and fox odour (freezing) stress were observed in the course of the present studies, these were not quantified in any systematic manner. However, a careful characterization of the behavioural responses to different stressors in relation to the sequence of DA release in the BLA, mPFC and NAc might provide useful information. The main strength of *in vivo* voltammetry, the technique used in the present studies to monitor DA release, is that it has excellent temporal resolution. Thus, it would be entirely feasible to conduct a detailed temporal analysis of stressor-induced DA release in these three structures.

The present study suggests that BLA DA directly modulates the NAc DA response to predator odour but does so indirectly via the mPFC in response to a physical stressor. As stated previously, an important factor here might be the different coping behaviours elicited by these two stressors. Whereas animals exposed to fox urine will typically remained immobile, those subjected to tail pinch stress typically responded by chewing on the clothes pin. Studies suggest that the amygdala is involved in mediating passive coping responses such as freezing (Roozendaal et al, 1991) while a DA-sensitive mechanism in the mPFC has been implicated in active coping and displacement behaviours, such as chewing (Carlson et al., 1993; Berridge et al., 1999). Alternatively, the fact that BLA DA modulates NAc DA transmission directly in response to predator odour and indirectly in response to a physical threat may be due to differences in the information content received by the amygdala regarding these stressors. The amygdala receives direct input from two distinct olfactory pathways that allows this structure access to unprocessed sensory information concerning odours. The majority of olfactory information received by the amygdala is conveyed by a direct projection from the olfactory bulbs (Price, 2003). The amygdala also receives olfactory input via the vomeronasal organ, a region that also plays an important role in olfaction. This structure sends a projection to the accessory olfactory bulb that, in turn, projects predominantly to the amygdala (Swanson and Petrovich, 1998). The vomeronasal organ has traditionally been associated with

detecting species-specific olfactory cues, such as those of a conspecific or a sexually-receptive mate, although it is possible that the vomeronasal organ is activated in response to certain molecules contained in the urine of other species such as predators (Brennan and Keverne, 2004). In contrast, the amygdala receives processed sensory input regarding other sensory modalities via projections from various associative cortical regions, including the mPFC (McDonald, 1998).

The finding that BLA DA modulation of the mPFC DA stress response is lateralized to the right hemisphere is congruent with other lines of evidence indicating that the right meso-PFC DA projection plays a preferential role in mediating physiological and behavioural responses to stressors (Carlson et al., 1993; Sullivan and Gratton 1998; Berridge et al., 1999; Brake et al., 2000; Thiel and Schwarting, 2001). There is little available evidence on the possible asymmetrical nature of interactions between BLA and mPFC DA function. Although BLA DA modulation of stressor-induced mPFC DA release was determined by examining the effects of bilateral BLA DA depletion in the present studies, it is known that the BLA projections to the mPFC are predominantly ipsilateral (Granato et al., 1991), suggesting that the effects observed were due to DA depletion of the right BLA. However, determining the effects of unilateral BLA DA depletion on the mPFC DA stress response would be of use in clarifying this issue. The effects of bilateral, left or right mPFC DA depletion on amygdaloid DA transmission in response to stress were, however, examined by Sullivan and Szechtman (1995). In this study, bilateral DA depletion of the mPFC was shown to increase left but decrease right amygdala DA metabolism. Moreover, left mPFC DA depletion increased amygdala DA metabolism bilaterally, although DA depletion in the right mPFC had no effect on DA transmission in the right amygdala. Thus, the functional relationship between amygdala and mPFC DA transmission appears to occur in a lateralized manner.

In the present studies, the potentiating effect of BLA D1 receptor antagonism on tail pinch stress-induced NAc DA release was abolished by

concomitant infusion of intra-mPFC D1 and D2/D3 DA receptor agonists, suggesting that BLA DA modulation of the NAc DA stress response is mediated indirectly via a DA-dependent mechanism in the mPFC. It remains unknown, however, which DA receptor subtype(s) in the mPFC mediates this effect, given that the effects of separate infusions of D1 and D2/D3 receptor agonists were not determined in the present study. One previous study has shown that mPFC D1, but not D2, receptor blockade potentiated the NAc DA stress response (Doherty and Gratton, 1996), suggesting that the effects seen in the present studies may be mediated by mPFC D1 receptors.

It appears that BLA DA depletion had a greater effect on stressor-induced DA release in both the mPFC and NAc than did intra-BLA D1 receptor antagonism. Apart from differences in methodology (bilateral DA depletion vs. unilateral D1 receptor antagonist infusion), the reasons for this difference are not obvious. One possible explanation is that the full post-synaptic effect of DA may require the co-activation of D1 and D2 to occur. Although the synergistic nature of D1 and D2 receptor signalling in the BLA has not been examined, previous studies in the striatum have revealed that prior activation of D1 receptors is necessary in order for D2 receptor activation to occur (Clark and White, 1987). Thus, in the present study, intra-BLA infusion of a non-specific DA receptor antagonist, or co-infusion of D1 and D2 receptor antagonists, may have resulted in greater effects compared to D1 receptor antagonist infusion alone. Another possibility is that the greater effects on the mPFC and NAc DA stress responses after BLA DA depletion were due to the partial depletion of BLA NE. As indicated above, amygdaloid NE transmission plays an important role in mediating the physiological (Quirarte et al., 1998) and behavioural (Tanaka et al., 2000) responses to stressors, although the possibility that BLA NE can influence mPFC and NAc DA transmission has yet to be addressed. The effects of selective BLA NE depletion, or intra-BLA infusion of NE receptor antagonists, on stressor-induced mPFC and NAc DA release should perhaps be examined in future studies.

How does BLA DA influence stressor-induced mPFC and NAc DA release? It is hypothesized that DA in the BLA modulates the mPFC and NAc DA stress responses by virtue of its effects on local neuronal activity which, in turn, influences the indirect projections from this region to DA neurons in the VTA. Local application of DA or a D1 receptor agonist inhibits the firing rate of BLA projection neurons, presumably due to increased activity in local GABA interneurons or recurrent collaterals of inhibitory intercalated cells (Rosenkranz and Grace, 1999, 2002a; Paré et al., 2003). As stated above, there are several possible pathways by which the BLA can modulate the activity of VTA DA neurons. It is possible that the BLA influences stressor-induced mPFC and NAc DA release by acting on the CeA, which projects directly and indirectly to the VTA (Maeda and Mogenson, 1981; Wallace et al., 1992; Fadel and Deutch, 2002). The BLA may also modulate the NAc DA response to predator odour stress directly via a glutamatergic-dependent mechanism in the NAc (Floresco et al., 1998; Howland et al., 2002) or indirectly by affecting NAc output to the VTA (Walaas and Fonnum, 1980; Kalivas et al., 1993). In response to a physical stressor, however, it appears that BLA modulation of NAc DA release occurs indirectly by influencing DA release in the mPFC. The BLA projects to the mPFC which, in turn, projects to the VTA; directly to meso-PFC DA neurons and indirectly to meso-accumbens DA neurons via local GABA interneurons (Carr and Sesack, 2000; see Figure 1 above).

6.2.2. Central DA systems and information processing

After determining that, in response to stressors, a functional relationship exists between DA transmission in the BLA, mPFC and NAc, we sought to address the possibility that BLA DA modulates different reflexive and learned types of information processing, which are themselves disrupted by stressful stimuli and are reportedly mediated by mPFC and NAc DA function. These studies indicate that BLA DA transmission modulates PPI, a form of automatic sensory processing, and suggest the possibility that stressor-induced disruption of PPI may be mediated, in part, by activation of the DA projection to the BLA.

They also suggest that impairment of LI and habituation of the ASR, two distinct types of learned information processing, elicited by stressful stimuli may not depend on BLA DA transmission. However, the fact that BLA DA function was shown to exert an influence on the initial responsivity to startling stimuli adds to a growing body of evidence indicating that DA transmission in the BLA plays an important role in mediating the perceived aversive nature of potentially threatening stimuli (Ashford and Jones, 1976; Lamont and Kokkinidis, 1998; Nader and LeDoux, 1999; Guarracci et al, 1999, 2000; Greba and Kokkinidis, 2001; Greba et al, 2001).

As mentioned above, diminished mPFC (Bubser and Koch, 1994; Koch and Bubser, 1994; Ellenbroek et al., 1996; Crain et al., 2003) and enhanced NAc (Swerdlow et al., 1990a, b, 1992; Wan and Swerdlow, 1993; Wan et al., 1994; Hart et al., 1998) DA transmission have been shown to impair PPI. Given the evidence that BLA D1 receptor antagonism diminishes and enhances mPFC and NAc DA transmission, respectively, it was expected that this treatment would also disrupt PPI. However, in the present studies intra-BLA infusion of a D1 receptor antagonist facilitated PPI, suggesting that BLA DA modulates PPI independently of changes in NAc and mPFC DA transmission. One possibility is that BLA DA receptor activation modulates PPI via changes in the functional activity of the ventral pallidum, a structure known to receive a projection from the BLA and to modulate PPI (Maslowski-Cobuzzi and Napier, 1994; Wan and Swerdlow, 1997; Kretschmer and Koch, 1998).

The opposite effects of BLA D1 and D2/D3 receptor blockade on PPI are likely due to differences in local neuronal activity caused by BLA D1 and D2 receptor activation. From the present studies it is expected that activation of BLA D1 and D2 receptors would disrupt and enhance PPI, respectively. As indicated previously, BLA D1 and D2 receptor activation inhibits and facilitates the activity of projection neurons, respectively (Rosenkranz and Grace, 2002a). Moreover, decreased BLA neuronal activity in general may result in disrupted PPI. Excitotoxic lesions to the BLA and intra-BLA infusion of NMDA receptor antagonists reduce PPI (Wan and Swerdlow, 1997; Bakshi and Geyer, 1998,

1999; Fendt et al., 2000). However, local BLA $GABA_A$ receptor blockade, which would be expected to disinhibit BLA pyramidal cell activity, also impairs PPI; this finding has been taken to suggest that BLA NMDA receptor blockade may occur preferentially at receptors located on local GABA interneurons, which would then result in a disinhibition of BLA projection neurons (Fendt et al., 2000). One possible explanation for this apparent discrepancy may lie in the finding that intra-amygdaloid infusion of both NMDA and GABA receptor antagonists appear to facilitate BLA DA transmission (Rao et al., 1990; Chu and Lin, 1996), suggesting that BLA glutamate and GABA modulation of PPI occurs indirectly via changes in local DA function.

Antagonism of BLA DA receptors had no effect on LI in the present studies. Similarly, other studies conducted to date have failed to demonstrate a role for mPFC DA transmission in modulating LI (Ellenbroek et al., 1996; Broersen et al., 1999; Lacroix et al., 2000a), suggesting that the DA projections to the BLA and mPFC are not involved in modulating this form of information processing. The indirect DA receptor agonist AMPH impairs LI when administered systemically during the pre-exposure and conditioning stages of training in several paradigms (Joseph et al., 2000), including the CTA paradigm used in the present studies (Ellenbroek et al., 1996; Russig et al., 2003). This impairment presumably occurs as a consequence of increased NAc DA transmission (Solomon and Staton, 1982; Young et al., 1993; Joseph et al., 2000). Moreover, it appears that repeated administration of AMPH during training is necessary to disrupt LI (Warburton et al., 1996; Weiner, 2003). It is possible that meso-amygdaloid and meso-PFC DA can modulate LI indirectly by affecting NAc DA transmission under conditions of increased central DA transmission, although this hypothesis has not been tested. The effects of BLA or mPFC DA depletion on AMPH-induced disruptions in LI could be examined to test this hypothesis. Alternatively, the effects of manipulating BLA or mPFC DA transmission on stress-induced impairment of LI could be examined.

It is unclear why BLA D1 and D2/D3 receptor antagonism had opposite effects on PPI but had the same effect on startle reactivity, although studies

examining the role of BLA DA transmission in aversive learning have also shown that both D1 and D2 receptor blockade in the BLA disrupts fear conditioning (Guarraci et al., 1999, 2000; Greba and Kokkinidis, 2001; Greba et al., 2001). Perhaps the role of BLA DA in mediating the association of emotional significance with environmental stimuli in general requires the activation of several local DA receptor subtypes. For example, selective activation of the D3 receptor subtype in the amygdala is thought to play an important role in appetitive conditioning (Hitchcott et al., 1997a; Hitchcott and Phillips, 1998a, b, c; Phillips et al., 2002).

Although the present studies did not examine the role of BLA DA in working memory, previous studies have reported an involvement of the BLA in modulating this function (Peinado-Manzano, 1990; Ohno et al., 1992; Ingles et al., 1993; Ono et al., 1993; Barros et al., 2002; Addy et al., 2003; May-Simera and Levin, 2003). Given the central role of mPFC DA in working memory and the fact that BLA DA can modulate mPFC DA transmission, it is entirely conceivable that working memory is influenced indirectly by the DA input to the BLA. Although studies in animals have not yet tested this hypothesis, one study conducted in human subjects has found that engaging in a working memory task elicits DA release in the amygdala (Fried et al., 2001).

REFERENCES (from General Introduction and Discussion)

Abekawa T, Ohmori T, Ito K and Koyama T (2000) D1 dopamine receptor activation reduces extracellular glutamate and GABA concentrations in the medial prefrontal cortex. Brain Res 867:250-254.

Abercrombie ED, Keefe KA, DiFrischia DS and Zigmond MJ (1989) Differential effect of stress on *in vivo* dopamine release in striatum, nucleus accumbens, and medial frontal cortex. J Neurochem 52:1655-1658.

Addy NA, Nakijama A and Levin ED (2003) Nicotinic mechanisms of memory: effects of acute local DHbetaE and MLA infusions in the basolateral amygdala. Brain Res Cogn Brain Res 16:51-57.

Aghajanian GK and Bunney BS (1977) Dopamine "autoreceptors": pharmacological characterization by microiontophoretic single unit recording studies. Naunyn Schmiedebergs Arch Pharmacol 297:1-7.

al Maskati HA and Zbrozyna AW (1989) Stimulation in prefrontal cortex area inhibits cardiovascular and motor components of the defence reaction in rats. J Auton Nerv Syst 28:117-125.

Aultman JM and Moghaddam B (2001) Distinct contributions of glutamate and dopamine receptors to temporal aspects of rodent working memory using a clinically relevant task. Psychopharmacology 153:353-364.

Anden NE, Grabowska-Anden M and Liljenberg B (1983) Demonstration of autoreceptors on dopamine neurons in different brain regions of rats treated with gammabutyrolactone. J Neural Transm 58:143-152.

Anderson AK, Christoff K, Panitz D, de Rosa E and Gabrieli JDE (2003) Neural correlates of the automatic processing of threat facial signals. J Neurosci 23:5627-5633.

Antelman SM, Szechtman H, Chin P and Fisher AE (1975) Tail-pinch-induced eating, gnawing and licking behaviour in rats: dependence on the nigrostriatal dopamine system. Brain Res 99:319-337.

Ariano MA, Monsma FJ Jr, Barton AC, Kang HC, Haugland RP and Sibley DR (1989) Direct visualization and cellular localization of D1 and D2 dopamine receptors in rat forebrain by use of fluorescent ligands. Proc Natl Acad Sci USA 86:8570-8574.

Arnsten AFT and Goldman-Rakic PS (1998) Arch Gen Psychiatry 55:362-368.

Asan E (1997) Ultrastructural features of tyrosine-hydroxylase-immunoreactive afferents and their targets in the rat amygdala. Cell Tissue Res 288:449-469.

Ashford J and Jones BJ (1976) The effects of intra-amygdaloid injections of 6-hydroxydopamine on avoidance responding in rats. Br J Pharmacol 56:255-261.

Aultman JM and Moghaddam B (2001) Distinct contributions of glutamate and dopamine receptors to temporal aspects of rodent working memory using a clinically relevant task. Psychopharmacology 153:353-364.

Bacon SJ, Headlam AJ, Gabbott PL and Smith AD (1996) Amygdala input to medial prefrontal cortex (mPFC) in the rat: a light and electron microscope study. Brain Res 720:211-219.

Bakshi VP and Geyer MA (1999) Alpha-1-adrenergic receptors mediate sensorimotor gating deficits produced by intra-cerebral dizocilpine administration in rats. Neuroscience 92:113-121.

Bakshi VP and Geyer MA (1998) Multiple limbic regions mediate the disruption of prepulse inhibition produced in rats by the noncompetitive NMDA antagonist dizocilpine. J Neurosci 18:8394-8401.

Barrot M, Marinelli M, Abrous DN, Rouge-Pont F, Le Moal M and Piazza PV (1999) Functional heterogeneity in dopamine release and in the expression of Fos-like proteins within the rat striatal complex. Eur J Neurosci 11:1155-1166.

Bashore TR, Rebec GV and Groves PM (1978) Alterations of spontaneous neuronal activity in the caudate-putamen, nucleus accumbens and amygdaloid complex of rats produced by D-amphetamine. Pharmacol Biochem Behav 8:467-474.

Bassareo V, De Luca MA and Di Chiara G (2002) Differential expression of motivational stimulus properties by dopamine in nucleus accumbens shell versus core and prefrontal cortex. J Neurosci 22:4709-19.

Bassareo V and Di Chiara G (1999) Modulation of feeding-induced activation of mesolimbic dopamine transmission by appetitive stimuli and its relation to motivational state. Eur J Neurosci 11:4389-4397.

Beart PM, MacDonald D and Gundlach AL (1979) Mesolimbic dopaminergic neurones and somatodendritic mechanisms. Neurosci Lett 15:165-170.

Beaulieu S, Di Paolo T, Cote J and Barden N (1987) Participation of the central amygdaloid nucleus in the response of adrenocorticotropin secretion to immobilization stress: opposing roles of the noradrenergic and dopaminergic systems. Neuroendocrinology 45:37-46.

Beck KD, Brennan FX and Servatius RJ (2002) Effects of stress on nonassociative learning processes in male and female rats. Integr Physiol Behav Sci 37:128-139.

Beck CH and Fibiger HC (1995) Conditioned fear-induced changes in behavior and in the expression of the immediate early gene c-fos: with and without diazepam pretreatment. J Neurosci 15:709-720.

Ben-Ari Y and Le Gal La Salle G (1974) Lateral amygdala unit activity: II. Habituating and non-habituating neurons. Electroencephalogr Clin Neurophysiol 37:463-472.

Ben-Ari Y and Kelly JS (1976) Dopamine evoked inhibition of single cells of the feline putamen and basolateral amygdala. J Physiol (Lond) 256:1-21.

Berendse HW, Galis-de Graaf Y and Groenewegen HJ (1992) Topographical organization and relationship with ventral striatal compartments of prefrontal corticostriatal projections in the rat. J Comp Neurol 316:314-347.

Berendse HW and Groenewegen HJ (1990) The organization of the thalamostriatal projections in the rat, with special emphasis on the ventral striatum. J Comp Neurol 299:187-228.

Berridge CW and Dunn AJ (1989) Restraint-stress-induced changes in exploratory behavior appear to be mediated by norepinephrine-stimulated release of CRF. J Neurosci 9:3513-3521.

Berridge CW, Mitton E and Roth RH (1999) Engagement in a non-escape (displacement) behavior elicits a selective and lateralized suppression of frontal cortical dopaminergic utilization in stress. Synapse 32:187-197.

Blanchard RJ, Blanchard DC, Rodgers J and Weiss SM (1990) The characterization and modelling of anti-predator defensive behavior. Neurosci Biobehav Rev 14:463-472.

Bland ST, Hargrave D, Pepin JL, Amat J, Watkins LR and Maier SF (2003) Stressor controllability modulates stress-induced dopamine and serotonin efflux and morphine-induced serotonin efflux in the medial prefrontal cortex. Neuropsychopharmacology 28:1589-1596.

Bohus B, Koolhaas JM, Luiten PGM, Korte SM, Roozendaal B and Wiersma A (1996) The neurobiology of the central nucleus of the amygdala in relation to neuroendocrine and autonomic outflow. Prog Brain Res 107:447-460.

Brake WG, Noel MB, Boksa P and Gratton A (1997) Influence of perinatal factors on the nucleus accumbens dopamine response to repeated stress during adulthood: an electrochemical study in the rat. Neuroscience 77:1067-1076.

Brake WG, Sullivan RM and Gratton A (2000) Perinatal distress leads to lateralized medial prefrontal cortical dopamine hypofunction in adult rats. J Neurosci 20:5538-5543.

Branchereau P, van Bockstaele EJ, Chan J and Pickel VM (1996) Pyramidal neurons in rat prefrontal cortex show a complex synaptic response to single electrical stimulation of the locus coeruleus region: evidence for antidromic activation and GABAergic inhibition using *in vivo* intracellular recording and electron microscopy. Synapse 22:313-331.

Braunstein-Bercovitz H, Dimentman-Ashkenazi I and Lubow RE (2001) Stress affects the selection of relevant from irrelevant stimuli. Emotion 1:182-192.

Breiter HC, Etcoff NL, Whalen PJ, Kennedy WA, Rauch SL, Buckner RL, Strauss MM, Hyman SE and Rosen BR (1996) Response and habituation of the human amygdala during visual processing of facial expression. Neuron 17:875-887.

Brennan PA and Keverne EB (2004) Something in the air? New insights into mammalian pheromones. Curr Biol 14:R81-89.

Brinley-Reed M, Mascagni F and McDonald AJ (1995) Synaptology of prefrontal cortical projections to the basolateral amygdala: an electron microscopic study in the rat. Neurosci Lett 202:45-48.

Brinley-Reed M and McDonald AJ (1999) Evidence that dopaminergic axons provide a dense innervation of specific neuronal subpopulations in the rat basolateral amygdala. Brain Res 850:127-135.

Broersen LM, Feldon J and Weiner I (1999) Dissociative effects of apomorphine infusions into the medial prefrontal cortex of rats on latent inhibition, prepulse inhibition and amphetamine-induced locomotion. Neuroscience 94:39-46.

Brog JS, Salyapongse A, Deutch AY and Zahm DS (1993) The patterns of afferent innervation of the core and shell in the "accumbens" part of the rat ventral striatum: immunohistochemical detection of retrogradely transported fluoro-gold. J Comp Neurol 338:255-278.

Bubser M and Koch M (1994) Prepulse inhibition of the acoustic startle response of rats is reduced by 6-hydroxydopamine lesions of the medial prefrontal cortex. Psychopharmacology 113:487-492.

Buijs RM and van Eden CG (2000) The integration of stress by the hypothalamus, amygdala and prefrontal cortex: balance between the autonomic nervous system and the neuroendocrine system. Prog Brain Res 126:117-132.

Bull DR, Bakhtiar R and Sheehan MJ (1991) Characterization of dopamine autoreceptors in the amygdala: a fast cyclic voltammetric study in vitro. Neurosci Lett 134:41-44.

Cabib S and Puglisi-Allegra S (1996) Different effects of repeated stressful experiences on mesocortical and mesolimbic dopamine metabolism. Neuroscience 73:375-380.

Callaway CW, Hakan RL and Henriksen SJ (1991) Distribution of amygdala input to the nucleus accumbens septi: an electrophysiological investigation. J Neural Transm 83:215-225.

Campeau S and Davis M (1995) Involvement of the central nucleus and basolateral amygdaloid complex of the amygdala in fear conditioning measured with fear-potentiated startle in rats trained concurrently with auditory and visual conditioned stimuli. J Neurosci 15:2301-2311.

Campeau S, Hayward MD, Hope BT, Rosen JB, Nestler EJ and Davis M (1991) Induction of the c-fos proto-oncogene in rat amygdala during unconditioned and conditioned fear. Brain Res 565:349-352.

Canedo A (1982) Subcortical influences upon prefrontal cortex of the cat. Brain Res 232:449-454.

Cannon WB (1929) Organization for physiological homeostasis. Physiol Rev 9:399-431.

Carlson JN, Fitzgerald LW, Keller Jr RW and Glick SD (1993) Lateralized changes in prefrontal cortical dopamine activity induced by controllable and uncontrollable stress in the rat. Brain Res 630:178-187.

Carr DB and Sesack SR (2000) Projections from the rat prefrontal cortex to the ventral tegmental area: target specificity in the synaptic associations with mesocortical and mesoaccumbens neurons. J Neurosci 20:3864-73.

Carter CJ (1982) Topographical distribution of possible glutamatergic pathways from the frontal cortex in the striatum and substantia nigra in rats. Neuropharmacology 21:383-393.

Cassell MD, Chittick CA, Siegel MA and Wright DJ (1989) Collateralization of the amygdaloid projections of the rat prelimbic and infralimbic cortices. J Comp Neurol 279:235-248.

Cassell MD and Wright DJ (1986) Topography of projections from the medial prefrontal cortex to the amygdala in the rat. Brain Res Bull 17:321-333.

Cheng JJ, de Bruin JP and Feenstra MG (2003) Dopamine efflux in nucleus accumbens shell and core in response to appetitive classical conditioning. Eur J Neurosci 18:1306-1314.

Chiodo LA, Bannon MJ, Grace AA, Roth RG and Bunney BS (1984) Evidence for the absence of impulse-regulating somatodendritic and synthesis-modulating nerve terminal autoreceptors on subpopulations of mesocortical dopamine neurons. Neuroscience12:1-16.

Christie MJ, Summers RJ, Stephenson JA, Cook CJ and Beart PM (1987) Excitatory amino acid projections to the nucleus accumbens septi in the rat: a retrograde transport study utilizing [3H]aspartate and [3H]GABA. Neuroscience 22:425-439.

Chu TF and Lin MT (1996) Picrotoxin induces both hypertension and dopamine release in the rat amygdala. Neurosci Lett 218:169-172.

Clark D and White FJ (1987) D1 dopamine receptor - the search for a function: a critical evaluation of the D1/D2 dopamine receptor classification and its functional implications. Synapse 1:347-388.

Claustre Y, Rivy JP, Dennis T, and Scatton B (1986) Pharmacological studies on stress-induced increase in frontal cortical dopamine metabolism in the rat. J Pharmacol Exp Ther 238:693-700.

Coco ML, Kuhn CM, Ely TD and Kilts CD (1992) Selective activation of mesoamygdaloid dopamine neurons by conditioned stress: attenuation by diazepam. Brain Res 590:39-47.

Conti LH, Murry JD, Ruiz and Printz MP (2002) Effects of corticotropin-releasing factor on prepulse inhibition of the acoustic startle response in two rat strains. Psychopharmacology 161:296-303.

Coutureau E, Blundell PJ and Killcross S (2001) Basolateral amygdala lesions disrupt latent inhibition in rats. Brain Res Bull 56:49-53.

Cowan RL, Sesack SR, Van Bockstaele EJ, Branchereau P, Chan J and Pickel VM (1994) Analysis of synaptic inputs and targets of physiologically characterized neurons in rat frontal cortex: combined intracellular recording and immunolabelling. Synapse 17:101-114.

Cragg SJ and Greenfield SA (1997) Differential autoreceptor control of somatodendritic and axon terminal dopamine release in substantia nigra, ventral tegmental area, and striatum. J Neurosci 17:5738-5746.

Crain SK, Shoemaker JM, Goins JC, Ma LT, Noh H and Swerdlow NR (2003) D1 blockade in prefrontal cortex disrupts startle gating in rats: anatomical characterization. Soc Neurosci Abstracts 858.18.

Cuadra G, Zurita A, Gioino G and Molina V (2001) Influence of different antidepressant drugs on the effect of chronic variable stress on restraint-induced dopamine release in frontal cortex. Neuropsychopharmacology 25:384-394.

Cuadra G, Zurita A, Lacerra C and Molina V (1999) Chronic stress sensitizes frontal cortex dopamine release in response to a subsequent novel stressor: reversal by naloxone. Brain Res Bull 48:303-308.

Damsma G, Pfaus JG, Wenkstern D, Phillips AG and Fibiger HC (1992) Sexual behavior increases dopamine transmission in the nucleus accumbens and striatum of male rats: comparison with novelty and locomotion. Behav Neurosci 106:181-91.

D'Angio M, Serrano A, Driscoll P and Scatton B (1988) Stressful environmental stimuli increase extracellular DOPAC levels in the prefrontal cortex of hypoemotional (Roman high-avoidance) but not hyperemotional (Roman low-avoidance) rats. An in vivo voltammetric study. Brain Res 451:237-247.

Datla KP, Ahier RG, Young AM, Gray JA and Joseph MH (2002) Conditioned appetitive stimulus increases extracellular dopamine in the nucleus accumbens of the rat. Eur J Neurosci 16:1987-1993.

Davis M (1992) The role of the amygdala in fear and anxiety. Annu Rev Neurosci 15:353-375.

Davis M (1980) Neurochemical modulation of sensory-motor reactivity: acoustic and tactile startle reflexes. Neurosci Biobehav Rev 4:241-263.

Davis M and Aghajanian GK (1976) Effects of apomorphine and haloperidol in the acoustic startle response in rats. Psychopharmacology 47:217-233.

Davis M, Hitchcock JM, Bowers MB, Berridge CW, Melia KR and Roth RH (1994) Stress-induced activation of prefrontal cortex dopamine turnover: blockade by lesions of the amygdala. Brain Res 664:207-210.

Decker MW, Curzon P and Brioni JD (1995) Influence of separate and combined septal and amygdala lesions on memory, acoustic startle, anxiety, and locomotor activity in rats. Neurobiol Learn Mem 64:156-168.

Defagot MC, Malchiodi EL, Villar MJ and Antonelli MC (1997) Distribution of D4 dopamine receptor in rat brain with sequence-specific antibodies. Mol Brain Res 45:1-12.

Del Arco A and Mora F (2001) Dopamine release in the prefrontal cortex during stress is reduced by the local activation of glutamate receptors. Brain Res Bull 56:125-130.

Delatour B and Gisquet-Verrier P (1996) Prelimbic cortex specific lesions disrupt delayed-variable response tasks in the rat. Behav Neurosci 110:1282-1298.

Deminière JM, Taghzouti K, Tassin JP, Le Moal M and Simon H (1988) Increased sensitivity to amphetamine and facilitation of amphetamine self-administration after 6-hydroxy-dopamine lesions of the amygdala. Psychopharmacology 94:232-236.

Deniau JM, Menetry A and Thierry AM (1994) Indirect nucleus accumbens input to the prefrontal cortex via the substantia nigra pars reticulata: a combined anatomical and electrophysiological study in the rat. Neuroscience 61:533-545.

Deniau JM, Thierry AM and Feger J (1980) Electrophysiological identification of mesencephalic ventromedial tegmental (VMT) neurons projecting to the frontal cortex, septum, and nucleus accumbens. Brain Res 189:315-326.

Deutch AY (1991) Heterogeneity of the prefrontal cortical dopamine system in responsiveness to stress. Soc Neurosci Abstracts 17:529.

Deutch AY and Cameron DS (1992) Pharmacological characterization of dopamine systems in the nucleus accumbens core and shell. Neuroscience 46:49-56.

Deutch AY, Clark WA and Roth RH (1990) Prefrontal cortical dopamine depletion enhances the responsiveness of mesolimbic dopamine neurons to stress. Brain Res 521:311-315.

Deutch AY, Lee MC, Gillham MH, Cameron DA, Goldstein M and Iadarola MJ (1991) Stress selectively increases fos protein in dopamine neurons innervating the prefrontal cortex. Cereb Cortex 1:273-292.

Deutch AY, Tam SY and Roth RH (1985) Footshock and conditioned stress increase 3,4-dihydroxyphenylacetic acid (DOPAC) in the ventral tegmental area but not substantia nigra. Brain Res 333:143-146.

Ding DC, Gabbott PL and Totterdell S (2001) Differences in the laminar origin of projections from the medial prefrontal cortex to the nucleus accumbens shell and core regions in the rat. Brain Res 917:81-89.

Diorio D, Viau V and Meaney MJ (1993) The role of the medial prefrontal cortex (cingulate cortex) in the regulation of hypothalamic-pituitary-adrenal responses to stress. J Neurosci 13:3839-3847.

Dirks A, Groenink L, Iutje Schipholt M, van der Gugten J, Hijzen TH, Geyer MA and Olivier B (2002) Reduced startle reactivity and plasticity in transgenic mice overexpressing corticotropin-releasing hormone. Biol Psychiatry 51:583-590.

Doherty MD and Gratton A (1999) Effects of medial prefrontal cortical injections of GABA agonists and antagonists on the local and nucleus accumbens dopamine responses to stress. Synapse 32:288-300.

Doherty MD and Gratton A (1996) Medial prefrontal cortical D1 receptor modulation of the meso-accumbens dopamine response to stress: an electrochemical study in freely-behaving rats. Brain Res 715:86-97.

Doherty MD and Gratton A (1992) High-speed chronoamperometric measurements of mesolimbic and nigrostriatal dopamine release associated with repeated daily stress. Brain Res 586:295-302.

Dolan RJ and Vuilleumier P (2003) Amygdala automaticity in emotional processing. Ann N Y Acad Sci 985:348-355.

Dunn AJ and File SE (1984) Cold restraint alters dopamine metabolism in frontal cortex, nucleus accumbens and neostriatum. Physiol Behav 31:511-513.

Ellenbroek BA, Budde S and Cools AR (1996) Prepulse inhibition and latent inhibition: the role of dopamine in the medial prefrontal cortex. Neuroscience 75:535-542.

Ellenbroek BA, Knobbout DA and Cools AR (1997) The role of mesolimbic and nigrostriatal dopamine in latent inhibition as measured with the conditioned taste aversion paradigm. Psychopharmacology 129:112-20.

Engel GL (1977) Emotional stress and sudden death. Psychol Today 11:114-118.

Fadel J and Deutch AY (2002) Anatomical substrates of orexin-dopamine interactions: lateral hypothalamic projections to the ventral tegmental area. Neuroscience 111:379-387.

Fallon JH, Koziell DA and Moore RY (1978) Catecholamine innervation of the basal forebrain. II. Amygdala, suprarhinal cortex and entorhinal cortex. J Comp Neurol 180:509-532.

Fallon JH and Moore RY (1978) Catecholamine innervation of the basal forebrain. IV. Topography of the dopamine projection to the basal forebrain and neostriatum. J Comp Neurol 180:545-580.

Feenstra MG, Teske G, Botterblom MH and De Bruin JP (1999) Dopamine and noradrenaline release in the prefrontal cortex of rats during classical aversive and appetitive conditioning to a contextual stimulus: interference by novelty effects. Neurosci Lett 272:179-182.

Fendt M, Schwienbacher I and Koch M (2000) Amygdaloid N-methyl-D-aspartate and gamma-aminobutyric acid(A) receptors regulate sensorimotor gating in a dopamine-dependent way in rats. Neuroscience 98:55-60.

File SE, Zangrossi H, Sanders FL and Mabbutt PS (1993) Dissociation between behavioural and corticosterone responses on repeated exposures to cat odor. Physiol Behav 54:1109-1111.

Finch DM (1996) Neurophysiology of converging synaptic inputs from the rat prefrontal cortex, amygdala, midline thalamus, and hippocampal formation onto single neurons of the caudate/putamen and nucleus accumbens. Hippocampus 6:495-512.

Fischer H, Wright CI, Whalen PJ, McInerney SC, Shin and Rauch SL (2003) Brain habituation during repeated exposure to fearful and neutral faces: a functional MRI study. Brain Res Bull 59:387-392.

Floresco SB, Blaha CD, Yang CR and Phillips AG (2001a) Dopamine D1 and NMDA receptors mediate potentiation of basolateral amygdala-evoked firing of nucleus accumbens neurons. J Neurosci 21:6370-6376.

Floresco SB, Blaha CD, Yang CR and Phillips AG (2001b) Modulation of hippocampal and amygdalar-evoked activity of nucleus accumbens neurons by dopamine: cellular mechanisms of input selection. J Neurosci 21:2851-2860.

Floresco SB, Yang CR, Phillips AG and Blaha CD (1998) Basolateral amygdala stimulation evokes glutamate receptor-dependent dopamine efflux in the nucleus accumbens of the anesthetized rat. Eur J Neurosci 10:1241-1251.

Freed C, Revay R, Vaughan RA, Kriek E, Grant S, Uhl GR and Kuhar MJ (1995) Dopamine transporter immunoreactivity in rat brain. J Comp Neurol 359:340-349.

Freeman AS and Bunney BS (1987) Activity of A9 and A10 dopaminergic neurons in unrestrained rats: further characterization and effects of apomorphine and cholecystokinin. Brain Res 405:46-55.

French SJ and Totterdell S (2003) Individual nucleus accumbens-projection neurons receive both basolateral amygdala and ventral subicular afferents in rats. Neuroscience 119:19-31.

French SJ and Totterdell S (2002) Hippocampal and prefrontal cortical inputs monosynaptically converge with individual projection neurons of the nucleus accumbens. J Comp Neurol 446:151-165.

Fried I, Wilson CL, Morrow JW, Cameron KA, Behnke ED, Ackerson LC and Maidment NT (2001) Increased dopamine release in the human amygdala during performance of cognitive tasks. Nat Neurosci 4:201-206.

Frysztak RJ and Neafsey EJ (1991) The effect of medial frontal cortex lesions on respiration, "freezing", and ultrasonic vocalizations during conditioned emotional responses in rats. Cereb Cortex 1:418-425.

Frysztak RJ and Neafsey EJ (1994) The effect of medial frontal cortex lesions on cardiovascular conditioned emotional responses in the rat. Brain Res 643:181-193.

Funada M and Hara C (2001) Differential effects of psychological stress on activation of the 5-hydroxytryptamine- and dopamine-containing neurons in the brain of freely moving rats. Brain Res 901:247-251.

Fuxe K, Jacobsen KX, Hoistad M, Tinner B, Jansson A, Staines WA and Agnati LF (2003) The dopamine D1 receptor-rich main and paracapsular intercalated nerve cell groups of the rat amygdala: relationship to the dopamine innervation. Neuroscience 119:733-746.

Garcia R, Vouimba RM, Baudry M and Thompson RF (1999) The amygdala modulates prefrontal cortex activity relative to conditioned fear. Nature 402:294-296.

Garcia-Rill E (1986) The basal ganglia and the locomotor regions Brain Res Rev 11:47-63.

Gariano RF, Sawyer SF, Tepper JM, Young SJ and Groves PM (1989) Mesocortical dopaminergic neurons. 2. Electrophysiological consequences of terminal autoreceptor activation. Brain Res Bull 22:517-523.

Garris PA, Collins LB, Jones SR and Wightman RM (1993) Evoked extracellular dopamine *in vivo* in the medial prefrontal cortex. J Neurochem 61:637-647.

Garris PA and Wightman RM (1994a) Different kinetics govern dopaminergic transmission in the amygdala, prefrontal cortex, and striatum: an *in vivo* voltammetric study. J Neurosci 14:442-450.

Garris PA and Wightman RM (1994b) *In vivo* voltammetric measurement of evoked extracellular dopamine in the rat basolateral amygdaloid nucleus. J Physiol (Lond) 478:239-249.

Garris PA and Wightman RM (1995) Distinct pharmacological regulation of evoked dopamine efflux in the amygdala and striatum of the rat in vivo. Synapse 20:269-279.

Geijo-Barrientos E and Pastore C (1995) The effects of dopamine on the sub-threshold electrophysiological responses of rat prefrontal cortex neurons *in vitro*. Eur J Neurosci 7:358-366.

German DC, Dalsass M and Kiser RS (1980) Electrophysiological examination of the ventral tegmental (A10) area in the rat. Brain Res 181:191-197.

Geyer MA and Braff DL (1987) Startle habituation and sensorimotor gating in schizophrenia and related animal models. Schizophrenia Bull 13:643-668.

Geyer MA, Krebs-Thomson K, Braff DL and Swerdlow NR (2001) Pharmacological studies of prepulse inhibition models of sensorimotor gating deficits in schizophrenia: a decade in review. Psychopharmacology 156:117-154.

Geyer MA, Petersen LR, Rose GJ, Horwitt DD, Light RK, Adams LM, Zook JA, Hawkind RL and Mandell AJ (1978) The effects of LSD and mescaline-derived hallucinogens on sensory-integrative function: tactile startle. J Pharmacol Exp Ther 207:837-847.

Geyer MA, Swerdlow NR, Mansbach RS and Braff DL (1990) Startle response models of sensorimotor gating and habituation deficits in schizophrenia. Brain Res Bull 25:485-498.

Gibbs CM, Prescott and Powell DA (1992) A comparison of multiple-unit activity in the medial prefrontal and agranular insular cortices during Pavlovian heart rate conditioning in rabbits. Exp Brain Res 89:599-610.

Giorgi O, Lecca D, Piras G, Driscoll P and Corda MG (2003) Dissociation between mesocortical dopamine release and fear-related behaviours in two psychogenetically selected lines of rats that differ in coping strategies to aversive conditions. Eur J Neurosci 17:2716-2726.

Goldstein LE, Rasmusson AM, Bunney BS and Roth RH (1996) Role of the amygdala in the coordination of behavioral, neuroendocrine, and prefrontal cortical monoamine responses to psychological stress in the rat. J Neurosci 16:4787-4798.

Gonon F (1997) Prolonged and extrasynaptic excitatory action of dopamine mediated by D1 receptors in the rat striatum in vivo. J Neurosci 17:5972-5978.

Gonzalez-Islas C and Hablitz JJ (2003) Dopamine enhances EPSCs in Layer II-III pyramidal neurons in rat prefrontal cortex. J Neurosci 867-875.

Gonzalez-Islas C and Hablitz JJ (2001) Dopamine inhibition of evoked IPSCs in rat prefrontal cortex. J Neurophysiol 86:2911-2918.

Gonzales C and Chesselet MF (1990) Amygdalonigral pathway: an anterograde study in the rat with phaseolus vulgaris leucoagglutinin (PHA-L). J Comp Neurol 297:182-200.

Gorelova N and Yang CR (1997) The course of neural projection from the prefrontal cortex to the nucleus accumbens in the rat. Neuroscience 76:689-706.

Goto Y and O'Donnell P (2002) Timing-dependent limbic-motor synaptic integration in the nucleus accumbens. Proc Natl Acad Sci USA 99:13189-13193.

Grace AA and Moore H (1998) Regulation of information flow in the nucleus accumbens: a model for the pathophysiology of schizophrenia. In: Lenzenweger MF and Dworkin RH (eds) Origins and development of schizophrenia: advances in experimental psychopathology. American Psychological Association, Washington, pp. 123-157.

Grace AA and Onn S-P (1989) Morphology and electrophysiological properties of immunocytochemically identified rat dopamine neurons recorded in vitro. J Neurosci 9:3463-3481.

Granato A, Santarelli M and Minciacchi D (1991) Bihemispheric organization of amygdalo-cortical projections in the rat. Neurosci Lett 127:53-56.

Granon S, Passetti F, Thomas KL, Dalley JW, Everitt BJ and Robbins TW (2000) Enhanced and impaired attentional performance after infusion of D1 dopaminergic receptor agents into rat prefrontal cortex. J Neurosci 20:1208-1215.

Granon S, Vidal C, Thinus-Blanc C, Changeux J-P and Poucet B (1994) Working memory, response selection, and effortful processing in rats with medial prefrontal lesions. Behav Neurosci 108:883-891.

Gray TS and Bingaman EW (1996) The amygdala: corticotropin-releasing factor, steroids, and stress. Crit Rev Neurobiol 10:155-168.

Greba Q, Gifkins A and Kokkinidis L (2001) Inhibition of amygdaloid dopamine D2 receptors impairs emotional learning measured with fear-potentiated startle. Brain Res 899:218-226.

Greba Q and Kokkinidis L (2001) Peripheral and intraamygdalar administration of the dopamine D_1 receptor antagonist SCH 23390 blocks fear-potentiated startle but not shock reactivity or the shock sensitization of acoustic startle. Behav Neurosci 114:262-272.

Grobin AC and Deutch AY (1998) Dopaminergic regulation of extracellular gamma-aminobutyric acid levels in the prefrontal cortex of the rat. J Pharmacol Exp Ther 285:350-357.

Groenewegen HJ, Vermeulen-van der Zee E, Te Kortschot A and Witter MP (1987) Organization of the projections from the subiculum to the ventral striatum in the rat. A study using anterograde transport of phaseolus vulgaris-leucoagglutinin. Neuroscience 23:103-120.

Groenewegen HJ, Wright CI and Beijer AVJ (1996) The nucleus accumbens: gateway for limbic structures to reach the motor system? Prog Brain Res 107: 485-511.

Guarraci FA, Frohardt RJ, Falls WA and Kapp BS (2000) The effects of intra-amygdaloid infusions of a D_2 dopamine receptor antagonist on Pavlovian fear conditioning. Behav Neurosci 114:647-651.

Guarraci FA, Frohardt RJ and Kapp BS (1999) Amygdaloid D_1 dopamine receptor involvement in Pavlovian fear conditioning. Brain Res 827:28-40.

Guarraci FA and Kapp BS (1999) An electrophysiological characterization of ventral tegmental area dopaminergic neurons during differential pavlovian fear conditioning in the awake rabbit. Behav Brain Res 99:169-179.

Gulledge AT and Jaffe DB (1998) Dopamine decreases the excitability of layer V pyramidal cells in the rat prefrontal cortex. J Neurosci 18:9139-9151.

Gulledge AT and Jaffe DB (2001) Multiple effects of dopamine on layer V pyramidal cell excitability in rat prefrontal cortex. J Neurophysiol 86:586-595.

Hajnal A and Lenard L (1997) Feeding-related dopamine in the amygdala of freely moving rats. Neuroreport 8:2817-2820.

Hariri AR, Bookheimer SY and Mazziotta JC (2000) Modulating emotional responses: effects of a neocortical network on the limbic system. Neuroreport 11:43-48.

Hariri AR, Mattay VS, Tessitore A, Fera F and Weinberger DR (2003) Neocortical modulation of the amygdala response to fearful stimuli. Biol Psychiatry 53:494-501.

Harmer CJ and Phillips GD (1999) Enhanced dopamine efflux in the amygdala by a predictive, but not a non-predictive, stimulus: facilitation by prior repeated D-amphetamine. Neuroscience 90:119-130.

Hart S, Zreik M, Carper R and Swerdlow NR (1998) Localizing haloperidol effects on sensorimotor gating in a predictive model of antipsychotic potency. Pharmacol Biochem Behav 61:113-119.

Hellman PA, Crider A and Solomon PR (1983) Interaction of tail-pressure stress and D-amphetamine in disruption of the rat's ability to ignore an irrelavant stimulus. Behav Neurosci 97:1017-1021.

Henke PG (1980) Facilitation and inhibition of gastric pathology after lesions in the amygdala of rats. Physiol Behav 25:575-579.

Hennessy MB and Foy T (1987) Nonedible material elicits chewing and reduces the plasma corticosterone response during novelty exposure in mice. Behav Neurosci 101:237-245.

Herman JP, Guillonneau D, Dantzer R, Scatton B, Semerdjian-Rouqier L and Le Moal M (1982) Differential effects of inescapable footshocks and of stimuli previously paired with inescapable footshocks on dopamine turnover in cortical and limbic areas of the rat. Life Sci 30:2207-2214.

Hitchcock J and Davis M (1986) Lesions of the amygdala but not of the cerebellum or red nucleus block conditioned fear as measured with the potentiated startle paradigm. Behav Neurosci 100:11-22.

Hitchcott PK, Bonardi CM and Phillips GD (1997a) Enhanced stimulus-reward learning by intra-amygdala administration of a D3 dopamine receptor agonist. Psychopharmacology 133:240-248.

Hitchcott PK, Harmer CJ and Phillips GD (1997b) Enhanced acquisition of discriminative approach following intra-amygdala d-amphetamine. Psychopharmacology 132:237-246.

Hitchcott PK and Phillips GD (1998a) Effects of intra-amygdala R(+) 7-OH-DPAT on intra-accumbens d-amphetamine-associated learning. I. Pavlovian conditioning. Psychopharmacology 140:300-309.

Hitchcott PK and Phillips GD (1998b) Effects of intra-amygdala R(+) 7-OH-DPAT on intra-accumbens d-amphetamine-associated learning. II. Instrumental conditioning. Psychopharmacology 140:310-318.

Hitchcott PK and Phillips GD (1998c) Double dissociation of the behavioural effects of R(+) 7-OH-DPAT infusions in the central and basolateral amygdala nuclei upon Pavlovian and instrumental conditioned appetitive behaviours. Psychopharmacology 140:458-469.

Hogg S and File SE (1994) Responders and nonresponders to cat odor do not differ in other tests of anxiety. Pharmacol Biochem Behav 49:219-222.

Horger BA and Roth RH (1996) The role of mesoprefrontal dopamine neurons in stress. Crit Rev Neurobiol 10:395-418.

Hori K, Tanaka J and Nomura M (1993) Effects of discrimination learning on the rat amygdala dopamine release: a microdialysis study. Brain Res 621:296-300.

Horn AS (1990) Dopamine uptake: a review of progress in the last decade. Prog Neurobiol 34:387-400.

Horvitz (2002) Dopamine gating of glutamatergic sensorimotor and incentive motivational input signals to the striatum. Behav Brain Res 65-74.

Horvitz (2000) Mesolimbocortical and nigrostriatal dopamine responses to salient non-reward events. Neuroscience 96:651-656.

Howland JG, Taepavarapruk P, Phillips AG (2002) Glutamate receptor-dependent modulation of dopamine efflux in the nucleus accumbens by basolateral, but not central, nucleus of the amygdala in rats. J Neurosci 22:1137-1145.

Hurley KM, Herbert H, Moga MM and Saper CB (1991) Efferent projections of the infralimbic cortex of the rat. J Comp Neurol 308:249-276.

Ikemoto S and Panksepp J (1999) The role of nucleus accumbens dopamine in motivated behavior: a unifying interpretation with special reference to reward-seeking. Brain Res Brain Res Rev 31:6-41.

Ikemoto S and Panksepp J (1996) Dissociations between appetitive and consummatory responses by pharmacological manipulations of reward-relevant brain regions. Behav Neurosci 110:331-345.

Imperato A, Cabib S and Puglisi-Allegra (1993) Repeated stressful experiences differently affect the time dependent responses of the mesolimbic dopamine system to the stressor. Brain Res 601:333-336.

Imperato A, Puglisi-Allegra S, Casolini P, Zocchi A and Angelucci L (1989) Stress-induced enhancement of dopamine and acetylcholine release in limbic structures: role of corticosterone. Eur J Pharmacol 165:337-338.

Ingles JL, Beninger RJ, Jhamandas K and Boegman RJ (1993) Scopolamine injected into the rat amygdala impairs working memory in the double Y-maze. Brain Res Bull 32:339-344.

Inglis FM and Moghaddam B (1999) Dopaminergic innervation of the amygdala is highly responsive to stress. J Neurochem 72:1088-1094.

Inoue T, Tsuchiya K and Koyama T (1994) Regional changes in dopamine and serotonin activation with various intensity of physical and psychological stress in the rat brain. Pharmacol Biochem Behav 49:911-920.

Ishikawa A and Nakamura S (2003) Convergence and interaction of hippocampal and amygdalar projections within the prefrontal cortex in the rat. J Neurosci 23:9987-9995.

Jackson ME, Frost AS and Moghaddam B (2001) Stimulation of prefrontal cortex at physiologically relevant frequencies inhibits dopamine release in the nucleus accumbens. J Neurochem 78:920-923.

Jackson ME and Moghaddam B (2001) Amygdala regulation of nucleus accumbens dopamine output is governed by the prefrontal cortex. J Neurosci 21:676-681.

Japha K and Koch M (1999) Picrotoxin in the medial prefrontal cortex impairs sensorimotor gating in rats: reversal by haloperidol. Psychopharmacology 144:347-354.

Jeanblanc J, Hoeltzel A and Louilot A (2002) Dissociation in the involvement of dopaminergic neurons innervating the core and shell subregions of the nucleus accumbens in latent inhibition and affective perception. Neuroscience 111:315-323.

Jentsch JD and Taylor JR (1999) Impulsivity resulting from frontostriatal dysfunction in drug abuse: implications for the control of behaviour by reward-related stimuli. Psychopharmacology 146:373-390.

Jodo E, Chiang C and Aston-Jones G (1998) Potent excitatory influence of prefrontal cortex activity on noradrenergic locus coeruleus neurons. Neuroscience 83:63-79.

Joel D, Weiner I and Feldon J (1997) Electrolytic lesions of the medial prefrontal cortex in rats disrupt performance on an analog of Wisconsin Card Sorting Test but do not disrupt latent inhibition: implications for animal models of schizophrenia. Behav Brain Res 85:187-201.

Johnson SW and North RA (1992) Two types of neurone in the rat ventral tegmental area and their synaptic inputs. J Physiol (Lond) 450:455-468.

Jones SR, Garris PA, Kilts CD and Wightman RM (1995) Comparison of dopamine uptake in the basolateral amygdaloid nucleus, caudate-putamen, and nucleus accumbens of the rat. J Neurochem 64:2581-2589.

Jones SR, O'Dell SJ, Marshall JF and Wightman RM (1996) Functional and anatomical evidence for different dopamine dynamics in the core and shell of the nucleus accumbens in slices of rat brain. Synapse 23:224-231.

Jongen-Relo AL, Kaufmann S and Feldon J (2003) A differential involvement of the shell and core subterritories of the nucleus accumbens of rats in memory processes. Behav Neurosci 117:150-168.

Jongen-Relo AL, Kauffmann S and Feldon J (2002) A differential involvement of the shell and core subterritories of the nucleus accumbens of rats in attentional processes. Neuroscience 111:95-109.

Joseph MH, Peters SL, Moran PM, Grigoryan GA, Young AMJ and Gray JA (2000) Modulation of latent inhibition in the rat by altered dopamine transmission in the nucleus accumbens at the time of conditioning. Neuroscience 101:921-930.

Kalivas PW, Bourdelais A, Abhold R and Abbott L (1989) Somatodendritic release of endogenous dopamine: in vivo dialysis in the A10 dopamine region. Neurosci Lett 100:215-220.

Kalivas PW, Churchill L and Klitenick MA (1993) GABA and enkephalin projection from the nucleus accumbens and ventral pallidum to the ventral tegmental area. Neuroscience 57:1047-1060.

Kalivas PW and Duffy P (1995) Selective activation of dopamine transmission in the shell of the nucleus accumbens by stress. Brain Res 675:325-328.

Kaneyuki H, Yokoo H, Tsuda A, Yoshida M, Mizuki Y, Yamada M and Tanaka M (1991) Psychological stress increases dopamine turnover selectively in mesoprefrontal dopamine neurons of rats: reversal by diazepam. Brain Res 557:154-61.

Karreman M and Moghaddam B (1996) The prefrontal cortex regulates the basal release of dopamine in the limbic striatum: an effect mediated by ventral tegmental area. J Neurochem 66:589-598.

Kelley AE, Domesick VB and Nauta WJH (1982) The amygdalostriatal projection in the rat - an anatomical study by anterograde and retrograde tracing methods. Neuroscience 7:615-630.

Kilts CD, Anderson CM, Ely TD and Nishita JK (1987) Absence of synthesis-modulating nerve terminal autoreceptors on mesoamygdaloid and other mesolimbic dopamine neuronal populations. J Neurosci 7:3961-3975.

King D and Finlay JM (1997) Loss of dopamine terminals in the medial prefrontal cortex increased the ratio of DOPAC to DA in tissue of the nucleus accumbens shell: role of stress. Brain Res 767:192-200.

King D, Zigmond MJ and Finlay JM (1997) Effects of dopamine depletion in the medial prefrontal cortex on the stress-induced increase in extracellular dopamine in the nucleus accumbens core and shell. Neuroscience 77:141-153.

Kiyatkin EA (1988) Functional properties of presumed dopamine-containing and other ventral tegmental area neurons in conscious rats. Int J Neurosci 42:21-43.

Kiyatkin EA and Rebec GV (1999) Striatal neuronal activity and responsiveness to dopamine and glutamate after selective blockade of D1 and D2 dopamine receptors in freely moving rats. J Neurosci 19:3594-3609.

Kiyatkin EA and Rebec GV (1996) Dopaminergic modulation of glutamate-induced excitations of neurons in the neostriatum and nucleus accumbens of awake, unrestrained rats. J Neurophysiol 75:142-153.

Kiyatkin EA and Zhukov VN (1988) Impulse activity of mesencephalic neurons on nociceptive stimulation in awake rats. Neurosci Behav Physiol 18:393-400.

Koch M (1993) Microinjections of the metabotropic glutamate receptor agonist, trans(+-)-1-amino-cyclopentane-1,3-dicarboxylate (trans-ACPD) into the amygdala increase the acoustic startle response of rats. Brain Res 629:176-179.

Koch M (1999) The neurobiology of startle. Prog Neurobiol 59:107-128.

Koch M and Bubser M (1994) Deficient sensorimotor gating after 6-hydroxydopamine lesion of the rat medial prefrontal cortex is reversed by haloperidol. Eur J Neurosci 6:1837-1845.

Koch M and Ebert U (1998) Deficient sensorimotor gating following seizures in amygdala-kindled rats. Biol Psychiatry 44:290-297.

Kodsi MH and Swerdlow NR (1997) Reduced prepulse inhibition after electrolytic lesions of nucleus accumbens subregions in the rat. Brain Res 773:45-52.

Kodsi MH and Swerdlow NR (1994) Quinolinic acid lesions of the ventral striatum reduce sensorimotor gating of acoustic startle in rats. Brain Res 643:59-65.

Kretschmer BD and Koch M (1998) The ventral pallidum mediates disruption of prepulse inhibition of the acoustic startle response induced by dopamine agonists, but not by NMDA antagonists. Brain Res 798:204-210.

Krettek JE and Price JL (1978) A description of the amygdaloid complex in the rat and cat with observations on intra-amygdaloid axonal connections. J Comp Neurol 178:255-280.

Krettek JE and Price JL (1977) Projections from the amygdaloid complex to the cerebral cortex and thalamus in the rat and cat. J Comp Neurol 172:687-722.

Lacroix L, Broerson LM, Weiner I and Feldon J (1998) The effects of excitotoxic lesion of the medial prefrontal cortex on latent inhibition, prepulse inhibition, food hoarding, elevated plus maze, active avoidance and locomotor activity in the rat. Neuroscience 84:432-443.

Lacroix L, Broersen LM, Feldon J and Weiner I (2000a) Effects of local infusions of dopaminergic drugs into the medial prefrontal cortex of rats on latent inhibition, prepulse inhibition and amphetamine induced activity. Behav Brain Res 107:111-121.

Lacroix L, Spinelli S, Heidbreder CA and Feldon J (2000b) Differential role of the medial and lateral prefrontal cortices in fear and anxiety. Behav Neurosci 114:119-1130.

Lacroix L, Spinelli S, White W and Feldon J (2000c) The effects of ibotenic acid lesions of the medial and lateral prefrontal cortex on latent inhibition, prepulse inhibition and amphetamine-induced hyperlocomotion. Neuroscience 97:459-468.

Lamont EW and Kokkinidis L (1998) Infusion of the dopamine D_1 receptor antagonist SCH 23390 into the amygdala blocks fear expression in a potentiated startle paradigm. Brain Res 795:128-136.

Lavin A and Grace AA (2001) Stimulation of D1-type dopamine receptors enhances excitability in prefrontal cortical pyramidal neurons in a state-dependent manner. Neuroscience 104:335-346.

Law-Tho D, Hirsch JC and Crepel F (1994) Dopamine modulation of synaptic transmission in rat prefrontal cortex: an in vitro electrophysiological study. Neurosci Res 21:151-160.

LeDoux JE (2000) Emotion circuits in the brain. Annu Rev Neurosci 23:155-184.

LeDoux JE, Cicchetti P, Xagoraris A and Romanski LM (1990) The lateral amygdaloid nucleus: sensory interface of the amygdala in fear conditioning. J Neurosci 10:1062-1069.

Leitner DS (1989) Multisensory deficits in rats produced by exposure to cold swim stress. Behav Neurosci 103:151-157.

Levey AI, Hersch SM, Rye DB, Sunahara RK, Niznik HB, Kitt CA, Price DL, Maggio R, Brann MR and Ciliax BJ (1993) Localization of D1 and D2 dopamine receptors in brain with subtype-specific antibodies. Proc Natl Acad Sci USA 90:8861-8865.

Levine MS, Li Z, Cepeda C, Cromwell HC and Altemus KL (1996) Neuromodulatory actions of dopamine on synaptically evoked neostriatal responses in slices. Synapse 24:65-78.

Lewis BL and O'Donnell P (2000) Ventral tegmental area afferents to the prefrontal cortex maintain membrane potential 'up' states in pyramidal neurons via D1 dopamine receptors. Cereb Cortex 10:1168-1175.

Loughlin SE and Fallon JH (1984) Substantia nigra and ventral tegmental projections to cortex: topography and collateralization. Neuroscience 11:425-435.

Louilot A, Le Moal M and Simon H (1989) Opposite influences of dopaminergic pathways to the prefrontal cortex or the septum on dopaminergic transmission in the nucleus accumbens: an *in vivo* voltammetric study. Neuroscience 29:45-56.

Louilot A, Simon H, Taghzouti K and Le Moal M (1985) Modulation of dopaminergic activity in the nucleus accumbens following facilitation or blockade of the dopaminergic transmission in the amygdala: a study by *in vivo* differential pulse voltammetry. Brain Res 346:141-145.

Luan Phan K, Liberzon I, Welsh RC, Britton JC and Taylor SF (2003) Habituation of rostral anterior cingulate cortex to repeated emotionally salient pictures. Neuropsychopharmacology 28:1344-1350.

Maeda H and Mogenson GJ (1981) Electrophysiological responses of the ventral tegmental area to electrical stimulation of amygdala and septum. Neuroscience 6:367-376.

Mair RG, Koch JK, Newman JB, Howard JR and Burk JA (2002) A double dissociation within striatum between serial reaction time and radial maze delayed nonmatching performance in rats. J Neurosci 22:6756-6765.

Mangiavacchi S, Masi F, Scheggi S, Leggio B, De Montis MG and Gambarana C (2001) Long-term behavioral and neurochemical effects of chronic stress exposure in rats. J Neurochem 79:1113-1121.

Maren S, Aharonov G and Fanselow MS (1997) Neurotoxic lesions of the dorsal hippocampus and Pavlovian fear conditioning in rats. Behav Brain Res 88:261-274.

Maroun M and Richter-Levin G (2003) Exposure to acute stress blocks the induction of long-term potentiation of the amygdala-prefrontal cortex pathway in vivo. J Neurosci 23:4406-4409.

Maslowski-Cobuzzi RJ and Napier TC (1994) Activation of dopaminergic neurons modulates ventral pallidal responses evoked by amygdala stimulation. Neuroscience 62:1103-1120.

Matsuda Y and Fujimura K (1996) Recurrent inhibition in amygdalo-cortical projection neurons of the rat via collaterals of fast-conducting axons. Neurosci Res 25:385-389.

May-Simera H and Levin ED (2003) NMDA systems in the amygdala and piriform cortex and nicotinic effects on memory function. Brain Res Cogn Brain Res 17:475-483.

McCullough LD, Sokolowski JD and Salamone JD (1993) A neurochemical and behavioral investigation of the involvement of nucleus accumbens dopamine in instrumental avoidance. Neuroscience 52:919-925.

McDonald AJ (1998) Cortical pathways to the mammalian amygdala. Prog Neurobiol 55:257-332.

McDonald AJ (1996) Glutamate and aspartate immunoreactive neurons of the rat basolateral amygdala: colocalization of excitatory amino acids and projections to the limbic circuit. J Comp Neurol 365:367-379.

McDonald AJ (1991a) Topographical organization of amygdaloid projections to the caudatoputamen, nucleus accumbens, and related striatal-like areas of the rat brain. Neuroscience 44:15-33.

McDonald AJ (1991b) Organization of amygdaloid projections to the prefrontal cortex and associated striatum in the rat. Neuroscience 44:1-14.

McDonald AJ (1987) Organization of amygdaloid projections to the mediodorsal thalamus and prefrontal cortex: a fluorescence retrograde transport study in the rat. J Comp Neurol 262:46-58.

McDonald AJ, Mascagni F and Guo L (1996) Projections of the medial and lateral prefrontal cortices to the amygdala: a phaseolus vulgaris leucoagglutin study in the rat. Neuroscience 71:55-75.

McDonald LM, Moran PM, Vythelingum GN, Joseph MH, Stephenson JD and Gray JA (2002) Latent inhibition is attenuated by noise and partially restored by a $5HT_{2A}$ receptor antagonist. Behav Pharmacol 13:663-667.

McGaugh JL, Ferry B, Vazdarjanova A and Roozendaal B (2000) Amygdala role in modulation of memory storage. In: Aggleton JP (Ed), The amygdala: a functional analysis. Oxford University Press, Oxford, pp. 391-445.

McGregor A, Baker G and Roberts DC (1994) Effect of 6-hydroxydopamine lesions of the amygdala on intravenous cocaine self-administration under a progressive ratio schedule of reinforcement. Brain Res 646:273-278.

Meltzer HY, Matsubara S and Lee JC (1989) Classification of typical and atypical antipsychotic drugs on the basis of dopamine D-1, D-2 and serotonin2 pKi values. J Pharmacol Exp Ther 251:238-246.

Merali Z, McIntosh J, Kent P, Michaud D and Anisman H (1998) Aversive and appetitive events evoke the release of corticotropin-releasing hormone and bombesin-like peptides at the central nucleus of the amygdala. J Neurosci 18:4758-4766.

Miller JD, Sanghera MK and German DC (1981) Mesencephalic dopaminergic activity in the behaviorally conditioned rat. Life Sci 29:1255-1265.

Missale C, Nash SR, Robinson SW, Jaber M and Caron M (1998) Dopamine receptors: from structure to function. Physiol Rev 78:189-225.

Mitchell J and Gratton A (1991a) Mesolimbic dopamine release elicited by activation of the accessory olfactory system: a high-speed chronoamperometric study. Neurosci Lett 140: 81-84.

Mitchell J and Gratton A (1991b) Opioid modulation and sensitization of dopamine release elicited by sexually relevant stimuli: a high speed chronoamperometric study in freely behaving rats. Brain Res 551: 20-27.

Moga MM, Herbert H, Hurley KM, Yasui Y, Gray TS and Saper CB (1990) Organization of cortical, basal forebrain, and hypothalamic afferents to the parabrachial nucleus in the rat. J Comp Neurol 295:624-661.

Mogenson GJ, Jones LD and Yim CY (1980) From motivation to action: functional interface between the limbic system and the motor system. Prog Neurobiol 14:69-97.

Mogenson GJ and Nielsen MA (1983) Evidence that an accumbens to subpallidal GABAergic projection contributes to locomotor activity. Brain Res Bull 11:309-314.

Montaron MF, Deniau JM, Menetrey A, Glowinski J and Thierry AM (1996) Prefrontal cortex inputs of the nucleus accumbens-nigro-thalamic circuit. Neuroscience 71:371-382.

Moore H, Rose HJ and Grace AA (2001) Chronic cold stress reduces the spontaneous activity of ventral tegmental dopamine neurons. Neuropsychopharmacology 24:410-419.

Morgan MA and LeDoux JE (1995) Differential contribution of dorsal and ventral medial prefrontal cortex to the acquisition and extinction of conditioned fear in rats. Behav Neurosci 109:1650-1657.

Morón JA, Brockington A, Wise RA, Rocha BA and Hope BT (2002) Dopamine uptake through the norepinephrine transporter: evidence from knock-out mouse lines. J Neurosci 22:389-395.

Morris JS, DeGelder B, Weiskrantz L and Dolan RJ (2001) Differential extra-geniculostriate and amygdala responses to presentation of emotional faces in a cortically blind field. Brain 124:1241-1252.

Morris JS, Ohman A and Dolan RJ (1999) A subcortical pathway to the right amygdala mediating "unseen" fear. Proc Natl Acad Sci US 96:1680-1685.

Morris JS, Ohman A and Dolan RJ (1998) Conscious and unconscious emotional learning in the human amygdala. Nature 393:467-470.

Morrow BA, Elsworth JD, Lee EJ and Roth RH (2000a) Divergent effects of putative anxiolytics on stress-induced fos expression in the mesoprefrontal system of the rat. Synapse 36:143-154.

Morrow BA, Redmond AJ, Roth RH and Elsworth JD (2000b) The predator odor, TMT, displays a unique, stress-like pattern of dopaminergic and endocrinological activation in the rat. Brain Res 864:146-151.

Morrow BA, Roth RH and Elsworth JD (2000c) TMT, a predator odor, elevates mesoprefrontal dopamine metabolic activity and disrupts short-term working memory in the rat. Brain Res Bull 52:519-523.

Morrow BA, Elsworth JD, Rasmusson AM and Roth RH (1999) The role of mesoprefrontal dopamine neurons in the acquisition and expression of conditioned fear in the rat. Neuroscience 92:553-564.

Morrow BA, Lee EJ, Taylor JR, Elsworth JD, Nye HE and Roth RH (1997) (S)-(-)-HA-966, a gamma-hydroxybutyrate-like agent, prevents enhanced mesocorticolimbic dopamine metabolism and behavioral correlates of restraint stress, conditioned fear and cocaine sensitization. J Pharmacol Exp Ther 283:712-721.

Muir JL, Everitt BJ and Robbins TW (1996) The cerebral cortex of the rat and visual attentional function: dissociable effects of mediofrontal, cingulate, anterior dorsolateral and parietal cortex lesions on a five choice serial reaction time task in rats. Cereb Cortex 6:470-481.

Mulder AB, Hodenpijl MG and Lopes da Silva FH (1998) Electrophysiology of the hippocampal and amygdaloid projections to the nucleus accumbens of the rat: convergence, segregation, and interaction of inputs. J Neurosci 18:5095-5102.

Murase S, Grenhoff J, Chouvet G, Gonon FG and Svensson TH (1993) Prefrontal cortex regulates burst firing and transmitter release in rat mesolimbic dopamine neurons studied in vivo. Neurosci Lett 157:53-56.

Murphy BL, Arnsten AFT, Goldman-Rakic PS and Roth RH (1996a) Increased dopamine turnover in the prefrontal cortex impairs spatial working memory performance in rats and monkeys. Proc Natl Acad Sci USA 93:1325-1329.

Murphy BL, Arnsten AFT, Jentsch JD and Roth RH (1996b) Dopamine and spatial working memory in rats and monkeys: pharmacological reversal of stress-induced impairment. J Neurosci 16:7768-7775.

Murphy CA, Pezze M, Feldon J and Heidbreder C (2000) Differential involvement of dopamine in the shell and core of the nucleus accumbens in the expression of latent inhibition to an aversively conditioned stimulus. Neuroscience 97:469-477.

Nader K and LeDoux JE (1999) Inhibition of the mesoamygdala dopaminergic pathway impairs the retrieval of conditioned fear associations. Behav Neurosci 113:891-901.

Nicola SM, Surmeier J and Malenka RC (2000) Dopaminergic modulation of neuronal excitability in the striatum and nucleus accumbens. Annu Rev Neurosci 23:185-215.

O'Donnell (2003) Dopamine gating of forebrain neural ensembles. Eur J Neurosci 17:1-7.

O'Donnell P and Grace AA (1995) Synaptic interactions among excitatory afferents to nucleus accumbens neurons: hippocampal gating of prefrontal cortical input. J Neurosci 15:3622-3639.

O'Donnell P and Grace AA (1998) Phencyclidine interferes with the hippocampal gating of nucleus accumbens neuronal activity *in vivo*. Neuroscience 87:823-830.

O'Donnell P, Greene J, Pabello N, Lewis BL and Grace AA (1999) Modulation of cell firing in the nucleus accumbens. Ann N Y Acad Sci 877:157-175.

Ohno M, Yamamoto T and Watanabe S (1993) Amygdaloid NMDA and muscarinic receptors involved in working memory performance of rats. Physiol Behav 54:993-997.

Ostrander MM, Richtand NM and Herman JP (2003) Stress and amphetamine induce Fos expression in medial prefrontal cortex neurons containing glucocorticoid receptors. Brain Res 990:209-214.

Ottersen OP (1982) Connections of the amygdala of the rat. IV: Corticoamygdaloid and intraamygdaloid connections as studied with axonal transport of horseradish peroxidase. J Comp Neurol 205:30-48.

Pacák K and Palkovits M (2001) Stessor specificity pf central neuroendocrine responses: implications for stress-related disorders. Endocrine Rev 22:502-548.

Paré D, Royer S, Smith Y and Lang EJ (2003) Contextual inhibitory gating of impulse traffic in the intra-amygdaloid network. Ann N Y Acad Sci 985:78-91.

Passetti F, Dalley JW and Robbins TW (2003) Double dissociation of serotonergic and dopaminergic mechanisms on attentional performance using a rodent five-choice reaction time task. Psychopharmacology 165:136-145.

Peinado-Manzano MA (1990) The role of the amygdala and the hippocampus in working memory for spatial and non-spatial information. Behav Brain Res 38:117-134.

Pérez-Jaranay JM and Vives F (1991) Electrophysiological study of the response of medial prefrontal cortex neurons to stimulation of the basolateral nucleus of the amygdala in the rat. Brain Res 564:97-101.

Perrot-Sinal TS, Ossenkopp K-P and Kavaliers M (1999) Brief predator odour exposure activates the HPA axis independent of locomotor changes. NeuroReport 10:775-780.

Petrovich GD, Canteras NS and Swanson LW (2001) Combinatorial amygdalar inputs to hippocampal domains and hypothalamic behavioural systems. Brain Res 38:247-289.

Petrovich GD, Risold PY and Swanson LW (1996) Organization of projections from the basomedial nucleus of the amygdala: a PHAL study in the rat. J Comp Neurol 374:387-420.

Pezze MA, Bast T and Feldon J (2003) Significance of dopamine transmission in the rat medial prefrontal cortex for conditioned fear. Cereb Cortex 13: 371-380.

Pfaus JG, Damsma G, Wenkstern D and Fibiger HC (1995) Sexual activity increases dopamine transmission in the nucleus accumbens and striatum of female rats. Brain Res 693:21-30.

Phillips AG, Ahn S and Floresco SB (2004) Magnitude of dopamine release in medial prefrontal cortex predicts accuracy of memory on a delayed response task. J Neurosci 24:547-553.

Phillips GD, Harmer CJ and Hitchcott PK (2002) Blockade of sensitisation-induced facilitation of appetitive conditioning by post-session intra-amygdala nafadotride. Behav Brain Res 134:249-257.

Phillips RG and LeDoux JE (1992) Differential contribution of amygdala and hippocampus to cued and contextual fear conditioning. Behav Neurosci 106:274-285.

Pinto A and Sesack SR (2000) Limited collateralization of neurons in the rat prefrontal cortex that project to the nucleus accumbens. Neuroscience 97:635-642.

Pirot S, Godbout R, Mantz J, Tassin J-P, Glowinski J and Thierry A-M (1992) Inhibitory effects of ventral tegmental area stimulation on the activity of prefrontal cortical neurons: evidence for the involvement of both dopaminergic and GABAergic components. Neuroscience 49:857-865.

Pistis M, Muntoni AL, Pillolla G and Gessa GL (2002) Cannabinoids inhibit excitatory inputs to neurons in the shell of the nucleus accumbens: an in vivo electrophysiological study. Eur J Neurosci 15:1795-1802.

Pitkänen A, Savander V and LeDoux JE (1997) Organization of intra-amygdaloid circuitries in the rat: an emerging framework for understanding functions of the amygdala. Trends Neurosci 20:517-523.

Poellinger A, Thomas R, Lio P, Lee A, Makris N, Rosen BR and Kwong KK (2001) Activation and habituation in olfaction - an fMRI study. Neuroimage 13:547-560.

Powell DA, Watson K and Maxwell B (1994) Involvement of subdivisions of the medial prefrontal cortex in learned cardiac adjustments in rabbits. Behav Neurosci 108:294-307.

Price JL (2003) Comparative aspects of amygdala connectivity. Ann N Y Acad Sci 985:50-58.

Pycock CJ, Carter CJ and Kerwin RW (1980) Effect of 6-hydroxydopamine lesions of the medial prefrontal cortex on neurotransmitter systems in subcortical sites in the rat. J Neurochem 34:91-99.

Quirarte GL, Galvez R, Roozendaal B and McGaugh JL (1998) Norepinephrine release in the amygdala in response to footshock and opioid peptidergic drugs. Brain Res 808:134-140.

Quirk GJ, Likhtik E, Guillaume Pelletier J and Paré D (2003) Stimulation of medial prefrontal cortex decreases the responsiveness of central amygdala output neurons. J Neurosci 23:8800-8807.

Quirk GJ, Russo GK, Barron JL and Lebron K (2000) The role of ventromedial prefrontal cortex in the recovery of extinguished fear. J Neurosci 20:6225-6231.

Raber J, Koob GF and Bloom FE (1995) Interleukin-2 (IL-2) induces corticotropin-releasing factor (CRF) release from the amygdala and involves a nitric oxide-mediated signaling; comparison with the hypothalamic response. J Pharmacol Exp Ther 272:815-824.

Rada P and Hernandez L (1990) Opposite changes of dopamine turnover in prefrontal cortex and nucleus accumbens after amygdaloid kindling. Neurosci Lett 117:144-148.

Radulovic J, Kammermeier J and Spiess J (1998) Relationship between fos production and classical fear conditioning: effects of novelty, latent inhibition, and unconditioned stimulus preexposure. J Neurosci 18:7452-7461.

Rao TS, Kim HS, Lehman J, Martin LL and Wood PL (1990) Interactions of phencyclidine receptor agonist MK-801 with dopaminergic system: regional studies in the rat. J Neurochem 54:1157-1162.

Ray A and Henke PG (1991) The basolateral amygdala, dopamine and gastric stress ulcer formation in rats. Brain Res 558:335-338.

Ray A, Henke PG and Sullivan RM (1988) Effects of intra-amygdalar dopamine agonists and antagonists on gastric stress lesions in rats. Neurosci Lett 84:302-306.

Ray A, Henke PG and Sullivan RM (1987) The central amygdala and immobilization stress-induced gastric pathology in rats: neurotensin and dopamine. Brain Res 409:398-402.

Redmond AJ, Morrow BA, Elsworth JD and Roth RH (2002) Selective activation of the A10, but not A9, dopamine neurons in the rat by the predator odor, 2,5-dihydro-2,4,5-trimethylthiazoline. Neurosci Lett 328:209-212.

Revay R, Vaughan R, Grant S and Kuhar MJ (1996) Dopamine transporter immunohistochemistry in median eminence, amygdala, and other areas of the rat brain. Synapse 22:93-99.

Richardson NR and Gratton A (1998) Changes in medial prefrontal cortical dopamine levels associated with response-contingent food reward: an electrochemical study in rat. J Neurosci 18:9130-9138.

Richardson NR and Gratton A (1996) Behavior-relevant changes in nucleus accumbens dopamine transmission elicited by food reinforcement: an electrochemical study in rat. J Neurosci 16:8160-8169.

Rizvi TA, Ennis M, Behbehani MM and Shipley MT (1991) Connections between central nucleus of the amygdala and the midbarin periaqueductal gray: topography and reciprocity. J Comp Neurol 303:121-131.

Robbins TW (2000) Chemical neuromodulation of frontal-executive functions in humans and other animals. Exp Brain Res 133:130-138.

Room P, Russchen FT, Groenewegen HJ and Lohman AH (1985) Efferent connections of the prelimbic (area 32) and the infralimbic (area 25) cortices: an anterograde tracing study in the cat. J Comp Neurol 242:40-55.

Roozendaal B, Koolhaass JM and Bohus B (1990) Differential effect of lesioning of the central amygdala on the bradycardia and behavioural response of the rat in relation to conditioned social and solitary stress. Behav Brain Res 41:39-48.

Roozendaal B, Koolhaass JM and Bohus B (1991) Attenuated cardiovascular, neuroendocrine, and behavioural responses after a single footshock in central amygdaloid lesioned male rats. Physiol Behav 50:771-775.

Rosenkranz JA, Moore H and Grace AA (2003) The prefrontal cortex regulates lateral amygdala neuronal plasticity and responses to previously conditioned stimuli. J Neurosci 23:11054-11064.

Rosenkranz JA and Grace AA (2002a) Cellular mechanisms of infralimbic and prelimbic prefrontal cortical inhibition and dopaminergic modulation of basolateral amygdala neurons in vivo. J Neurosci 22:324-337.

Rosenkranz JA and Grace AA (2002b) Dopamine-mediated modulation of odour-evoked amygdala potentials during Pavlovian conditioning. Nature 417:282-287.

Rosenkranz JA and Grace AA (2001) Dopamine attenuates prefrontal cortical suppression of sensory inputs to the basolateral amygdala of rats. J Neurosci 21:4090-103.

Rosenkranz JA and Grace AA (1999) Modulation of basolateral amygdala neuronal firing and different drive by dopamine receptor activation in vivo. J Neurosci 19:11027-39.

Russig H, Kovacevic A, Murphy CA and Feldon (2003) Haloperidol and clozapine antagonise amphetamine-induced disruption of latent inhibition of conditioned taste aversion. Psychopharmacology 170:263-270.

Salamone JD and Correa M (2002) Motivational views of reinforcement: implications for understanding the behavioural functions of dopamine. Behav Brain Res 137:3-25.

Sanders BJ, Wirtz-Nole C, DeFord SM and Erling BF (1994) Central amygdaloid lesions attenuate cardiovascular responses to acute stress in rats with borderline hypertension. Physiol Behav 56:709-713.

Sarter M and Markowitsch HJ (1984) Collateral innervation of the medial and lateral prefrontal cortex by amygdaloid, thalamic, and brain-stem neurons. J Comp Neurol 224:445-460.

Sarter M and Markowitsch HJ (1983) Convergence of basolateral amygdaloid and mediodorsal thalamic projections in different areas of the frontal cortex in the rat. Brain Res Bull 10:607-622.

Schauz C and Koch M (2000) Blockade of NMDA receptors in the amygdala prevents latent inhibition of fear-conditioning. Learn Mem 7:393-399.

Scheggi S, Leggio B, Masi F, Grappi S, Gambarana C, Nanni G, Rauggi R and De Montis MG (2002) Selective modifications in the nucleus accumbens of dopamine synaptic transmission in rats exposed to chronic stress. J Neurochem 83:895-903.

Schulkin L, McEwen BS and Gold PW (1994) Allostasis, amygdala, and anticipatory angst. Neurosci Biobehav Rev 18:385-396.

Schultz W (1998) Predictive reward signal of dopamine neurons. J Neurophysiol 80:1-27.

Scibilia RJ, Lachowicz JE and Kilts CD (1992) Topographic nonoverlapping distribution of D1 and D2 dopamine receptors in the amygdaloid nuclear complex of the rat brain. Synapse 11:146-154.

Seamans JK, Durstewitz D, Christie BR, Stevens CF and Sejnowski TJ (2001) Dopamine D1/D5 receptor modulation of excitatory synaptic inputs to layer V prefrontal cortex neurons. Proc Natl Acad Sci USA 98:301-306.

Selye H (1936) A syndrome produced by diverse nocious agents. Nature 138:32.

Sesack SR, Deutch AY, Roth RH and Bunney BS (1989) Topographical organization of the efferent projections of the medial prefrontal cortex in the rat: an anterograde tract-tracing study with phaseolus vulgaris leucoagglutinin. J Comp Neurol 290:213-242.

Sesack SR, Hawrylak VA, Matus C, Guido MA and Levey AI (1998) Dopamine axon varicosities in the prelimbic division of the rat prefrontal cortex exhibit sparse immunoreactivity for the dopamine transporter. J Neurosci 2697-2708.

Sesack SR and Pickel VM (1992) Prefrontal cortical efferents in the rat synapse on unlabeled neuronal targets of catecholamine terminal in the nucleus accumbens septi and on dopamine neurons in the ventral tegmental area. J Comp Neurol 320:145-160.

Sesack SR, Snyder CL and Lewis DA (1995) Axon terminals immunolabelled for dopamine or tyrosine hydroxylase synapse on GABA-immunoreactive dendrites in rat and monkey cortex. J Comp Neurol 363:264-280.

Shepard PD and German DC (1984) A subpopulation of mesocortical dopamine neurons possess autoreceptors. Eur J Pharmacol 114:401-402.

Shimada Kitayama S, Walther D and Uhl G (1992) Dopamine transporter mRNA: dense expression in ventral midbrain neurons. Mol Brain Res 13:359-362.

Shinonaga Y, Takada M and Mizuno N (1994) Topographic organization of collateral projections from the basolateral amygdaloid nucleus to both the prefrontal cortex and nucleus accumbens in the rat. Neuroscience 58:389-397.

Shoemaker JM, Pitcher L, Noh HR and Swerdlow NR (2003) Quetiapine produces a prolonged reversal of the sensorimotor gating-disruptive effects of basolateral amygdala lesions in rats. Behav Neurosci 117:136-143.

Simon H, Taghzouti K, Gozlan H, Studler JM, Louilot A, Herve D, Glowinski J, Tassin JP and Le Moal M (1988) Lesion of dopaminergic terminals in the amygdala produces enhanced locomotor response to D-amphetamine and opposite changes in dopaminergic activity in prefrontal cortex and nucleus accumbens. Brain Res 447:335-340.

Smith Y, Pare JF and Paré D (2000) Differential innervation of parvalbumin-immunoreactive interneurons of the basolateral amygdaloid complex by cortical and intrinsic inputs. J Comp Neurol 416:496-508.

Smith WJ, Stewart J and Pfaus JG (1997) Tail pinch induces fos immunoreactivity within several regions of the male rat brain: effects of age. Physiol Behav 61:717-723.

Solomon PR and Staton DM (1982) Differential effects of microinjections of d-amphetamine into the nucleus or the caudate putamen on the rat's ability to ignore an irrelevant stimulus. Biol Psychiatry 17:743-756.

Sotty F, Sandner G and Gosselin O (1996) Latent inhibition in conditioned emotional response: c-fos immunolabelling evidence for brain areas involved in the rat. Brain Res 737:243-254.

Spehlmann R and Norcross K (1984) Decreased sensitivity of neurons in the basolateral amygdala to dopamine and noradrenaline iontophoresis after a kindling stimulus. Exp Neurol 83:204-210.

Stanwood GD, Artymyshyn RP, Kung MP, Kung HF, Lucki I and McGonigle P (2000) Quantitative autoradiographic mapping of rat brain dopamine D3 binding with [(125)I]7-OH-PIPAT: evidence for the presence of D3 receptors on dopaminergic and nondopaminergic cell bodies and terminals. J Pharmacol Exp Ther 295:1223-1231.

Starke K, Gothert M and Kilbinger H (1989) Modulation of neurotransmitter release by presynaptic autoreceptors. Physiol Rev 69:864-989.

Sterling P and Eyer J (1981) Allostasis: a new paradigm to explain arousal pathology. In: Fisher S, Reason HS, eds. Handbook of life, stress, cognition, and health. New York: John Wiley and Sons.

Storozheva ZI, Afanas'ev II, Proshin AT and Kudrin VS (2003) Dynamics if intracellular dopamine contents in the rat brain during the formation of conditioned contextual fear and extinction of an acoustic startle reaction. Neurosci Behav Physiol 33:307-312.

Sullivan RM and Dufresne M (2002) Effects of unilateral dopamine receptor blockade in medial prefrontal cortex on stress-induced HPA activitiy in handled and nonhandled rats. Soc Neurosci Abstracts 864.7.

Sullivan RM and Gratton A (2002a) Prefrontal cortical regulation of hypothalamic-pituitary-adrenal function in the rat and implications for psychopathology: side matters. Psychoneuroendocrinology 27:99-114.

Sullivan RM and Gratton A (2002b) Behavioural effects of excitotoxic lesions of ventral medial prefrontal cortex in the rat are hemisphere-dependent. Brain Res 927:69-79.

Sullivan RM and Gratton A (1999) Lateralized effects of medial prefrontal cortex lesions on neuroendocrine and autonomic stress responses in rats. J Neurosci 19:2834-2840.

Sullivan RM and Gratton A (1998) Relationships between stress-induced increases in medial prefrontal cortical dopamine and plasma corticosterone levels in rats: role of cerebral laterality. Neuroscience 83:81-91.

Sullivan RM and Szechtman H (1995) Asymmetrical influence of mesocortical dopamine depletion on stress ulcer development and subcortical dopamine systems in rats: implications for psychopathology. Neuroscience 65:757-766.

Svingos AL, Periasamy S and Pickel VM (2000) Presynaptic dopamine D(4) receptor localization in the rat NAc shell. Synapse 36:222-232.

Swanson LW and Petrovich GD (1998) What is the amygdala? Trends Neurosci 21:323-331.

Swerdlow NR, Braff DL, Masten VL and Geyer MA (1990a) Schizophrenic-like sensorimotor gating abnormalities in rats following dopamine infusion into the nucleus accumbens. Psychopharmacology 101:414-420.

Swerdlow NR, Caine SB and Geyer MA (1992) Regionally selective effects of intracerebral dopamine infusion on sensorimotor gating of the startle reflex in rats. Psychopharmacology 108:189-195.

Swerdlow NR and Koob GF (1987) Lesions of the dorsomedial nucleus of the thalamus, medial prefrontal cortex and pedunculopontine nucleus. Effects on locomotor activity mediated by nucleus accumbens-ventral pallidal circuitry. Brain Res 412:233-243.

Swerdlow NR, Mansbach RS, Geyer MA, Pulvirenti L, Koob GF and Braff DL (1990b) Amphetamine disruption of prepulse inhibition of acoustic startle is reversed by depletion of mesolimbic dopamine. Psychopharmacology 100:413-416.

Taber MT and Fibiger HC (1995) Electrical stimulation of the prefrontal cortex increases dopamine release in the nucleus accumbens of the rat: modulation by metabotropic glutamate receptors. J Neurosci 15:3896-3904.

Tai CT, Cassaday HJ, Feldon J and Rawlins JNP (1995) Both electrolytic and excitotoxic lesions of nucleus accumbens disrupt latent inhibition of learning in rats. Neurobiol Learn Mem 64:36-48.

Takagishi M and Chiba T (1991) Efferent projections of the infralimbic (area 25) region of the medial prefrontal cortex in the rat: an anterograde tracer PHA-L study. Brain Res 566:26-39.

Tanaka M, Yoshida M, Emoto H and Ishii H (2000) Noradrenaline systems in the hypothalamus, amygdala and locus coeruleus are involved in the provocation of anxiety: basic studies. Eur J Pharmacol 405:397-406.

Terreberry RR and Neafsey EF (1987) The rat medial frontal cortex projects directly to autonomic regions of the brainstem. Brain Res Bull 19:639-649.

Thiel CM and Schwarting RK (2001) Dopaminergic lateralisation in the forebrain: relations to behavioural asymmetries and anxiety in male Wistar rats. Neuropsychobiology 43:192-199.

Thierry AM, Tassin JP, Blanc G and Glowinski J (1976) Selective activation of the mesocortical dopamine system by stress. Nature 263:242-244.

Trulson ME and Preussler DW (1984) Dopamine-containing ventral tegmental area neurons in freely moving cats: activity during the sleep-waking cycle and effects of stress. Exp Neurol 83:367-377.

Turner BH and Herkenham M (1991) Thalamoamygdaloid projections in the rat: a test of the amygdala's role in sensory processing. J Comp Neurol 313:295-325.

van de Kar LD, Piechowski RA, Rittenhous PA and Gray TS (1991) Amygdaloid lesions: differential effect on conditioned stress and immobilization-induced increases in corticosterone and retinin secretion. Neuroendocrinology 54:89-95.

van der Kooy D, Koda LY, McGinty JF, Gerfen CR and Bloom FE (1984) The organization of projections from the cortex, amygdala, and hypothalamus to the nucleus of the solitary tract in rat. J Comp Neurol 224:1-24.

Vincent SL, Khan Y, Benes FM (1995) Cellular colocalization of dopamine D1 and D2 receptors in the rat medial prefrontal cortex. Synapse 19:112-120.

Vincent SL, Khan Y and Benes FM (1993) Cellular distribution of dopamine D1 and D2 receptors in rat medial prefrontal cortex. J Neurosci 13:2551-2564.

Vuilleumier P, Armony J, Clarke K, Husain M, Driver J and Dolan R (2002) Neural response to emotional faces with and without awareness: event-related fMRI in a parietal patient with visual extinction and spatial neglect. Neuropsychologia 40:2156.

Vuilleumier P, Armony J, Driver J and Dolan R (2001a) Effects of attention and emotion on face processing in the human brain: an event-related fMRI study. Neuron 30:829-841.

Vuilleumier P, Sagiv N, Hazeltine E, Poldrack RA, Swick D, Rafal RD and Gabrieli JD (2001b) Neural fate of seen and unseen faces in visuospatial neglect: a combined event-related functional MRI and event-related potential study. Proc Natl Acad Sci USA 98:3495-3500.

Wadenberg ML, Ericson E, Magnusson O and Ahlenius S (1990) Suppression of conditioned avoidance behavior by the local application of (-)sulpiride into the ventral, but not the dorsal, striatum of the rat. Biol Psychiatry 28:297-307.

Walaas I and Fonnum F (1980) Biochemical evidence for gamma-aminobutyrate containing fibers from the nucleus accumbens to the substantia nigra and ventral tegmental area in the rat. Neuroscience 5:325-336.

Wallace DM, Magnuson DJ and Gray TS (1992) Organization of amygdaloid projections to brainstem dopaminergic, noradrenergic, and adrenergic cell groups in the rat. Brain Res Bull 28:447-454.

Wallace KJ and Rosen JB (2000) Predator odor as an unconditioned fear stimulus in rats: elicitation of freezing by trimethylthiazoline, a component of fox feces. Behav Neurosci 114:912-922.

Wan FJ, Geyer MA and Swerdlow NR (1994) Accumbens D2 modulation of sensorimotor gating in rats: assessing anatomical localization. Pharmacol Biochem Behav 49:155-163.

Wan F-J and Swerdlow NR (1997) The basolateral amygdala regulates sensorimotor gating of acoustic startle in the rat. Neuroscience 76:715-724.

Wan FJ and Swerdlow NR (1993) Intra-accumbens infusion of quinpirole impairs sensorimotor gating of acoustic startle in rats. Psychopharmacology 113:103-109.

Wang J and O'Donnell P (2001) D(1) dopamine receptors potentiate NMDA-mediated excitability increase in layer V prefrontal cortical pyramidal neurons. Cereb Cortex 11:452-462.

Wang RY (1981) Dopaminergic neurons in the rat ventral tegmental area. I. Identification and characterization. Brain Res Rev 3:123-140.

Warburton EC, Mitchell SN, Joseph MH (1996) Calcium dependence of sensitised dopamine release in rat nucleus accumbens following amphetamine challenge: implications for the disruption of latent inhibition. Behav Pharmacol 7:119-129.

Weiner I (2003) The "two-headed" latent inhibition model of schizophrenia: modeling positive and negative symptoms and their treatment. Psychopharmacology 169:157-197.

Weiner I, Gal G and Feldon J (1999) Disrupted and undisruptable latent inhibition following shell and core lesions. Ann N Y Acad Sci 877:723-727.

Weiner I, Gal G, Rawlins JN and Feldon J (1996a) Differential involvement of the shell and core subterritories of the nucleus accumbens in latent inhibition and amphetamine-induced activity. Behav Brain Res 81:123-133.

Weiner I, Tarrasch R and Feldon J (1996b) Basolateral amygdala lesions do not disrupt latent inhibition. Behav Brain Res 72:73-81.

Wepsic JG and Austin GM (1971) The neurophysiological effects of amphetamine upon the cat amygdala. In: Neurobiology of the amygdala (Eleftheriou BE, ed), pp 623-640. New York: Plenum.

West AR and Grace AA (2002) Opposite influence of endogenous dopamine D1 and D2 receptor activation on activity states and electrophysiological properties of striatal neurons: studies combining *in vivo* intracellular recordings and reverse microdialysis. J Neuroscience 22:294-304.

Whalen PJ, Rauch SL, Etcoff NL, McInerney SC, Lee MB and Jenike MA (1998) Masked presentations of emotional facial expressions modulate amygdala activity without explicit knowledge. J Neurosci 18:411-418.

White FJ (1996) Synaptic regulation of mesocorticolimbic dopamine neurons. Annu Rev Neurosci 19:405-436.

White FJ and Wang RY (1984) A10 dopamine neurons: role of autoreceptors in determining firing rate and sensitivity to dopamine agonists. Life Sci 34:1161-1170.

Wolf ME, Galloway MP and Roth RH (1986) Regulation of dopamine synthesis in the medial prefrontal cortex: studies in brain slices. J Pharmacol Exp Ther 236:699-707.

Wolf ME and Roth RH (1987) Dopamine neurons projecting to the medial prefrontal cortex possess release-modulating autoreceptors. Neuropharmacology 26:1053-1059.

Wolf ME and Roth RH (1990) Autoreceptor regulation of dopamine synthesis. Ann NY Acad Sci 604:323-343.

Wright CI, Fischer H, Whalen PJ, McInerney S, Shin LM and Rauch SL (2001) Differential prefrontal cortex and amygdala habituation to repeatedly presented emotional stimuli. Neuroreport 12:379-383.

Wright CI and Groenewegen HJ (1996) Patterns of overlap and segregation between insular cortical, intermediodorsal thalamic and basal amygdaloid afferents in the nucleus accumbens of the rat. Neuroscience 73:359-373.

Wright CI and Groenewegen HJ (1995) Patterns of convergence and segregation in the medial nucleus accumbens of the rat: relationships of prefrontal cortical, midline thalamic, and basal amygdaloid afferents. J Comp Neurol 361:383-403.

Wu YL, Yoshida M, Emoto H and Tanaka M (1999) Psychological stress selectively increases extracellular dopamine in the 'shell', but not in the 'core' of the rat nucleus accumbens: a novel dual-needle probe simultaneous microdialysis study. Neurosci Lett 275:69-72.

Yamamoto BK and Novotney S (1998) Regulation of extracellular dopamine by the norepinephrine transporter. J Neurochem 71:274-280.

Yang CR, Seamans JK and Gorelova N (1999) Developing a neuronal model for the pathophysiology of schizophrenia based on the nature of electrophysiological actions of dopamine in the prefrontal cortex. Neuropsychopharmacology 21:161-194.

Yee BK (2000) Cytotoxic lesion of the medial prefrontal cortex abolishes the partial reinforcemrnt extinction effect, attenuates prepulse inhibition of the acoustic startle reflex and induces transient hyperlocomotion, while sparing spontaneous object recognition memory in the rat. Neuroscience 95:675-689.

Yim CY and Mogenson GJ (1989) Low doses of accumbens dopamine modulate amygdala suppression of spontaneous exploratory activity in rats. Brain Res 477:202-210.

Yim CY and Mogenson GJ (1988) Neuromodulatory action of dopamine in the nucleus accumbens: an in vivo intracellular study. Neuroscience 26:403-415.

Yim CY and Mogenson GJ (1986) Mesolimbic dopamine projection modulates amygdala-evoked EPSP in nucleus accumbens neurons: an in vivo study. Brain Res 369:347-352.

Yim CY and Mogenson GJ (1982) Response of nucleus accumbens neurons to amygdala stimulation and its modification by dopamine. Brain Res 239:401-415.

You ZB, Tzschentke TM, Brodin E and Wise RA (1998) Electrical stimulation of the prefrontal cortex increases cholecystokinin, glutamate, and dopamine release in the nucleus accumbens: an in vivo microdialysis study in freely moving rats. J Neurosci 18:6492-6500.

Young AM, Joseph MH and Gray JA (1993) Latent inhibition of conditioned dopamine release in rat nucleus accumbens. Neuroscience 54:5-9.

Young AMJ and Rees KR (1998) Dopamine release in the amygdaloid complex of the rat, studied by brain microdialysis. Neurosci Lett 249:49-52.

Zahm (1999) Functional-anatomical implications of the nucleus accumbens core and shell subterritories. Ann N Y Acad Sci 877:113-128.

Zahm DS and Brog JS (1992) On the significance of subterritories in the "accumbens" part of the rat ventral striatum. Neuroscience 50:751-767.

Zahrt J, Taylor JR, Mathew RG and Arnsten AF (1997) Supranormal stimulation of D1 dopamine receptors in the rodent prefrontal cortex impairs spatial working memory performance. J Neurosci 17:8528-8535.

Zangrossi H and File SE (1992) Behavioural consequences in animal tests of anxiety and exploration of exposure to cat odour. Brain Res Bull 29:381-388.

Zheng P, Zhang X-X, Bunney BS and Shi W-X (1999) Opposite modulation of cortical *N*-methyl-D-aspartate receptor-mediated responses by low and high concentrations of dopamine. Neuroscience 91:527-535.

Zhou F-M and Hablitz JJ (1999) Dopamine modulation of membrane and synaptic properties of interneurons in rat cerebral cortex. J Neurophysiol 81:967-976.