THE INVOLVEMENT OF DOPAMINE NEUROTRANSMISSION IN MOOD IN HUMANS: ADMINISTRATION OF L-3,4-DIHYDROXYPHENYLALANINE TO HEALTHY VOLUNTEERS

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ABSTRACT

A large body of evidence indicates that dopamine (DA) neurotransmission regulates approach toward rewards and reward-related cues. The best-cited hypothesis proposes that DA accomplishes this by mediating the pleasurable effects of a variety of natural and drug rewards. This "anhedonia hypothesis" has received support from some pre-clinical models of reward and a few drug challenge studies in humans. However, direct assessment of DA's role in mood and other subjective states in healthy humans has been largely limited to the use of psychostimulant drugs, which elevate brain levels of multiple neurotransmitters in addition to DA. This thesis is comprised of one study which examined the effect of more selectively elevated DA neurotransmission, as produced by administration of the immediate DA precursor, L-DOPA, in healthy human volunteers. L-DOPA failed to alter mood and other subjective states. These results add to the evidence that DA neurotransmission does not directly influence mood in healthy humans.

ABRÉGÉ

La contribution précise de récompense et de motivation de la neurotransmission de la dopamine (DA) n'est pas entièrement comprise. La meilleure hypothèse citée propose que la DA forme un trait d'union des effets agréables d'une variété de récompenses naturelles et narcotiques. Cette hypothèse « anhédoniste » a reçu l'appui de quelques modèles précliniques de récompense et de quelques études chez l'humain mettant la drogue en question. Cependant, l'évaluation directe du rôle de la DA sur la disposition et autres états subjectifs chez l'humain en santé a été principalement limitée à l'utilisation de drogues psychostimulantes, ce qui élève le niveau de neurotransmetteurs multiples en plus de la DA dans le cerveau. La présente thèse comprend une étude qui examine l'effet d'une neurotransmission sélectivement plus élevée de la DA, produite par l'administration du précurseur immédiat de la DA, L-DOPA, chez des volontaires en santé. L-DOPA n'a modifié ni disposition ni autres états subjectifs. Ces résultats s'ajoutent à l'évidence la neurotransmission de DA n'influence pas directement la disposition chez l'humain en santé.

INTRODUCTION

1.0 Dopamine biochemistry

Dopamine (DA), norepinephrine (NE) and epinephrine are collectively referred to as catecholamines due to the presence of a common catechol or hydroxylated aromatic ring nucleus in each of the molecules. Catecholamines function as neurotransmitters in the central nervous system and they are also biologically active in a variety of peripheral body tissues. DA, for example, is found primarily in the brain, but also to some extent in the kidneys (Missale et al 1998). Catecholamines share a common biosynthetic pathway, beginning with the essential amino acid phenylalanine (Kuhar et al 2006). Within the liver, phenylalanine is a substrate for phenylalanine hydroxylase (PH). PH adds an hydroxyl group to produce tyrosine. In catecholamine neurons, tyrosine is a substrate for the rate-limiting enzyme in DA synthesis, tyrosine hydroxylase (TH). The addition of the second hydroxl group produces dihydroxyphenylalanine (L-DOPA). L-DOPA, in turn, is a substrate for DOPA decarboxylase, which rapidly converts the precursor into DA. In neurons that release DA, this is the terminal step in catecholamine synthesis. The majority of DA neurons are found in two adjacent and somewhat overlapping brainstem nuclei, the ventral tegmental area (VTA) and the substantia nigra (SN; Kuhar et al 2006). DA neurons from the former area project to a variety of cortical and sub-cortical regions, including the prefrontal cortex, amygdala and ventral striatum (VS), while DA neurons from the latter structure project mainly to the dorsal striatum (Kuhar et al 2006). In other brainstem neurons, catecholamine synthesis does not stop with the formation of DA. Some of these neurons possess the enzyme DA β-hydroxylase (DßH), which converts DA into NE, while a minority of others also possess the enzyme phenylethanolamine N-methyltransferase, which converts NE into epinephrine (Kuhar et al 2006). Catecholamine synthesis in the periphery involves the same enzymes.

Of particular relevance to the present discussion are the storage, release and post-synaptic signalling features of the DA system. DA is most commonly synthesized in the pre-synaptic terminal of DA neurons, though synthesis also occurs in the cell body. Following DA synthesis in the cytosol, the neurotransmitter is actively transported into vesicles via the vesicular monoamine transporter (VMAT). DA release can be "phasic" which occurs in response to increases in the firing rate of DA neurons or "tonic" which is not activity-dependent and contributes to the basal level of DA present in synaptic and extra-synaptic areas (Grace et al 2007). Synaptic DA levels are generally regulated by pre-synaptic DA release and post-release clearance mechanisms. The latter involves reuptake of DA into the pre-synaptic terminal by the DA transporter (DAT) and ultimately its degradation into inactive metabolites by the enzyme monoamine oxidase (MAO). In most brain regions, DA can also be metabolized in an extraneuronal fashion by the enzyme catechol-O-methyltransferase (COMT) which is present in the synaptic cleft. Clearance by COMT is the dominant mechanism in the prefrontal cortex and clearance by DAT is the dominant mechanism in the striatum (Matsumoto et al 2003). DA exerts its post-synaptic effects by binding to one of the five different DA receptor subtypes (Missale et al 1998). These are divided into two major families, the D1-like (D1 and D5) and D2-like receptors (D2, D3 and D4). All of the DA receptors are metabotropic receptors that signal through the creation of second messenger molecules, such as cAMP, which influence a variety of chemical cascades that in turn affect downstream targets such as gene transcription and receptor activity. DA receptors can be found pre-synaptically where they function as autoreceptors that regulate DA release or post-synaptically where they convey molecular signals to other neurons (Kuhar et al 2006).

2.0 Dopamine, reward and the anhedonia hypothesis

A series of groundbreaking studies conducted in the 1950s with electrical brain stimulation (EBS) served as a critical catalyst for investigations into the

neurobiology of reward and motivation. This approach was combined with a new operant conditioning paradigm to explore the potential involvement of cortical and sub-cortical structures in reward and punishment. Skinner's behavioural theory of reinforcement (Skinner 1938) allowed for the objective measurement of behavioural responses related to reward and punishment. Briefly, a reinforcer was defined as any stimulus that served to increase the probability and frequency of actions that preceded its presentation (Skinner 1938). Thus, the frequency with which an animal responded by pressing a lever in a box, called instrumental responding, could be taken as a measure of the "rewarding effects" of a stimulus presented to that animal. In a landmark study, Olds and Milner (1954) combined EBS and operant conditioning and found that rats responded more frequently and vigorously on the operant lever in order to self-stimulate a variety of cortical and sub-cortical regions, including the lateral hypothalamus, cingulate cortex and brainstem. In stark contrast, though, rats did not increase their level of responding in order to receive EBS in other areas of the brain, including motor and sensory cortex. These and other observations made it clear that the brain contains specific anatomical substrates and circuits that correspond to basic biological drives, including sex, drinking and feeding (Coons et al 1965; Glickman & Schiff 1967; Olds 1956; Olds & Milner 1954).

Work over the next decade led to the suggestion that a specific neurotransmitter mediated reward processing in the brain. Evidence for this proposition came from anatomical and pharmacological studies involving the EBS self-administration paradigm. First, the mechanism by which EBS of the median forebrain bundle enhanced instrumental self-administration behaviour in rats appeared to involve stimulation of noradrenergic fibers of passage (Dresse 1966) and the consequent release of NE from these nerve terminals (Stein & Wise 1969). Second, drugs that altered NE neurotransmission produced dramatic changes in EBS self-administration behaviour. Specifically, drugs that augmented NE neurotransmission, such as amphetamine and MAO inhibitors, increased instrumental responding for EBS (Poschel 1969; Stein 1964), while drugs that

attenuated NE neurotransmission, such as DβH inhibitors, reserpine and alpha methylparatyrosine (AMPT), decreased instrumental responding for EBS (Gibson et al 1970; Wise & Stein 1969). These and other observations formed the foundation of the NE hypothesis of reward (Poschel & Ninteman 1963; Stein 1964).

Around the same time, DA was gaining attention as a potential neurotransmitter. Although DA was initially believed to function only as a precursor for NE synthesis, this view started to change when Arvid Carlsson and colleagues (1957) found that L-DOPA restored motor activity in reserpine-treated rabbits. While this study left open the possibility that L-DOPA produced its effect by elevating NE rather than DA levels, two subsequent studies provided strong evidence that DA was in fact the critical mediator. Tissue culture experiments revealed that L-DOPA more potently elevates DA levels compared to NE levels in the brain (Carlsson et al 1958) and that these neurotransmitters are synthesized in discrete, non-overlapping brain regions (Carlsson et al 1957). Since the latter study demonstrated that DA is synthesized to a high degree in the striatum and this brain region was known to be an important substrate for motor function, it was proposed that DA neurotransmission plays a key role in motor activity. The efficacy of L-DOPA as a treatment for the motor symptoms in Parkinson's disease (PD) strengthened this notion further.

Following the general acceptance of DA as a neurotransmitter, critical evidence emerged suggesting that it too was involved in reward. DA was first implicated in reward function based on the observation that electrode placement in brainstem nuclei that contained the cell bodies of DA neurons was sufficient to generate robust self-administration of EBS in rats (Crow 1972a; Crow 1972b; German & Bowden 1974). Next came the observation that systemic amphetamine administration enhanced instrumental responding for EBS when electrodes were placed in one of the loci of DA neurotransmission, the SN, as well as in the hypothalamus, which was believed to contain mainly noradrenergic fibers of passage (Phillips & Fibiger 1973). A role for DA in this behavioural phenomenon

was suspected since both isomers of amphetamine were equally effective at increasing instrumental behaviour for EBS despite the fact that d-amphetamine exerted more potent effects on NET compared to l-amphetamine. These two major findings from the EBS studies prompted the creation of a broader catecholamine hypothesis of reward, which posited that both DA and NE were important neurotransmitters for reward function.

Investigators then conducted carefully controlled anatomical and pharmacological studies over the next decade in pursuit of confirmatory evidence for this new hypothesis. Surprisingly, though, a role for NE in mediating the rewarding effects of EBS was not supported by most of the evidence. Drugs that attenuated NE neurotransmission appeared to disrupt instrumental responding for EBS by altering arousal rather than reward function (Fouriezos et al 1978; Franklin 1978; Roll 1970). For example, in the study by Roll (1970), the DβH inhibitor disulfiram dramatically altered arousal as evidenced by the observation that rats fell asleep during brief pauses between EBS self-administration sessions. The key finding from this study was that disulfiram-treated rats resumed normal levels of instrumental responding for EBS when awoken by handling and placed back in front of the lever, suggesting that the rewarding efficacy of EBS remained the same, but that the lower levels of instrumental responding previously reported (Wise & Stein 1969) were due to the sedative effects of the drug. Furthermore, specific lesions to the NE fibers of the dorsal component of the median forebrain bundle failed to disrupt instrumental responding for EBS when the electrode was placed in either the locus coeruleus, a major locus of NE cell bodies in the brainstem, or the lateral hypothalamus, a structure densely innervated by NE fibers (Corbett et al 1977). A subsequent anatomical study determined that the cell bodies of NE neurons in the locus coeruleus did not overlap with the locations of electrodes in this region of the brainstem that supported self-administration of EBS (Corbett & Wise 1979). Since EBS did not appear to depend on activation of NE neurotransmission to generate rewarding effects, the role of this neurotransmitter in reward function started to come into question.

In contrast, similar experimental approaches provided some support for the idea that DA neurotransmission was an important part of the mechanism by which EBS produced its rewarding effects, though this was not without controversy. A series of drug challenge studies demonstrated that DA receptor antagonists strongly disrupted performance in EBS paradigms (Fibiger et al 1976; Franklin 1978; Franklin & McCoy 1979; Gallistel & Karras 1984; Rolls et al 1974; Wauquier et al 1972; Zarevics et al 1977). Initially, this performance deficit was attributed to an effect of DA receptor antagonists on motor activity rather than reward function (Fibiger 1978; Fibiger et al 1976; Rolls et al 1974). For example, in the study by Fibiger et al (1976), the DA receptor antagonists haloperidol and pimozide both significantly reduced instrumental responding for EBS of the lateral hypothalamus. Since the number of lever presses dropped following drug administration and remained depressed throughout the test session, the authors concluded that the performance deficit was due to an effect of the drugs on motor activity. If the DA receptor antagonists disrupted performance because of an effect on reward function, the authors reasoned, an extinction curve characterized by an initial increase, followed by a progressive decrease, in instrumental responding should have been observed.

Subsequent studies that were specifically designed to tease apart the effect of DA receptor antagonists on motor activity and reward function provided crucial evidence to suggest that these drugs were in fact altering reward function while leaving the capacity to respond intact. A notable series of experiments by Fouriezos et al (1978) provided compelling evidence. In the first experiment, the DA receptor antagonists pimozide and butaclomol both significantly and gradually decreased the instrumental response rate for EBS of the lateral hypothalamus. The resemblance of the pattern of drug effects to the extinction effect produced by reducing the current intensity of EBS implied that DA receptor antagonists reduced the rewarding effects of EBS in a similar manner. Indeed, the parallel between the effects of drugs and non-reward on instrumental responding is very important when interpreting the results of self-administration studies, since

it is assumed that the animal gradually ceases to respond for a reward while under the influence of a drug because it comes to experience that reward in the same way that it experiences non-reward. In the second experiment, Fouriezos et al (1978) observed that pimozide-treated rats initially responded at higher rates when they came back into contact with the lever after a brief timeout period that followed the initial extinction phase, though no EBS was available. The high levels of responding suggested that the pimozide-induced performance decrement in the previous experiment was not due to a drug-induced motor effect. In the third experiment, Fouriezos et al (1978) used a different self-administration paradigm to extract specific measures of motor and reward performance. In this paradigm, rats had to run down a long alley in order to press a lever and receive EBS. Running latency provided a measure of the ability to initiate a motor sequence, while running speed and self-stimulation rate provided measures of the ability to execute complex motor sequences. At the beginning of the extinction trials, pimozide-treated rats had normal running latencies, running speeds and self-stimulation rates when compared to vehicle-treated controls. However, as the session progressed, running latencies increased and both running speeds and self-stimulation rates decreased significantly compared to controls. These results suggested that pimozide-treated rats decrease self-administration of EBS due to an effect of pimozide on the rewarding efficacy of EBS and not because of a drug-induced inability to initiate and execute motor responses.

The high rates of instrumental responding required in EBS self-administration studies are a major limitation in reward studies, since even minor drug effects on motor performance can result in severe performance impairments. Consequently, an approach called the reward summation function was developed in an effort to reduce the impact of high response rate requirements and enhance the ability to detect the effect of experimental manipulations on reward function (Edmonds & Gallistel 1974; Edmonds & Gallistel 1977; Edmonds et al 1974). Using this approach, pimozide was shown to dramatically reduce the rewarding effects of EBS as evidenced by a shift to the right of the reward summation curve

(Franklin 1978; Franklin & McCoy 1979; Gallistel & Karras 1984), providing further evidence that DA receptor antagonists disrupt instrumental responding for EBS by impacting reward function rather than motor activity. Further pharmacological support for the proposition that DA was involved in EBS came from observations that DA augmenting drugs enhanced the rewarding efficacy of EBS as evidenced by dramatic increases in instrumental response rates or responding to lower current thresholds (Crow 1970; Gallistel & Karras 1984; German & Bowden 1974; Phillips & Fibiger 1973; Poschel & Ninteman 1964; Stephens & Herberg 1975). Additionally, an anatomical mapping study conducted by Corbett and Wise (1980) found that EBS self-administration was best supported by placement of electrodes in parts of the VTA, a brainstem region containing dense populations of DA neurons. Collectively, these studies showed that DA neurotransmission was an important component of the brain circuitry that mediates the rewarding effects of EBS.

Concurrent with studies investigating EBS reward mechanisms, researchers began pursuing the idea that DA neurotransmission was also involved in mediating the rewarding effects of a variety of drug and natural rewards. The first indication that abused drugs tapped into the brain's reward system came from the demonstration that amphetamine modulated responding for EBS (Stein 1964). Subsequently, it was shown that laboratory animals responded vigorously in an instrumental self-administration paradigm to receive injections of psychostimulant drugs (Pickens & Harris 1968). The possibility that direct activation of DA neurotransmission mediated the rewarding effects of psychostimulant drugs came from three separate lines of evidence. First, the DA receptor agonists apomorphine and piribedil sustained self-administration (Baxter et al 1974; Davis & Smith 1977; Wise et al 1976; Yokel & Wise 1978). Second, lesions to the ascending fibers of the DA pathway effectively eliminated the ability of psychostimulant drugs to sustain self-administration (Lyness et al 1979; Roberts et al 1977; Roberts et al 1980). Third and perhaps most striking was the ability of DA receptor antagonists to severely disrupt the prototypical high rates of

instrumental responding for psychostimulant drugs and DA receptor agonists in the self-administration paradigm (Baxter et al 1974; Davis & Smith 1977; de Wit & Wise 1977; Risner & Jones 1976; Risner & Jones 1980; Wilson & Schuster 1972; Yokel & Wise 1975; Yokel & Wise 1976; Yokel & Wise 1978). For example, de Wit and Wise (1977) trained rats to lever press for cocaine and then tested these animals following pre-treatment with one of a wide range of doses of pimozide or saline. A very distinctive pattern of drug effects emerged in this study. Specifically, rats treated with the lowest dose of pimozide significantly increased their rate of responding compared to saline-treated rats, whereas rats treated with the high doses of pimozide dramatically increased their rate of responding at the outset of testing, but then eventually stopped responding altogether. The increased responding for cocaine observed in the rats treated with a low dose of pimozide suggested that the animals no longer found the previous dose of cocaine sufficiently rewarding since this behavioural pattern mirrored the commonly observed effect of lowering the dose of a psychostimulant drug. In this case, laboratory animals will increase their rate of responding in an effort to maintain a consistent blood level of the drug and to presumably optimize the drug's rewarding effects. Additionally, the behavioural pattern of rats treated with high doses of pimozide, characterized by an initial robust increase in responding followed by a complete cessation of responding, resembled the extinction effect observed when animals previously trained to receive a reward are tested under conditions of non-reward. This pattern was also taken to suggest that the rewarding effects of cocaine were severely diminished by pre-treatment with a DA receptor antagonist. Combined with the growing evidence that neither lesions to the ascending fibers of the NE system (Roberts et al 1977) nor administration of NE antagonists (Davis & Smith 1975; Davis & Smith 1977; de Wit & Wise 1977; Risner & Jones 1976; Risner & Jones 1980; Yokel & Wise 1975; Yokel & Wise 1976; Yokel & Wise 1978) compromised self-administration of DA-augmenting drugs, it became clear that DA, but not NE, played an important role in mediating the rewarding effects of psychostimulant drugs. Following

observations that DA receptor antagonists disrupted instrumental responding for natural rewards, such as food and water (Gerber et al 1981; Wise & Schwartz 1981; Wise et al 1978a; Wise et al 1978b), in much the same way that these drugs disrupted instrumental responding for artificial rewards, such as psychostimulant drugs and EBS, it appeared likely that DA neurotransmission was a common element in the brain circuitry that responded to nearly all rewards.

Wise (1982) integrated the findings from investigations into the effect of DA receptor antagonists on EBS, drug and natural reward and formulated the anhedonia hypothesis of DA's involvement in reward. The main purpose of the anhedonia hypothesis was to explain the robust performance-lowering effect of DA receptor antagonists on instrumental responding for a variety of rewards. The major thrust of the hypothesis was that DA receptor antagonists profoundly altered an animal's level of "motivational arousal" by disrupting the rewarding effects of unconditioned stimuli as well as conditioned stimuli associated with reward. By rewarding impact, Wise meant the ability of these stimuli to produce a hedonic reaction and to reinforce behaviours that led to the acquisition and consumption of the unconditioned stimulus. The hypothesis was developed on the basis of several major behavioural patterns that emerged from studies examining the effect of DA receptor antagonists on reward. First, the response pattern of animals following pre-treatment with DA receptor antagonists resembled that of animals tested under the condition of non-reward. Specifically, in extinction trials involving omission of a previously reinforced reward, normal drug-free animals will initially respond at a high rate, but after failing to receive the reward, these animals gradually cease to respond. The same response pattern was observed following pre-treatment with DA receptor antagonists despite the fact that the reward was still available. Wise argued that this similarity in response patterns, termed "extinction mimicry," occurred because animals treated with DA receptor antagonists came to experience the reward the same way as a normal drug-free animal came to experience non-reward. In other words, it appeared that the reward had lost its hedonic value following treatment with DA receptor antagonists.

Results from studies involving psychostimulant drugs were particularly striking since consistently elevated rates of responding were observed in animals pre-treated with low doses of DA receptor antagonists, while an initial large burst of responding followed by a complete cessation of responding was seen in animals pre-treated with high doses of DA receptor antagonists. This was taken to suggest that DA receptor antagonism reduced the rewarding effects of these drugs and, consequently, animals increased responding in order to acquire a higher dose of the drug and presumably achieve the same magnitude of rewarding effect that previously occurred at the lower drug dose. The effects of DA receptor antagonism on instrumental responding for reward also resembled two other phenomena observed following non-reward in normal, drug-free animals: spontaneous recovery and decreased resistance to extinction. The former refers to a renewal of high rates of responding at the beginning of a new test session following an extinction trial, while the latter refers to a cumulative reduction in responding over successive extinction trials. Again, the similar behavioural patterns were taken to support the proposition that animals treated with DA receptor antagonists essentially valued the reward as much as a normal drug-free animal valued non-reward. These features were also important because they helped to rule out the alternative hypothesis that DA receptor antagonists affected instrumental responding by impairing motor activity rather than altering reward function. Second, at least with natural rewards, animals required multiple exposures to reward while under the influence of a DA receptor antagonist before a performance decrement was observed (Mason et al 1980; Wise et al 1978a). Additionally, normal levels of instrumental responding could be reinstated in these same animals if they were tested in a drug-free condition that occurred between test sessions involving pre-treatment with a DA receptor antagonist (Mason et al 1980). Taken together, these results demonstrated that animals needed to experience the reward while under the influence of a DA receptor antagonist before the drug would impact instrumental responding for that reward. It appeared that animals decreased instrumental responding in this situation

because the hedonic value of the reward was lower following DA blockade in comparison to a drug-free state. Third, decreased instrumental responding could be observed in the same animal following a transfer from several days of experience in a non-reward condition to a test session where the animal was pre-treated with a DA receptor antagonist (Gerber et al 1981; Wise et al 1978a). This transfer effect was strongly suggestive of the existence of a shared property between the experience of non-reward and the experience of reward following pre-treatment with a DA receptor antagonist. Fourth, DA receptor antagonists also progressively diminish the ability of conditioned stimuli to elicit instrumental responding for reward (Gray & Wise 1980).

A major argument against the anhedonia hypothesis was that DA receptor antagonists disrupted instrumental responding for reward not through an effect on reward per se, but rather by compromising motor function (Fibiger et al 1976). However, this was essentially ruled out by the fact that high instrumental response rates were initially observed following pre-treatment with DA receptor antagonists and again during tests of spontaneous recovery. Moreover, in experiments specifically designed to separate motor and reward functions, motor activity only decreased in animals pre-treated with DA receptor antagonists following several trials of normal responding and, most importantly, experience with the reward (Fouriezos et al 1978; Wise et al 1978a).

Although the main intent of the anhedonia hypothesis was to account for DA's role in reward as objectively measured by operant conditioning paradigms in laboratory animals, Wise and colleagues also openly speculated about a potential role of DA as a mediator of the subjective state of pleasure (Wise 1980; Wise 1982; Wise et al 1978b). This seemed to be a logical extension of the framework they presented to explain the modulatory effect of DA receptor antagonists on instrumental responding for reward, since hedonic reactions, including pleasure, presumably occur following interaction with rewards. This proposition also found some support from contemporary studies in humans, specifically the observations that DA receptor antagonists diminished

amphetamine-induced euphoria in drug users (Gunne et al 1972; Jonsson 1972; Jonsson et al 1971) and induced dysphoria in some patients with schizophrenia (Singh 1976). Moreover, humans reported feeling pleasure-like effects following EBS of brain regions innervated by DA neurons (Heath 1972). Thus, by the beginning of the 1980s, several distinct lines of evidence were suggestive of a role of DA neurotransmission in mediating positive mood states, such as pleasure.

3.0 Dopamine and positive mood states

3.1 Pre-clinical evidence against the anhedonia hypothesis

With respect to DA's involvement in pleasure, the anhedonia hypothesis was considered speculative. To the extent that it is possible to model and measure such subjective experiences in laboratory animals, none of the original experiments whose results form the basis of the anhedonia hypothesis actually did so. The proposition that DA mediated the pleasure associated with rewards mainly rested on the assumptions that pleasure always follows reward consumption and animals experience pleasure in the same way that humans do. Wise (1985) himself admitted this in a reformulation of the anhedonia hypothesis: "the assumption that pleasure is attenuated by neuroleptics is thus not a data-based assumption in the traditional sense. It is largely based on personal subjective experience; pleasure is a state which usually seems to accompany reward (Wise 1985, page 182)." Clearly, the question of what role, if any, DA plays in positive mood states needs to be answered with evidence from studies in humans. Nevertheless, recent pre-clinical research has helped address this question by striving to elucidate the exact nature of DA's involvement in reward, motivation and hedonic processes.

Two lines of indirect evidence and one direct line of evidence have emerged from pre-clinical studies which cast doubt on the hypothesized role of DA as a mediator of positive mood states, including pleasure. First, the timing of DA neuron firing and DA release do not coincide with reward consumption. If DA mediated pleasure, DA neuron firing should occur just prior to, and DA

release during, interaction with a reward that is currently being consumed since that is the time when pleasure would be expected to be maximal. Experimental findings, though, do not support this prediction. For example, DA release in the nucleus accumbens (NAcc), a region of the VS that is densely innervated by VTA DA neurons, typically increases and then peaks prior to consumption of food or drug reward (Gratton & Wise 1994; Kiyatkin & Gratton 1994; Kiyatkin & Stein 1996; Kiyatkin et al 1993; Phillips et al 1993; Richardson & Gratton 1996). Moreover, following multiple exposures, DA release begins to increase and then peak after presentation of visual or auditory cues that have been repeatedly paired with food or drug reward (Gratton & Wise 1994; Phillips et al 1993; Richardson & Gratton 1996). Similarly, electrophysiological studies have found that the firing rate of midbrain DA neurons does not increase following reward consumption, except when the reward is presented unexpectedly or during the initial stages of learning a task that involves reward (Ljungberg et al 1991; Ljungberg et al 1992; Mirenowicz & Schultz 1994; Schultz et al 1993; Schultz & Romo 1990). After extensive learning, midbrain DA neurons fire robustly and consistently to the presentation of cues associated with reward, but no increases in the firing rate are observed in response to the reward itself (Ljungberg et al 1991; Ljungberg et al 1992; Mirenowicz & Schultz 1994; Schultz et al 1993; Schultz & Romo 1990). Second, a growing body of evidence implicates DA in aversive motivation (Ikemoto & Panksepp 1999; Salamone 1994a). Briefly, DA is released in the NAcc in response to a variety of aversive stimuli or stressful conditions, including foot or tail shock, tail pinch, restraint, forced exercise and anxiogenic drugs (Abercrombie et al 1989; Bertolucci-D'Angio et al 1990; D'Angio et al 1987; Imperato et al 1992; Imperato et al 1991; Kalivas & Duffy 1995; McCullough & Salamone 1992; Scatton et al 1988; Sorg & Kalivas 1991; Young et al 1993). Similar to reward-predicting conditioned stimuli, cues that are repeatedly presented in association with aversive stimuli also come to elicit DA release in the NAcc (Young et al 1993). Moreover, DA receptor antagonists impair avoidance responding (Ader & Clink 1957; Beninger et al 1980; Cook & Weidley 1957;

Davidson & Weidley 1976; White et al 1992). Taken together, these findings demonstrate that DA neurotransmission is not uniquely involved in reward processing or appetitive motivation.

The biggest pre-clinical challenge to the proposition that DA is a neurochemical mediator of pleasure has come from a series of studies using the taste reactivity test, which assesses the affective responses of animals after ingestion of sweet and bitter solutions. Briefly, the pattern of orofacial responses typically observed after an animal ingests a sweet solution are thought to reflect a positive evaluation akin to "liking" (hedonic reactions) whereas orofacial responses observed after an animal ingests a bitter solution are thought to reflect a negative evaluation akin to "disliking" (aversive reactions; Berridge & Robinson 1998). Similar orofacial responses are observed across species, including humans (Berridge & Robinson 1998). Though it allows for a more direct assessment of how neurotransmitters, such as DA, affect hedonic processes in animal models, it is important to note that the taste reactivity test is not an index of subjective pleasure. In humans, orofacial responses to taste stimuli are highly correlated with subjective ratings of "liking" and "disliking," but they also occur normally in anencephalic infants (Berridge 1996; Steiner 1973). These and other findings suggest that the neural mechanisms underpinning orofacial responses to taste stimuli might be independent from those that mediate subjective hedonic experiences. Thus, while the taste reactivity test is a useful tool to investigate the neurobiology of basic hedonic processes, it can only provide limited insight into the role of DA in positive mood states, which are inherently subjective experiences.

With this caveat aside, several studies have examined the influence of experimentally-altered DA neurotransmission on positive and negative affect as measured by the taste reactivity test. According to the anhedonia hypothesis, methods that augment DA neurotransmission should increase hedonic reactions to sweet tastes, whereas methods that attenuate DA neurotransmission should do the opposite. The pattern of results, however, contravenes these predictions. DA

augmenting drugs, such as amphetamine and apomorphine, do not increase the number of hedonic reactions (Tindell et al 2005; Treit & Berridge 1990; Wyvell & Berridge 2000), nor does a robust elevation of DA levels with a hyperdopaminergic DAT knockout mouse (Pecina et al 2003). DA receptor antagonists, such as pimozide and haloperidol, fail to decrease the number of hedonic reactions (Pecina et al 1997; Treit & Berridge 1990) as do neurochemical-induced lesions of DA projections that substantially deplete DA levels (Berridge & Robinson 1998; Berridge et al 1989). Collectively, these findings suggest that DA neurotransmission is not involved in the neural mechanisms that underpin basic hedonic processes.

3.2 Neuropsychiatric disorders and mood

Three neuropsychiatric disorders in which DA dysfunction is thought to be a component of the disease pathophysiology provide some insight into the potential role of DA neurotransmission in mood. First, altered DA neurotransmission has been implicated in the pathophysiology of depression and bipolar disorder, though no simple association between low DA levels and depressive symptoms has been demonstrated (Dunlop & Nemeroff 2007; Leyton 2009). Rather, there is some evidence to suggest that DA dysfunction is present in a sub-group of depressed patients who exhibit psychomotor retardation (Meyer et al 2001; Meyer et al 2006). Second, PD, which involves pronounced decreases in DA neurotransmission and profound motor deficits, is also associated with mood and motivational disturbances (Aarsland et al 2005; Weintraub et al 2005). These latter symptoms likely emerge secondary to motor problems and are typically ameliorated with DA replacement therapy. Intriguingly, a small percentage of medicated PD patients develop a hypomanic-like syndrome, commonly called "DA dysregulation syndrome" (DDS), which is characterized by mood elevation, compulsive drug-taking and dramatic increases in goal-directed behaviours (Giovannoni et al 2000). As with bipolar mania, the precise contribution of increased DA neurotransmission to positive mood is not entirely clear. However,

one recent study with PD patients found an association between the magnitude of L-DOPA-induced DA release in the VS and subjective ratings of "drug wanting," but not "drug liking," suggesting that augmented DA neurotransmission does not contribute directly to the increased positive mood observed in PD patients with DDS (Evans et al 2006). Third, patients with schizophrenia, a psychiatric disorder thought to involve abnormally elevated striatal DA neurotransmission, do not experience euphoria as the anhedonia hypothesis would predict. However, these patients often complain of lowered mood and motivation following treatment with antipsychotic drugs, an effect sometimes referred to as "neuroleptic-induced dysphoria" (Lewander 1994; Singh 1976; Singh & Smith 1973) and these symptoms correlate with the degree of medication-induced DA D2 receptor blockade (Bressan et al 2002; de Haan et al 2000; Mizrahi et al 2007). Collectively, these lines of clinical evidence provide only weak support for the proposition that DA neurotransmission is involved in mood regulation.

3.3 Dopaminergic agents: selectivity and mechanisms of action

DA neurotransmission can be experimentally increased in humans through the administration of a variety of drugs. For the purpose of this review, these drugs will be divided into three main classes: specific DA augmenters, non-specific DA augmenters and DA receptor agonists. In comparison to the non-specific DA augmenters, drugs such as L-DOPA and tolcapone are relatively devoid of effects on neurotransmitters other than DA. L-DOPA, the gold standard in the treatment of PD, is the immediate metabolic precursor to DA. L-DOPA administration increases DA synthesis in the brain, though the magnitude of this effect is more pronounced in animal models of PD compared to healthy intact animals (Rodriguez et al 2007). Surprisingly, L-DOPA administration does not appear to have a significant effect on NE synthesis in vivo in laboratory animals (Bartholini et al 1969; Butcher & Engel 1969; Doshi & Edwards 1981; Goshima et al 1991; Schoenfeld & Uretsky 1973). Tolcapone elevates synaptic levels of DA through its inhibition of COMT, an enzyme that degrades catecholamines

from functionally active neurotransmitters to inactive metabolites (Karoum et al 1994; Matsumoto et al 2003). This pharmacological mechanism more selectively enhances DA neurotransmission when tolcapone is administered in conjunction with L-DOPA, as evidenced by its clinical utility as an adjunctive therapy in PD (Ceravolo et al 2002). The psychostimulant drugs amphetamine and methylphenidate and the antidepressant drugs bupropion and nomifensine are included in the non-specific DA augmenter category since these drugs also significantly affect the levels of neurotransmitters other than DA. Amphetamine is a potent enhancer of pre-synaptic DA release via a combination of distinct mechanisms, including blockade of DAT and VMAT as well as inhibition of MAO (Sulzer et al 2005). Amphetamine also increases levels of NE and serotonin through its actions on VMAT and MAO along with blockade of their respective transporters, NET and SERT (Heal et al 2009; Sulzer et al 2005). Methylphenidate, a derivative of amphetamine and a commonly prescribed medication for the treatment of attention deficit hyperactivity disorder, robustly elevates DA and NE levels via a reuptake inhibition mechanism (Heal et al 2009). An abundance of pre-clinical evidence suggests that bupropion, used clinically as an antidepressant and smoking cessation aid, is a reuptake inhibitor of DA and NE, and to a lesser extent serotonin, as well as a nicotinic acetylcholine receptor antagonist (Arias et al 2009; Paterson 2009). However, in humans the extent to which its mechanism of action depends on elevated DA levels remains a matter of controversy since therapeutic doses administered to healthy volunteers do not appear to significantly alter striatal DA levels (Egerton et al 2010; Paterson 2009). Nomifensine, once a promising candidate antidepressant that had to be withdrawn from clinical use due to its abuse liability and side effects, is a reuptake inhibitor of DA and NE and, to a lesser extent, serotonin (Brogden et al 1979; Hanks 1977).

A plethora of DA receptor agonists are commercially available, but only a handful of these (apomorphine, bromocriptine, pramipexole and pergolide) have been used in carefully designed drug challenge studies probing the involvement of

DA neurotransmission in mood regulation in healthy humans. DA receptor agonists are mainly used in the treatment of PD (Kvernmo et al 2008), though a case has been made for their use either alone or as an adjunct to antidepressants in the treatment of depression (Willner 1997). Most DA receptor agonists exert their pharmacological effects by binding to several distinct types of DA receptors. For example, pergolide and apomorphine are considered mixed DA receptor agonists since these drugs bind with relatively high affinities to both the D1-like and D2-like families of DA receptors (Kvernmo et al 2008). In contrast, bromocriptine and pramipexole have considerably higher receptor binding affinities for the D2-like compared to D1-like receptor family (Kvernmo et al 2008). Pramipexole is the most selective D2 receptor agonist currently available since it is essentially devoid of activity at D1 and D5 receptors (Kvernmo et al 2008). Receptor binding promiscuity is a major limitation of the DA receptor agonists for two reasons. First, with the exception of pharmacological subtraction paradigms in which the behavioural effects of a mixed D1/D2 agonist are subtracted from the behavioural effects of a more selective D2 receptor agonist to uncover those behavioural effects most likely mediated through D1 receptor transmission, there is no way at present to accurately localize specific behavioural effects to specific sub-types of DA receptors in studies with humans. Second, receptor binding promiscuity is unfortunately not only limited to the DA family of receptors, since many of these agonists also have some affinity for serotonin and NE receptors, though typically to a much lesser extent.

3.4 The effects of experimentally-increased DA neurotransmission on mood and subjective states in humans

If the anhedonia hypothesis of DA function were correct, drugs that augment DA neurotransmission should produce increases in positive mood states. Early support for this hypothesis came from the clinical observations that repeat, high dose L-DOPA administration induced a hypomanic-like state in bipolar depressed patients (Bunney et al 1971; Goodwin et al 1970; Murphy et al 1971)

and in a subset of patients with PD (Calne et al 1969; O'Brien et al 1971) and the drug reversed the "pseudodepressions" that developed following reserpine administration (Degkwitz et al 1960). Around the same time, a series of studies demonstrated that neuroleptics could diminish the euphorigenic effects of amphetamine (Jonsson 1972; Jonsson et al 1971), pointing to DA as the neurochemical mediator of these mood-elevating effects. Collectively, these separate lines of evidence raised the possibility that increased DA neurotransmission could be a direct mediator of positive mood states in humans.

In healthy subjects, by far the most robust and consistent pattern of effects on mood and other subjective states has been observed in studies that have administered the psychostimulant drugs amphetamine or methylphenidate. Amphetamine potently and consistently increases positive mood, as indexed by the POMS measure Elated-Depressed and the VAS items "Rush," "High," and "Euphoria," and arousal, as indexed by the POMS measure Energetic-Tired and the VAS items "Excited," "Energetic," "Mind-Racing," and "Alert" (Acheson & de Wit 2008; Brauer & de Wit 1997; Chait 1993; de Wit et al 2002; Leyton et al 2007). For example, in a placebo-controlled study of 39 healthy volunteers conducted by Chait et al (1993), moderate doses of amphetamine (7.5 to 20 mg) produced marked effects on the POMS (increased scores on the Anxiety, Vigor, Friendliness, Elation and Arousal sub-scales), ARCI (increased scores on the BG, A, MBG and LSD scales) and VAS (increased scores on the items "Stimulated," "High," and "Anxious"). The same pattern of drug effects is typically seen following administration of methylphenidate (for a review see Kollins et al 2001), though there is some evidence to suggest that the magnitude of drug effects, particularly on measures of euphoria, is higher for amphetamine compared to methylphenidate when equivalent doses are administered (Brown et al 1978; Chait 1994; Martin et al 1971; Rush et al 2001; Smith & Davis 1977). More pronounced effects on measures of euphoria are generally observed following administration of higher doses of methylphenidate (for example, Volkow et al 1999; Volkow et al 2006). Collectively, these studies demonstrate the robust

mood-elevating and stimulant effects of the psychostimulant drugs amphetamine and methylphenidate. Since both drugs exert their pharmacological effects on multiple neurotransmitter systems, it is impossible to attribute the observed changes in positive mood to changes in the activity of one neurotransmitter system, such as DA.

In comparison, the non-specific DA augmenters bupropion and nomifensine have considerably weaker and far more variable effects on mood and other subjective states in healthy humans. Bupropion is structurally similar to amphetamine, but within the range of doses administered clinically or in experimental studies with humans (50 to 400 mg), it does not have the same constellation or magnitude of effects (Acheson & de Wit 2008; Miller & Griffith 1983; Peck et al 1979; Rush et al 1998). Five published studies involving healthy humans have examined the effects of bupropion on mood and other subjective states. In general, high doses of bupropion (200 to 400 mg) produce mild stimulant-like effects, but are generally devoid of euphorigenic effects, whereas low doses (below 200 mg) do not have any observable effects on mood and other subjective states (Acheson & de Wit 2008; Gobbi et al 2003; Miller & Griffith 1983; Peck et al 1979; Rush et al 1998). For example, in a combined sample of 33 smokers and non-smokers who were otherwise neurologically and psychiatrically healthy, Acheson and de Wit (2008) found that a low dose of bupropion (150 mg) did not have any significant effects on the POMS, ARCI or DEQ. In contrast, a high dose of bupropion (300 mg) significantly increased scores on the POMS Arousal subscale and the DEQ items "Feel Drug," "Like Drug" and "Want More Drug." Notably, neither dose of bupropion had an effect on three putative measures of euphoria: the POMS subscale Elated-Depressed, the ARCI subscale MBG and the DEQ item "High." Two studies have found hints of an effect of bupropion on measures of euphoria (Gobbi et al 2003; Rush et al 1998), but these findings are neither particularly strong nor consistent. In the first study, Gobbi et al (2003) used a chronic dosing regimen whereby healthy volunteers administered one of two doses of bupropion daily for one week. Relative to placebo,

participants who ingested 150 mg per day had significantly higher scores on the POMS Arousal subscale and a trend toward higher scores on the POMS Elated-Depressed subscale. It is interesting to note that the higher dose of bupropion (300 mg per day) did not significantly affect either of these subscales. In a study of healthy volunteers who were administered escalating doses of bupropion on separate days following a washout period, Rush et al (1998) found that participants who ingested high doses of bupropion (200 and 400 mg) had significantly increased scores on the DEQ item "Elated" compared to the placebo session. However, neither of these doses significantly altered scores on the POMS subscale Elated-Depressed, thus calling into question the robustness of bupropion's effect on euphoria. In contrast to bupropion, studies assessing the effect of nomifensine on mood and other subjective states in healthy humans are more consistent. All of the four published placebo-controlled studies were conducted in the 1980s to assess nomifensine's potential clinical viability as an antidepressant drug. In these studies, VAS were employed as part of a larger battery of cognitive and physiological measures. None of these studies found statistically significant differences between nomifensine (50 to 100 mg) and placebo for any of the VAS measures (Culig et al 1983; Hamilton et al 1983; Siegfried & Taeuber 1984; Taeuber et al 1979). Taken together, the studies reviewed above suggest that potent and non-selective DA augmenters, such as the psychostimulant drugs amphetamine and methylphenidate, have strong and consistent mood-elevating and stimulant-like effects in healthy humans. In contrast, the relatively weaker and non-selective DA augmenters, such as bupropion and nomifensine, are devoid of euphorigenic effects and only one of these (bupropion) has mild stimulant-like effects in healthy humans.

Several studies have been conducted to assess the effect of DA receptor agonists on mood and other subjective states in healthy volunteers (summarized in table 1). A majority of these studies did not set out to investigate the role of DA neurotransmission in mood regulation, but rather employed mood and subjective state measures in order to control for the potential confound of drug side effects

on cognitive task performance. In many of these studies, VAS were commonly used to measure dimensions of mood related to arousal and less emphasis was placed on assessment of positive mood dimensions. Additionally, a few of these studies administered novel mood rating scales, such as the Adjective Mood Scale (AMS; Muller et al 1998). This is a major limitation of these studies since it is difficult to determine which items on these unique scales correspond to measurements of positive mood and how they might compare to positive mood items on more frequently used and validated instruments such as the VAS and POMS. Despite these limitations, a consistent picture has emerged from the group of studies which assessed the effect of DA receptor agonists on mood and other subjective states in healthy humans. In general, the mixed D1 and D2 receptor agonists apomorphine and pergolide and the relatively selective D2 receptor agonists pramipexole and bromocriptine do not produce mood-elevating effects in healthy humans. Only one study has been conducted in healthy volunteers with apomorphine (Blin et al 1990). In this study, nine healthy men were administered a subcutaneous dose of 10 μg per kg. Compared to placebo treatment, apomorphine did not significantly alter VAS ratings pertaining to arousal and positive mood. Similarly, in the four placebo-controlled studies which administered pergolide to healthy volunteers, none found strong evidence of a mood-elevating effect (Breitenstein et al 2006; Muller et al 1998; Roesch-Ely et al 2005; Upadhyaya et al 2003). In fact, two of these studies (Muller et al 1998; Roesch-Ely et al 2005) detected a mild mood-lowering effect of pergolide as assessed by the AMS. Since neither of these studies employed VAS to measure potential side effects, such as nausea, dizziness and drowsiness, it is impossible to determine if these contributed to the mild mood-lowering effect that was detected. The only hint of a mild mood-elevating effect of pergolide came from a study by Breitenstein et al (2006) in which 0.1 mg of pergolide was administered daily for five days to a group of 40 healthy men and women just prior to training on an associative learning task. Acute administration of pergolide did not significantly affect mood as measured by the Positive and Negative Affect Scale. However,

compared over all of the training sessions, participants in the pergolide group had stable measures of positive mood whereas participants in the placebo group started out with similar positive mood scores and these consistently decreased during each of the subsequent training sessions. The authors interpreted this as evidence of flattened affect following inhibition of phasic DA release via stimulation of D2 autoreceptors with a low dose of pergolide. Alternatively, it is possible that chronic administration of pergolide produced a mild mood-elevating effect which was protective against the general mood-lowering effect of the cognitive task training.

The relatively selective DA D2 receptor agonists bromocriptine and pramipexole appear to have mild mood-lowering effects at most. Of the seven published studies which examined the effect of bromocriptine on mood and other subjective states, only one found evidence of a mild mood-lowering effect (Mehta et al 2001 *vs*. Abduljawad et al 1998; Cools et al 2007; Franken et al 2008; Micallef et al 2009; Muller et al 1998; Roesch-Ely et al 2005). In the study by Mehta et al (2001) in a group of 20 healthy men, a low dose of bromocriptine (1.25 mg) significantly decreased scores on the VAS factor "Contentedness" compared to the placebo session. This could be a spurious finding since this effect was not detected in any of the other studies which either administered bromocriptine at the same dose (Abduljawad et al 1998; Cools et al 2007) or at a higher dose (2.5 mg; Franken et al 2008; Micallef et al 2009; Muller et al 1998; Roesch-Ely et al 2005). Of the three published studies which examined the effect of the most selective D2 receptor agonist pramipexole on mood and other subjective states in healthy humans, only one found evidence of a mild mood-lowering effect of the drug (Hamidovic et al 2008). In this study, low (0.25 mg) and high (0.5 mg) doses of pramipexole were administered to a group of 10 healthy men and women. The high dose of pramipexole, but not the low dose, significantly decreased scores on the ARCI subscales related to euphoria and energy, the POMS subscale Vigor and the empirically derived factor Positive Mood. The authors hypothesized that the sedative side effect of pramipexole was

responsible for the observed mood-lowering effect of the drug, possibly through an elaborate mechanism involving stimulation of pre-synaptic DA D3 autoreceptors and a consequent disruption of NE neurotransmission. Further evidence for a non-specific effect of pramipexole on positive mood dimensions came from a study by Pizzagalli et al (2008) in which 0.5 mg of the drug was administered to a sample of 32 healthy men and women. A mild mood-lowering effect of the drug was observed as evidenced by significantly increased VAS ratings of "Mental Slowness" and "Tension" following pramipexole compared to placebo, but these effects were no longer significant after scores were adjusted for adverse drug effects. Taken together, the results of the studies which administered the relatively selective DA D2 receptor agonists bromocriptine and pramipexole suggest that these drugs at most have a mild mood-lowering effect in healthy humans. The effect appears to be non-specific and likely due to the side effect profile of both drugs.

Compared to pharmacological challenge studies conducted with non-specific DA augmenters and DA D2 receptor agonists, relatively fewer studies have been conducted with specific DA augmenters, such as L-DOPA and tolcapone. Nevertheless, the reported studies have consistently demonstrated a lack of effect of elevated DA neurotransmission on mood and other subjective states. For example, in a study of 25 healthy men, Roussos et al (2009) did not detect an effect of 200 mg of tolcapone on any of the POMS subscales, nor was a differential drug effect observed when participants were classified according to the presence of a polymorphism coding for either a high or low activity form of the COMT enzyme. Two other studies which administered tolcapone to healthy volunteers failed to find an effect of the drug on mood and other subjective states (Apud et al 2007; Giakoumaki et al 2008). Similarly, of the three studies which administered low doses of L-DOPA to healthy humans, none found evidence of a drug effect on mood and other subjective states (Andreu et al 1999; Micallef et al 2009; Pine et al 2010). These studies are limited by the use of only one dose of L-DOPA and dissimilar measures of mood and other subjective states across studies.

Specifically, the study by Andreu et al (1999) did not measure any positive mood dimensions and the more recent studies by Micallef et al (2009) and Pine et al (2010) did not have overlapping VAS measures or other standardized mood rating scales. Thus, there is an obvious need for additional studies to more fully characterize the effect of the selective DA augmenter L-DOPA on mood and other subjective states in healthy humans.

Table 1. The effect of dopamine-enhancing agents on positive mood states in healthy humans.

Drug	Mechanism of Action	Dose	Study	n	Mood Measures	Effect on Positive Mood	Details
Apomorphine	Mixed D1/D2 agonist	10 µg/kg	Blin (1990)	9	VAS	≠	
Bromocriptine	D2 agonist	1.25 mg	Morcom (2010)	32	VAS	NR	VAS items corresponding to motivation and energy No drug effects on any measure
		2.5 mg	Micallef (2009)	12	VAS	≠	
		2.5 mg	Franken (2008)	21	VAS PANAS	≠	
		1.25 mg	Cools (2007)	22	VAS	≠	
		2.5 mg	Roesch-Ely (2005)	40	AMS	≠	
		1.25 mg	Mehta (2001)	20	VAS	↓	Bromocriptine ↓ VAS Contented and ↑ VAS Sad and Antagonistic scores
		1.25 mg	Abduljuwad (1998)	12	VAS	≠	
		2.5 mg	Muller (1998)	16	AMS STAI	≠	Not clear what these scales actually measure
L-DOPA	Selective DA augmenter	100 mg	Micallef (2009)	12	VAS	≠	
		150 mg	Pine (2010)	14	VAS	≠	
		200 mg	Andreu (1999)	22	VAS	NR	Only measured VAS "Drowsiness"
Lisuride	D2 agonist	0.2 mg	van der Post (2004)	12	VAS	↓	Adverse effects, such as nausea, vomiting and headache No sedative effect
Pergolide	Mixed D1/D2 agonist	0.1 mg	Breitenstein (2006)	40	PANAS	≠	Drugs administered daily for 5 days No acute drug effect (assessed on day 1) Pergolide group had stable positive mood during training sessions on days 2-5, whereas placebo group had ↓ positive mood during training sessions on all days
		0.1 mg	Roesch-Ely (2005)	40	AMS	≠	
		0.05 mg	Upadhyaya (2003)	15	VAS	≠	
		0.1 mg	Muller (1998)	16	AMS STAI	↓	Not clear what these scales actually measure
Pramipexole	D2 agonist	0.5 mg	Micallef (2009)	12	VAS	≠	
		0.25 mg, 0.5 mg	Hamidovic (2008)	10	POMS ARCI DEQ	↓	0.5 mg ↓ euphoria and energy as measured by ARCI, ↓ POMS vigor and positive mood and ↓ item "like drug" on DEQ
		0.5 mg	Pizzagalli (2008)	32	VAS	≠	
Tolcapone	COMT inhibitor	200 mg	Roussos (2009)	25	POMS	≠	No COMT genotype X drug interaction effect for any POMS item
		200 mg	Giakoumaki (2008)	23	POMS	≠	No COMT genotype X drug interaction effect for any POMS item
		100 mg day 1 followed by 200 mg x 6 days	Apud (2007)	47	POMS	≠	No COMT genotype X drug interaction effect for any POMS item

For the purpose of this table, measures of positive mood include the ARCI MBG subscale, POMS “Elated” subscale, and the VAS items “High,” “Rush,” “Euphoria,” “Contentedness,” “Like Drug,” and “Good Effects.” Abbreviations: AMS, Adjective Mood Scale. ARCI, Addiction Research Center Inventory. NR, not reported. PANAS, Positive and Negative Affect Scales. POMS, Profile of Mood States. VAS, Visual Analog Scales. STAI, State Trait Anxiety Inventory.

3.5 The effects of experimentally-decreased DA neurotransmission on mood in humans

DA neurotransmission can be experimentally decreased in humans in two main ways, either through pharmacological blockade of DA receptors or through a reduction of DA biosynthesis. The latter can be accomplished by administering drugs that inhibit tyrosine hydroxylase (AMPT) or through dietary depletion of amino acids, such as tyrosine and phenylalanine, which are essential for DA synthesis (the acute phenylalanine tyrosine depletion method; APTD). In humans, the first evidence of an association between decreased DA neurotransmission and lowered mood came from a series of clinical observations in the 1970s with schizophrenic patients. In some patients, administration of antipsychotic drugs quickly led to the development of a constellation of negative subjective symptoms, including dislike of the medication, apathy, hostility and depression (Singh 1976; Singh & Smith 1973; Van Putten & May 1978). This syndrome was dubbed "neuroleptic-induced dysphoria" (Singh & Smith 1973). Some evidence suggests that these negative subjective symptoms are related to the sedative effects that arise from the pharmacological action of older antipsychotic drugs on the histamine and NE neurotransmitter systems (Lewander 1994). However, these symptoms have also been observed following administration of newer antipsychotic drugs which are relatively devoid of sedative side effects (Voruganti et al 2000), suggesting that some other mechanism is responsible for the mood-lowering effect of antipsychotic drugs. In support of the proposition that altered DA neurotransmission contributes to the effect of antipsychotic drugs on mood in schizophrenic patients, three neuroimaging studies have found evidence of a positive association between the striatal D2 receptor occupancy of these drugs and negative mood symptoms in schizophrenic patients (Bressan et al 2002; de Haan et al 2000; Mizrahi et al 2007). Collectively, these clinical findings provide some, albeit weak, support for the notion that DA neurotransmission plays a role in positive mood regulation.

An abundance of studies have been conducted in healthy humans to examine the effect of relatively selective DA receptor antagonists, such as haloperidol and amisulpride, on aspects of cognitive function and mood (table 2). Since some of these studies were more concerned with the effect of DA receptor blockade on cognitive function, an emphasis was placed on measuring drug side effects rather than positive mood states. In fact, several studies failed to measure positive mood at all (for example, Mehta et al 1999; Mehta et al 2004; Mehta et al 2005; Mehta et al 2008). In the studies that measured a much broader set of mood dimensions, none of the DA receptor antagonists consistently affected positive mood. For example, neither amisulpride nor sulpiride were found to alter positive mood in the six studies that used these drugs (Jocham et al 2011; Legangneux et al 2000; McClelland et al 1990; Peretti et al 1997; Ramaekers et al 1999; van der Post et al 2004). In the two studies that administered chlorpromazine to healthy humans and examined its effect on mood, one found evidence of a mood-lowering effect (McClelland et al 1990), while the other did not (Hughes et al 1999). In contrast to three lower doses of pimozide which did not produce any subjective effects (Brauer & de Wit 1995; Brauer & de Wit 1996), administration of a high dose of pimozide (8 mg) significantly reduced scores on the POMS "Elated-Depressed" and "Vigor" subscales and a composite measure of positive mood (Brauer & de Wit 1997). In a large sample of healthy humans, Saeedi et al (2006) found evidence of a mild mood-lowering effect of haloperidol. In this study, participants who received a high dose of haloperidol (5 mg) had significantly decreased VAS "Contentment" scores compared to those who received placebo. VAS "Contentment" scores did not differ between participants who received lower doses of haloperidol (1 mg or 3 mg) and those who received placebo. Notably, none of these doses of haloperidol produced a sedative effect. This is an important point because the other three studies that found evidence of a mood-lowering effect of haloperidol also observed a drug-induced sedative effect (Liem-Moolenaar et al 2010; Magliozzi et al 1985; McClelland et al 1990). From these results it is unknown whether haloperidol-induced sedation contributed to the

observed mood-lowering effect, since the aforementioned studies did not examine this with an analysis of covariance. Nevertheless, these positive findings must be considered against a backdrop of several studies that failed to detect an effect of haloperidol on positive mood (for example, Enggasser & de Wit, 2001; Krystal et al 1999; Wachtel et al 2002). Taken together, these results suggest that DA receptor blockade, at least at the moderate level accomplished in these studies, does not appreciably modulate positive mood states in healthy humans. The possibility remains that a higher magnitude of DA receptor blockade must be achieved before an effect on positive mood will be observed in healthy humans. However, this will be difficult to test in future studies because of the risk of adverse drug effects at higher doses.

By far the most consistent results have come from studies that decreased DA neurotransmission by reducing biosynthesis of the neurotransmitter. Administration of AMPT to healthy humans has been shown to robustly decrease positive mood and arousal in several studies (Laruelle et al 1997; Verhoeff et al 2001; Verhoeff et al 2003; though see Krahn et al 1999; McCann et al 1995; Zimmerman et al 1996). However, since AMPT is a competitive inhibitor of tyrosine hydroxylase, it attenuates DA and NE levels to a similar extent. Consequently, the mood-lowering effect of the drug cannot be solely ascribed to changes in DA tone. In contrast, studies conducted with the APTD method, which more selectively decreases DA neurotransmission, have largely failed to detect a mood-lowering effect of the manipulation except following a psychosocial stressor. Specifically, only two out of ten published studies observed a mild mood-lowering effect following APTD compared to the balanced condition (Harmer et al 2001; McLean et al 2004). However, in a study by Leyton et al (2000), participants had significantly lower scores on the POMS "Elated-Depressed" subscale in the APTD condition when mood was measured following stress induction with a public speaking task. Thus, decreased DA neurotransmission appears to produce a mild mood-lowering effect at best and perhaps only when it occurs in the context of an environmental stressor. The

possibility remains that a higher magnitude of DA depletion is required before a robust and consistent mood-lowering effect is observed in healthy humans, since, in the absence of a drug or psychological challenge, APTD might reduce synaptic DA levels by only 10-20% (Montgomery et al 2003). Collectively, the results from drug challenge studies that have attenuated DA neurotransmission in healthy humans suggest that DA only plays a minor role, if any, in the regulation of positive mood states.

Table 2. The effect of relatively selective dopamine-decreasing agents on positive mood states in healthy humans.

Dopamine-decreasing agent	Mechanism of Action	Study	Dose	n	Mood Measures	Effect on Positive Mood	Details/Other Effects
AMPT	Tyrosine hydroxylase inhibitor	McCann (1995)	6000 mg	41	POMS VAS	≠	Sedative effect
		Laruelle (1997)	8000 mg	9	VAS	↓	Sedative effect
		Verhoeff (2001)	4500 mg	6	POMS VAS	↓	Sedative effect
		Verhoeff (2003)	5200 mg	6	POMS VAS	↓	Sedative effect
APTD	Dietary depletion of dopamine precursors	Leyton (2000)		26	POMS VAS	↓	Only significant following psychosocial stressor No sedative effect
		Harmer (2001)		12	VAS	↓	No sedative effect
		Harrison (2002)		13	POMS VAS	≠	No sedative effect
		Grevet (2002)		12	POMS VAS	≠	No sedative effect
		McLean (2004)		39	VAS	↓	No sedative effect
		Harrison (2004)		13	VAS	≠	No sedative effect
		Lythe (2005)		12	VAS	≠	No sedative effect
		Mehta (2005)		14	VAS	NR	Sedative effect
		Vrshek-Schallhorn (2006)		37	POMS VAS	≠	No sedative effect
		Scholes (2007)		12	VAS	≠	No sedative effect
		Mann (2008)		16	VAS	≠	No sedative effect
		van Ruitenbeek (2009)		16	VAS	NR	No sedative effect
		Newhouse (2010)		11	POMS	≠	No mood-lowering effect following psychosocial stressor
Amisulpiride	D2/D3 antagonist	Mattila (1996)	50 and 200 mg	18	VAS	NR	No sedative effect
		Peretti (1997)	50 and 100 mg	12	VAS	≠	50 mg had sedative effect
		Ramaekers (1999)	50 and 400 mg X 5 days	21	ARCI	≠	
		Legangneux (2000)	50 mg	17	VAS	≠	No sedative effect
		Barrett (2004)	300 mg	32	VAS	NR	No sedative effect
		Jocham (2011)	200 mg	16	VAS	≠	No sedative effect
Chlorpromazine	D2 antagonist	McClelland (1990)	50 mg	12	VAS	↓	Sedative effect
		Danion (1992)	12.5 and 25 mg	72	VAS	NR	No sedative effect
		Mattila (1994)	50 mg	12	VAS	NR	Sedative effect
		Green (1999)	50, 75 and 100 mg	12	VAS	NR	Sedative effect (75 and 100 mg)
		Hughes (1999)	50 mg	12	VAS	≠	Sedative effect
		McCartan (2001)	100 mg	46	VAS	NR	Sedative effect
		Barrett (2004)	100 mg	32	VAS	NR	Sedative effect
Haloperidol	D2 antagonist	Magliozzi (1985)	0.125 mg/kg (IV) 0.5 mg/kg	16	POMS ARCI	↓	Sedative effect
		McClelland (1990)	3 mg	12	VAS	↓	Sedative effect

		Malaspina (1994)	2 mg (IM)	7	POMS	≠	Sedative effect
		Vitello (1997)	2 mg	12	VAS	NR	No sedative effect
		Lynch (1997)	2, 4 and 6 mg	15	VAS	NR	4 mg dose produced sedative effect
		Peretti (1997)	1 and 2 mg	12	VAS	≠	No sedative effect
		Williams (1997)	0.5 and 1 mg (IV)	166	VAS	≠	No sedative effect
		Meyer-Lindenberg (1997)	300 mg	12	VAS	NR	No sedative effect
		Kumari (1998)	5 mg	57	UMACL	≠	Sedative effect?
		Abduljawad (1998)	3 mg	12	VAS	≠	No sedative effect
		Krystal (1999)	5 mg	20	VAS	≠	Sedative effect
		Beuzen (1999)	3 mg/day X 4 days	14	VAS	≠	Sedative effect
		Ramaekers (1999)	4 mg X 5 days	21	ARCI	↓	↓ ARCI MBG subscale scores on day 5 only
		Legangneux (2000)	2 mg	17	VAS	≠	No sedative effect
		McCartan (2001)	1 mg (IV)	48	VAS	NR	No sedative effect
		Enggasser (2001)	3 mg	17	VAS ARCI	≠	No sedative effect
		Wachtel (2002)	3 mg	18	POMS VAS ARCI	≠	Sedative effect
		Saeedi (2006)	1, 3 and 5 mg	59	POMS VAS	↓	5 mg ↓ VAS "Contentment" No sedative effect
		Wezenberg (2007)	2.5 mg	15	VAS	≠	No sedative effect
		D'Souza (2008)	0.057 mg/kg	28	VAS	≠	No sedative effect
		Franken (2008)	2 mg	21	VAS	≠	
		Liem-Moolenar (2010)	3 mg	12	VAS	↓	Sedative effect
Pimozide	D2 antagonist	Brauer (1995)	4 mg	12	POMS VAS ARCI	≠	No sedative effect
		Brauer (1996)	1 and 2 mg	10	POMS VAS ARCI	≠	No sedative effect
		Brauer (1997)	8 mg	12	POMS VAS ARCI	↓	No sedative effect
Sulpiride	D2 antagonist	McClelland (1990)	400 mg	12	VAS	≠	No sedative effect
		Meyer-Lindenberg (1997)	300 mg	12	VAS	NR	No sedative effect
		Mehta (1999)	200 and 400 mg	34	VAS	NR	No sedative effect
		van der Post (2004)	400 mg	12	VAS	≠	No sedative effect
		Mehta (2004)	400 mg	35	VAS	NR	No sedative effect
		Mehta (2005)	400 mg	18	VAS	NR	No sedative effect
		Mehta (2008)	200 and 400 mg	10	VAS	NR	No sedative effect
		Morcom (2010)	400 mg	32	VAS	NR	VAS items assessed motivation and energy No drug effects observed

For the purpose of this table, measures of positive mood include the ARCI MBG subscale, POMS “Elated” subscale, and the VAS items “High,” “Rush,” “Euphoria,” “Contentedness,” “Like Drug,” and “Good Effects.” Unless otherwise stated, drugs were administered orally. Only relatively selective DA antagonists are included in this table; drugs with significant activity at other neurotransmitter receptors are omitted. Abbreviations: ARCI, Addiction Research Center Inventory. NR, Not Reported. POMS, Profile of Mood States. UMACL, UWIST Adjective Checklist. VAS, Visual Analog Scales.

3.6 The effects of experimentally-decreased DA neurotransmission on the mood-elevating effects of abused drugs in humans

Concomitant administration of DA decreasing treatments and abused drugs is another approach that has been used to evaluate the potential role of DA in positive mood states. Most studies have been negative, though, and this lack of influence has been observed with multiple methods for diminishing DA neurotransmission (table 3). While early studies found intriguing evidence that DA-decreasing drugs could blunt the euphorigenic effects of high doses of amphetamine in regular users of the drug (Gunne et al 1972; Jonsson 1972; Jonsson et al 1971), this finding could not be replicated in subsequent studies with healthy volunteers (Brauer & de Wit, 1995; Brauer & de Wit 1996; Brauer & de Wit 1997; Jacobs & Silverstone 1986; Leyton et al 2007; though see McTavish et al 1999) or cocaine users (Evans et al 2001; Haney et al 2001; Leyton et al 2005; Nann-Vernotica et al 2001; Sherer et al 1989; Stine et al 1997; though see Romach et al 1999). It is important to note that all of the studies with healthy volunteers administered lower doses of amphetamine than the original in-patient studies, thus leaving open the possibility that DA blockade only modulates the euphorigenic effects of psychostimulant drugs when these are administered at relatively high doses. Additionally, despite the fact that the doses of DA receptor antagonists used in a majority of these studies falls within the clinical range that is associated with a high degree of DA receptor blockade, it is still possible that a higher magnitude of DA receptor blockade is required in order to diminish the euphorigenic effects of commonly abused drugs. This possibility will be difficult to test in future studies since higher doses of all currently available experimental methods to decrease DA neurotransmission are likely to produce significant unwanted side effects (Brauer & de Wit 1997; Evans et al 2001; Leyton et al 2000). In general, though, experimentally decreased DA neurotransmission does not appear to alter the mood-elevating effects of psychostimulant drugs or other commonly abused drugs, including ketamine (Krystal et al 1999), THC (D'Souza et al 2008), ethanol (Barrett et al 2008; Enggasser & de Wit 2001; Leyton et al

2000; though see Ahlenius et al 1973), and nicotine (Casey et al 2006; Chausmer et al 2003; Venugopalan et al 2010). Collectively, these findings do not support the proposition that DA is a key mediator of positive mood states, including pleasure.

Table 3. The effect of dopamine-decreasing drugs on the mood-elevating effects of abused drugs in humans.

Dopamine Blocker	Abused Drug	Study	Participants	Mood Measures	Effect on Positive Mood	Details/Other Effects
Ecopipam (Selective D1/D5 antagonist)	Cocaine	Romach (1999)	15 cocaine-dependent volunteers	VAS	↓	Acute dosing High dose ecopipam ↓ cocaine-induced increases in VAS "Good Drug Effect" and "High" scores
	Cocaine	Haney (2001)	10 cocaine-dependent volunteers	VAS	↑	Ecopipam ↑ cocaine-induced ratings of VAS "High" and "Good Drug Effect" Chronic dosing
	Cocaine	Nann-Vernotica (2001)	10 cocaine-dependent volunteers	VAS POMS ARCI	≠	Chronic dosing
	Nicotine	Chausmer (2003)	10 volunteers with cocaine and nicotine dependence	VAS	≠	
Flupenthixol (Non-selective DA antagonist)	Cocaine	Evans (2001)	31 cocaine abusers	VAS	≠	
Fluphenazine (Non-selective DA antagonist)	AMPH	Brauer (1995)	12 healthy volunteers	VAS POMS ARCI	≠	
Haloperidol (D2/D3 antagonist)	Cocaine	Sherer (1989)	5 cocaine abusers	VAS ARCI	≠	
	Ketamine	Krystal (1999)	20 healthy volunteers	VAS	≠	
	THC	D'Souza (2008)	28 healthy volunteers and cannabis users	VAS	≠	
	Ethanol	Enggasser (2001)	17 social drinkers	ARCI VAS	≠	Haloperidol blocked alcohol-induced euphoria in sub-group of drinkers who reported stimulant effects following ethanol
	METH	Wachtel (2002)	35 healthy volunteers	VAS POMS ARCI	≠	
	MDMA	Liechti (2000)	14 healthy volunteers	OAV-ASC	↓	
Pimozide (D2 antagonist)	AMPH	Jonsson (1972)	24 AMPH abusers	VAS	↓	Acute and chronic (1 week) effects
	AMPH	Jacobs (1986)	12 healthy volunteers	VAS	≠	
	AMPH	Brauer (1995)	12 healthy volunteers	VAS POMS ARCI	≠	
	AMPH	Brauer (1996)	10 healthy volunteers	VAS POMS ARCI	≠	Low dose pimozide (4 mg)
	AMPH	Brauer (1997)	12 healthy volunteers	VAS POMS ARCI	≠	High dose pimozide (8 mg)
APTD	AMPH	McTavish (1999)	15 healthy volunteers	VAS	↓	

	Ethanol	Leyton (2000)	39 healthy volunteers	VAS POMS	≠	
	METH	McTavish (2001)	16 healthy volunteers		≠	
	Nicotine	Casey (2006)	15 men with nicotine dependence	VAS POMS	≠	
	AMPH	Leyton (2007)	14 healthy volunteers	VAS POMS	≠	
	Cocaine	Leyton (2005)	8 cocaine abusers	VAS POMS	≠	APTD ↓ cocaine craving
	Ethanol	Barrett (2008)	16 social drinkers	VAS	≠	
AMPT (tyrosine hydroxylase inhibitor)	AMPH	Jonsson (1971)	29 AMPH abusers	VAS	↓	High single dose AMPH (IV 200 mg)
	Ethanol	Ahlenius (1973)	10 healthy volunteers	Observer	↓	Alcohol-induced increases in "Elation" and "Happy" were blocked by AMPT (observer ratings only; effect not found with self ratings)
	Cocaine	Stine (1997)	10 cocaine abusers	VAS POMS	≠	

For the purpose of this table, measures of positive mood include the ARCI MBG subscale, POMS “Elated” subscale, and the VAS items “High,” “Rush,” “Euphoria,” “Contentedness,” “Like Drug,” and “Good Effects.” Abbreviations: AMPH, amphetamine. AMPT, alpha-methylparatyrosine. APTD, acute phenylalanine tyrosine depletion. ARCI, Addiction Research Center Inventory. MDMA, 3,4-Methylenedioxymethamphetamine or ecstasy. METH, methamphetamine. OAV-ASC, Altered State of Consciousness rating scale. POMS, Profile of Mood States. THC, tetrahydrocannabinol. VAS, visual analog scales.

4.0 Individual differences: dopamine, approach-related personality traits and mood

4.1 Dopamine and approach-related personality traits

In the early 1970s, Jeffrey Gray profoundly altered the course of psychology research when he postulated the existence of three basic behavioural systems that underpinned personality (Gray 1973). Since some evidence linked specific brain circuits to each of these basic behavioural systems, individual differences in the reactivity of these systems were proposed to result from inter-individual variability in their underlying neurobiology. Gray (1973) speculated that individual differences in personality traits emerged from individual differences in the neurobiological substrates that directly mediated the reactivity of these basic behavioural systems. Gray's behavioural activation system (BAS) and later Panksepp's foraging-expectancy command system (Panksepp 1986b) were proposed to influence an animal's sensitivity to incentive stimuli in its environment and to regulate its approach to reward. On the basis of accumulating evidence from EBS and neurochemistry studies that implicated DA neurotransmission and elements of its associated reward circuitry in the control of approach and exploratory behaviour and incentive motivation (Bardo et al 1996; Beninger 1983; Berridge & Robinson 1998; Salamone et al 2007), several researchers have more recently postulated the involvement of DA neurotransmission in "approach-related personality traits" in humans, such as novelty seeking, sensation seeking, impulsivity and extraversion (Cloninger 1987; Depue & Collins 1999; Zuckerman & Kuhlman 2000).

The most compelling evidence collected to date in support of this proposition has come from a pre-clinical model of approach-related personality traits. In laboratory animals, novelty seeking behaviour can be assessed with several performance-based tests, such as open field and place preference tests. Since a high degree of inter-individual variability exists on these performance measures, rats can be categorized as either "high responders" (HR) or "low responders" (LR; Dellu et al 1996; Piazza et al 1989). The HR model is thought to

be analogous to measures of approach-related personality traits in humans, since both tools appear to assess approach and exploratory behaviours (Dellu et al 1996). Neurochemistry and electrophysiology experiments using this model have yielded evidence indicating that HR rats are characterized by a midbrain DA system that is more reactive than LR rats. Specifically, HR rats show significantly higher NAcc DA release following either acute or chronic administration of psychostimulant drugs compared to their LR counterparts (Chefer et al 2003; Hooks et al 1992; Hooks et al 1991). HR rats have been shown to have higher VTA DA neuron firing rates (Marinelli & White 2000) and NAcc D1 receptor density (Hooks et al 1994) compared to LR rats. D2 receptor density has been found to be lower in the NAcc of HR compared to LR rats (Hooks et al 1994), which further suggests that DA neurotransmission is enhanced in this group of rats since these receptors are thought to function mainly as autoreceptors that control DA release. Using a different experimental approach, a recent study found that D2/D3 receptor binding was also significantly reduced in "impulsive" compared to "non-impulsive" rats (Dalley et al 2007). To the extent that these pre-clinical models are analogous to human personality traits, these results suggest that midbrain DA neurotransmission might be elevated in humans who possess high levels of approach-related personality traits compared to those who possess lower levels of these traits.

In humans, two main lines of indirect evidence link variability in approach-related personality traits to individual differences in DA neurotransmission. First, several neuroimaging studies have found evidence of associations between approach-related personality traits and indices of DA neurotransmission. In brief, the magnitude of striatal DA release induced by amphetamine or alcohol challenge has been shown to positively correlate with individual differences in personality traits, such as novelty seeking and impulsivity (Boileau et al 2003; Boileau et al 2006; Buckholtz et al 2010a; Buckholtz et al 2010b; Leyton et al 2002). Two recent studies have also found evidence of baseline differences in DA neurotransmission between individuals

who score high or low on scales measuring approach-related personality traits, such as impulsivity and sensation seeking (Buckholtz et al 2010b; Gjedde et al 2010). Of particular interest is the study by Buckholtz and colleagues (2010) who found an association between D2/D3 receptor binding in the VTA and SN and impulsivity, as measured by Barrett's Impulsivity Scale, as well as the magnitude of amphetamine-induced striatal DA release. Based on the results of a model they developed which incorporated these findings, the authors proposed that "high impulsive" individuals have fewer D2 autoreceptors in the VTA which decreases inhibition of DA neurons in this brain region and consequently facilitates enhanced DA release in the striatum. Taken together, these neuroimaging findings suggest that individuals who possess high levels of approach-related personality traits might be characterized by enhanced reactivity of the midbrain DA system in comparison to individuals who possess low levels of these traits. Second, drug challenge studies have shown that experimentally altered DA neurotransmission modulates the ability to sustain interest in rewards. Specifically, selective attention and responding for reward-paired cues is increased by DA augmenting drugs (de Wit et al 2002; Servan-Schreiber et al 1998) and decreased by DA attenuating drugs (Ahveninen et al 2000; Clark et al 1986; Kahkonen et al 2001; Leyton et al 2007; Magliozzi et al 1989; McLean et al 2004; Saeedi et al 2006; Shelley et al 1997). These findings parallel pre-clinical observations implicating DA neurotransmission in goal-directed or approach behaviour and thus provide further, albeit indirect, evidence in humans that DA neurotransmission might be a critical component underlying approach-related personality traits.

4.2 Approach-related personality traits and the mood-elevating effects of psychostimulant drugs

There is a high degree of inter-individual variability in the subjective and mood-elevating effects of abused drugs (de Wit et al 1986), but the causes of this variation remain poorly understood. Since these effects are thought to be important in the development of drug addiction, researchers have sought to

determine the factors underlying this variation. Among the possible factors are individual differences in approach-related personality traits. However, attempts to predict a differential subjective drug response depending on individual differences in approach-related personality traits have so far been mixed. Three studies have found positive associations (Hutchison et al 1999; Sax & Strakowski 1998; White et al 2006) while four studies have not (Alessi et al 2003; Chait 1993; Corr & Kumari 2000; Uhlenhuth et al 1981). It is important to note that different personality scales were typically used in each of these studies and not all studies were designed explicitly to test associations between approach-related personality traits and the mood-elevating effects of amphetamine. Thus, no definitive conclusions can be made on the basis of this evidence. The results of recent neuroimaging studies, which have consistently found associations between the magnitude of DA release in the ventral striatum and individual differences in both the mood-elevating effects of amphetamine (Abi-Dargham et al 2003; Boileau et al 2007; Drevets et al 2001; Laruelle et al 1995; Martinez et al 2003; Munro et al 2006; Oswald et al 2005; Oswald et al 2007; Volkow et al 1999) as well as approach-related personality traits (Boileau et al 2003; Buckholtz et al 2010a; Buckholtz et al 2010b; Leyton et al 2002), suggest that in some way variation in mood-elevating effects is systematically related to variation in approach-related personality traits.

5.0 Purpose of the present study

Whether or not elevated DA neurotransmission directly mediates positive mood states in healthy humans remains an open question for two reasons. First, several recent neuroimaging studies have found associations between psychostimulant drug-induced increases in striatal DA release and the mood-elevating effects of these drugs (Abi-Dargham et al 2003; Boileau et al 2007; Drevets et al 2001; Laruelle et al 1995; Martinez et al 2003; Munro et al 2006; Oswald et al 2005; Oswald et al 2007; Volkow et al 1999). These findings have revived interest in the proposition that DA plays a critical role in positive mood

states, particularly pleasure. Second, previous drug challenge studies have either administered psychostimulant drugs, which act on multiple neurotransmitters in addition to DA, or DA receptor agonists or antagonists, which target specific DA receptor subtypes. Thus, it has been difficult to determine the precise contribution of DA to mood and other subjective states.

The present study was conducted to determine the effect of a more selective DA augmenter, L-DOPA, on mood and other subjective states in a large group of healthy humans. Approach-related personality traits were used as proxies of DA neurotransmission since these traits have been shown to correlate with the magnitude of drug-induced striatal DA release (Boileau et al 2003; Boileau et al 2006; Buckholtz et al 2010a; Buckholtz et al 2010b; Leyton et al 2002). If elevated DA neurotransmission produced pleasurable effects, it was expected that the effects would be largest in those individuals who scored high on questionnaires assessing approach-related personality traits.

THE DOPAMINE AUGMENTER L-DOPA DOES NOT AFFECT POSITIVE MOOD IN HEALTHY HUMAN VOLUNTEERS

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Running Head: L-DOPA and mood

ABSTRACT

Dopamine neurotransmission influences approach toward rewards and reward-related cues. The best cited interpretation of this effect proposes that dopamine mediates the pleasure that commonly accompanies reward. This hypothesis has received support in some animal models and a few studies in humans. However, direct assessments of the effect of transiently increasing dopamine neurotransmission have been largely limited to the use of psychostimulant drugs, which elevate brain levels of multiple neurotransmitters in addition to dopamine. In the present study we tested the effect of more selectively elevating dopamine neurotransmission, as produced by administration of the immediate dopamine precursor, L-DOPA (0, 100/25, 200/50 mg, Sinemet), in healthy human volunteers. Neither dose altered positive mood. The results suggest that dopamine neurotransmission does not directly influence positive mood in humans.

INTRODUCTION

Mesolimbic dopamine (DA) neurotransmission influences the ability of rewards to elicit focused interest and approach [1-5]. One early and still frequently cited interpretation is that the neurotransmitter mediates pleasure [6]. This possibility was first suggested following observations that neuroleptic medications decreased amphetamine-induced subjective "high" in stimulant drug abusers [7-9] and produced a sense of "psychic indifference" in patients with schizophrenia [10] while extended treatment with high doses of L-DOPA led to hypomanic states in patients with bipolar mood disorders [11]. Subsequently, a series of carefully controlled animal studies indicated that increases in DA neurotransmission augmented instrumental responding for electrical stimulation of the brain (ESB) [12] while decreased DA neurotransmission disrupted responding for drugs, food, and ESB [13-18]. The latter effects were not attributable to compromised motor function since low doses of DA receptor antagonists increased instrumental responding while higher doses produced biphasic increases and decreases. These observations led to the suggestion that DA receptor antagonists reduced the ability to experience pleasure [6].

Some recent work is at least consistent with the "anhedonia hypothesis." For example, individual differences in the magnitude of drug-induced striatal DA responses correlate with approach-related personality traits [19-22] and the substance's positive subjective effects [23-31]. In the converse experiments, mood-lowering effects of antipsychotic medications are predicted by their extent of DA D2 receptor blockade [32-34].

Other work, though, has seemed inconsistent with a role of DA in pleasure. First, in both humans [35,36] and laboratory animals [3,37] DA release in the ventral striatum can also be evoked by aversive stimuli. Second, in operant conditioning paradigms, DA release increases and then peaks just prior to a lever press for reward and then gradually decreases thereafter [38,39]. With experience, DA comes to be released in response to cues associated with the reward [38-40] but not when actually receiving the reward [40,41]. Third, an extensive series of studies has indicated that neither DA antagonists nor DA lesions alter responses in the 'taste reactivity' paradigm, an animal model of eating-related pleasure [2,42,43]. Finally, the majority of studies have failed to replicate an ability of neuroleptic medications or other DA lowering manipulations to decrease drug-induced pleasure in humans [44-58].

Given the above controversies, the present study aimed to test the effect of a more selective DA augmenter, L-DOPA, on mood states in healthy human volunteers. Since individual differences in approach-related traits predict differences in DA reactivity, it was further hypothesized that those who scored higher on these traits would exhibit greater mood elevation.

METHODS

Ethics Statement

The study was carried out in accordance with the Declaration of Helsinki and was approved by the Research Ethics Board of the McGill University Hospital Centre. All subjects gave informed written consent.

Subjects

Fifty participants were recruited from the McGill University campus through online classified advertisements. Forty-eight men and women (29 females and 19 males; mean age 21.9 ± 3.7 years) completed the study. One participant was excluded due to vomiting at the beginning of the test session and another was excluded because of failure to comprehend the task instructions. All were healthy, as determined by a physical exam, standard laboratory tests, and an interview with the Structured Clinical Interview for DSM-IV, axis I [59]. None had a personal history of axis I psychiatric disorders. On the test day, all subjects tested negative on a urine drug screen sensitive to cocaine, opiates, phencyclidine, barbiturates, Δ^9-tetrahydrocannabinol, and amphetamines (Triage Panel for Drugs of Abuse, Biosite Diagnostics©, San Diego, CA).

Procedure

Participants completed the personality questionnaires on the same day as the psychiatric interview, while the test session took place on a separate day. Participants also completed a battery of cognitive tasks during the test session, but

these results will be reported elsewhere. Participants were assigned to one of three drug groups (n = 16 per group): placebo, L-DOPA/carbidopa (Sinemet, 100mg /25 mg) or L-DOPA/carbidopa (Sinemet, 200 mg/50 mg), in a randomized, double blind, between-groups design. A combination drug, including the peripheral decarboxylase inhibitor carbidopa, was used to prevent the conversion of L-DOPA to DA before it entered the brain. Low doses of L-DOPA were administered in an effort to avoid the potential confound of side effects such as nausea, vomiting and dizziness. On the test day, participants arrived in the laboratory at 11:30 AM and completed baseline subjective state questionnaires and drug screening. At 12:30 PM, participants ingested two green capsules containing either placebo or one of the two doses of L-DOPA. Participants completed the mood questionnaires at three additional times: 45 minutes, 105 minutes and 165 minutes post-capsule ingestion. Cognitive testing commenced 45 minutes following ingestion of the capsules, coinciding with the time to peak blood concentration of L-DOPA, and lasted until 3:30 PM. Female participants who were not taking oral contraceptives were tested within 10 days of the start of menstruation because previous studies have shown that females are more sensitive to reward in the follicular compared to the luteal phase of the menstrual cycle [60-62].

Personality Measures

All subjects completed the Tridimensional Personality Questionnaire (TPQ) [63], Substance Use Risk Profile (SURPS) [64] and the Neuroticism-Extroversion-Openness Five Factor Inventory (NEO-FFI) [65]. Of specific

interest in the present study were the TPQ Novelty Seeking factor and two of its subscales (Exploratory-Excitability and Impulsiveness), the SURPS factors Impulsivity and Sensation Seeking, and the NEO-FFI factor Extraversion. Each drug group was further sub-divided into high and low groups based on a median split of these personality factor scores for each subject.

Mood and Subjective Effects Measures

Subjective effects were measured with the bipolar Profile of Mood States (POMS), a sensitive measure of small rapid changes in mood [66,67], and a visual analog scale (VAS) labeled “Nauseous”. The POMS is comprised of 72 adjectives that describe various mood states. Participants indicate the extent to which they feel these states at each time point on a scale ranging from 0 (“not at all”) to 4 (“extremely”). The POMS items are then converted into 6 empirically derived sub-scales: Elated-Depressed, Composed-Anxious, Agreeable-Hostile, Confident-Unsure, Energetic-Tired and Clearheaded-Confused. Both questionnaires were administered at four times on the test day: at baseline, and at 45, 105 and 165 minutes post-capsule ingestion.

DATA ANALYSIS

Data analyses were conducted using SPSS Statistics (version 18.0; IBM, Chicago, Illinois). Each drug group was further subdivided based on a median split of scores for the approach-related personality traits of Impulsivity, Extraversion, Sensation Seeking and Novelty Seeking, yielding high and low groups for each factor. Three separate analyses were conducted for TPQ Novelty Seeking: the total score as well as scores for the Exploratory-Excitability (NS1) and Impulsiveness (NS2) subscales. Three-way mixed design ANOVAs were used to assess the effects of drug group (independent factor, 3 levels: placebo, 100 mg L-DOPA, 200 mg L-DOPA) and personality trait sub-group (independent factor, 2 levels: high and low) across time (repeated factor, 4 levels: baseline, + 45 minutes, +105 minutes and +165 minutes) for all of the mood and subjective effects measures. Two-way independent groups ANOVAs were used to assess the effects of drug group and personality trait subgroup on POMS absolute peak change scores, calculated as the largest difference between any of the three time points and baseline. Post-hoc Least Significant Differences (LSD) tests were used whenever an ANOVA yielded a significant result. The significance for all statistical tests was $p < 0.05$.

RESULTS

There were no significant Group x Time interaction effects for any of the POMS subscales (all ps > 0.05, see Table 1), nor were there significant main effects of personality (all ps > 0.05). A three-way Group x Personality sub-group x Time interaction raised the possibility that NS2 predicted differential POMS Agreeable-Hostile responses to L-DOPA, but this effect was no longer significant when VAS "Nauseous" scores were entered as covariates ($F_{6, 114} = 0.804$, $p > 0.05$). Effects on nausea were mild (peak change = 1.4 / 10), and statistically significant for the 200 mg L-DOPA dose only ($F_{6, 126} = 2.839$, $p < 0.05$) (see Table 1).

DISCUSSION

In the present study, the immediate DA precursor, L-DOPA, did not affect positive subjective states in healthy human volunteers, neither in the groups as a whole nor in subgroups based on DA-related personality traits. These findings extend the results from previous drug challenge studies. In contrast to non-specific DA augmenters, such as psychostimulant drugs, which reliably and potently elevate mood in healthy human volunteers [31,55,68-70], accumulating evidence indicates that more selective DA agonists do not (Table 2).

The inability to detect effects of L-DOPA on positive mood does not preclude a relationship between DA neurotransmission, personality traits and goal-directed behavior [11,19-22,71,72]; indeed, enhancements in goal-directed behavior may lead to elevated mood [11,71-73]. However, the present results suggest that drug-induced mood-elevating effects are more closely related to neurotransmitters other than DA [3,37,71-78], perhaps serotonin, norepinephrine, glutamate, GABA, endocannabinoids and endogenous opioids [2,79-84].

If DA's influence on reward seeking behaviors is not accounted for by enhanced pleasure, this raises the question of why it has these effects. Perhaps the best-supported alternative interpretation from the animal literature proposes that DA enhances the incentive salience of reward related cues, increasing their ability to elicit focused interest and effortful seeking [2,43,85]. This conclusion is largely based on extensive evidence that decrements in DA neurotransmission reduce the willingness to work for rewards [37,85] without changing responses in an index of feeding related pleasure [2,43]. Accumulating work in humans supports this

interpretation also [71, Table 2]. For example, in a series of studies conducted here, decreasing DA neurotransmission disrupted the tendency of subjects to respond preferentially to reward-related cues [55] and decreased the willingness to work for abused drugs and monetary reward on progressive ratio breakpoint schedules [53,58]; each of these effects was produced without reductions in pleasure. Indeed, the majority of studies in humans have failed to replicate an ability of various DA lowering manipulations to diminish drug-induced pleasure [45-58].

The present results should be considered in light of the following. First, there was no direct measure of the ability of L-DOPA to increase DA, leaving open the possibility that mood changes were not detected because L-DOPA failed to increase DA levels. However, this seems unlikely since similar doses of L-DOPA given to healthy human volunteers induce behavioural effects [86-88] and increase striatal DA synthesis [89]. Pre-clinical studies confirm that L-DOPA increases extracellular DA levels in the intact brains of healthy laboratory animals, albeit to a lesser extent than in animal models of Parkinson's disease [90]. Although, to our knowledge, there are no reports of L-DOPA induced DA release in healthy humans, in patients with Parkinson's disease robust L-DOPA induced DA responses are seen [91]; intriguingly, these effects are largest in those who have developed pathological gambling and the "DA dysregulation syndrome" [92,93]. Moreover, in these patients, larger L-DOPA-induced DA responses are associated with higher novelty- and fun-seeking personality traits, greater L-DOPA-induced psychomotor activation, and greater drug "wanting" but

not drug "liking" [92]. Testing the effect of larger increases in DA neurotransmission in healthy human volunteers will be difficult, though, since higher doses of all currently available drugs that selectively augment DA neurotransmission are limited by side effects such as nausea, vomiting, dizziness and drowsiness. Indeed, this limitation guided our selection of L-DOPA doses in the present study. Second, we used a median split to determine the high and low sub-groups for each of the approach-related personality traits. It might be necessary to recruit participants from the more extreme ends of the normative population distribution for each of these traits in order to detect a differential effect of a DAergic drug since individual differences in DA neurotransmission might be more pronounced in these more extreme ends of the distribution. This noted, a *post hoc* examination of our more extreme upper and lower quartiles also failed to identify an effect on mood (all p-values ≥ 0.15). Finally, it is possible that an effect on mood would have been seen with a larger sample size. However, this is considered unlikely. The single largest effect size was peak change to 'Energetic-Tired' scores ($d = 0.339$), and this would have required a sample of 138. All other effects would require samples larger than 200. Following corrections for multiple comparisons, these numbers increase further again.

In conclusion, then, L-DOPA failed to produce changes in positive mood states in a group of healthy human volunteers. These findings add to an accumulating literature suggesting that increases in DA neurotransmission are not sufficient to directly generate positive emotions.

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Table 1. The effect of dopamine-enhancing agents on positive mood states in healthy humans.

Drug	Mechanism of Action	Dose	Study	n	Mood Measures	Effect on Positive Mood	Details
Apomorphine	Mixed D1/D2 agonist	10 µg/kg	Blin (1990)	9	VAS	≠	
Bromocriptine	D2 agonist	1.25 mg	Morcom (2010)	32	VAS	NR	VAS items corresponding to motivation and energy No drug effects on any measure
		2.5 mg	Micallef (2009)	12	VAS	≠	
		2.5 mg	Franken (2008)	21	VAS PANAS	≠	
		1.25 mg	Cools (2007)	22	VAS	≠	
		2.5 mg	Roesch-Ely (2005)	40	AMS	≠	
		1.25 mg	Mehta (2001)	20	VAS	↓	Bromocriptine ↓ VAS Contented and ↑ VAS Sad and Antagonistic scores
		1.25 mg	Abduljuwad (1998)	12	VAS	≠	
		2.5 mg	Muller (1998)	16	AMS STAI	≠	Not clear what these scales actually measure
L-DOPA	Selective DA augmenter	100 mg	Micallef (2009)	12	VAS	≠	
		150 mg	Pine (2010)	14	VAS	≠	
		200 mg	Andreu (1999)	22	VAS	NR	Only measured VAS "Drowsiness"
Lisuride	D2 agonist	0.2 mg	van der Post (2004)	12	VAS	↓	Adverse effects, such as nausea, vomiting and headache No sedative effect
Pergolide	Mixed D1/D2 agonist	0.1 mg	Breitenstein (2006)	40	PANAS	≠	Drugs administered daily for 5 days No acute drug effect (assessed on day 1) Pergolide group had stable positive mood during training sessions on days 2-5, whereas placebo group had ↓ positive mood during training sessions on all days
		0.1 mg	Roesch-Ely (2005)	40	AMS	≠	
		0.05 mg	Upadhyaya (2003)	15	VAS	≠	
		0.1 mg	Muller (1998)	16	AMS STAI	↓	Not clear what these scales actually measure
Pramipexole	D2 agonist	0.5 mg	Micallef (2009)	12	VAS	≠	
		0.25 mg, 0.5 mg	Hamidovic (2008)	10	POMS ARCI DEQ	↓	0.5 mg ↓ euphoria and energy as measured by ARCI, ↓ POMS vigor and positive mood and ↓ item "like drug" on DEQ
		0.5 mg	Pizzagalli (2008)	32	VAS	≠	
Tolcapone	COMT inhibitor	200 mg	Roussos (2009)	25	POMS	≠	No COMT genotype X drug interaction effect for any POMS item
		200 mg	Giakoumaki (2008)	23	POMS	≠	No COMT genotype X drug interaction effect for any POMS item
		100 mg day 1 followed by 200 mg x 6 days	Apud (2007)	47	POMS	≠	No COMT genotype X drug interaction effect for any POMS item

For the purpose of this table, measures of positive mood include the ARCI MBG subscale, POMS “Elated” subscale, and the VAS items “High,” “Rush,” “Euphoria,” “Contentedness,” “Like Drug,” and “Good Effects.” Abbreviations: AMS, Adjective Mood Scale. ARCI, Addiction Research Center Inventory. NR, not reported. PANAS, Positive and Negative Affect Scales. POMS, Profile of Mood States. VAS, visual analog scales. STAI, State Trait Anxiety Inventory.

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DISCUSSION

In the present study, L-DOPA failed to alter subjective ratings of positive mood in a large group of healthy humans. These findings support the results from other studies where selectively increasing or decreasing DA neurotransmission also did not elevate or diminish positive mood (tables 1 and 2). These findings stand in contrast to the ability of non-selective DA augmenters, such as psychostimulant drugs, to potently elevate positive mood in humans (Acheson & de Wit 2008; de Wit et al 2002; Hamidovic et al 2009; Leyton et al 2007; Volkow et al 1999). Collectively, the evidence strongly suggests that DA neurotransmission does not mediate the pleasure that commonly follows consumption of various natural and drug rewards. Instead, DA neurotransmission appears to mediate other aspects of reward, including approach and exploratory behaviours and incentive salience attribution (Beninger 1983; Berridge 2007; Grace et al 2007; Ikemoto & Panksepp 1999; Redgrave et al 1999; Robbins et al 1989; Salamone 1994b; Salamone et al 2007; Schultz 2007; Wise & Rompre 1989).

The present findings do not preclude any role for DA in mood regulation. DA neurotransmission might indirectly affect positive mood states through its direct modulation of incentive salience attribution (Leyton 2009). Additionally, pharmacologically altered DA neurotransmission might contribute to the energizing and pro-motivational effects of some antidepressant drugs (Dunlop & Nemeroff 2007).

Accumulating evidence, though, suggests that neurotransmitters other than DA might be more directly involved in mood. The fact that DA decreasing drugs do not alter the mood-elevating effects of psychostimulant drugs (table 3) implies that NE and/or serotonin mediate these effects, since psychostimulant drugs also potently increase the levels of these neurotransmitters. At present, clinical and drug challenge studies provide some support for this proposition. Briefly, serotonin and NE are thought to be involved in the pathophysiology of mood disorders (Brunello et al 2003; Lambert et al 2000; Nemeroff 2002) and drugs that

target these systems are effective antidepressants (Dremencov et al 2009). In healthy humans, dietary manipulations that augment or attenuate brain serotonin levels affect positive mood states, though the effects are typically weak and only occur in some individuals (Ruhe et al 2007; Young & Leyton 2002). Two recent studies found that selective NE drugs alter the mood-elevating effects of amphetamine (Sofuoglu et al 2009a; Sofuoglu et al 2008a), but whether these drugs impact mood when administered alone has not been examined to date. In pre-clinical studies using the taste reactivity test, serotonin agonists have been shown to modulate both positive and aversive hedonic responses (Treit & Berridge 1990). Selective NE drugs have not been tested with this paradigm to date.

Non-monoamine neurotransmitters, such as opioids, cannabinoids, GABA and glutamate, have also been implicated in mood regulation. Briefly, in pre-clinical studies using the taste reactivity test, opioid receptor agonists have been shown to consistently enhance positive hedonic "liking" responses (Kelley et al 2002; Pecina & Berridge 1995; Pecina & Berridge 2005; Pecina et al 2006). In healthy humans, opioid receptor agonists produce mixed euphoric and dysphoric effects (Hill & Zacny 2000; Walker et al 2001; Zacny & de Wit 2009; Zacny & Gutierrez 2003; Zacny & Lichtor 2008) and opioid release correlates with subjective ratings during mood-induction paradigms (Koepp et al 2009; Zubieta et al 2003). Additionally, both opioid receptor agonists and antagonists alter the subjective responses to a wide range of abused drugs (Brauer et al 1999; Cooper et al 2010; Comer et al 2002; Comer et al 2005; Haney 2007; Haney et al 2003; Jayaram-Lindstrom et al 2004; Jayaram-Lindstrom et al 2008; King & Meyer 2000; McCaul et al 2000; Na & Lee 2002; Ray & Hutchison 2007; Setiawan et al 2011; Sullivan et al 2006; Walsh et al 2001; Wewers et al 1998; though see Wachtel et al 2000). Cannabinoid neurotransmission appears to be involved in mood regulation based on three lines of evidence. First, cannabinoids modulate positive hedonic reactions to sucrose in the taste reactivity test (Mahler et al 2007). Second, dysfunctional cannabinoid neurotransmission is thought to

contribute to the pathophysiology of mood disorders and drugs that act on this system might be useful as antidepressant drugs (Bambico et al 2009; Hill & Gorzalka 2009). Third, in healthy humans, a variety of drugs that alter cannabinoid neurotransmission, such as THC and cannabinoid receptor agonists, have mood-elevating effects (Karschner et al 2011; Kaufmann et al 2010; Wachtel et al 2002; Zuurman et al 2009; Zuurman et al 2010; Zuurman et al 2008).

At present there is also some evidence to suggest that the ubiquitous neurotransmitters GABA and glutamate might play a role in mood regulation. Specifically, in pre-clinical studies using the taste reactivity paradigm, injection of a metabotropic glutamate receptor 2/3 antagonist into the medial shell of the NAcc decreases (Richard & Berridge 2011) and injection of GABA receptor agonists into the parabrachial nucleus of the brainstem increases the number of positive hedonic "liking" responses to sucrose (Berridge 1988; Soderpalm & Berridge 2000). Drugs that modulate GABA or glutamate neurotransmission have been shown to alter the subjective responses to abused drugs in some (Cousins et al 2001; Hart et al 2004; Jackson et al 2009; Sofuoglu et al 2011; Sofuoglu et al 2005a; Sofuoglu et al 2005b) but not all studies (Bisaga & Evans 2006; Haney et al 2005; Haney et al 2006; Nutt et al 2007; Sofuoglu et al 2008b; Sofuoglu et al 2009b). Glutamate and GABA dysfunction are thought to contribute to the pathophysiology of mood disorders (Bielau et al 2007; Brambilla et al 2003; Hashimoto et al 2007; Yuksel & Ongur 2010) and drugs that affect these neurotransmitter systems show some promise as antidepressant or mood-stabilizing treatments (Brambilla et al 2003; Pilc et al 2008; Sanacora et al 2003; Sanacora et al 2008; Zarate et al 2010).

There are two limitations in the present study. First, there was no direct measure of DA levels. This leaves open the possibility that L-DOPA did not produce any mood changes because it did not sufficiently increase DA levels. However, it is unlikely that L-DOPA failed to increase DA levels since previous drug challenge studies conducted in healthy humans found effects of L-DOPA on cognitive tasks (Eisenegger et al 2010; Floel et al 2008; Pine et al 2010) and a

recent pre-clinical study has shown that L-DOPA increases DA levels in healthy intact rodent brains (Rodriguez et al 2007). Another possibility is that more robust increases in DA levels are required to produce mood changes in healthy humans. This will be extremely difficult to test in future studies since all currently available DA enhancing drugs produce significant unwanted side effects, such as nausea, vomiting and drowsiness, when administered at high doses. Second, participants were categorized as "high" or "low" for each approach-related personality trait based on a median split. This might have limited our ability to detect a differential drug effect on mood and other subjective states, since there was not significant variability in scores on these measures. It might be necessary to recruit participants from the extreme ends of the normative population distribution for each of these traits in order to accentuate the putative differences in baseline DA neurotransmission.

In conclusion, the present study demonstrated that augmented DA neurotransmission, as produced by administration of the DA precursor L-DOPA, does not alter mood or other subjective states in healthy humans. Moreover, a differential drug effect on mood was not detected after categorizing participants based on individual differences in the approach-related personality traits of impulsivity, novelty seeking, sensation seeking and extraversion. This study adds to the growing body of evidence suggesting that DA is not a mediator of positive mood states, such as pleasure. Additional studies are needed to elucidate the nature of the relationship between individual differences in DA neurotransmission, approach-related personality traits and subjective responses to DA enhancing drugs.

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