Role of the Dopaminergic and Cholinergic Systems of the Rat Neostriatum in Learning and Associative Memory functions

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ABSTRACT

The experiments in this thesis investigated the neuropharmacology of memory in the caudate nucleus, using the conditioned emotional response (CER) with visual and olfactory conditioned stimuli (CS).

In experiment 1, post-training, intrastriatal microinjections of both amphetamine and LY 171555, but not SKF 38393: (1) into the posteroventral area improved memory of a visual, but not an olfactory, CER; (2) into the ventrolateral area improved memory of an olfactory, but not a visual, CER. In experiment 2, sulpiride, but not SCH 23390, blocked the memory improving effect of amphetamine. These findings are consistant with the hypothesis that dopamine D2 receptor stimulation mediates the memory enhancement effect of amphetamine in the neostriatum.

In three experiments on a visual CER, pre-training intrastriatal micro-injections of scopolamine impaired acquisition; post-training micro-injections improved consolidation; and pre-testing micro-injections impaired retrieval. These findings are consistant with the hypothesis that striatal muscarinic receptor stimulation mediates some aspects of acquisition and retrieval of sensory-motor memory, and that blockade of these receptors following training has an effect on memory consolidation similar to that of D2 receptor stimulation.

In experiment 6, destruction of the dopaminergic nigrostriatal neurons abolished the memory improving effect of

intrastriatal post-training micro-injections of scopolamine and AFDX-384, a specific muscarinic M2 antagonist. These results suggest that the post-training memory improvement produced by muscarinic blockade may be mediated by an M2 receptor, known to be located on dopaminergic nigro-striatal terminals.

Résumé

Les expériences de la présente thèse ont étudié la neuropharmacologie de la mémoire dans le noyau caudé en utilisant la réponse émotionnelle conditionnée (REC) et des stimuli conditionnels (SC) visuel et olfactif.

Dans l'expérience 1, des micro-injections intra-striatales d'amphétamine et de LY 171555, mais pas de SKF 38393, juste aprés l'apprentissage,: (1) dans la région postéroventrale améliorèrent la mémoire d'une REC visuelle mais pas d'une REC olfactive; (2) dans la région ventrolatérale améliorèrent la mémoire d'une REC olfactive mais pas d'une REC visuelle. Dans l'expérience 2, sulpiride, mais pas SCH 23390, bloqua l'amélioration de mémoire causée par l'amphétamine. Ces résultats sont consistent avec l'hypothèse que la stimulation du récepteur dopaminergique D2 constitue le substrat neuronal de cet effet d'amélioration de la mémoire par l'amphétamine dans le néostriatum.

Dans trois expériences portant sur une REC visuelle, la micro-injection avant l'apprentissage de scopolamine interferra avec l'acquisition; la micro-injection juste aprés l'apprentissage améliora la consolidation; et la micro-injection juste avant le rappel interferra avec la récupération. Ces résultats sont consistant l'hypothèse que la stimulation des récepteurs muscariniques constitue le substrat neuronal d'au moins certaines aspects de l'acquisition et de la récupération de la mémoire sensori-motrice dans le

néostriatum, et que le blockage de ces récepteurs aprés l'apprentissage a un effet sur la consolidation de la mémoire similaire à celui de la stimulation des récepteurs dopaminergiques D2.

Dans l'expérience 6, la destruction des neurones dopaminergiques nigro-striataux élimina l'amélioration de la mémoire causée par des micro-injections apres apprentissage de scopolamine et d'AFDX-384, un antagoniste spécifique du récepteur muscarinique M2. Ces résultats suggèrent que cette amélioration de la mémoire par le blockage muscarinique juste apres l'apprentissage puisse avoir comme substrat neuronal le récepteur muscarinique M2 dont la présence sur les terminaux dopaminergiques nigro-striataux a été suggeré.

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PREFACE

When I first came to McGill University in September of 1985, I was determined to work on the neurological basis of memory and learning. Like many others I had been following closely the research on the hippocampus and the limbic system as possible sites for such functions. In my first weeks in McGill, Dr. Norman White introduced me to the caudate nucleus and explained why he thought this structure to be an important part of an alternative memory system, a system dealing mostly with simple sensory-motor learning. Some of his own early work with previous graduate students on electrical self-stimulation and amphetamine micro-injections were among the most important evidence supporting such a position. Since those days my conception of learning and memory in the brain has been completely altered.

From the accumulated evidence, it was clear that the neostriatum was an important part of the neurological system underlying associative learning and that dopamine release from nigro-striatal terminals might mediate post-training memory improving effect of amphetamine. However, what was not known at the time was the extent of its contribution as well as the underlying mechanisms. The demonstration in my Master's thesis that specific sites in the neostriatum seem to mediate the acquisition of sensory specific information was a major piece of evidence implicating the matrix compartment of the neostriatum with its pattern of anatomical relations to the

cortex, in sensory-motor memory. The missing element was the understanding of the mechanism for memory formation and consolidation, that is, for creating permanent sensory-motor (S-R) connections on the basis of experience. The purpose of this thesis is to begin to describe that mechanism.

In the end, as the reader will see, what had started as an attempt at clarifying the involvement of dopamine and acetylcholine in associative function in the striatum, has become an integrative model of how normal S-R learning might occur in the neostriatum of the rat. The model involves the different neurotransmitter systems and revolves around the changes in cAMP activity induced by stimulation of D2 autoreceptors and their effects on the dopaminergic-cholinergic balance. Finally, in addition to allowing for the explanation of the observed drug effects reported in the present thesis, this model also suggests explanations for several other learning phenomena and permits some interesting predictions.

My greatest appreciation is extended to my supervisor, Dr. Norman White, for his help in both supporting and guiding my research. Working with him was not only a great scientific experience but also an important part of growing up. His presence and especially his understanding of my sometime particular personality were more than appreciated. None of this would have been possible without him behind me.

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Chapter 1

Introduction

THE NATURE OF MEMORY

The idea of a memory consolidation process was first proposed by George Müller and Alfons Pilzecker (1901). They based their theory on the observation that human subjects had difficulties recalling a list of words if they were asked to learn a second list of words immediately after the first one. These authors suggested that the most recently presented words interfered with the recall of the older ones. This phenomenon was called retroactive interference and it was thought that the interference prevented the fixation or consolidation of the memory of the first set of words. This led to the proposal that short-term memories were gradually transformed into long-term memories.

More recently, D.O. Hebb (1949, 1955) proposed a physiological mechanism of consolidation. Hebb speculated that groups of neurons called cell assemblies, fired by the presentation of stimuli and the performance of responses, re-excited themselves repeatedly via numerous interconnections causing the initial burst of activity to persist for some time. This "reverberatory" neural activity was thought to produce permanent synaptic changes in the network of cells. Therefore, Hebb suggested, memories can be represented in the nervous system in two distinct forms: short-term (the labile electrical activity) and long-term (the changed synaptic relationships). In Müller and Pilzecker's paradigm, according to this hypothesis the presentation of the second list of

words impaired retention of the first list by disrupting the labile activity of the short-term stage, preventing the formation of long-term memory.

Human head injury studies

Early evidence supporting the existence of a consolidation process initially came from clinical studies of human head injury cases. McDougall (1901) was the first to suggest that retrograde amnesia observed following head injuries might be related to the consolidation process. For McDougall, trauma produced a deficit that was similar in nature, albeit exaggerated, to the retroactive interference of Müller and Pilzecker. Russell and Nathan (1946), in their extensive review of cases of head injury (1,029 patients), showed that 87% of human patients who suffered head injury had difficulties recalling events that occurred shortly before the trauma, although older memories were completely intact. They hypothesized the existence of a process that strengthens memories with the passage of time, thus making them less vulnerable to interference or trauma such as head injury.

Electro-convulsive shock

The next step in understanding memory consolidation was made possible by the discovery that electroconvulsive shock (ECS) could produce retrograde amnesia in humans (Zubin and Barrera, 1941) and in the rat (Duncan, 1949). ECS allowed for

the first experimental studies of memory and consolidation. Research on ECS-induced retrograde amnesia in animals used the one-trial passive avoidance paradigm almost exclusively. For example, in the widely used step-down test (Pearlman et al, 1961), animals were placed on a platform surrounded by an electrified grid. When animals stepped down onto the grid, they received a shock and returned to the platform. Immediately or after some delay, ECS was applied to the animals. Twenty-four hours later, the animals were again placed on the platform and their latency to step down was measured. While control animals usually stayed on the platform for the duration of the test, ECS-treated rats stepped down as or nearly as quickly as they had the previous day, acting as if they had forgotten both the shock and the ECS. Such results are typically seen as suggesting that the foot shock and the stimuli associated with it were still represented in the labile form at the time of the ECS. Thus, the disruption of normal neural activity induced by the ECS destroyed the labile memory trace before it could be consolidated into long-term memory. Further supporting this explanation is the fact that any substantial delay between the shock and the ECS decreases the amnesia produced by the ECS (McGaugh and Gold, 1976; McGaugh and Landfield, 1970). These findings have been replicated and extended using a variety of amnesic treatments, such as convulsants (Pentylenetetrazol: Krivanek and McGaugh, 1969; Krivanek, 1971), anaesthetics (Ether: Herz, 1969.

Halothane: Penrod and Boice, 1971) and spreading depression (the reduction of electrical activity of cortical structures by the application of potassium chloride to the surface of the cortex: Bures and Buresova, 1963; Albert, 1966). Although these amnesic treatments that produce a general disruption of the activity of the brain supported consolidation theory and provided information about the physiological mechanisms of consolidation, they did not provide clues about their possible localization.

Electrical brain stimulation

Subsequent studies have shown that memory consolidation can also be affected by post-training electrical stimulation of discrete brain areas (EBS), using chronically implanted electrodes. As EBS affects axons, dendrites, and cell bodies in a way that never occurs normally as the result of volleys of nerve impulses, experimenters using localized EBS made the assumption that such stimulation would disrupt ongoing neural activity the vicinity of the stimulating electrode by scrambling normal spatio-temporal firing patterns, while indirectly facilitating or inhibiting neural activity in interconnected neural structures distal to the site of stimulation (Doty, 1969). It was thus expected that any effect on mnemonic processes would be a direct function of a disturbance of on-going neural activity at the locus of stimulation and indirectly a function of changes in excitation

and inhibition in remotely activated neural systems. This new research tool enabled investigators to identify structures that might be involved in mnemonic processes. The neural regions which produce amnesia when stimulated are the amygdala (McDonough and Kesner, 1971; Bresnahan and Routtenberg, 1972; Gold et al, 1975; Baker et al, 1981), the hippocampus (Hirano, 1965; Kesner and Doty, 1968; McDonough and Kesner, 1971), the frontal cortex (Routtenberg and Sloan, 1972; Santos-Anderson and Routtenberg, 1976), substantia nigra (Routtenberg and Holzman, 1973; Fibiger and Phillips, 1976) and striatum (Gold and King, 1972; Wilburn and Kesner, 1972; Herz et al, 1975).

Even more interestingly, several studies showed that post-training stimulation of some areas of the brain can produce improvements in retention among which are the amygdala (Olton and Wolf, 1981; Berman and Kesner, 1981; Kesner and Andrus, 1982), the hippocampus (Destrade and Cardo, 1974; Destrade and Jaffard, 1978), substantia nigra (Major and White, 1978), and the hypothalamus (Destrade and Jaffard, 1978; Major And White, 1978)).

One of the important findings of the EBS studies was the discovery that the caudate nucleus seemed to be involved in memory acquisition and consolidation. Much of the earlier work on EBS of the caudate nucleus had focused on the elicitation of motor movements (Forman and Ward, 1957; Buchwald and Erwin, 1957) as promoted by the concept of the striatum as solely a motor control centre (Lashey, 1950; Hassler, 1956). Arrest of

movement, contraversive head turning, and phasic limb and facial movements were noted by a number of investigators (see review by Laursen, 1963). Similar behaviors, including repetitive, stereotyped movement patterns, have been observed following injections of drugs into the caudate nucleus (Randrup and Munkvad, 1967; Snyder et al, 1970).

When applied during training, EBS intensities and frequencies below those producing motor movements have resulted in learning and retention deficits. However, EBS during training cannot be unequivocally interpreted in terms of memory. Still, deficits have been found with passive avoidance, maze learning, and visual discrimination tasks (Kesner and Wilburn, 1974). In a progressively more difficult visual discrimination task, Buchwald and co-workers (1961) demonstrated that low frequency stimulation of caudate nuclei of cats during learning reduced the cats' accuracy and delayed initiation of the response. The deficits were characteristic only of those trials on which EBS was delivered after termination of the visual stimulus. Thus interference with cue registration apparently is not critical for impairment of visual discrimination. However, as already mentioned above, because stimulation was given during the learning trials in studies such as this one, it is difficult to separate the effects of stimulation on cue-access and registration from effects on memory consolidation.

Using post-training caudate nucleus stimulation avoids

confounding effects on cue registration and storage processes. Wyers and his co-workers (Wyers et al, 1968) measured the time rats required to traverse a runway and press a bar to get water. They compared animals given bilateral caudate nucleus stimulation 0.1 second to 30 seconds after an intense foot-shock with animals given only the foot-shock. The following day, the caudate-stimulated rats approached and drank from the tube far more rapidly than controls. These results were interpreted as evidence for retroactive interference with memory consolidation in the caudate nucleus. Additional experiments (Wyers and Deadwyler, 1970) using longer intervals between foot-shock and EBS (30, 120, 300 sec. and 15 min.) and repeated trials demonstrated a temporal gradient of interference with performance. Gold and King (1972) also found a temporal gradient of retrograde amnesia using rats in a passive avoidance task. With 60 Hz., 1.5 mA. post-training bilateral caudate nucleus stimulation for 1 sec., they obtained a passive avoidance deficit at a 15 minute interval between foot-shock and EBS, but not at 60 minutes. Bilateral, post-training caudate nucleus stimulation also interfered with rats' learning of a complex maze for appetitive reinforcement (Peeke and Herz, 1971). In order of ascending interference with learning, EBS conditions used were (1) single shocks after the rat had eaten for 30 sec., (2) single shocks after each choice point, and (3) 4 to 9 pulses at 1 sec. after the rat had eaten. EBS delayed 10 minutes after the animal had

eaten was without effect. In another appetitive reinforcement procedure, caudate nucleus stimulation with single shocks at 4 to 12 minutes, but not more than 12 minutes, after extinction sessions prolonged drinking spout contact time, and number of licks during subsequent sessions was higher (Herz and Peeke, 1971). If the primary consequence of such stimulation were a general motor inhibition, number of licks would have been diminished by caudate nucleus stimulation. The greater activity of the experimental subjects was taken as evidence for disruption of the memory of non-reinforcement. All of these findings suggest that post-training electrical stimulation of the caudate nucleus produces disruption while delayed stimulation does not, therefore implicating this structure in one important aspect of the memory process: consolidation.

Electrical self-stimulation

During the same years, researchers (Olds and Milner, 1954) demonstrated that a rat with an electrode inserted into the medial forebrain bundle (MFB) would press a treadle to stimulate itself. In fact, animals would forgo food essential to their survival in order to obtain brain stimulation of the MFB (Routtenberg, 1962). Lesions of the MFB were shown to reduce self-stimulation and, more important, to damage two components of the dopamine system of the midbrain: the ventral tegmentum and the substantia nigra, pars compacta (Routtenberg

and Holzman, 1973). These findings led the authors to suggest that the dopamine system of the midbrain might be part of a memory system.

However, Major and White (1978) showed that retention of a water-finding task was facilitated by a post-training, non-contingent session of self-stimulation through electrodes implanted in the nigro-striatal bundle or directly into the substantia nigra, pars compacta; electrodes implanted in the medial part of lateral hypothalamus or in the preoptic area also supported self-stimulation but had no effect on retention. These results led the authors to conclude that the effect on consolidation produced by stimulation of the nigro-striatal pathway was not dependent on the affective properties of rewarding self-stimulation but represented an effect on some memory consolidation process.

The demonstrations that electrical stimulation of the NBS increases dopamine turnover in the caudate nucleus (Korf et al, 1976), that self-stimulation in the substantia nigra is blocked by the injection into the caudate nucleus of the drug haloperidol, which selectively blocks dopamine transmission (Broekkamp, 1976), and that the memory consolidation produced by self-stimulation of the NSB was abolished by pimozide (a dopaminergic blocker, White and Major, 1978) suggest that the effects of electrical stimulation and self-stimulation of the NSB on memory may be dependent on dopamine activity in the caudate.

Lesion studies

Although there had been several earlier reports of learning impairments accompanying bilateral temporal-lobe damage (Glees & Griffeth, 1952; Terzian and Dalle Ore, 1955), intensive study of the phenomenon only began after the publication of papers by Scoville and Milner (1957) and Penfield and Milner (1958). These authors reported that bilateral surgical removal of medial temporal-lobe structures, or unilateral removals where the contralateral hippocampal region had previously been damaged by epileptic seizures, produce severe anterograde amnesia.

However, further observations (Milner, 1962) led to the discovery of several spared learning and memory abilities in temporal-lobe and hippocampal patients. They have normal digit-span and can remember simple items for as long as rehearsal is allowed. More important, Milner (1962) showed that these amnesic patients learn and retain a new visuo-motor skill (mirror drawing) normally, though they did not remember anything about the training sessions. More recently, Cohen and Corkin (1981) have demonstrated that amnesic patients improve from day to day in solving the "Tower of Hanoi" puzzle, though again they have no recollection of having seen it before.

Research with hippocampectomized animals also revealed spared learning abilities. For example, hippocampal rats were unimpaired in the acquisition of simple brightness discrimination (Silveira and Kimble, 1968) or visual

discrimination (Winocur, 1979). Hippocampally lesioned rats also acquired aversively motivated passive (Winocur and Bindra, 1976) and active avoidance tasks (Duncan and Duncan, 1971) normally.

A number of the major findings concerning memory and learning deficits resulting from neostriatal lesions made over the years are summarized in Table 1. In fact, a variety of neostriatal lesions have been shown to affect motor behaviors as well as to retard learning of numerous types of learning tasks. However, because of the variability in the results, not to say inconsistencies, it is difficult to draw any clear generalizations from these data beyond the fact that these lesions disrupt many types of tasks. Furthermore, most of these studies, as pointed out by Pisa and co-workers (1981), failed to take into account the regional differences within the neostriatum shown by Webster (1961) earlier. Generally, the lesions made in these studies were not very well defined or localized to a single area of the neostriatum. Furthermore, coagulation, aspiration and ablation lesion techniques destroy everything at the lesion site. In addition to destroying striatal cells (without any discrimination as to type), these lesions interrupt all the fibers of passage, such as the corticofugal and thalamofugal fibers (Divac, 1972; Iversen, 1979). During ablation, a large quantity of cortical tissue surrounding the neostriatum is destroyed. Still, electrolytic lesions can be a useful tool for the study of neostriatal

TABLE 1

NEOSTRIATAL LESION STUDIES: MEMORY AND LEARNING EFFECTS.

SPATIAL MEMORY

LESION	EFFECTS	AUTHORS
anteromedian neostriatum	retention deficit in delayed spatial alternation (DSA)	Wilmark et al, 1973
lateral neostriatum	no deficits in DSA	same
dorsomedian caudate	retention deficit in DSA	Divac and Rosvold, 1967
	performance deficit in DSA	Divac, 1972
ventral area	deficits in learning and performance of Non-DSA (NDSA)	Chorover and Gross, 1963
dorsal area	deficits in learning and performance of NDSA	Gross et al, 1965
dorsocentral neostriatum	no effects on NDSA	Schwartz et al, 1979

INHIBITION OF CONDITIONED APPETITIVE RESPONSES

unspecified neostriatal	retarded extinction	Schmaltz and Issacson 1972
same	impaired reversal of position	Kolb, 1977
same	impaired rate of bar-pressing in fixed interval schedule	Hansing et al, 1968
same	impaired differential reinforcement of reduced frequency schedules	Neill et al, 1974
same	discrimination of luminosity impaired	Price and Fibiger, 1975

dorsal neostriatum	no effect on differential reinforcement of reduced frequency schedules	Neill et al, 1974
ventral neostriatum	impaired differential reinforcement of reduced frequency schedules	same

NON-SPATIAL MEMORY

extended lesion of caudate's head	abnormal persistence to produce a response reinforced before in a task of simple Go-NoGo alternation	Butters and Rosvold, 1968

SPATIAL DISCRIMINATION

extended dorsal lesion	deficits in learning of maze	Battig, 1963 Borst, 1970
ventral lesion	no deficit in learning of maze	Chorover and Gross, 1963 Gross et al, 1965
unspecified neostriatal	no deficit in learning of position habit within a T-maze	Mikulas, 1966

NON-SPATIAL DISCRIMINATION

anterodorsal neostriatum	no effect on discrimination of luminosities in maze	Hannon and Bader, 1974 Kirkby, 1969
same	impaired shuttle-box free operant paradigm	Schwartzbaum and Donovick, 1968
same	impaired discrimination of position learned before the lesion	Mikulas, 1969
posteroventral caudate	serious impairment of visual discrimination of forms	Divac et al, 1967
head caudate	no effect on visual reversal of objects	same

AVERSIVE CONDITIONING

ventral neostriatum	deficits in passive, one-way and two-way avoidance	Kirkby and Klimble, 1968
dorsal neostriatum	deficits in passive, one-way and two-way avoidance	Kirkby and Polgar, 1974 Neill and Ross, 1974
dorsal neostriatum	deficits in passive and two-way avoidance	Winocur, 1974 Winocur and Mills, 1969

function when used cautiously and with the proper controls.

It is possible to identify differences in the effects of lesions made in different parts of the neostriatum, suggesting that the neostriatum is not functionally homogeneous. Moreover, the wide variety of behavioral deficits caused by the lesions make it difficult to attribute them to a particular sensory or motor function. These points can be illustrated by a comparison of the effects of lesions of the dorsal and ventral neostriatum, using data from experiments listed in Table 1.

Dorsal lesions of the neostriatum caused deficits in maze learning (Battig, 1963; Borst, 1970) and in the learning and performance of non-delayed spatial alternation (NDSA) (Gross et al, 1965). Lesions of the dorsal neostriatum, while causing deficits in two-way active and passive avoidance, did not affect one-way avoidance (Winocur, 1974; Mitcham and Thomas, 1972; Winocur and Mills, 1970). Neill and co-workers (1974) demonstrated that lesions of the dorsal neostriatum did not impair behavior on differential reinforcement of reduced frequency schedules (DRRFS). Finally, lesions of the dorsal neostriatum also lead to significant increases in spontaneous locomotion of animals during the night period while leaving the day period locomotion unchanged (Whitter and Orr, 1962).

In contrast to the deficits caused by dorsal lesions, lesions of the ventral neostriatum caused no apparent deficit in maze learning (Chorover and Gross, 1963; Gross et al,

1965). Ventral lesions also caused significant impairments of DRRFS tasks (Neill et al, 1974). It was concluded that these DRRFS deficits could be compared to those observed after an orbito-frontal decortication (Kolb, 1977), one of the corresponding cortical areas. Lesions of the ventral neostriatum produced deficits in all types of avoidance tasks, passive, one-way or two-way (Kirkby and Klimble, 1968). Ventral lesions resulted, like dorsal lesions, in learning and performance deficits in NDSA tasks (Chorover and Gross,1963). Finally, lesions of the ventral neostriatum were shown to decrease night locomotion while leaving day locomotion unchanged (Neill et al, 1974). It must be noted, however, that the modifications (increase or decrease) observed as a result of both types of lesion, ventral and dorsal, appeared only a week or so after the lesions were made and disappeared after one month.

The differences observed in the effects of ventral and dorsal lesions of the neostriatum suggest the existence of a functional heterogeneity within this structure. However, the deficits observed after neostriatal lesions are so numerous and differ so greatly from one to another that it is difficult to attribute them to any consistent effects on sensory or motor functions. Thus, dorsal lesions affected not only spatial and locomotion functions but also impaired avoidance tasks (except one-way avoidance). Such multiple effects, especially the specificity of the avoidance deficits, cannot

be explained easily as impairments of sensory or motor functions. It may be the fact that all of these tasks require some memory function that can explain the deficits produced in all of them by a single lesion. It is, therefore, suggested that these effects could be attributable to an effect on associative memory. Still, other explanations might also possible.

More recently, injections of kainic acid, a rigid analogue of the excitatory neurotransmitter glutamate involved in the cortico-striatal afference (Divac et al, 1977), into the neostriatum have been used to cause the degeneration of local intrinsic neurons without causing any apparent damage to fibres of passage or to the terminals of extrinsic neurons (Olney et al, 1975; Coyle and Schwarcz, 1976; Mason et al, 1978a, 1978b, 1978c).

Several studies have evaluated the effects of kainic acid injection on learning and memory. In the rostral neostriatum, kainic acid-induced lesions produced impaired learning and retention of 1-way and 2-way active avoidance (Pisa et al, 1978), of simple go-nogo alternation (Pisa et al,1981), and abnormally long extinction of a learned bar-pressing response previously continually reinforced (Sanberg et al, 1979). However, most common appetitive behaviors were unaffected. Injections of kainic acid into the ventral neostriatum reduced retention of delayed spatial alternation (Dunnett and Iversen 1979, 1980). The most interesting finding was the deficit in

go-nogo alternation observed after a rostral injection. This tends to suggest a memory deficit independent of spatial orientation alternation. Furthermore, this phenomenon cannot result from a deficit in motor inhibition since the same lesion did not affect the extinction of a learned running response (Pisa et al, 1981).

However, it should be noted that kainic acid is not without problems. Even with very small doses, which destroyed striatal neurons without affecting the fibres of passage, large cell losses were found in the neocortex, hippocampus, pyriform cortex and amygdala (Divac and Oberg, 1979), making the interpretation of the effects of the lesions ambiguous.

Dual-mode memory theories

Taking into account this accumulating evidence as well as the evidence of spared learning abilities in hippocampized animals, several investigators have proposed "dual-mode" hypotheses of memory. In suggesting such hypotheses, researchers have tried to account for the above mentioned findings from lesion and stimulation studies. On the one hand, the cognitive theory of learning and memory (Tolman, 1930; Hirsh, 1980) views learned behavior not as evoked by external stimuli but rather as guided by the relational information encoded in its representation. Cognitive memory function has traditionally been associated with the hippocampus (O'Keefe and Nadel, 1978). On the other hand, the associative theory of

learning and memory (Watson, 1913; Hull, 1943) views the acquisition of associations between stimuli and responses (ie S-R memory) as the basis of learning. It views behavior as automatically evoked by the presence of external stimuli that are part of the association.

Because of the evidence of its involvement in memory (ECS, EBS, ESS, lesions) the caudate nucleus appeared as a likely candidate for neural basis of the S-R memory system. In addition to the evidence from electrical stimulation studies reviewed earlier, caudate lesions have been shown to impair acquisition of various operant tasks (Chorover and Gross, 1963; Neill and Grossman, 1970, Winocur, 1974).

Finally, the demonstration that stimulation of the nigro-striatal bundle which causes an increase in dopamine turnover in the caudate nucleus (Korf et al, 1976) can improve consolidation of associative memory (White and Major, 1978; Major and White, 1978) supports the role of this structure in S-R memory. However, this alone does not answer the question of the nature of the mechanisms involved.

INTERNAL ORGANIZATION OF THE NEOSTRIATUM

Cell Types

The caudate-putamen is generally referred to as the striatum or neostriatum, and this designation is especially relevant in the rat, where it forms a large "striated" mass, penetrated by dispersed fibre bundles, representing

corticofugal and corticopetal projections. With the progressive phylogenetic development of the cerebral cortex, many of these projection fibres gradually collect into a massive fibre plate, the internal capsule, which subdivides the striatum more or less completely into two parts, the caudate nucleus and putamen. However, the distinction between caudate and putamen may be largely topographic; the cytoarchitectural features, apparently, are identical in the two subdivisions, which, furthermore, are rostrally continuous with each other thanks to bridges of striatal neurons that separate the bundles of the internal capsule. The functional differences that exist between the caudate nucleus and putamen are in part related to the fact that the two subdivisions receive their neocortical input from different parts of the cerebral cortex; the putamen receives most of its neocortical input from the sensory-motor cortex, whereas the caudate is more closely related to cortical regions known as "association cortex". Nevertheless, anatomical and histochemical data favour the view that the caudate and putamen represent two parts of the same anatomical entity. Consequently, in the rat, no attempt is made to identify the two subdivisions (Heimer et al, 1985).

It was thought for a long time, on the basis of cytological and ultrastructural characteristics revealed by the Nissl methods and Golgi impregnations, that a medium size spiny neuron was the most common and probably only type of

cell in this region of the central nervous system (Marchi, 1886). Until recently, conceptions of the internal organization of the striatum were limited to this fact.

More recently, correlated light and electron microscopic studies have revealed that the neostriatum contains several different morphologic cell types, but their classification has been problematic, and in the past it has been especially difficult to make the important distinction between interneurons and projection neurons. Recently, however, it has become possible to stain neurons selectively and to trace axonal projections by the use of intracellular staining techniques, and to identify projection neurons by injecting retrograde tracers into putative termination sites of neostriatal neurons.

Most descriptions of striatal neurons are based on the size of the soma and the appearance of the neuronal processes with special emphasis on the occurrence and frequency of dendritic spines. Several classification schema have been proposed (Mori, 1966; Fox et al, 1971: four types; Ramon y Cajal, 1911; five types; Kemp and Powell, 1971: six types; Lu and Brown, 1977: seven types).

Dimova and co-workers (1980) using ultrafine sections and a new technique to analyze Golgi impregnations classified striatal cells into medium size cells with four subtypes and the giant cells. This classification tends to agree with the count made by Pasik and co-workers (1979) who classified the

cells as spiny I and II and aspiny I, II and III.

The A-I type is cholinergic as demonstrated by the fact it can be found in the areas of the neostriatum where the concentration of acetylcholine is high (McGeer et al, 1971). Type A-I cells are the most common type in the neostriatum and can often be found in chains. This type differs from other types because its total absence of nuclear inclusions, microfibrils and crystalloid bundles (Dimova et al, 1980). Furthermore, it receives many special afferents. First, the topographically organized glutamaergic cortico-striatal cells terminate on these cells (Hattori et al, 1979). In a similar fashion, GABAergic thalamostriatal and dopaminergic nigrostriatal fibres project to the type A-I neurons (Hattori et al, 1980; Kocsis et al, 1977).

It appears possible therefore that type A-I cells might be one of the important elements critical for the integration of the many different inputs to the neostriatum. Such an integration is a requirement for the establishment of S-R associations in this structure.

The other two aspiny neuron types also seem to be interneurons. However, the giant type A-II is somewhat of a mystery. It resembles medium sized spiny neurons in that it possesses somatic spines and moderate spine density of the proximal dendrite that decreases with distance from the soma (Chang et al, 1982). It has also been proposed on the basis of its resemblance to giant GABAergic cells found in the

cerebellum that the type A-II could have a similar function, a GABAergic inhibition of excitatory neurons (Hattori et al, 1979). Type A-III is known to be GABAergic (McGeer and McGeer, 1975) and projects to type S-I and S-II output neurons (Hattori et al, 1979).

Some afferent fibres, as well as interneurons such as A-III, make contacts with efferent neurons in the neostriatum as demonstrated in a study using intracellular injections of horseradish peroxidase (Kocsis et al, 1977). These efferent neurons are the two spiny types suggested by Pasik and co-workers (1979). This is in agreement with electrophysiological data suggesting that there are at least two types of striatal efference, striato-nigral and striato-pallidal (Mallian and Purpura, 1967; Levine et al, 1974). It appears that S-I and S-II fibres constitute the only sources of output from the neostriatum. The S-I efference is inhibitory. It uses GABA as neurotransmitter (Kim et al, 1971; Follum et al, 1978) and innervates the substantia nigra as well as the globus pallidus (Grofova, 1979). Type S-II seems to be excitatory. Some evidence suggests substance P as the possible neurotransmitter for S-II fibres (Hong et al, 1971; Kamasawa et al, 1977) while others propose that leu-enkephalin may be a neurotransmitter in the striato-pallidal S-II fibres (Fonnum and Walaas, 1979).

Recently, Chang and co-workers (1982) have described dwarf (5um - 10um) neurons, which have both dendritic spines and an identifiable axon. The difficulty in observing these

small neurons is emphasized by the fact that very few examples were obtained.

Striatal Compartments

The "matrix", one of the two striatal compartments, has a high AchE activity (Herkenham and Pert, 1981; Graybiel et al, 1981) as well as a dense plexus of fibres displaying somatostatin-like immunoreactivity. The dopaminergic projection to the matrix originates in the dorsal part of the substantia nigra pars compacta (Gerfen et al, 1987). It also receives thalamic fibres (Herkenham and Pert, 1981; Royce, 1978), and topographically organized projections from the sensory and motor cortical areas (Ragsdale and Graybiel, 1981; Donoghue and Herkenham, 1983). These last projections come primarily from the sensory-motor areas (Goldman and Nauta, 1977; Jones et al, 1977; Kunzle, 1975). The matrix projects primarily to the substantia nigra pars reticulata, the source of the non-dopaminergic nigro-thalamic and nigrotectal system (Gerfen et al, 1987). According to some researchers (Gerfen, 1985) it is in this pattern of organization that can be found the basis for the sensory-motor function of the neostriatum as demonstrated by electrophysiological data (Hikosaka, 1983).

The other compartment is characterized by patches of dense opiate receptor binding (Herkenham and Pert, 1981), and is rich in enkephalin- and substance P-like immunoreactivity (Graybiel et al, 1981). The dopaminergic projection to this

"patch" compartment develops earlier than that to the matrix (Gerfen, 1984; Gerfen et al, 1987) and originates instead in the ventral part of pars compacta and in pars reticulata of the substantia nigra (Gerfen et al, 1987). Studies have shown that dopaminergic neurons originating in the ventral tegmental area project to the ventral striatum which may consist largely of a type of patch tissue (Gerfen, 1985). The patches also receive afferents from limbic areas: the medial frontal prelimbic cortex which, in turn, is innervated by direct limbic inputs from the amygdala (Krettek and Price, 1977; Gerfen, 1984), the hippocampus (Swanson and Cowan, 1977; Swanson, 1981) and the amygdala (Kelley et al, 1982; Phillipson and Griffiths, 1985). Patches project to the substantia nigra pars compacta, the source of the nigrostriatal dopaminergic system (Gerfen et al, 1987). They also project diffusely to the substantia nigra pars reticulata (Fishell and Van der Kooy, 1989).

White (1990) suggests that the pattern of organization of the matrix compartment, its connections and its relationship with sensory-motor function are additional evidence for an associative S-R type memory function for the neostriatum. To attribute an S-R associative memory function to this structure requires only the demonstration that the matrix contains a mechanism for memory formation and consolidation, that is, for creating permanent sensory-motor (S-R) connections on the basis of experience.

PROJECTIONS TO THE NEOSTRIATUM

Two of the projections to the neostriatum seem to play an important role in this possible mechanism for S-R memory formation and consolidation: the cortico-striatal projection, because of its highly organized topographical sensory and motor input to the neostriatum; and the nigro-striatal projection, because of its demonstrated ability to support brain self stimulation and to produce memory improvement.

Cortico-Striatal Projection

The cortico-striatal projection was demonstrated with silver staining techniques in various species including the rat (Carman et al, 1965; Webster, 1961). In general, the fibres are ipsilateral (Webster, 1961; Kemp and Powell, 1970); however, in the rat, it is possible to identify a modest contralateral projection originating in the sensory-motor cortex (Carman et al, 1965; Veenings et al, 1980).

Donoghue and Herkenh (1985) have recently re-examined the corticostriatal projection and its relation to patches and matrix compartments in the rat neostriatum. They observed three patterns of corticostriatal projections which varied as a function of the specific cortical area of origin. Medial prefrontal cortex showed a preferential bilateral termination in enkephalinergic patches; agranular motor cortex and cingulate cortex showed bilateral terminations in matrix areas of the caudate-putamen, with the cingulate cortex projecting

to the dorsal and medial striatum and the motor cortex projecting to the lateral third of the head of the caudate-putamen (Domesick, 1969). Finally, ipsilateral projections from primary somatosensory and visual cortex reach striatal matrix zones in the body of the caudate-putamen caudal to the zone receiving projections from the motor cortex. Somatosensory terminals are dense in the dorsal and lateral parts of the caudate-putamen, while the sparse projections of visual cortex reach the dorsomedial striatum.

Hedreen (1977) found that the cell bodies of the cortico-striatal projections are located in layers 3 to 5 of the cortex. They are pyramidal cells, 14 to 16 micrometers in diameter. This is taken as evidence that the cortico-striatal projection constitutes an independent neural system rather than being a collateral projection of another pathway, such as the cortico-spinal system. The terminals of the cortico-striatal cells seem to group themselves within the neostriatum in clusters, each cluster representing the terminals of fibres originating in one particular group of cortical cells (Kemp and Powell, 1971; Jones et al, 1977). The corticostriatal projection fibres apparently terminate on, and excite, the medium sized spiny striatal neurons (Buchwald et al, 1973; Kitai, 1981) as well as on the A-I cholinergic interneurons (Hattori et al, 1980), and there is good evidence that they use glutamate as their transmitter (Divac et al, 1977; Fonnum et al, 1981; Spencer, 1976).

Nigro-striatal Projection

The earliest evidence of the existence of a nigro-striatal projection came from several retrograde degeneration studies in which the death of cells in the substantia nigra was observed following lesions of the neostriatum (Ferraro, 1928; Mettler, 1942; Anden et al, 1964). More recently, the Flack-Hillarp histochemical fluorescence technique was used to demonstrate the existence of dopaminergic cells (Anden et al, 1966; Dahlstrom and Fuxe, 1964) in the substantia nigra. Fallon and Moore (1978 a, 1978 b), using anterograde transport-autoradiographic tracing and horseradish peroxidase retrograde transport methods, studied the major DA-forebrain systems, including the nigrostriatal system arising from Dahlstrom and Fuxe's (1964) A8 and A9 cell groups. The authors reported that the DA neurons projecting to the neostriatum followed a topography organized in three planes, dorsal-ventral, medial-lateral and anterior-posterior. DA cells were found almost exclusively in the substantia nigra - ventral tegmental Area complex (SN-VTA). Still, some DA cells located ventrally in the pars reticulata of the substantia nigra that project to the neostriatum were found. Similarly, ventral cells of the SN-VTA complex project to the neostriatum. The medial-lateral topography is organized such that the medial regions of the SN-VTA complex project to the medial parts of the neostriatum while lateral regions project to the lateral neostriatum. Finally, in the anterior-posterior plane,

anterior parts of the SN-VTA complex project more anteriorly whereas the posterior SN-VTA projects posteriorly in the neostriatum. Another characteristic of the nigrostriatal projection is that the cells projecting to the neostriatum have their somas distributed in discrete clusters within the substantia nigra while their terminals distribute themselves through the entire neostriatum without any sign of clustering (Kemp and Powell, 1966). Two types of terminals are formed, one of which is a large terminal making an asymmetric synapse predominantly on spines, and a second small "en passant" terminal making symmetrical contacts with several types of postsynaptic elements (Kaiya and Namba, 1981; Pickel et al, 1979). The dopaminergic terminals appear to synapse with GABAergic and cholinergic neurons in the caudate-putamen (Hattori et al, 1976).

CHEMICAL MANIPULATION OF THE NEOSTRIATUM

Dopaminergic Manipulations

The primary action of amphetamine is to stimulate activity in catecholaminergic synapses primarily by causing an increase in the release of the endogenous neurotransmitters norepinephrine and dopamine into the synapse and then preventing their deactivation by reuptake into the nerve terminal, thereby prolonging their synaptic activity (Fuxe and Ungerstedt, 1970; Biel and Bopp, 1978).

Peripheral injections of amphetamine have been shown to affect motor behaviors, including increases in locomotor activity, the emergence of certain species-typical behaviors, and a tendency for all behaviors to be repeated in a stereotyped way (Fink and Smith, 1980; Rebec and Bashore, 1984). The evidence that amphetamine-induced stereotyped behavior is mediated by release of dopamine from neurons which innervate the striatum has been extensively reviewed previously (Randrup and Munkvad, 1970). In addition to amphetamine, a variety of other drugs also produce the stereotyped behavior syndrome. These drugs include methamphetamine, methylphenidate, pipradol, apomorphine and cocaine (Randrup and Munkvad, 1970). Consistent with the view that stereotypy is mediated by a dopaminergic mechanism, many of these drugs have been shown to increase the release of dopamine into a ventriculocisternal perfusate (McKenzie and Szerb, 1968; Chiueh and Moore, 1974, 1975). Finally, evidence that the neostriatum is involved in amphetamine stereotypy comes from demonstrations that it can be attenuated by intracaudate injections of neuroleptics such as haloperidol (Fog et al, 1968; Pijnenburg et al, 1975) and that 6-OHDA lesions of the caudate nucleus produce a reduction of amphetamine-induced stereotypy (Creese and Iversen, 1974; Asher and Aghajanian, 1974; Kelly et al, 1975). Similarly, intranigral injections of 6-OHDA also block amphetamine-induced stereotypy (Creese and Iversen, 1972, 1975; Fibiger et

al, 1973).

Peripheral injections of amphetamine also produce effects on learning and memory, including increases in rates of acquisition, facilitation of consolidation and improved retrieval (Gorelick et al, 1975).

Numerous experiments have demonstrated facilitatory effects on the consolidation of memory when amphetamine is administered shortly after a training session. Post-training amphetamine facilitates the consolidation of an avoidance-discrimination response (Doty and Doty, 1966). The effects of amphetamine on discrimination might be related to the complexity of the task as suggested by Hall's finding (1969) that post-training amphetamine failed to affect consolidation of a two-choice visual discrimination task while it facilitated consolidation of a three-choice discrimination task. However, LY 171555, a dopaminergic D2 agonist, when injected after training, improved memory for both appetitive and adversive tasks (Packard & White, 1989). Similarily, amphetamine has been reported to facilitate the consolidation of passive avoidance responses. For example, Johnson and Waite (1971) found that post-training methamphetamine facilitated the consolidation of a single-trial inhibitory avoidance response. In this experiment, the effect was not apparent until 7 days following training which suggests that amphetamine might facilitate the maintenance of consolidated information. Similar effects of post-training amphetamine were

found with shuttle-box avoidance (Evangelista and Izquierdo, 1971) and in a conditioned emotional response (Carr and White, 1984). However, it is important to note that evidence suggests that amphetamine exerts a dose-dependent bidirectional effect on memory consolidation processes. Krivanek and McGaugh (1969) reported that post-training amphetamine injection (0.5 - 2.0 mg\kg) facilitated consolidation of an appetitive discrimination response in mice, while doses of 2.5 mg\kg proved ineffective. Even higher doses of amphetamine (3 - 50 mg\kg) were shown to disrupt the consolidation of a single-trial inhibitory avoidance response (Weissman, 1967).

The results of these experiments in which amphetamine is administered shortly after training have been interpreted as indicating that amphetamine facilitates the consolidation of recently acquired information, that this facilitation is not specific to one type of memory task and works with both appetitively and aversively motivated tasks, and that amphetamine exerts a dose-dependent bidirectional action on consolidation, since memory disruption is observed at higher doses.

Early implication of neostriatal dopamine in the memory improving effect of post-training amphetamine came from an experiment in which direct injection of amphetamine immediately after training into the striatum was shown to improve a conditioned emotional response (Carr and White, 1984). Another experiment (Viaud and White, 1989) supports

further the role of neostriatal dopamine in memory consolidation, and, at the same time, supports the hypothesis that the topographically organized cortico-striatal afference to the matrix is involved in associative memory. Rats were trained on one of two conditioned emotional response tasks: one in which a visual stimulus was paired with shock, the other in which an olfactory stimulus was paired with shock. Intra-cerebral microinjections of amphetamine into the posterior ventral part of the caudate nucleus, also called "dorsolateral striatum", which is innervated by neurons from the visual associative areas of the occipital cortex, improved retention of the visual, but not the olfactory conditioning. The same injection in the lateral ventral part of the caudate, the area that is innervated by neurons from the olfactory associative area of the parietal cortex, improved retention for the olfactory, but not the visual conditioning. This double dissociation implicates the topographically organized cortico-striatal innervation of the matrix compartment in the striatal memory function affected by post-training amphetamine injections.

All this accumulated evidence that post-training injections of amphetamine (Doty and Doty, 1966; Krivanek and McGaugh, 1969; Evangelista and Izquierdo, 1971; Martinez et al, 1980; Martinez et al, 1983; McGaugh, 1989) as well as intrastriatal post-training microinjections of amphetamine (Carr and White, 1984; Viaud and White, 1989) have an

improving effect on associative memory consolidation suggests that striatal catecholamine release, possibly including both dopamine and noradrenaline (Biel & Bopp, 1978), may mediate this potentiation of associative memory consolidation. This hypothesis is strongly supported by a study in which dopamine specific lesions of the nigrostriatal neurons, produced by injecting 6-OHDA into substantia nigra, blocked the post-training memory improving action of amphetamine (White, 1988). However, until recently, little was known about specific neurochemical mechanisms that might be involved.

There is now considerable evidence for the existence of at least two, and probably more, categories of dopamine (DA) receptors (or binding sites) in the brain: type D1, coupled with adenylate cyclase, and type D2, not coupled or negatively coupled with adenylate cyclase (Spano et al, 1978; Spano et al, 1979; Kebabian and Calne, 1979; Seeman, 1981).

However, until recently, the relative involvement of these DA receptor subtypes in central dopaminergic neurotransmission remained uncertain due to the lack of specific drugs for the different DA receptors. More recently, several drugs have been found that discriminate these two dopamine binding sites, among them two compounds apparently specific to D1, SKF 38393, and D2, LY 171755, receptors (Setler et al, 1978; Tsuruta et al, 1981; Watling and Dowling, 1981). Further studies within the neostriatum using these two compounds, and others, revealed that stimulation of the D1

receptor increases C-AMP formation (Kebabian et al, 1982) while stimulation of the D2 dopamine receptors decreases the same C-AMP formation (Stoof and Kebabian, 1981).

Additional evidence supporting D2 dopamine receptor sites as the substrate of the post-training amphetamine memory improving effect in the neostriatum comes from studies showing that a subtype of D2 dopamine receptors, called autoreceptors, are located on the dopaminergic nigrostriatal terminals where they control the synthesis and release of dopamine by these terminals (Roth, 1984; Nowycky & Roth, 1978; Lehman et al, 1983; Salah et al, 1989). These are the same terminals destroyed by 6-OHDA injection into substantia nigra and whose destruction blocks post-training memory improvement of amphetamine (White, 1988). Finally, Packard and White (1989) have shown that apomorphine, LY 171555 and BH-T590 (a specific dopaminergic autoreceptor agonist) all improved memory when injected after training.

Cholinergic manipulations

The role of central cholinergic neurons, especially those found in the striatum, in learning and memory also has long been of interest (see Hagan and Morris 1987 for review). This interest was rekindled by recent reports of a positive correlation between mental status and cholinergic markers in brains of Alzheimer's disease deceased patients (Perry et al, 1978). In addition to many peripheral injection studies,

direct micro-injections of acetylcholine (McLennan and York, 1966) and of choline (Prado-Alcala and Cobos-Zapian, 1979) have been used to increase neostriatal cholinergic activity. Injections of scopolamine, which blocks cholinergic transmission (Prado-Alcala et al, 1979), of potassium chloride, which produces a generalized interference with neural activity (Prado-Alcala et al, 1979), and of atropine (McLennan and York, 1966) have been used to decrease neostriatal cholinergic activity.

The centrally acting muscarinic blocking agents, atropine and scopolamine, have been found to disrupt the acquisition of active avoidance (Herz, 1960), successive discrimination (Whitehouse, 1964, 1967), maze (Pazzagli and Pepeu, 1964), and passive-avoidance responses (Meyers, 1965; Dilts and Berry, 1967). When these agents are injected prior to training and retention is measured some time later (i.e., when the drug effects have subsided), deficits in performance have been observed. Buresova and his collaborators (1964) found that atropine (6 mg/kg) disrupted the retention of a passive-avoidance task in rats. This effect was greatest when the injection-training interval was 20 minutes, a time at which the maximal alterations of EEG activity were observed. Atropine and scopolamine are known to produce a dissociation between behavior and EEG, consisting of the appearance of synchronous high-voltage slow waves without concomitant induction of behavioral sleep or drowsiness (Longo, 1956,

1966). Intraventricular administration of the selective muscarinic antagonist pirenzepine impaired passive avoidance learning when given 20 minutes before training (Caulfield et al, 1983). Pre-training scopolamine has also been found to disrupt pole-jump avoidance response (Gruber et al, 1957) and passive avoidance responses in rats (Bohdanecky and Jarvik, 1967) and mice (Calhoun and Smith, 1968).

Micro-injection studies also revealed deficits in instrumental responding following cholinergic blockade of the neostriatum with scopolamine (Prado-Alcala et al, 1972, 1978). Neill and Grossman (1970) showed that pre-training injections of 10 ug of scopolamine into the dorsal portion of the caudate nucleus impaired acquisition of an avoidance response while the same injection into the ventral part of the caudate nucleus improved acquisition. Others reported impairment of several instrumental tasks following application of anticholinergic drugs into the caudate nucleus: deficits on bar-pressing on a continuous reinforcement schedule and maze performance (Prado-Alcala et al, 1972), in active (Neill and Grossman, 1970) and passive avoidance (Cruz-Morales et al, 1978; Fernandez et al, 1977; Haycock et al, 1978), and in a complex spatial alternation task (Prado-Alcala et al, 1978). Furthermore, lesions of cholinergic neurons in the striatum have been shown to impair acquisition and retention of a passive avoidance response (Sandberg and Sandberg, 1984).

Studies have also demonstrated that increased striatal

cholinergic activity affects memory. An improvement in passive avoidance responding was found upon injecting choline into the neostriatum of rats (Fernandez et al, 1977); Prado-Alcala and Cobos-Zapian (1979) found a dose-dependent modification of performance on a bar-pressing task following injection of choline into the neostriatum of rats: small doses improved and large doses impaired lever pressing. These findings suggests that cholinergic agents might be acting on memory processes in quite different ways depending on the doses used as well as the time of administration.

Gould and Yatvin (1972, 1973), using X-irradiation as the US in a conditioned taste aversion task, found that atropine sulfate blocked the acquisition of conditioned aversion to saccharin. More important, they also found that atropine sulfate injected just before testing had a similar blocking effect suggesting that anticholinergic agents affect retrieval processes as well. Similarly, scopolamine administered prior to test session has been reported to disrupt spatial working retrieval (Beatty and Bierley, 1986). Finally, scopolamine significantly impaired retrieval of a radial maze in animals previously trained without the drug (Watts et al, 1981).

Scopolamine has also long been considered clinically to be a retrograde amnesic agent (Koelle, 1970). Glick and Zimmerberg (1971) using a single-trial passive avoidance task found that high doses of scopolamine (5 - 20 mg/kg) produced retrograde amnesia when administered up to 1 hr post-training.

Furthermore, these effects were shown to be time dependent, since injections 6 hr following training had no effect. In a conditioned emotional response task, post-training intracaudate injection of 5 ug of scopolamine impaired retention of a single shock-CS pairing (Haycock et al, 1973). Weissman (1967) also reported that a variety of anticholinergic agents produced retrograde amnesia, although less than that observed following electroconvulsive shock (ECS). Taken together, these results tend to suggest that high doses of anticholinergic agents such as scopolamine when administered post-training can produce an impairment in memory-storage processes.

However, several studies have failed to demonstrate amnesic effects when scopolamine was administered following training (Bohdanecky and Jarvik, 1967). In their review of the literature, Spencer and Lal (1983) even proposed tha centrally-acting muscarinic cholinergic antagonists such as scopolamine and atropine disrupt mechanisms of encoding and retrieval while sparing memory storage mechanisms. Furthermore, in a few other instances, post-training administration of low doses of atropine (2 to 10 mg/kg) have been reported to facilitate the retention of a shuttle-box avoidance response (Evangeslista and Izquierdo, 1971, 1972). Similarly, cholinergic agonist agents have been shown to impair consolidation. Physostigmine (1.0 mg/kg) administered following training disrupted an appetitive maze-learning

problem (Scratton and Petrinovich, 1963). Carbachol, a cholinomimetic agent, impaired the consolidation of a CER when injected in the caudate nucleus after training (Deadwyler et al, 1972). These results suggest the interesting possibility that muscarinic antagonists may produce a bidirectional action on memory-storage processes; at low doses they improve consolidation while at high doses they disrupt it. It should be kept in mind that atropine exerts effects on Ach activity which are much less potent than those of scopolamine (Longo, 1956, 1966) (2 to 10 mg/kg of atropine being equivalent of 0.1 to 0.5 mg/kg of scopolamine) and that most of the previously cited studies that showed retrograde amnesia with scopolamine or atropine used fairly high doses.

Finally, while it has been generally thought that the loss of muscarinic stimulation is the crucial aspect of Alzheimer's disease that results in memory impairment, the involvement of nicotinic receptors is supported by findings that nicotinic receptor binding is decreased in the brains of patients with Alzheimer's disease (Whitehouse et al, 1986). It is, therefore, not surprising that nicotinic receptor blockade has been found to impair cognitive function in a variety of tasks (Diltz and Berry, 1967; Flood et al, 1981; Blozovoski, 1983; Levin et al, 1987; Levin et al, 1989). However, most of these studies used systemically applied nicotinic agents which do not allow conclusions as to where and how they act to produce these impairments (Fibiger, 1991).

Another reason to be cautious with these results is that these studies have not investigated associative memory but rather used so-called cognitive tasks which are more related to the hippocampus as seen previously.

INTERACTION OF DOPAMINERGIC AND CHOLINERGIC SYSTEMS

The results of other pharmacological studies have suggested an antagonistic interaction between muscarinic and dopaminergic neuronal systems in the brain (Anisman, 1973; Carlton, 1963). Muscarinic receptor antagonists enhance and muscarinic receptor agonists depress the central stimulant actions of amphetamine-like drugs. In rodents, atropine, scopolamine, and other antimuscarinic drugs act synergistically with amphetamine on stereotyped behaviors (Arnfred and Randrup, 1968; Naylor and Costall, 1971; Klawans et al, 1972) and conditioned avoidance responding (Carlton, 1963; Carlton and Didamo, 1961). Atropine also enhances amphetamine self-administration in rats (Davis and Smith, 1975). On the other hand, cholinergic agents such as oxotremorine, physostigmine, or arecoline reduce stereotyped behaviors induced by amphetamine (Arnfred and Randrup, 1968; Colstall et al, 1972a, 1972b; Klawans et al, 1972) or methylphenidate (Janonsky et al, 1972); they also inhibit amphetamine-induced locomotor activity (Mennear et al, 1965).

Furthermore, several studies have shown similarities between the effects of scopolamine, atropine and amphetamine

on memory. Amphetamine disruption of well-learned responses is remarkably similar to the action of Ach antagonists atropine and scopolamine on such responses (Dews and Morse, 1961). Amphetamine has also been reported to disrupt the acquisition of passive avoidance (Cardo, 1959). Finally, both muscarinic antagonist agents and dopaminergic agonist agents seem to exert a dose dependent bidirectional action on memory-storage processes (Deadwyler et al, 1972; Evangeslista and Izquierdo, 1972; Krivanek and McGaugh, 1969; Weissman, 1967).

Little is known about the mechanisms and localization of this interaction between striatal dopaminergic and cholinergic systems. As a possible explanation for this synergism between dopaminergic agonists and muscarinic antagonists, the initial hypothesis was that muscarinic blocking drugs enhance the functional actions of dopaminergic agonists, such as amphetamine, by inhibiting further the cholinergic transmission process (Trabucchi et al, 1975). A more recent theory proposes that muscarinic antagonists affected dopamine release by acting on muscarinic receptors located on the dopaminergic nigrostriatal terminals (Ondrusek et al, 1981; Hagan et al, 1987).

Further supporting this interaction between dopaminergic and cholinergic systems, Scatton (1982) reported that LY 171555 but not SKF 38393 increases Ach and decreases homovanillic acid (HVA) and dihydroxyphenylacetic acid (DOPAC) levels in the neostriatum of rats after systemic injection. He

concluded that D2 but not D1 DA receptors are involved in dopaminergic control of striatal cholinergic transmission, a known element of this structure's memory function. Earlier, Sethy (1979) presented similar findings when he reported that acetylcholine content is increased by D2 dopamine receptor agonists and is decreased by D2 dopamine receptor antagonists. This dopaminergic regulation of neostriatal Ach levels is correlated with the presence of synaptic contacts between dopamine containing neurons with choline acetyltransferase-staining neuronal elements in the neostriatum (Hattori et al, 1976).

There is also evidence for a possible interaction between nicotinic and dopaminergic mechanisms in the striatum. It has been suggested that nicotinic receptors exist on the terminals of DA projections to the striatum (De Belleroche et al, 1979), and nicotinic stimulation stimulates DA efflux (Giorgulieff-Chesselet et al, 1979). This effect was seen even after treatment with tetrodotoxin, which implies that it acted on the presynaptic terminals of DA axons. Furthermore, McGurk and co-workers (1989) have reported that, although both nicotinic and muscarinic cholinergic systems are involved in radial-arm maze performance and antagonists of these receptors are additive in the deficits they cause, nicotinic and muscarinic interactions with dopaminergic systems are opposite in nature. However, the same cautions mentioned earlier apply to these studies since they used systemically administered nicotinic

agents and concentrated on cognitive rather than associative memory.

THE PRESENT STUDY

Based on the evidence suggesting that dopamine release from nigro-striatal terminals might mediate the post-training memory improving effect of amphetamine and that such release might be controlled by D2 dopamine autoreceptors located on these terminals, it was hypothesized that the post-training memory improving effect of dopaminergic stimulation in the neostriatum is mediated by D2 but not by D1 DA receptors. In experiment 1, the effects of post-training intrastriatal injections of amphetamine, a D1 agonist (SKF 38393) and a D2 agonist (LY 171555) into the posteroventral and ventrolateral sites on the retention of the visual and olfactory CERs were examined. This experiment also constituted an attempt at replicating previous findings suggesting that associative memory function in the neostriatum may be localized in terms of sensory modality, defined in terms of the specific cortical input of each neostriatal area (Viaud & White, 1989).

As further test of the hypothesis that DA D2 receptors are critical for memory-improving effects, in experiment 2, the effects of post-training injections of amphetamine alone or together with a D1 antagonist (SCH 23390) or a D2 antagonist (Sulpiride) into the posteroventral site on the retention of the visual CER were examined.

Based on the evidence suggesting that neostriatal cholinergic function is involved in the different stages of associative memory as well as on the evidence that muscarinic

blockade of the striatum has dose-dependent effects on memory, it was hypothesized that striatal muscarinic blockade with low doses of scopolamine would impair acquisition and retrieval while improving consolidation of associative memory. In experiment 3, the effect of pre-training injections of scopolamine into the posteroventral site on the acquisition of the visual CER were examined. In experiment 4, the effect of pre-testing injections of scopolamine into the posteroventral site on the retrieval of the visual CER were examined. In experiment 5, the effect of post-training injections of scopolamine into the posteroventral site on the consolidation of the visual CER were examined.

Based on the evidence that striatal dopaminergic agonists and muscarinic antagonists act synergistically on stereotyped behaviors and on conditioned avoidance responding; and on the evidence that destruction of the dopaminergic nigrostriatal terminals abolishes the post-training memory-improving action of amphetamine injection, it was hypothesized that the site of interaction of the two systems, dopaminergic and cholinergic, is the dopaminergic nigrostriatal terminal and, thus, that the post-training memory improvement effect of muscarinic blockade in the neostriatum is mediated by a M2 muscarinic receptor localized on the nigrostriatal terminal. In experiment 6, using animals in which dopaminergic striatal terminals had been previously lesioned with 6-OHDA, the effect of post-training injections of scopolamine and a M2 specific

muscarinic antagonist, AFDX-384, into the posteroventral site on the consolidation of the visual CER were examined.

Chapter 2

General Methods

The following sections describe the general methods and techniques used throughout the thesis. They apply to all the experiments except when stated otherwise in the descriptions of the individual experiments.

Subjects

Subjects were naive male hooded rats obtained from Charles River Canada Inc., weighing 325-350 gr. at the start of the experiments. The numbers of animals used in the individual experiments are indicated in the procedures for each experiment. They were housed in individual cages in a room with the lights on between 7 a.m. and 7 p.m. Purina Rat Chow and water were continuously available, except as indicated in the procedure.

Apparatus

The training chamber was a box (20 x 25 x 20 cm) made of clear Plexiglas mounted on four legs (3 cm long) so as to raise it above the floor. This made it possible to insert a dish containing Amyl Acetate under the floor of the chamber to provide an olfactory conditioned stimulus when required by the procedure. The chamber was situated inside an insulated wooden enclosure. The floor of the training chamber consisted of stainless steel rods. As required by the procedure, the rods could be connected to a Grason-Stadler shock generator (Model 700) which delivered a scrambled electrical shock. During

other phases of the procedure the grid floor was connected to a drinkometer circuit together with a stainless steel drinking tube protruding from a 2 cm diameter opening in a side wall of the training chamber. Normal chamber illumination was provided through a plastic window in the front of the wooden enclosure by the dim light of the laboratory. Two 25 Watt incandescent bulbs were suspended outside the training chamber (inside the enclosure) to provide a visual conditioned stimulus when required by the procedure.

Surgery

In all the animals cannulae were implanted unilaterally or bilaterally, as required by the experimental procedure, using standard stereotaxic techniques under sodium pentobarbital anaesthesia (55 mg/kg) supplemented by atropine sulphate (0.2 mg/kg). Coordinates were modifications based on experience from the atlas of Paxinos and Watson (1982) and measured from bregma (anterior-posterior and lateral) with the depth determined by lowering the precut cannula until the plastic sleeve touched the skull. As required by the experimental procedure, cannulae were aimed either at the posteroventral (PV) or the ventrolateral (VL) parts of the caudate nucleus. For the PV placement, the coordinates were: -0.3 mm anterior, 4.0 or -4.0 mm lateral and 6.5 mm below the skull. For the VL placement, the coordinates were: 0.6 mm anterior, 4.0 or -4.0 mm lateral and 6.1 mm below the skull.

Following surgery, a screw-on wire stylet was inserted in each cannula to keep it clean. After surgery, all animals were given one to three daily injections of penicillin (Derapen). They were given a minimum of one week to recover before the experiment started.

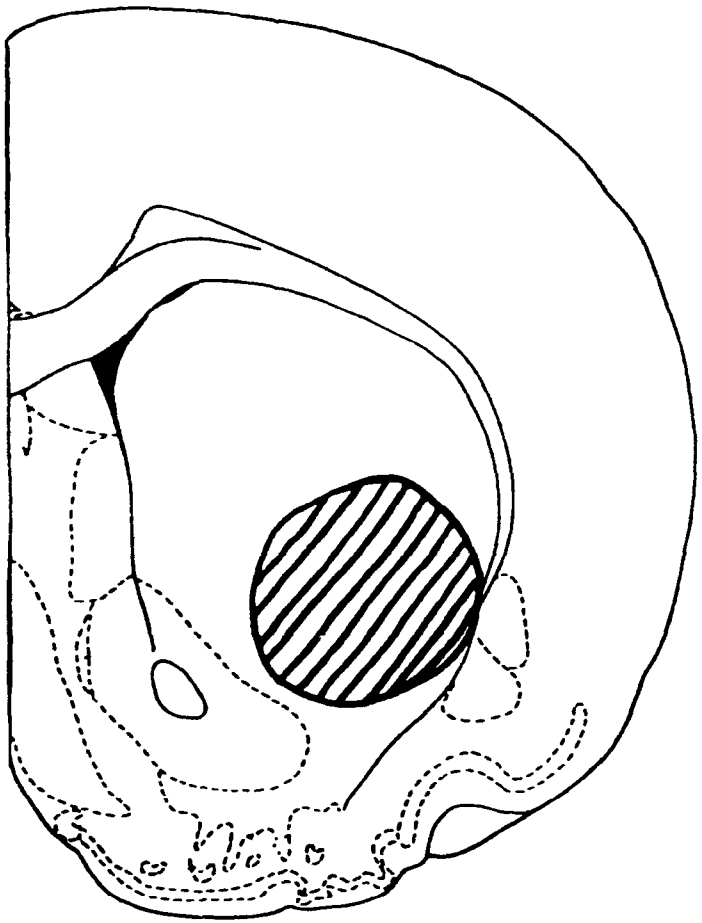
Histology

With the exception of experiment 6, after completion of all behavioral testing the brains of the animals were prepared for histological examination. Animals were anaesthetized with an overdose of chloral hydrate and perfused intracardially with physiological saline followed by 10% formalin. Their brains were removed from their skulls and stored in 10% formalin for at least three days. Twenty micron frozen sections were cut at 100 micron intervals and mounted for histological examination on pregeled slides. The mounted sections were then stained using a modified Kluver and Barrera (1953) technique.

Verification of placements was done using the atlas of Paxinos and Watson (1982). The areas for acceptable placements of the posteroventral and ventrolateral cannulae tips are shown in figure 1. The data of animals whose cannulae fell outside those areas were rejected from all statistical analyses.

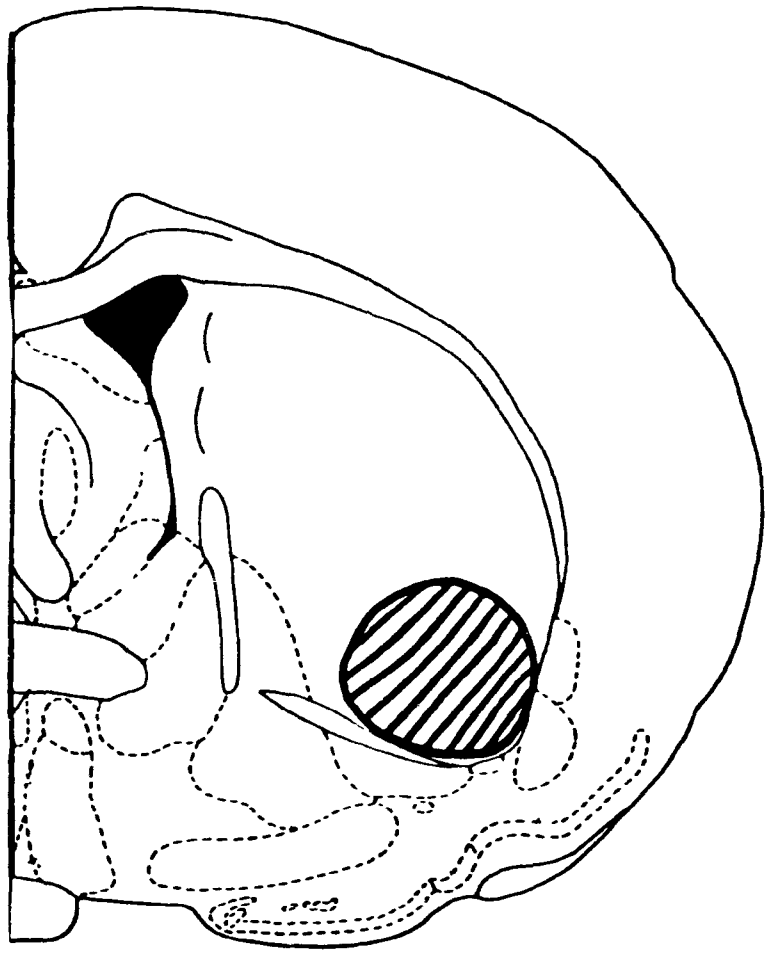
Figure 1. Tips locations of posteroventral and ventrolateral implanted cannulae. The hatched areas show the locations of the tips of the inner cannulae in the brains for all rats included in the different statistical analysis. In the anterior-posterior plane the placements for the ventrolateral cannulae ranged between 0.2 - 0.7 mm anterior to bregma; the placements for the posteroventral cannulae ranged between 0.3 - 0.8 mm posterior to bregma.

VENTROLATERAL



+0.7mm

POSTEROVENTRAL



−0.3mm

General Procedure

On day 1 of the experiment, water was removed from the animals' cages and, on the same day, each rat was handled for a few minutes. The next day, the handling was repeated and the rats were given free access to water for 20 minutes in their home cages. Twenty-four hours later, each animal was placed into the training chamber for 15 minutes with dim chamber illumination. The grid floor was connected to the drinkometer circuit. Water was available through the drinking tube, and the latency for each animal to complete 15 seconds of drinking was recorded. After this pre-exposure to the chamber, the animals were returned to their home cages and given free access to water for 20 minutes. This pre-exposure procedure was repeated on each of the next two days. If the drinking latency on the third day was above 100 seconds, an additional day of pre-exposure was given. Only rats with latencies of less than 100 seconds on day 3 or day 4 were used in the remainder of the experiment. The final pre-exposure day latencies were used to assign the animals to the different experimental groups in a manner that minimized the differences among the mean drinking latencies of the groups. The animals were allowed free access to water.

Twenty-four hours after the last day of pre-exposure, the rats were weighed and water was removed from their home cages. If any pre-training injections were required, they were done according to the procedure described in each experiment before

placing the animals into the chamber. Each rat was then placed into the training chamber. The grid floor was connected to the shock generator. As required by the procedure, each animal received a number of foot-shocks (0.8 mA for 0.5 sec.) at the rate of one per minute. After the last shock, the animals remained in the training chamber for 1 additional minute. For rats in a visual conditioned stimulus (VCS) group, the two 25 Watt bulbs in the enclosure were turned on (VCS+) for the full duration of the training session. For rats in an olfactory conditioned stimulus (OCS) group, amyl acetate was placed beneath the grid floor of the training chamber (OCS+) for the full duration of the training session. If post-training injections were required, they were performed as described in the procedure for each experiment after the animal was removed from the training chamber and put in his cage.

At the end of the training session (or, if required, after post-training injections), the animals were returned to their home cages. Rats in a delayed injection group were also returned to their home cages at the end of training. However, two hours later, they were injected as described in the procedure for each experiment.

Twenty-four hours after training, testing began. In cases where pre-testing injections were required, they were done according to the procedure described in each experiment. Each rat was placed into the chamber. During the testing sessions, the grid floor was connected to the drinkometer circuit. For

some of the animals in the VCS groups the lights were on (VCS+) while for some others they were off (VCS-). Similarly, for some of the animals in the OCS groups the smell was present (OCS+) while for some others no smell was present (OCS-). The rats were allowed to drink freely and the latency to drink for 15 seconds was measured and recorded. After 15 minutes in the chamber, each rat was returned to its home cage and allowed to drink for 20 minutes. This procedure was repeated on the next day.

Statistical Analysis

For each animal included in the analysis after histological verification, the drinking latencies for the two testing days were added together to give a single cumulative latency score. Prior to any further analysis, homogeneity of variance was checked using a F-max procedure. If a serious violation of the assumption homogeneity of variance was found ($p<0.05$), daily latencies were transformed to restore homogeneity and then added in a cumulative transformed latency. The transformation used was determined by the type of violation identified (Kruskal, 1978) and is described in each experiment. The untransformed or transformed scores were analyzed using one-way analyses of variance. Planned multiple comparisons were made with a modified t-test using the within-groups mean square from the analysis of variance (Kirk, 1968) thereby imposing the best estimate of the population variance (assuming the null hypothesis) on each comparison.

Chapter 3

Experiments:

Procedures and Results

POST-TRAINING INTRA-STRIATAL INJECTIONS OF AMPHETAMINE, SKF 38393 AND LY 141555

This experiment was an attempt to elucidate the mechanisms by which post-training, intrastriatal amphetamine produces memory improvement. To do so, the effects of post-training, intrastriatal injections of amphetamine, and SKF 38393 (a D1 agonist), and LY 141555 (a D2 agonist) into the posteroventral and ventrolateral striatal areas on the retention of the visual and olfactory CERs were examined.

Experimental Procedure

Animals with unilateral cannulae aimed at either the posteroventral site or at the ventrolateral site were used in this experiment. During training, each animal received 4 foot-shocks. The animals were micro-injected thirty seconds after training, over a period of one minute (50 seconds for injection plus 10 seconds for diffusion). Each injection consisted of 5 ug of d-amphetamine sulphate, 1 ug of LY171555, or 0.5, 1, or 2 ug of SKF38393, each dissolved in 0.3 ul of vehicle, or the vehicle alone. These doses were chosen after pilot experiments revealed that 1 ug of LY171555 had memory enhancing properties in the present paradigm, but that the same dose of SKF38393 did not exhibit these properties.

The training and testing conditions for each group together with the numbers of animals in each group are shown in table 2.

Table 2. CS for PV site is light; CS for VL site is smell; CS- indicates that the conditioned stimulus is absent; CS+ indicates that it is present; XCS+ indicates that the alternative conditioned stimulus is present; number of 0.8 mA \ 0.5 sec. shocks received during training; amphe=amphetamine; LY=LY 141555; drug doses in ug, volume of all injections is 0.3 ul. In parentheses are the numbers of animals originally trained and tested in each group; outside the parentheses are numbers of animals used in the statistical analysis after examination of the histological material.

TABLE 2

Experimental conditions and Groups

Group	Training Condition	Number Shocks	Post-Training Treatment	Testing Condition	Number PV	Number VI
1	CS+	6	saline	CS+	6 (8)	5 (8)
2	CS+	6	amphetamine (5.0)	CS+	5 (8)	6 (8)
3	CS+	6	SKF 38393 (0.5)	CS+	6 (8)	6 (8)
4	CS+	6	SKF 38393 (1.0)	CS+	6 (8)	6 (8)
5	CS+	6	SKF 38393 (2.0)	CS+	6 (8)	6 (8)
6	CS+	6	LY 171555 (1.0)	CS+	7 (8)	7 (8)
7	CS+	6	amphetamine (5.0)	CS-	6 (8)	7 (8)
8	CS+	6	LY 171555 (1.0)	CS-	6 (8)	6 (8)
9	CS+	6	delay.amphe (5.0)	CS+	6 (8)	7 (8)
10	CS+	6	delay.LY (1.0)	CS+	6 (8)	6 (8)
11	XCS+	6	amphetamine (5.0)	XCS+	6 (8)	5 (8)
12	XCS+	6	LY 171555 (1.0)	XCS+	7 (8)	6 (8)

Results

No violations of homogeneity of variance were found, so the untransformed behavioral data were analyzed. The data for the PV and VL sites groups are summarized in figure 2 and figure 3, respectively.

There were significant treatment effects for both the PV ($F(11, 61)=58.87$, $p<0.01$) and VL ($F(11, 61)=68.67$, $p<0.01$) injection sites. A similar set of multiple comparisons was made on selected groups in both the PV and VL analyses to test hypotheses about the effects of the injections specific to the visual CS for the PV group and to the olfactory CS for the VL group. Since the pattern of these results was the same for both sites, both sets of comparisons are described together. All significant comparisons reached the 0.01 level.

The mean latencies for the rats in the groups injected with amphetamine or with LY171555 were significantly longer than the mean latencies for the rats in the groups injected with saline. In contrast, there were no significant differences between the latencies for the rats in any of the groups injected with SKF38393 and those for the rats in the saline groups.

There were significant differences between the mean latencies for the rats tested in the presence and those tested in the absence of the CSs for both amphetamine and LY171555. The scores for the rats in the drug groups tested in the absence of the CSs were also significantly lower than those

Figure 2. Means of the cumulative daily latencies for animals trained with post-training micro-injections of amphetamine or LY 171555 or SKF 38393 in the postero-ventral neostriatum. The vertical lines on each bar are the standard errors of the mean. All groups except those in the rightmost panel were trained in the presence of the visual conditioned stimulus. Those in the rightmost panel were trained in the presence of the olfactory conditioned stimulus. The post-training microinjections are described on the abscissa: SAL=saline (0.3 ul); AMP=d-amphetamine (5ug); SKF=SKF38393 (amounts shown in ug); LY=LY141555 (1ug); AMP.D=delayed amphetamine (5ug); LY.D=delayed LY141555 (1ug)."+" indicates groups tested in the presence of the conditioned stimulus while "-" indicates groups tested in the absence of the conditioned stimulus.

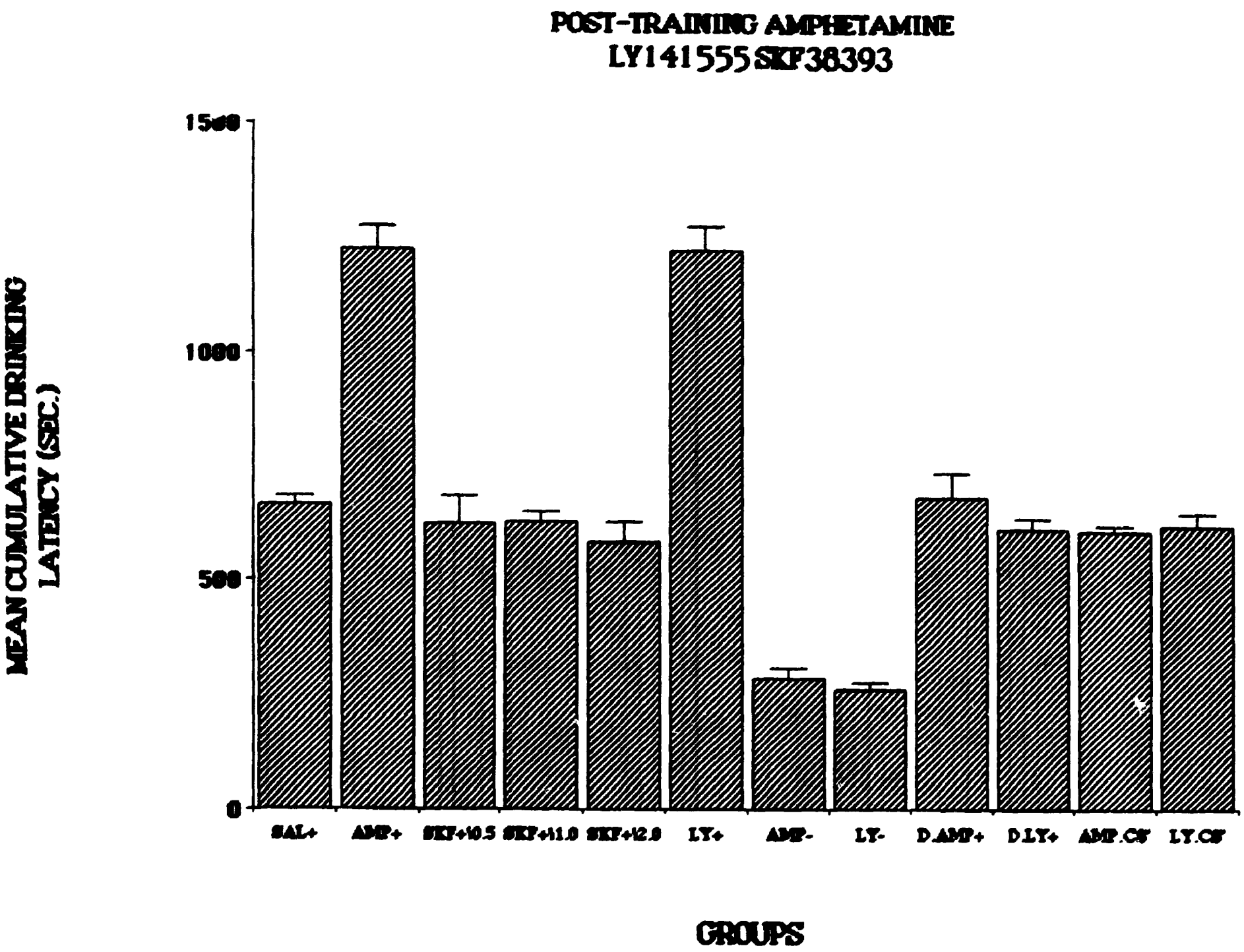
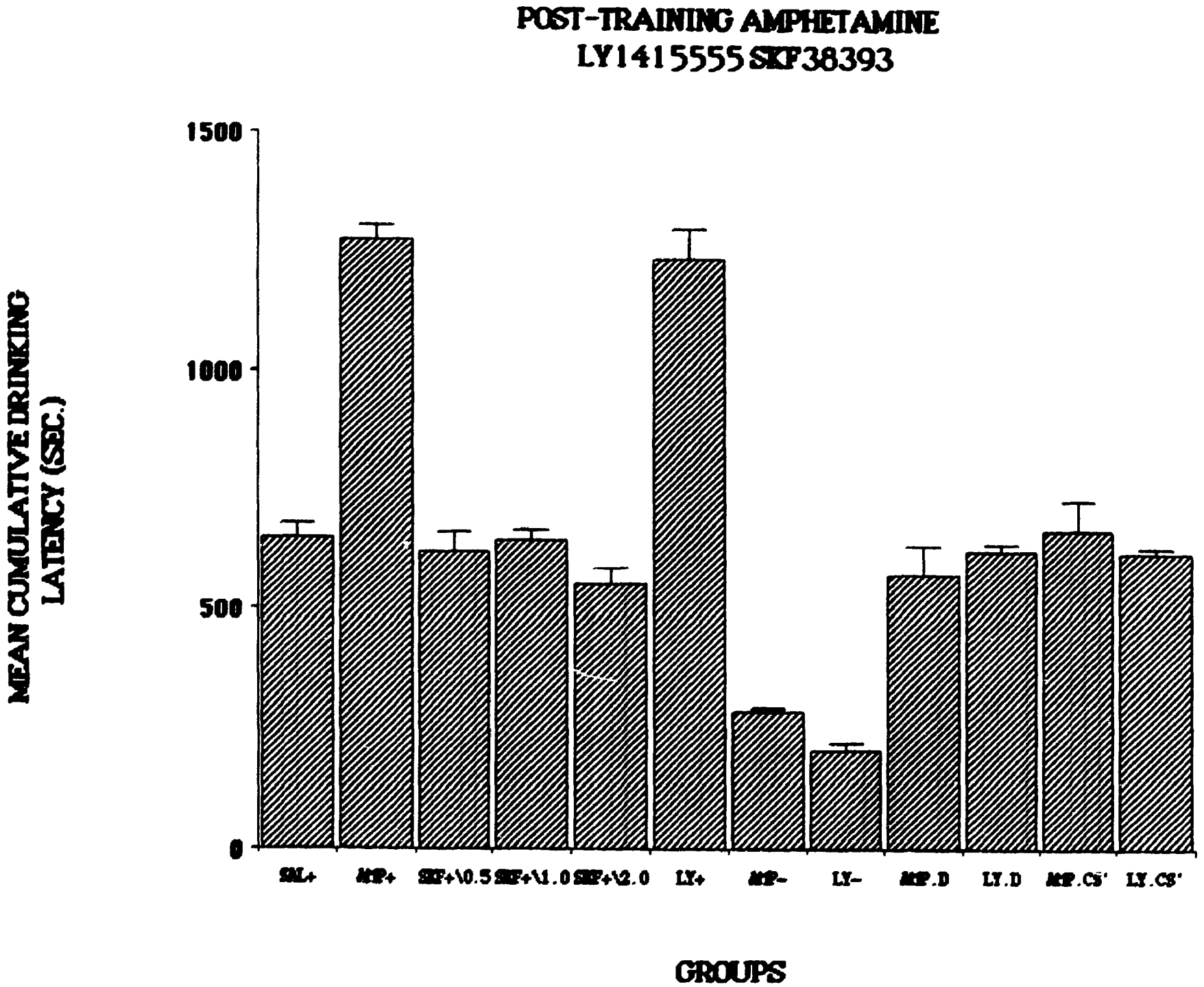

POST-TRAINING AMPHETAMINE
LY141555 SKF38393
MEAN CUMULATIVE DRINKING LATENCY (SEC.)
1500
1000
500
0
SAL+
AMP+
SKF+10.5
SKF+11.0
SKF+12.0
LY+
AMP-
LY-
D.AMP+
D.LY+
AMP.CS
LY.CS
GROUPS

Figure 3. Means of the cumulative daily latencies for animals trained with post-training micro-injections of amphetamine or LY 171555 or SKF 38393 in the ventro-lateral neostriatum. The vertical lines on each bar are the standard errors of the mean. All groups except those in the rightmost panel were trained in the presence of the olfactory conditioned stimulus. Those in the rightmost panel were trained in the presence of the visual conditioned stimulus. The post-training microinjections are described on the abscissa: SAL=saline (0.3 ul); AMP=d-amphetamine (5ug); SKF=SKF38393 (amounts shown in ug); LY=LY141555 (1ug); AMP.D=delayed amphetamine (5ug); LY.D=delayed LY141555 (1ug). "+" indicates groups tested in the presence of the conditioned stimulus while "-" indicates groups tested in the absence of the conditioned stimulus.


POST-TRAINING AMPHETAMINE
LY1415555 SKF38393
MEAN CUMULATIVE DRINKING LATENCY (SEC.)
1500
1000
500
0
SAL+
AMP+
SKF+\0.5
SKF+\1.0
SKF+\2.0
LY+
AMP-
LY-
AMP.D
LY.D
AMP.CS'
LY.CS'
GROUPS

for the rats in the saline groups tested in the presence of the CSs. These findings show that the increased latencies exhibited by the drug groups tested in the presence of the CSs were not due to effects of either drugs or the CSs alone, but that both conditions had to be present for the increase to occur.

Among the groups tested in the presence of the CSs, the mean latencies for the rats in the groups that received immediate injections of amphetamine or LY171555 were significantly longer than those for the rats that received delayed injections of the same drugs. This finding suggests that the increased latencies in the immediate drug groups were not due to any proactive effects of the drugs on the animals' test day behavior. Rather, it suggests, both the amphetamine and LY171555 effects were due to an interaction with neural processes that persisted for a limited time after the pairing of the CSs with the shocks. This finding is consistent with consolidation theory (McGaugh, 1966; McGaugh & Herz, 1972).

The findings for the groups tested with the opposite CSs support the hypothesis that the visual and olfactory CERs are mediated in different parts of the caudate nucleus. Thus, the scores for the PV animals that were tested with the OCS were significantly lower for both amphetamine and LY171555 than those for the PV animals that were tested with the VCS and received the same drugs. Similarly, the scores for the VL animals that were tested with VCS were significantly lower for

both amphetamine and LY171555 than those for the VL animals that were tested with OCS and received the same drugs.

POST-TRAINING INTRA-STRIATAL MICRO-INJECTIONS OF AMPHETAMINE ALONE OR MIXED WITH SCH23390 OR SULPIRIDE(-)

The second experiment constituted yet another attempt at elucidating the mechanisms of amphetamine's action. In this experiment, the effects of post-training injections of amphetamine alone or together with SCH 23390 (a D1 antagonist) or Sulpiride (a D2 antagonist) into the posteroventral striatal area on the retention of the visual CER were examined.

Experimental Procedure

Animals with unilateral cannulae aimed at the postero-ventral striatal site were used in this experiment. During training, each animal received 6 foot-shocks. The animals were micro-injected thirty seconds after training, over a period of one minute (50 seconds for injection plus 10 seconds for diffusion). Each injection consisted of 5 ug of d-amphetamine with 20 ug of sulpiride(-) or 5 ug of d-amphetamine with 0.5 pg of SCH 23390, each dissolved in 0.3 ul of vehicle, or the vehicle alone.

The training and testing conditions for each group together with the numbers of animals in each group are shown in table 3.

Table 3. CS- indicates that the conditioned stimulus is absent (light off); CS+ indicates that it is present (light on); XCS+ indicates that the alternative conditioned stimulus is present (smell); number of 0.8 mA / 0.5 sec. shocks received during training; drug doses in ug except for SCH 23390 (pg), volume of all injections is 0.3 ul. In parentheses are the numbers of animals originally trained and tested in each group; outside the parentheses are numbers of animals used in the statistical analysis after examination of the histological material.

TABLE 3

Experimental conditions and Groups

Group	Training Condition	Number Shocks	Post-Training Treatment	Testing Condition	Number
1	CS+	6	saline	CS-	7 (7)
2	CS+	6	saline	CS+	12 (13)
3	CS+	6	amphetamine (5.0)	CS+	5 (6)
4	CS+	6	amphetamine (5.0) + SCH 23390 (0.5)	CS+	5 (6)
5	CS+	6	amphetamine (5.0) + sulpiride (20.0)	CS-	6 (6)
6	CS+	6	amphetamine (5.0) + sulpiride (20.0)	CS+	5 (6)

Results

Verification of the homogeneity of variance prior to analysis revealed serious violations. Since the means and standard deviation of the drinking latencies were found to be proportional, a logarithmic transformation (log e(x)) was applied to the two daily latencies. Transformed scores were then added and analyzed. The data are summarized in figure 4.

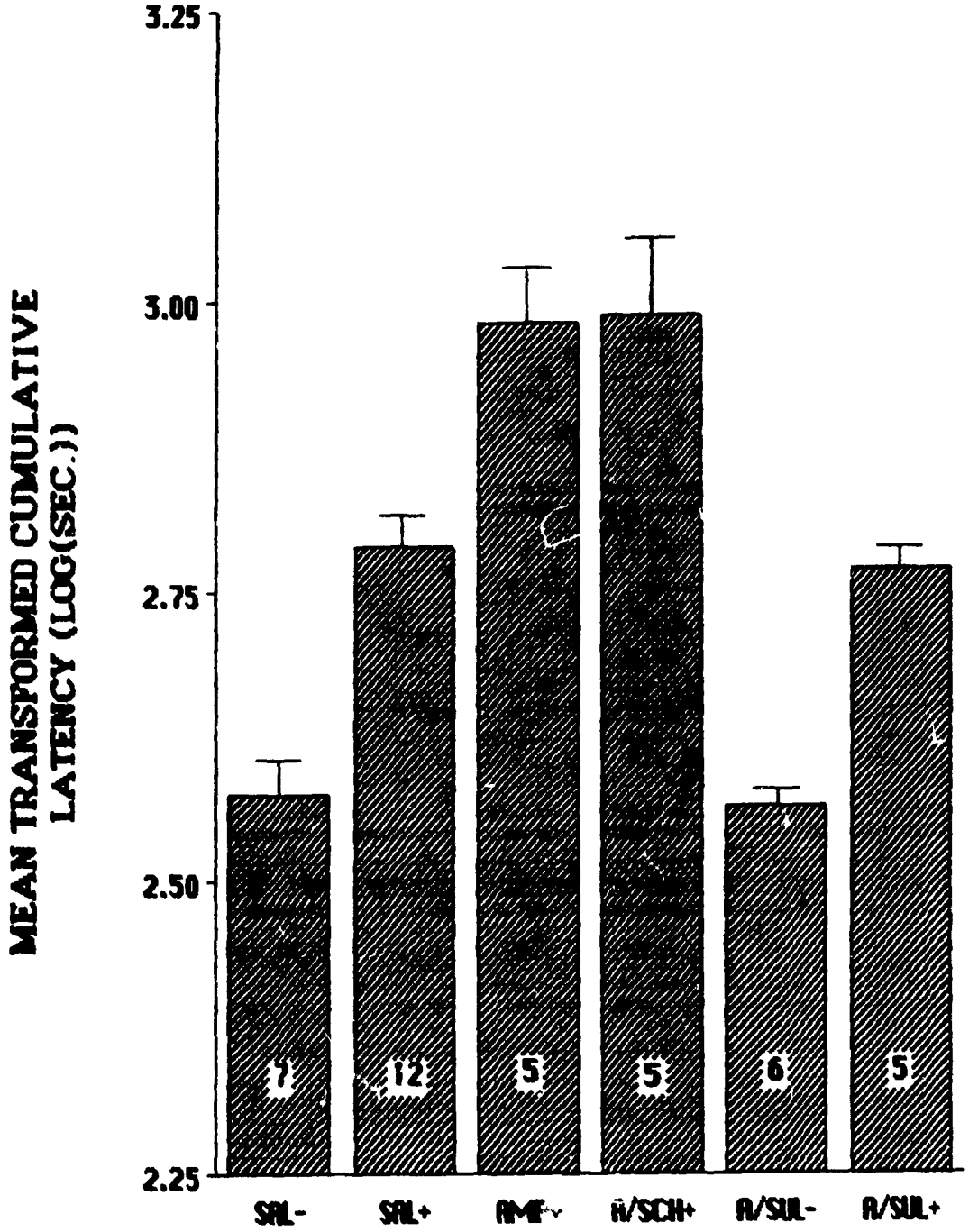
There was a significant overall treatment effect ($F(5, 35) = 26.12$, $p<0.01$). The saline groups tested in the presence of the visual CS had a significantly longer latency than the saline group tested in its absence ($p<0.01$), demonstrating that the increased latency occurred only in the presence of the CS.

Latencies for the animals injected with amphetamine alone and for those injected with amphetamine plus SCH 23390 and tested in the presence of the visual CS were not found to be significantly different ($p>0.05$). These two latencies were however found to be significantly ($p<0.01$) longer than that of the group injected with saline and tested in the presence of the CS. Taken together these findings confirm the previously demonstrated consolidation improving effect of post-training amphetamine. These findings also mean that this effect is independent of D1 receptors activation since their blockade by SCH 23390 failed to interfere with amphetamine's effect.

The cumulative mean transformed latency of animals injected with amphetamine together with sulpiride and tested

Figure 4. Means of the cumulative daily latencies for animals trained with post-training micro-injections of amphetamine alone or with SCH 23390 or with sulpiride(-) in the postero-ventral neostriatum. The vertical lines on each bar are the standard errors of the mean. The numbers inside each bar are the number of rats in each group. The post-training microinjections are described on the abscissa: SAL=saline (0.3ul); AMP=d-amphetamine (5ug); A/SCH=d-amphetamine & SCH23390 (5ug & 0.5pg); A/SUL=d-amphetamine & sulpiride(-) (5ug & 20ug)."+" means tested in the presence of the visual conditioned stimulus while "-" means tested in the absence of the visual conditioned stimulus.

EFFECT OF SCH23390 AND SULPIRIDE ON POST-TRAINING AMPHETAMINE



in the presence of the visual CS was found to be significantly shorter than that of the group injected with amphetamine and tested in the presence of the CS ($p<0.01$). In fact, animals injected with amphetamine together with sulpiride and tested in the presence of the CS were found not to be significantly different ($p>0.05$) from those injected with saline and tested in the presence of the CS. Finally, animals injected with amphetamine together with sulpiride and tested in the absence of the CS were found not to be significantly different ($p>0.05$) from those injected with saline and tested in the absence of the CS. These findings mean that amphetamine's effect on consolidation is dependent on D2 receptors activation since their blockade by sulpiride prevented the memory improving effect of amphetamine.

PRE-TRAINING INTRA-STRIATAL MICRO-INJECTIONS OF SCOPOLAMINE

This experiment was the first of a series of three experiments conducted to elucidate the role of the cholinergic striatal system in associative memory. More precisely, this experiment was design to test the effect of muscarinic blockade on the acquisition of associative memory. To do so, the effects of pre-training, intrastriatal injections of scopolamine into the posteroventral striatal area on the acquisition of the visual and olfactory CERs were examined.

Experimental Procedure

Animals with bilateral cannulae aimed at the postero-ventral striatal site were used in this experiment. On training day, 10 minutes prior to being placed in the training chamber, all the animals were micro-injected bilaterally simultaneously, using two syringes, over a period of one minute (50 seconds for injection and 10 seconds for diffusion). Each injection consisted of 0.1 ug of scopolamine dissolved in 0.3 ul of vehicle, or the vehicle alone. During training, each animal received 10 foot-shocks.

The training and testing conditions for each group together with the numbers of animals in each group are shown in table 4.

Table 4. CS- indicates that the conditioned stimulus is absent (light off); CS+ indicates that it is present (light on); XCS+ indicates that the alternative conditioned stimulus is present (smell); number of 0.8 mA / 0.5 sec. shocks received during training; drug doses in ug, volume of all injections is 0.3 ul. In parentheses are the numbers of animals originally trained and tested in each group; outside the parentheses are numbers of animals used in the statistical analysis after examination of the histological material.

TABLE 4

Experimental conditions and Groups

Group	Training Condition	Number Shocks	Pre-Training Treatment	Testing Condition	Number
1	CS+	10	saline	CS-	7 (7)
2	CS+	10	saline	CS+	7 (7)
3	CS+	10	scopolamine (0.1)	CS-	5 (6)
4	CS+	10	scopolamine (0.1)	CS+	6 (6)
5	XCS+	10	scopolamine (0.1)	XCS+	6 (6)

Results

Since no violations of the homogeneity of variance were found, untransformed behavioral data were analyzed. The data are summarized in figure 5.

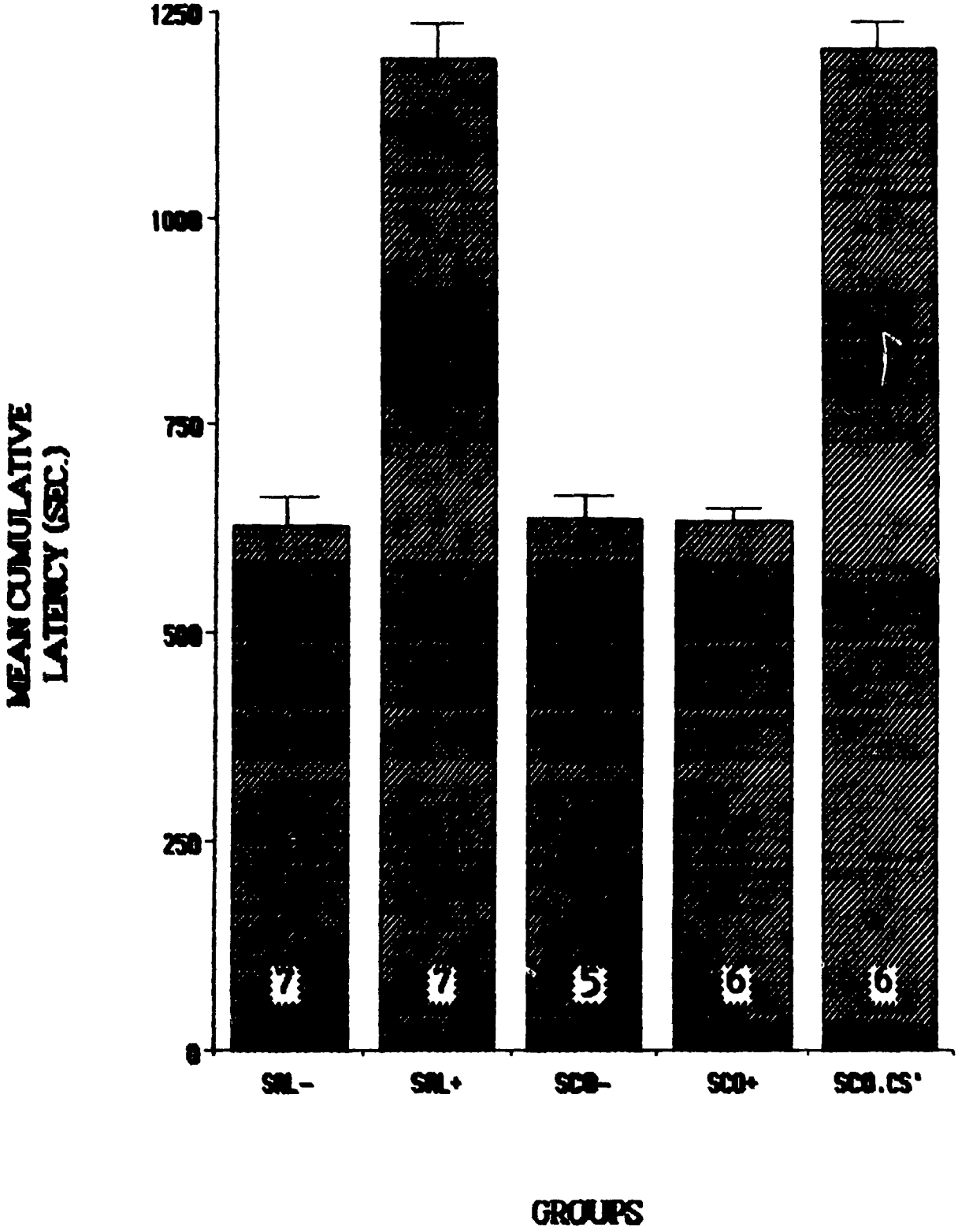
There was a significant overall treatment effect ($F(4, 26) = 75.92$, $p<0.01$). The saline group tested in the presence of the visual CS had a significantly longer latency than the saline group tested in its absence ($p<0.01$), demonstrating that the increased latency occurred only in the presence of the CS.

The group injected with scopolamine and tested in the presence of the visual CS exhibited a significantly shorter ($p<0.01$) mean latency than that of the group injected with saline and also tested in the presence of the visual CS. This difference means that the decreased latency observed in the group that received scopolamine prior to training did not depend upon the injection procedure itself but rather on a specific effect of the drug.

The latencies for the animals injected with scopolamine and tested in the presence of the visual CS were not reliably different from those of animals injected with scopolamine and tested in the absence of the CS ($p>0.05$). Taken together, these two groups' mean latencies were not reliably different ($p>0.05$) from that of the group injected with saline and tested in the absence of the visual CS. These findings mean that scopolamine injected in the postero-ventral striatal site

Figure 5. Means of the cumulative daily latencies for animals trained with pre-training micro-injections of scopolamine in the postero-ventral neostriatum. The vertical lines on each bar are the standard errors of the mean. The numbers inside each bar are the number of rats in each group. The pre-training microinjections are described on the abscissa: SAL=saline (0.3ul); SCO=scopolamine (0.1ug). "+" means tested in the presence of the visual conditioned stimulus while "-" means tested in the absence of the visual conditioned stimulus. "CS'" means that the group was trained and tested in the presence of the olfactory conditioned stimulus.

PRE-TRAINING INTRASTRIATAL
MICRO-INJECTION OF SCOPOLAMINE



impaired the acquisition of a visual CER.

The group injected with scopolamine, then trained and tested in the presence of the olfactory CS had a significantly longer mean latency ($p<0.01$) than the group injected with scopolamine, trained and tested in the presence of the visual CS. Moreover, the latencies for the scopolamine-OCS+ and saline-VCS+ groups were not reliably different ($p>0.05$). These findings mean that scopolamine injected into the postero-ventral striatal site had no effect on the acquisition of an olfactory CER.

POST-TRAINING STRIATAL INJECTIONS OF SCOPOLAMINE

This experiment was the second aimed at elucidating the role of the cholinergic striatal system in associative memory. More precisely, this experiment was design to test the effect of muscarinic blockade on the consolidation of associative memory. To do so, the effects of post-training, intrastriatal injections of scopolamine into the posteroventral striatal area on the consolidation of the visual and olfactory CERs were examined.

Experimental Procedure

Animals with bilateral cannulae aimed at the postero-ventral striatal site were used in this experiment. During training, each animal received 6 foot-shocks. The animals were bilaterally micro-injected thirty seconds after training, using two syringes, over a period of one minute (50 seconds for injection and 10 seconds for diffusion). As required by the procedure, some animals received the same injections but delayed two hours after the end of the training session. Each injection consisted of 0.1 ug of scopolamine dissolved in 0.3 ul of vehicle, or the vehicle alone.

The training and testing conditions for each group together with the numbers of animals in each group are shown in table 5.

Table 5. CS- indicates that the conditioned stimulus is absent (light off); CS+ indicates that it is present (light on); XCS+ indicates that the alternative conditioned stimulus is present (smell); number of 0.8 mA / 0.5 sec. shocks received during training; drug doses in ug, volume of all injections is 0.3 ul. In parentheses are the numbers of animals originally trained and tested in each group; outside the parentheses are numbers of animals used in the statistical analysis after examination of the histological material.

TABLE 5

Experimental conditions and Groups

Group	Training Condition	Number Shocks	Post-Training Treatment	Testing Condition	Number
1	CS+	6	saline	CS-	6 (12)
2	CS+	6	saline	CS+	12 (12)
3	CS+	6	scopolamine (0.1)	CS-	8 (12)
4	CS+	6	scopolamine (0.1)	CS+	8 (12)
5	CS+	6	delay scopolamine(0.1)	CS+	5 (6)
6	XCS+	6	scopolamine (0.1)	XCS+	6 (6)

Results

Verification of the homogeneity of variance prior to analysis revealed serious violation of the assumption. Since the means and standard deviation of the drinking latencies were found to be proportional, a logarithmic transformation (log e(x)) was applied to the two daily latencies. Cumulative transformed latencies were analyzed, and are summarized in figure 6.

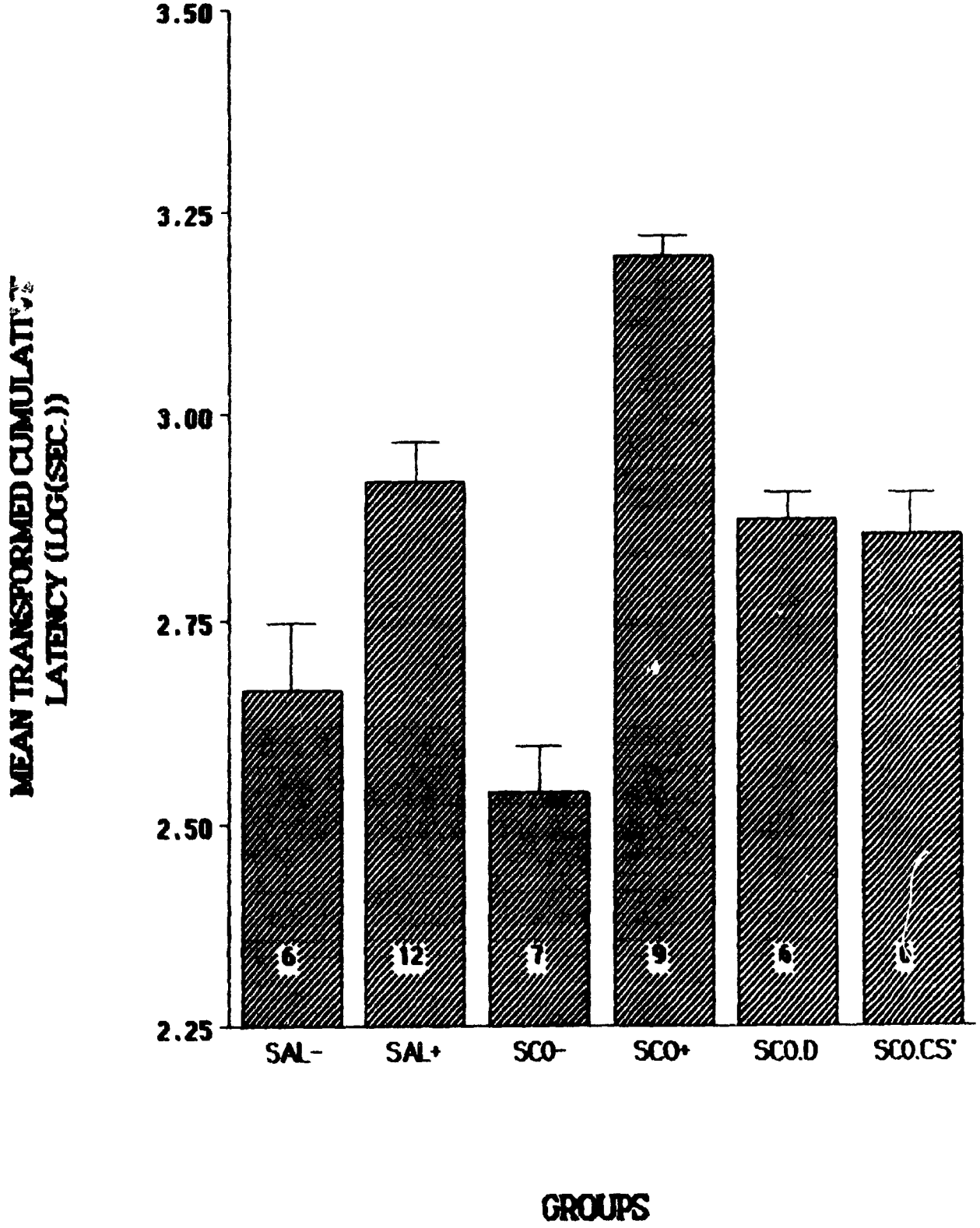
There was a significant overall treatment effect ($F(5, 40)= 13.96$, $p<0.01$). The saline group tested in the presence of the visual CS had a significantly longer latency than the saline group tested in its absence ($p<0.01$), showing that the increased latency occurred only in the presence of the CS.

The group injected with scopolamine and tested in the presence of the visual CS exhibited a mean cumulative latency significantly longer ($p<0.01$) than that of the group injected with saline and tested in the presence of the CS. This difference means that the increased latency observed in the group that received scopolamine immediately after training did not depend upon the injection procedure itself but rather on a specific effect of the drug.

The mean cumulative latency of the group injected with scopolamine and tested in the presence of the visual CS was also significantly longer ($p>0.01$) than that of the group that received a delayed injection of scopolamine and was tested in the presence of the CS. This shows that the effect of

Figure 6. Means of the cumulative daily latencies for animals trained with post-training micro-injections of scopolamine in the postero-ventral neostriatum. The vertical lines on each bar are the standard errors of the mean. The numbers inside each bar are the number of rats in each group. The post-training microinjections are described on the abscissa: SAL=saline (0.3ul); SCO=scopolamine (0.1ug). "+" means tested in the presence of the visual conditioned stimulus while "-" means tested in the absence of the visual conditioned stimulus. "CS'" means that the group was trained and tested in the presence of the olfactory conditioned stimulus while "DEL" means that the post-training microinjection was delayed two hours.

POST-TRAINING INTRASTRIATAL MICRO-INJECTION OF SCOPOLAMINE



scopolamine was restricted to processes occurring shortly after the shock-light pairing. This finding is consistent with consolidation theory (McGaugh, 1966; McGaugh & Herz, 1972) and also eliminates the possibility of proactive effects of scopolamine on the test session.

The mean cumulative latencies of the group injected with saline and tested in the presence of the visual CS and the group injected with scopolamine but trained and tested in the presence of the olfactory CS were not reliably different ($p>0.05$). The group injected with scopolamine and tested in the presence of the visual CS had a significantly longer mean cumulative latency ($p<0.01$) than these two groups. These findings mean that scopolamine injected in the postero-ventral striatal site had no effect on the consolidation of an olfactory CER.

PRE-TESTING INTRA-STRIATAL MICRO-INJECTIONS OF SCOPOLAMINE

This experiment was the third aimed at elucidating the role of the cholinergic striatal system in associative memory. More precisely, this experiment was design to test the effect of muscarinic blockade on the retrieval of associative memory. To do so, the effects of pre-testing, intrastriatal injections of scopolamine into the posteroventral striatal area on the retrieval of the visual and olfactory CERs were examined.

Experimental Procedure

Animals with bilateral cannulae aimed at the postero-ventral striatal site were used in this experiment. During training, each animal received 10 foot-shocks. On test day, 10 minutes prior to being placed in the training chamber, all the animals received bilateral micro-injections done simultaneously, using two syringes, over a period of one minute (50 seconds for injection and 10 seconds for diffusion). Each injection consisted of 0.1 u of scopolamine dissolved in 0.3 ul of vehicle, or the vehicle alone.

The training and testing conditions for each group together with the numbers of animals in each group are shown in table 6.

Results

Since no violations of the homogeneity of variance were

Table 6. CS- indicates that the conditioned stimulus is absent (light off); CS+ indicates that it is present (light on); XCS+ indicates that the alternative conditioned stimulus is present (smell); number of 0.8 mA / 0.5 sec. shocks received during training; drug doses in ug, volume of all injections is 0.3 ul. In parentheses are the numbers of animals originally trained and tested in each group; outside the parentheses are numbers of animals used in the statistical analysis after examination of the histological material.

TABLE 6

Experimental conditions and Groups

Group	Training Condition	Number Shocks	Pre-Testing Treatment	Testing Condition	Number
1	CS+	10	saline	CS-	6 (12)
2	CS+	10	saline	CS+	12 (12)
3	CS+	10	scopolamine (0.1)	CS-	10 (12)
4	CS+	10	scopolamine (0.1)	CS+	10 (12)
5	XCS+	10	scopolamine (0.1)	XCS+	6 (6)

found, untransformed behavioral data were analyzed. The data are summarized in figure 7.

There was a significant overall treatment effect ($F(4, 39) = 84.13$, $p<0.01$). The saline group tested in the presence of the visual CS had a significantly longer latency than the saline group tested in its absence ($p<0.01$), demonstrating that the increased latency occurred only in the presence of the CS.

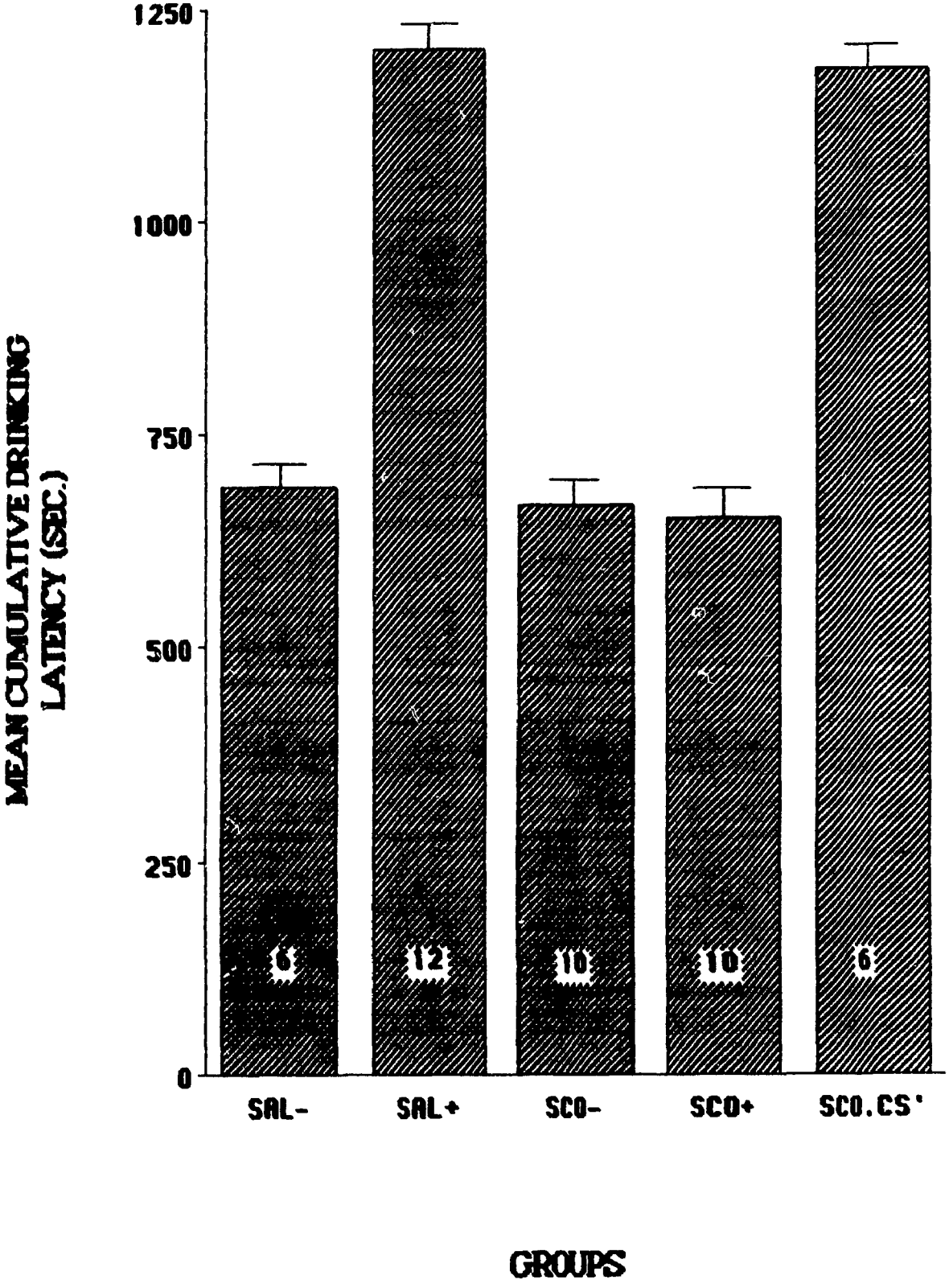
The group injected with scopolamine and tested in the presence of the visual CS exhibited a significantly shorter ($p<0.01$) mean latency than that of the group injected with saline and also tested in the presence of the visual CS. This difference means that the decreased latency observed in the group that received scopolamine prior to testing did not depend upon the injection procedure itself but rather on a specific effect of the drug.

The latencies for the animals injected with scopolamine and tested in the presence of the visual CS were not reliably different from those of animals injected with scopolamine and tested in the absence of the CS ($p>0.05$). Taken together, these two groups' mean latencies were not reliably different ($p>0.05$) from that of the group injected with saline and tested in the absence of the visual CS. These findings mean that scopolamine injected in the postero-ventral striatal site impairs the recall of a visual CER.

The group injected with scopolamine and trained and

Figure 7. Means of the cumulative daily latencies for animals trained with pre-testing micro-injections of scopolamine in the postero-ventral neostriatum. The vertical lines on each bar are the standard errors of the mean. The numbers inside each bar are the number of rats in each group. The pre-testing microinjections are described on the abscissa: SAL=saline (0.3ul); SCO=scopolamine (0.1ug). "+" means tested in the presence of the visual conditioned stimulus while "-" means tested in the absence of the visual conditioned stimulus. "CS'" means that the group was trained and tested in the presence of the olfactory conditioned stimulus.

PRE-TESTING INTRASTRIATAL MICRO-INJECTION OF SCOPOLAMINE



tested in the presence of the olfactory CS had a significantly longer mean latency ($p<0.01$) than the group injected with scopolamine and trained and tested in the presence of the visual CS. Moreover, the latencies for the scopolamine-OCS+ and saline-VCS+ groups were not reliably different ($p>0.05$). These findings mean that scopolamine injected into the postero-ventral striatal site had no effect on the recall of an olfactory CER.

POST-TRAINING INTRA-STRIATAL MICRO-INJECTIONS OF SCOPOLAMINE AND AFDX-384 IN ANIMALS WITH 6-OHDA LESIONS

This experiment was an attempt to elucidate the mechanisms by which post-training, intrastriatal scopolamine produces memory improvement. To do so, the effects of post-training, intrastriatal injections of scopolamine, and AFDX-384 into the posteroventral striatal area of previously 6-OHDA lesioned animals on the consolidation of the visual CER were examined.

Experimental Procedure

Rats were treated with pargyline HCl (50mg/kg) 30 minutes before anaesthetization done with sodium pentobarbital (55mg/kg) supplemented by atropine sulphate (0.2 mg/kg). 6-Hydroxydopamine HBr was made up as 6 ug/ul (base) in vehicle consisting of 0.3 mg/ml of ascorbic acid in 0.9% saline, and kept on ice in the dark before use. Unilateral injection of 6-hydroxydopamine solution or vehicle (sham lesion) was done into the medial forebrain bundle via a 30-gauge stainless-steel cannula attached by polyethylene tubing to a 5-ul Hamilton syringe. During injection, the 6-hydroxydopamine was shielded from light. For greater accuracy, stereotaxic coordinates were derived from the mean of two coordinate systems: 5.9 mm anterior, -2.3 mm lateral and 2.2 mm above the interaural zero; and -3.0 mm anterior, -2.0 mm lateral and 7.8 below the bregma (skull surface). The cannula was lowered

through a burr hole made in the skull to the injection site and, after a two minute delay, 2 ul was injected at the rate of 0.1 ul every 30 seconds. After a further 5 minutes to allow for diffusion the cannula was removed and the burr hole closed with bone wax. A unilateral cannula aimed at the postero-ventral striatal site was then implanted.

During training, each animal received 6 or 10 foot-shocks. With the exception of groups 1 and 2, all the animals were unilaterally micro-injected sixty seconds after training, over a period of one minute (50 seconds for injection plus 10 seconds for diffusion). Each injection consisted of 0.1 ug of scopolamine or 5 ug of AFDX-384 each dissolved in 0.3 ul of vehicle, or the vehicle alone.

The training and testing conditions for each group together with the numbers of animals in each group are shown in table 7.

Determination of dopamine depletion and CHAT activity

Upon completion of behavioral testing, determination of brain dopamine and ChAT activity was done. Rats were killed by cervical decapitation and the brain was rapidly removed and frozen in iso-butane at -50 Celsius. The brain was cut at the mid thalamic level and one 1.5 mm thick coronal section was taken with a freezing microtome. The section spanned from 0.5 mm anterior to 1.0 mm posterior to bregma (from Paxinos and Watson, 1982). The section was placed on ice-cold filter paper

Table 7. 6-OHDA indicates that the animal was lesioned with 6-OHDA; SHAM indicates that the animal was not lesioned with 6-OHDA but instead was micro-injected with vehicle only; CS- indicates that the conditioned stimulus is absent (light off); CS+ indicates that it is present (light on); number of 0.8 mA / 0.5 sec. shocks received during training; drug doses in ug, volume of all injections is 0.3 ul. In parentheses are the numbers of animals originally trained and tested in each group; outside the parentheses are numbers of animals used in the statistical analysis after examination of the histological material.

TABLE 7

Experimental conditions and Groups

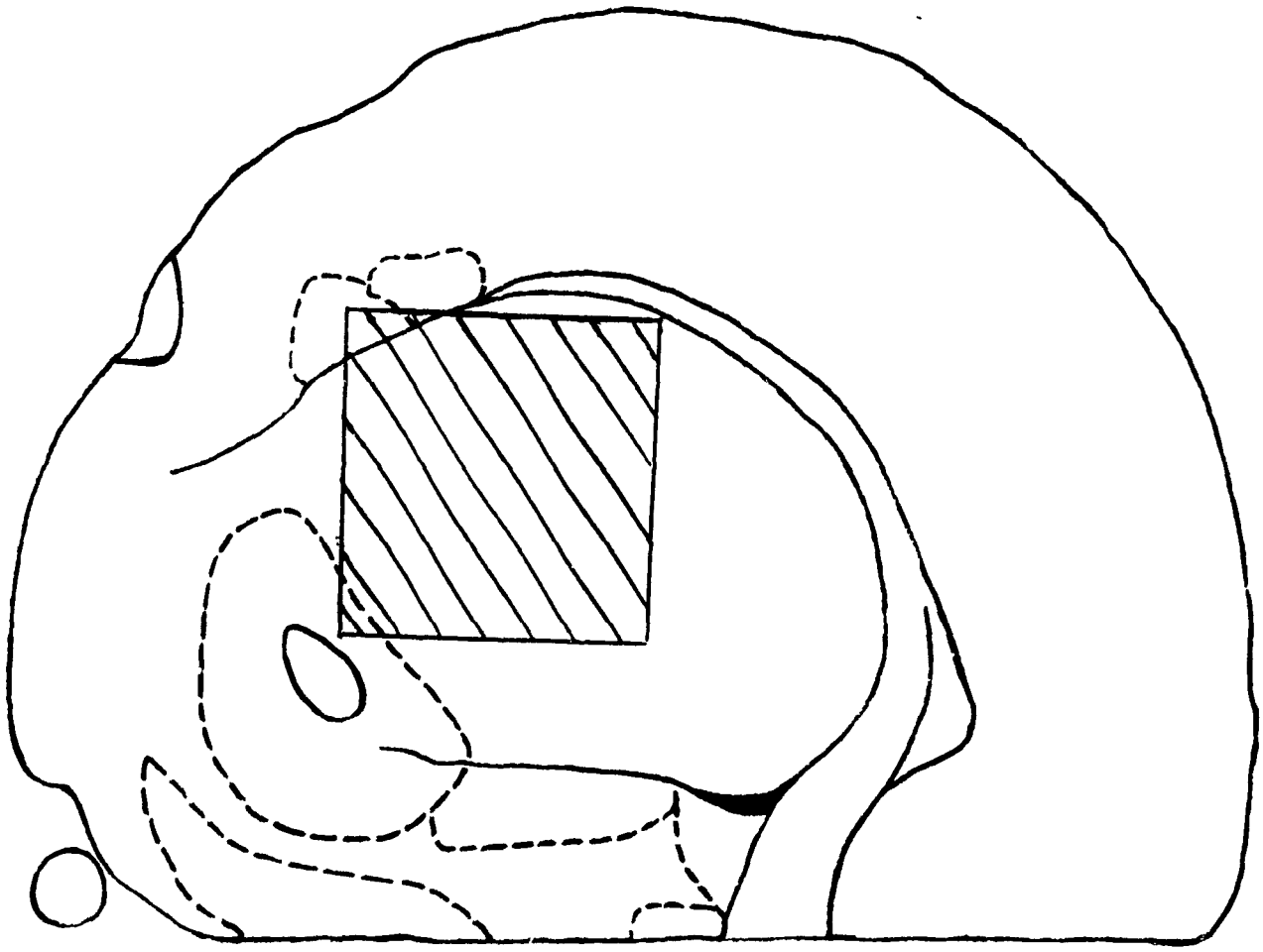
Group	Lesion	Training Condition	Number Shocks	Post-Training Treatment	Testing Condition	Number
1	6-OHDA	CS+	10	saline	CS-	7 (7)
2	6-OHDA	CS+	10	saline	CS+	7 (7)
3	6-OHDA	CS+	6	saline	CS+	7 (8)
4	6-OHDA	CS+	6	scopolamine (0.1)	CS+	5 (8)
5	6-OHDA	CS+	6	AFDX-384 (5.0)	CS+	5 (8)
6	SHAM	CS+	6	saline	CS+	6 (8)
7	SHAM	CS+	6	AFDX-384 (5.0)	CS+	7 (8)

dampened with saline. With the aid of binocular magnifiers, tissue samples were hand-dissected out on both sides of the brain from the area corresponding approximately to the posteroventral site, as illustrated in figure 8. Each dissected sample was then divided into two. One set of samples was used to determine dopamine depletion and the other Choline Acetyltransferase activity following 6-OHDA lesion. This procedure yielded mean tissue weights of 4.76 mg from the lesioned side and 5.14 mg from the control side.

For the determination of dopamine depletion, tissue samples from lesioned and control sides were weighed and disrupted by sonication in ice-cold in 150 ml of 0.1 M perchloric acid containing 40 ug DHBA as an internal standard. After 15 minutes of centrifugation (15000 rpm at 5 degrees C.), aliquots of 5 ul of the supernatant were injected directly into a reverse phase analytical column (Bondapak C18, 10 um, 3.9x150mm, Waters) with a mobile phase of 0.1 M sodium acetate, 0.02 M citric acid and 0.01 M sodium octyl sulphate to which was added 50 mg/L sodium EDTA and 2% methanol. The pH was 4.0. Quantification was by electrochemical detection. All measures were correct within a one percent error margin.

Choline acetyltransferase activity was measured using a modification of a radiometric method first developed by Fonnum (1969) and modified by Tucek (1978). Tissue samples from both sides were homogenized in 500 ul of a medium containing 200 mM NaCl, 40 mM Na Phosphate (pH 7.4) and 0.5 % Triton X-100. 35

Figure 8. Posteroventral striatal area dissected for neurochemical assay. Coronal sections of frozen brain were laid flat for dissection; this illustrations is taken from the atlas of Paxinos and Watson (1982), and the hatched area depicts the approximate appearance of the uppermost surface of the dissected area.



ul aliquots of the homogenate were transferred into duplicate Eppendorf incubation tubes located in an ice water bath. 15 ul of an incubation medium was added. Incubation medium was prepared by mixing 2 parts NaCl 4 M, 1 part choline chloride 0.625 M, 1 part eserine salicylate 10 mM, 5 parts [1-14C] acetyl-CoA 2.5 mM (specific radioactivity 1.5-3 Ci/mol), 2 parts human serum albumin solution (12.5 mg/ml) and 4 parts water. The incubation was done by transferring the tubes from the ice water bath to the dry incubator for 15 minutes. Temperature was 37 degrees C. The incubation was stopped by transferring the tubes back the ice water bath and by adding 500 ul of an ice cold solution of Na phosphate 10 mM (pH 7.4) and ACh chloride 0.2 mM. After all the reactions were stopped 500 ul of an extraction medium was added. The extraction medium consisted of 15mg/ml of sodium tetraphenylboron in 3-heptanone. The resulting solution was shaken 4 minutes and then centrifuged 4 minutes to separate the organic and aqueous phases. 300 ul aliquots of the organic phase were transferred to scintillation vials and 5 ml of ecolite added. Radioactivity was measured in a liquid scintillation spectrometer.

The results of dopamine depletion analysis showed that compared to the control side the posteroventral site on the lesioned side retained an average of 4.67 per cent of normal dopamine (control side = 55.99 ug/g; lesioned side = 2.61 ug/g). One animal was rejected from the statistical analysis

because it did not show any dopamine depletion following 6-OHDA injection. The results of ChAT activity analysis showed that compared to the control side the posteroventral site on the lesioned side retained an average of 95.9 per cent of normal ChAT activity (control side = 103.74 nmol/mg.protein/ hour; lesioned side = 99.48 nmol/mg.protein/ hour). Two animals were rejected because of abnormally low amounts of protein suggesting a manipulation error.

Results

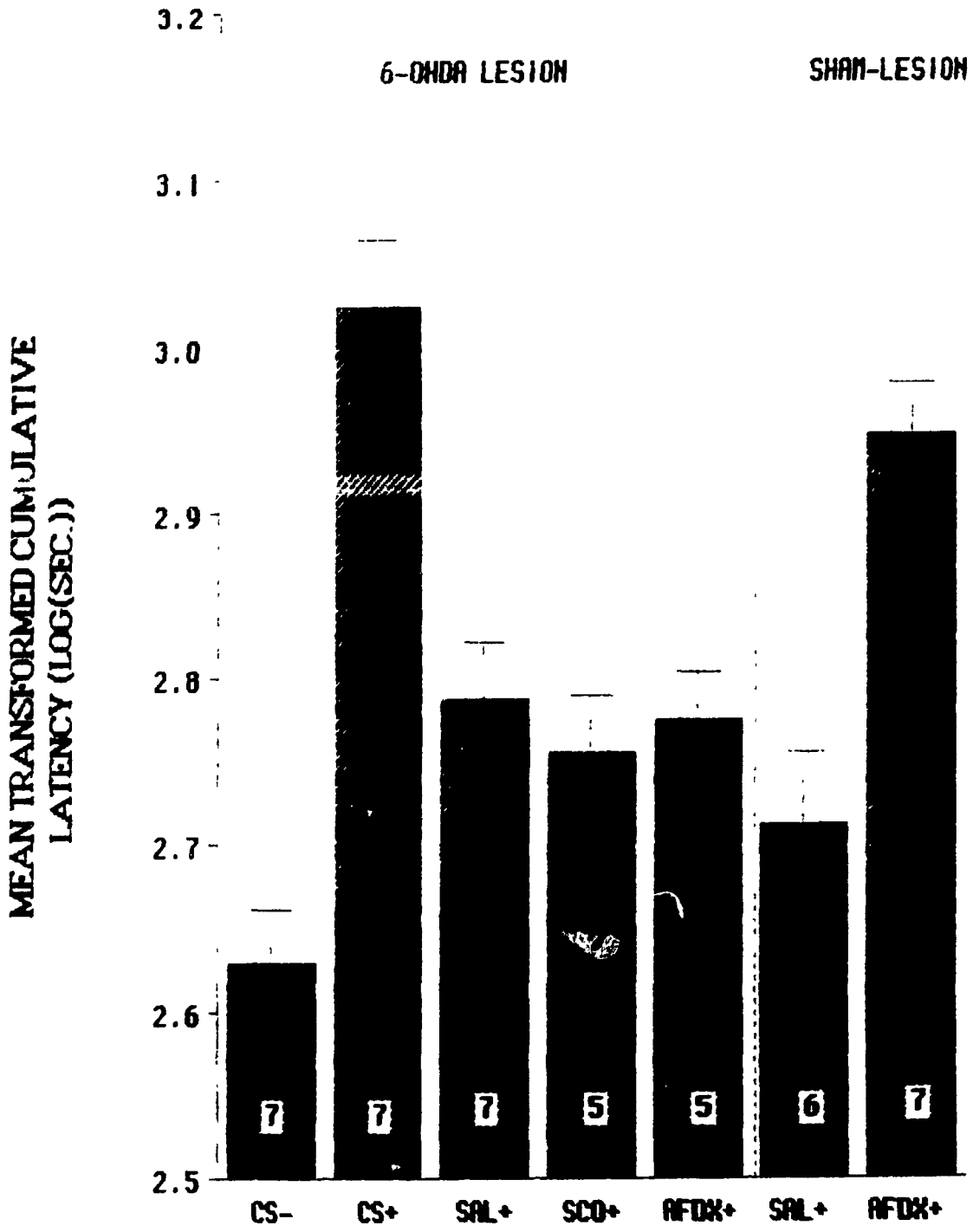
Verification of the homogeneity of variance prior to analysis revealed serious violations. Since the means and standard deviation of the drinking latencies were found to be proportional, a logarithmic transformation (log e(x)) was applied to the two daily latencies. Cumulative transformed latency scores were then analyzed, and are summarized in Figure 9.

There was a significant overall treatment effect ($F(4, 24) = 5.714$; $p<0.05$).

The lesioned group given 10 shocks and tested in the presence of the visual CS had a significantly longer latency than the lesioned group given 10 shocks and tested in its absence ($p<0.01$), demonstrating that the increased latency occurred only in the presence of the CS and that the unilateral 6-OHDA lesion did not impair the acquisition of the visual conditioned emotional response.

Figure 9. Means of the cumulative daily latencies for animals trained with post-training micro-injections of scopolamine or AFDX-384 in the postero-ventral neostriatum. Lesion means that animals had been lesioned unilateraly with 6-OHDA while Sham indicates that animals had received only vehicle injection. The vertical lines on each bar are the standard errors of the mean. The numbers inside each bar are the number of rats in each group. All groups were trained and tested in the presence of the visual conditioned stimulus. The post-training microinjections are described on the abscissa: SAL=saline (0.3ul); SCO=scopolamine (0.1ug); AFDX=AFDX-384 (5ug).

EFFECT OF 6-OHDA LESION ON POST-TRAINING SCOPOLAMINE AND AFDX-384



The cumulative mean latencies of lesioned and unlesioned animals injected with saline were found not to be significantly different ($p>0.05$). This result demonstrates that unilateral dopamine depletion of the posteroventral area of the striatum did not impair the learning and performance of a visual conditioned emotional response.

The cumulative mean latency of unlesioned animals injected with AFDX-384 was found to be significantly longer ($p<0.01$) than that of unlesioned animals injected with saline. This finding suggests that blockade of M2 muscarinic receptors is an event that promotes memory consolidation in the striatum.

Latencies for the lesioned animals injected with scopolamine and those injected with AFDX-384 were not found to be significantly different ($p>0.05$). Taken together these latencies were not different ($p>0.05$) from that of lesioned animals injected with the saline vehicle only. These findings demonstrate that destruction of striatal dopaminergic terminals blocks the memory improving effect of muscarinic antagonists.

These findings mean that the effect of muscarinic antagonists on memory consolidation in the striatum of the rat is dependent on dopaminergic terminals' integrity and may be mediated by the M2 muscarinic receptor located on these terminals.

Chapter 4

Discussion and Conclusion

DISCUSSION

The results of experiment 1 constitute a replication of earlier findings (Viaud & White, 1989) with direct intra-caudate microinjections of amphetamine, and extends them to the D2 agonist, LY 171555. Injection of these substances during the immediate post-training period facilitates the consolidation of memory for recently experienced pairings of a CS with shock. Moreover, this effect is specific to the sensory modality of the CS: injection into the PV area of the caudate improves retention of a CER with a visual CS but not of a CER with an olfactory CS. In contrast, injection into the VL area of the caudate improves memory for a CER with an olfactory CS, but not with a visual CS. An interesting implication of this double dissociation is the possibility that the cortical area of origin of the topographically organized cortico-striatal innervation (Webster, 1961; Hattori et al, 1979; Veening et al, 1980; McGeorge & Faull, 1989; Gerfen, 1989) determines the nature of the sensory information that is processed in each part of the caudate. The full implications of this possibility are seen when considering a possible interaction between the dopaminergic and glutamatergic afferent inputs to the neostriatum. These implications will be considered in the conclusion of this thesis.

The fact that the effects of LY171555 were quite comparable in amplitude to those of amphetamine and that

SKF38393 was without effect suggests that activation of caudate D2 receptors can account completely for the effect of amphetamine in this experimental paradigm. However, the possibility that D1 receptors might be involved in the post-training memory enhancement effect cannot be completely ruled out on the basis of these results alone. Although the present data provide no evidence for a role of caudate D1 receptors in associative memory consolidation, it is possible that higher doses of SKF38393 or that some other D1 agonist might produce an improvement of retention in this or some other memory paradigm. In fact, a memory enhancing effect of post-training intrastriatal injections of SKF38393 in a win-stay radial maze task was observed recently (Packard & White, 1990). This effect was observed with a higher dose of this drug than was used in the present experiment and, as these agonists tend to lose their specificity at higher doses, it is unclear if the effect was due exclusively to D1 receptor binding. Similar doses of SKF38393 have produced extensive damage to the area surrounding a cannula tip in the neostriatum of rats (Delfs et al, 1989). However, no evidence of such damage was observed by Packard and White (1990).

The results of experiment 2 further support a role for the D2 dopamine receptor in the memory enhancing effect of amphetamine. The fact that sulpiride completely abolished the post-training memory improving effect of amphetamine while SCH23390 did not affect it at all constitute additional

evidence that the activation of caudate D2 receptors can account completely for the effect of amphetamine in this experimental paradigm. Again, the present data provide no conclusive evidence concerning a role of caudate D1 receptors in associative memory consolidation. In fact, in a different paradigm, an amphetamine conditioned place preference, systemic SCH23390 (with significantly higher doses) as well as systemic sulpiride(-) were shown to block both the acquisition and the expression of this task (Hiroi and White, 1989). This again raises the possibility of D1 receptors involvement. However, since previous studies have linked this particular paradigm to the nucleus accumbens (Van der Kooy et al, 1982; Vaccarino et al,1985; White et al, 1991), it is possible to suggest that such data do not contradict the present conclusions.

This leaves the question of which one of the striatal D2 receptors is responsible for the post-training memory improvement effect of LY 171555. As previously noted, striatal D2 receptors are found on the terminals of dopaminergic nigro-striatal neurons, where they control the synthesis and release of dopamine (Roth, 1984; Salah et al, 1987). In addition to these presynaptic autoreceptors, D2 receptors can be found at two other locations.

The first of those two sites is probably on the terminals of glutamaergic cortico-striatal neurons (Schwarc et al, 1978; Theodorou et al, 1981). Although there is some controversy

concerning these findings (Trugman et al, 1986; Joyce & Marshall, 1987), there is functional evidence that dopamine can control glutamate release (Maura et al, 1988) and that dopamine release can be controlled by glutamate (Romo et al, 1986; Cheramy et al, 1986; Carter et al, 1988; Clow et al, 1989). These findings suggest that both systems might be interacting in a feedback-loop fashion.

The second post-synaptic location of D2 receptors is on the cell bodies of one or more species of post-synaptic neurons (Ohno et al, 1987), at least one of which is highly likely to be the striatal cholinergic interneuron (Joyce & Marshall, 1985; 1987). This receptor plays a role in the mediation of striatal acetylcholine release (Fujiwara et al, 1987; Stoof & Kebabian, 1982; Stoof et al, 1982), as well as in cholinergic neurotransmission within the striatum (Scatton, 1982; Drukarch et al, 1989). In addition, acetylcholine modulates dopamine function in the striatum (Schoffelmeer et al, 1988; Stoof et al, 1987) again suggesting that these two systems might be interacting in a feedback-loop fashion.

Some recent evidence implicates the pre-synaptic dopamine autoreceptor in the memory improving action of apomorphine (Ichihara et al, 1988a; Ichihara et al, 1988b). Furthermore, it has also been found that the selective activation of this receptor by very low doses of other dopamine agonists during the post-training period facilitates consolidation (Packard and White, 1989).

Therefore, based on the findings of experiments 1 and 2, and on the memory improving action of apomorphine (Ichihara et al, 1988a; Ichihara et al, 1988b), it can be suggested that the stimulation of the dopaminergic D2 autoreceptor located on the nigro-striatal dopaminergic terminals is a likely candidate as the site of the post-training memory effect of intrastriatal amphetamine. The fact that 6-OHDA lesions of the nigro-striatal dopaminergic terminals abolish the consolidation improvement effect of amphetamine (White, 1988) is also consistent with this hypothesis.

As described in the Introduction, there is ample reason, on the behavioral and pharmacological levels, to consider the role played in associative memory processes by the striatal cholinergic system, as well as its interaction with the dopaminergic system. In their review of the literature, Spencer and Lal (1983) proposed that anticholinergic drugs (i.e. scopolamine and atropine) disrupt learning and memory performance by interfering with or distorting encoding and retrieval processes while sparing memory storage. However, others have reported effects on storage and improvements of retention following post-training administration of the cholinergic antagonists atropine and scopolamine (Evangelista & Izquierdo, 1971; Singh et al, 1974; Matthies et al, 1975).

The findings reported in experiments 3, 4 and 5 are partially consistent with Spencer and Lal's hypothesis. Pre-training administration of scopolamine disrupted acquisition

(i.e. encoding) and pre-testing administration disrupted retrieval (i.e. decoding) but post-training administration improved retention (i.e. consolidation). On the one hand, the results of experiments 3 and 5 provide further support for the hypothesis proposed by several researchers (Buresova et al, 1964; Caulfield et al, 1983; Sandberg and Sandberg, 1984) that striatal cholinergic activity is involved in the acquisition and in the retrieval of new sensory-motor memories. On the other hand, the results of experiment 4 reveal a clear memory improving effect of post-training microinjections of low doses of scopolamine in the caudate nucleus. However, one must be cautious with the results from only a single dose of any drug (Fibiger, 1991).

It had been suggested that scopolamine might increase (or decrease) sensitivity or reactivity to footshock (Feigley et al, 1976). If this was the case then it would be impossible to interpret the observed performance impairments following pre-training and pre-testing administration of scopolamine. However, Smith (1978), in an automated version of the flinch-jump paradigm, observed no trend toward increased or decreased sensitivity following scopolamine injection and concluded that the changes in responding after scopolamine administration observed by previous researchers were contingent on the inclusion of an operant response in the dependent measure. Furthermore, in the present experiments, the lack of effect of pre-training and pre-testing posteroventral microinjections on

the olfactory CER seems to rule out any possible effect of striatal muscarinic blockade on sensitivity or reactivity to footshock. These results also rule out any possible explanation of the effect of muscarinic blockade in terms of general motivational, attentional, motor, or other non-memory-related changes (Cheal, 1981). Similarly, because the injections in experiment 4 were given after training, the results observed cannot be interpreted in terms of sensory, attentional or motor processes. Rather, they demonstrate clearly that the muscarinic antagonist scopolamine given after-training potentiates the consolidation process.

In an effort to understand how scopolamine administered after training might have acted to improve memory, we may look at another substance known to produce such memory facilitation: d-amphetamine (Carr and White, 1984; Viaud and White, 1989). An indirect dopaminergic agonist, amphetamine's primary action is to stimulate activity in catecholaminergic synapses by causing an increase in the release of the endogenous neurotransmitters norepinephrine and dopamine into the synapse and then preventing their deactivation by reuptake into the nerve terminal, thereby prolonging their synaptic activity. (Fuxe and Ungerstedt, 1970; Biel and Bopp, 1978). The findings in experiments 1 and 2, together with others (White, 1988; Packard and White, 1990), have suggested that increased stimulation of D2 autoreceptors located on the dopaminergic nigro-striatal terminals may be the basis of the

improved memory consolidation produced by post-training amphetamine.

Peripheral injections of amphetamine also strongly affect motor behaviors, including increased locomotor activity (Van Rossum et al, 1963) the emergence of certain species typical behaviors, and a tendency for many behaviors to be repeated in a stereotyped way (Van Rossum et al, 1962; Smith, 1963; Randrup and Munkvad, 1970; Fink and Smith, 1980; Rebec and Bashore, 1984). The main evidence that the caudate nucleus is involved in amphetamine-induced stereotypy comes from demonstrations that stereotypy is attenuated by intracaudate injections of dopamine antagonists (Fog et al, 1968; Pijnenburg et al, 1975). However, it is also known that cholinergic muscarinic antagonists such as scopolamine enhance the stereotypy produced by dopaminergic agonists (Arnfred and Randrup, 1968; Pycock et al, 1978). More precisely, infusion of the muscarinic cholinergic antagonists scopolamine and atropine into the ventral striatum potentiates apomorphine induced stereotypy (Scheel-Kruger & Arnt, 1985; Wolfarth and Kolasiewicz, 1977). This apparent synergism in the action of amphetamine and scopolamine has led to the suggestion that excitatory dopaminergic and inhibitory cholinergic agents act in a synergistic manner on motor function (Anisman, 1973; Carlton, 1963).

These data, together with the results of experiments 1 and 4 where both post-training amphetamine and post-training

scopolamine improve consolidation of the conditioned emotional response, lead to the suggestion that a synergism similar to the one demonstrated for motor function might exist between the actions of dopamine agonists and scopolamine on memory processes. According to this hypothesis, scopolamine administered after training in experiment 4 improved consolidation by acting on the same mechanism as amphetamine and LY 171555 in experiment 1, that is, by increasing D2 autoreceptor stimulation.

Initially, it had been thought that dopaminergic agonists and muscarinic antagonists acted synergistically in the striatum via the cholinergic interneurons. For example, Trabucchi and his collaborators (1975) suggested that muscarinic blockers enhance the functional actions of dopaminergic agonists, such as amphetamine, by further inhibiting the cholinergic transmission process. However, such an hypothesis cannot explain the similar effects on memory consolidation of both amphetamine and scopolamine in the light of evidence pointing to the D2 autoreceptor as the substrate of the effect of amphetamine on memory.

On the other hand, it is known that local application of muscarinic antagonists to the substantia nigra stimulates synthesis and utilization of dopamine in the neostriatum and reduces the turnover of dopamine in nigro-striatal dopaminergic neurones (Javoy et al, 1974) while activation of muscarinic receptors decreased K^+ -evoked dopamine release in

striatal slices (Westfall, 1974) or synaptosomes (De Belleroche and Bradford, 1978). Finally, Joseph and Roth (1989) showed that activation of muscarinic heteroreceptors with carbachol, an Ach agonist, inhibits neostriatal D2 autoreceptors, precisely those, stimulation of which, has been linked to the post-training memory consolidation improvement effect of amphetamine and LY 171555. Therefore, it seems reasonable to suggest that Ach antagonists such as scopolamine may have the hypothesized effect necessary to explain the similar effects on memory consolidation of amphetamine and scopolamine, and actually somehow stimulate D2 autoreceptors.

If scopolamine acts on memory consolidation by affecting striatal dopaminergic mechanisms, it might be predicted that pre-training and pre-testing manipulations of these receptors should have the same effects as pre-training and pre-testing scopolamine on acquisition and retrieval. Indeed, some studies have reported that pre-training amphetamine disrupts the acquisition and performance of a passive-avoidance response (Cardo, 1959) and of fixed-interval operant learning (Dews and Morse, 1961). Beatty and his co-workers (1984) showed that pre-testing administration of 2.0 mg/kg of amphetamine impaired reference memory in a radial maze task. More recently, using LY 171555, Levin and Bowman (1986) demonstrated that stimulation of D2 receptors before training impaired radial maze learning. Finally, as additional evidence of similar effects, a recent experiment showed that D2

stimulation with LY 171555 exacerbated the impairing effect of scopolamine on choice accuracy in the radial maze when the two drugs were given together twenty minutes before testing (Levin and Rose, 1990)

Therefore, based on the findings of experiments 3, 4 and 5 and on the previously accumulated evidence, it is suggested, with all the limitations implied by the use of a single dose of scopolamine, that striatal muscarinic blockade by scopolamine impairs acquisition and retrieval of a new sensory-motor association while improving its consolidation, thus acting in a manner similar to amphetamine and LY171555, probably by stimulating D2 autoreceptors.

The remaining question is the localization and actual mechanism of this hypothetical action of muscarinic antagonists on D2 autoreceptors.

At first, it was hypothesized (Wauquier et al, 1975) that scopolamine inhibited dopamine uptake - a mechanism that could account for the increased locomotion and stereotypy produced by scopolamine (Coyle and Snyder, 1969; Thornburg and Moore, 1973) as well as for the increased D2 autoreceptor stimulation necessary for memory consolidation improvement. However, it was shown that the ability of 6-OHDA to destroy dopaminergic fibres is not affected by anticholinergic drugs, suggesting that these drugs are not potent in vivo inhibitors of the uptake mechanisms system for dopamine (Breese and Traylor,

1971).

Another hypothesis was proposed on the basis of studies on circling behavior in unilaterally 6-OHDA lesioned rats. When these animals were given systemic injections of direct dopamine receptor agonists, they rotate away from the side of the lesion (Ungerstedt and Arbuthnott, 1970); but with the indirect agonist amphetamine rotation is toward the lesioned side. Amphetamine's action on rotation is known to be mediated by dopamine release from the intact nigro-striatal pathway. In such rats cholinergic agonists given systemically are inactive when given alone but inhibit amphetamine-induced rotation (Pycok et al, 1978). In co' trast, antagonists given alone induce moderate ipsiversive rotation (like amphetamine) and markedly facilitate amphetamine-induced rotation (Ungerstedt & Arbuthnott, 1970; Pycock et al, 1978; Ondrusek et al, 1981). Systemically administered cholinergic antagonists appear to exert their net effect through intact dopaminergic neurones, as scopolamine induced rotation is blocked by pre-treatment with the monoamine synthesis inhibitor alpha-methyl-P-tyrosine (Pycock et al, 1978; Ondrusek et al, 1981) and the dopamine antagonists haloperidol, chlorpromazine and pimozide (Kelly & Miller, 1975). Finally, inhibition of dopamine beta-hydroxylase failed to block the effect of scopolamine, indicating that its action was associated with pre-synaptic dopaminergic function (Ondrusek et al, 1981).

All of these findings are consistent with a report of

decreased density of muscarinic cholinergic receptors after 6-OHDA treatment (De Belleroche et al, 1979), suggesting that muscarinic receptors are located on pre-synaptic dopaminergic fibres. Furthermore, additional evidence from peripheral nervous system studies suggests that there are at least two types of muscarinic receptors: M1 receptors are postsynaptic and excitatory; M2 receptors are presynaptic and inhibitory (North et al, 1985). Recent studies have suggested that the muscarinic receptor located on pre-synaptic dopaminergic fibres may be of M2 type (Schoffelmeer et al, 1988). Using unilaterally 6-OHDA lesioned rats, Hagan and his co-workers (1987) showed that scopolamine and other muscarinic antagonists facilitated amphetamine-induced rotation and that this effect is correlated with the drugs' affinity for M2 binding sites.

The results of experiment 6, using animals in which dopaminergic striatal terminals had previously been lesioned with 6-OHDA, are consistent with the hypothesis that the effect of post-training muscarinic blockade on the consolidation of new sensory-motor associations is mediated by M2 muscarinic receptors located on the terminals of the dopaminergic nigro-striatal neurons, as suggested by the reported decreased density of striatal muscarinic cholinergic receptors after 6-OHDA treatment (De Belleroche et al, 1979). However, again, due to the use of only a single dose of AFDX-384, the interpretation of such results must be cautious.

Furthermore, considering the fairly large dose of AFDX-384 used (5 ug), it is not known if, at that dose, AFDX-384 is still very specific in its action.

Recent evidence shows that muscarinic and dopaminergic receptors are both coupled to dopamine-sensitive adenylate cyclase (Akiyama et al, 1986; Schoeffelmeer et al, 1988) and that stimulation or blockade of D2 receptors affects the coupling of M2 receptors to adenylate cyclase (Schoeffelmeer et al, 1988). Furthermore, it has been shown that forskolin, an activator of adenylate cyclase used to enhance cAMP levels, stimulates dopamine release in a dose-dependent manner in striatal slices (Lee et al, 1990). This suggests that the cAMP effector system is involved in mechanisms that decrease or increase dopamine release. Finally, since M2 receptors inhibit at least some aspects of adenylate cyclase activity in homogenates of different rat brain regions including the striatum (Gil and Wolfe, 1985; Olianas et al, 1982, 1983a, 1983b), it is possible that M2 antagonists such as AFDX-384 and scopolamine (non-specific) have an opposite effect on adenylate cyclase and stimulate dopamine release, acting like amphetamine or forskolin.

In another recent experiment (Packard et al, 1990), AFDX-116, also a specific M2 receptor antagonist, improved consolidation of a win-stay radial maze when administered systematically immediately after training. The authors suggested that the memory improvement might have involved the

blockade of M2 autoreceptors which would have resulted in increased Ach release. In light of the present finding, it seems unlikely that AFDX-116 acted on cholinergic interneurons to improve memory; more probably, as hypothesized here for AFDX-384, AFDX-116 acted on M2 receptors coupled with adenylate cyclase on the dopaminergic nigro-striatal terminals and increased dopamine release. Indeed, it has been shown that AFDX-116 is a potent blocker of the inhibiting effect of carbachol on adenylate cyclase activity (McKinney et al, 1989).

Finally, considering that the effects of muscarinic agonists and antagonists on memory in the striatum have often been shown to be dose-dependent (Longo, 1966; Prado-Alcala & Cobos-Zapian, 1979), it can be suggested that the memory improving effect of low doses of post-training scopolamine and atropine (Evangelista & Izquierdo, 1971; Singh et al, 1974; Matthies et al, 1975) can be explained by postulating a relatively specific action on M2 receptors located on the dopaminergic terminals. The impairing effect of larger doses of the substances (Glick and Zimmerberg, 1971; Haycock et al, 1973) may act by affecting muscarinic receptors located elsewhere, i.e. on the pre- and post-synaptic membranes of cholinergic interneurons. However, the present results do not allow for a conclusion on this hypothesis.

Therefore, based on the findings of experiment 6 and on

the accumulated evidence, it is suggested, with all the limitations implied by the use of only a single dose of scopolamine and AFDX-384 and the possibility that AFDX-384 might have lost its specificity at such a high dose, that the memory consolidation improving effect of striatal muscarinic blockade is mediated through M2 pre-synaptic receptors located on nigro-striatal dopaminergic terminals acting on adenylate cyclase to affect dopamine release. The details of this hypothesis are discussed in the final section of the thesis.

Finally, although the present studies do not provide any evidence for a role of striatal glutamatergic function in memory, the implication of the glutamatergic cortico-striatal innervation of the caudate in associative memory processes by the anatomical specificity of the effects of direct application of drugs to the structure make such a possibility worthy of further investigation.

Furthermore, several recent reports have shown that many associative memory tasks, possibly mediated by the neostriatum, can be disrupted by systemic injections of NMDA antagonists such as MK801 or AP5. Administration of MK801 prior to training disrupted the acquisition of a conditioned nictitating membrane response in the rabbit (Stillwell & Robinson, 1990). Acquisition of a three-lever sequence response was also disrupted by pre-training administration of MK-801 (Cohn & Cory-Slechta, 1990). AP5, administered before

training, blocked acquisition of Pavlovian fear conditioning in the rat, but, when administered immediately after the foot-shock pairing, it failed to block retentionof the behavior (Kim et al, 1990). The NMDA antagonists AP5 and AP7 given prior to passive avoidance acquisition resulted in amnesia (Danysz et al, 1988) while administration of glutamate into the brain enhanceed retention performance (Davis & Flood, 1987).

Recently, MK-801 has been shown to reduce the release of dopamine in a dose-dependent manner (Kashihara et al, 1990) while agonists such as L-glutamate and NMDA have been reported to liberate endogenous dopamine from striatum (Carter et al, 1988; Cheramy et al, 1986; Roberts & Anderson, 1979). Considering the apparently critical role played by dopamine in memory processes, the hypothesis that glutamatergic agents affect at least some type of memory through their action on dopamine suggests itself.

CONCLUSION

Based on the evidence that the neostriatum is an important part of the neurological system underlying associative learning and that dopamine release from nigro-striatal terminals might mediate post-training memory improving effect of amphetamine, the experiments in the present thesis attempted to identify some of the neurochemical mechanisms underlying this function of the neostriatum. As previously discussed in the introduction, White (1989) suggests that the pattern of organization of the matrix compartment, its connections and its relationship with sensory-motor function are perfectly suited for such a function. The only element missing was the demonstration that the matrix contains a mechanism for memory formation and consolidation, that is, for creating permanent sensory-motor (S-R) connections on the basis of experience. The purpose of this thesis was an attempt at finding that mechanism.

It seems clear that the three main neurochemical systems (dopaminergic, cholinergic, glutamatergic) of the neostriatum act together to mediate associative memory process in the neostriatum. For example, muscarinic agents regulate the turnover of dopamine in nigro-striatal dopaminergic neurones (Javoy et al, 1974), and activation of muscarinic receptors decreases K^+ -evoked dopamine release in striatal slices (Westfall, 1974) and synaptosomes (De Belleroche and Bradford, 1978). Similarly, D2 but not D1 dopaminergic receptors are

responsible for control of striatal cholinergic transmission (Scatton, 1982; Stoof et al, 1982). Thus, instead of acting independently, the dopaminergic and cholinergic (and possibly glutamatergic) elements in the neostriatum probably interact as part of a single system, with the D2 receptor playing a key role in the plasticity required for the acquisition, storage and retrieval of new associations in a manner that remains to be discussed.

Based on these ideas, a hypothetical model of how normal S-R learning might occur in the neostriatum and involve all three neurotransmitter systems can be proposed. This model must be able to explain both normal learning phenomena and the drug-induced results observed in the present experiments. The basis of the hypothesis is that changes in cAMP activity and their effects on the dopaminergic-cholinergic balance constitute the neural substrate of consolidation. Indeed, it has been suggested that receptor-mediated regulation of the intracellular levels of the second messenger cyclic AMP is an important mechanism by which hormones and neurotransmitters acting on the extracellular face of the plasma membrane produce long-lasting changes in cellular metabolism (Baron & Siegel, 1989). Furthermore, stimulation of the D2 autoreceptors located on the nigro-striatal dopaminergic terminals is known to lead to decreased cAMP activity, decreased dopamine activity, and increased acetylcholine activity. It is therefore suggested that stimulation of this

autoreceptor constitutes the key to the more or less permanent changes required for consolidation of sensory-motor memory in the striatum.

Since the model integrates a large number of pharmacological and behavioral data, a clear summary of the known effects of the release of each of the three neurotransmitters, dopamine, acetylcholine and glutamate at the level of neostriatal synaptic complex is a necessary pre-requisite to a presentation of the theory.

First, released glutamate causes the release of dopamine from the dopaminergic nigrostriatal terminals by acting directly on glutamatergic receptors located on those terminals (Roberts & Anderson, 1979, Romo et al, 1986; Cheramy et al, 1986; Carter et al, 1988; Clows et al, 1989), as well as the release of acetylcholine from the acetylcholinergic A-I interneuron (Hattori et al, 1979).

Second, released dopamine inhibits the release of glutamate from the cortico-striatal neurons by acting directly on a D2 type dopaminergic receptor located on the cortico-striatal terminals (Maura et al, 1988), and inhibits the release of more acetylcholine from the acetylcholinergic A-I interneuron (Stoof & Kebabian, 1982; Stoof et al, 1982; Fujiwara et al, 1987). Finally, dopamine stimulates D2 autoreceptors. These D2 receptors inhibit adenylate cyclase activity in the striatum (Stoof & Kebabian, 1981) and their

stimulation has a long-lasting inhibitory effect on cAMP formation in the striatum (Kelly & Nahorski, 1987). Through the release of dopamine it causes, amphetamine injected into the striatum would produce all of these effects. Before training or testing, amphetamine's released dopamine would inhibit or decrease the release of glutamate and inhibit the acetylcholinergic interneurons, both of which are critical elements of any acquisition and retrieval process. After training, in contrast, amphetamine would enhance the normal processes triggered by the natural release of dopamine (triggered by glutamate or by stimulation of the substantia nigra), including stimulation of the D2 autoreceptor linked to consolidation.

Third, released acetylcholine acts on other cholinergic A-I interneurons and causes them to release acetylcholine (McLennan & York, 1966; Prado-Alcala & Cobos-Zapian, 1979). On the dopaminergic nigro-striatal terminals, ACh acts on muscarinic M2 receptors to decrease dopamine release (Lee et al, 1990) probably by temporarily decreasing adenylate cyclase activity (Olinniana et al, 1983; Gil & Wolfe, 1985)), which in turn results in decreased D2 stimulation. On the other hand, scopolamine injections into the striatum produce opposite effects. They inhibit acetylcholinergic interneurons (Prado-Alcala et al, 1979) and cause increased dopamine release (Javoy et al, 1974; Ondrusek et al, 1981). Dopamine, in turn, produces all the above mentioned effects. Thus, in causing the

release of dopamine from the nigro-striatal terminals by acting on cAMP activity, scopolamine acts in the same way as amphetamine (which also causes the release of dopamine from the nigro-striatal terminals), inhibiting acetylcholinergic interneurons (directly and through the released dopamine) and stimulating, through the released dopamine, the D2 autoreceptor linked to memory consolidation. Therefore, it can be predicted that, as is the case with amphetamine, pre-training and pre-testing scopolamine would impair acquisition and retrieval processes while post-training injections would improve consolidation.

Figure 10 depicts the neuronal activity during and immediately after training in the neostriatum. The stimulation of appropriate cortical areas by the US (shock) and the CS (light leads to the release of glutamate by the cortico-striatal terminals at two specific sites, called synapses I and II, in the striatum while another site (e.g. sweet taste, synapse III) is left unaffected. At the first two sites, glutamate (indicated by continous arrows) released from the cortico-striatal neurons excites both the dopaminergic nigro-striatal terminals (continuous arrow 1) onto DA-I and DA-II, causing the release of dopamine (indicated by hatched arrows), and the cholinergic interneurons (continuous arrow 2) A-I and A-II, causing the release of acetylcholine (indicated by doted arrows).

The dopamine released by DA-I and DA-II affects (1) the glutamatergic cortico-striatal terminals G-I and G-II inhibiting further release of glutamate (hatched arrow 1); (2) the acetylcholine interneurons A-I and A-II which it hyperpolarizes, inhibiting release of acetylcholine (hatched arrow 2); and (3) the D2 auto-receptors located on the dopaminergic terminals DA-I and DA-II, stimulating them (hatched arrow 3).

The acetylcholine released by A-I affects (1) the acetylcholine interneurons A-II and A-III causing depolarization (doted arrow 1); (2) the M2 receptor located on the dopaminergic terminals DA-II and DA-III (doted arrow 2); and (3) the spiny type II efferent neuron which probably serves as an output to motor system (doted arrow 3). Evidence that pre-established connections between specific areas of the striatum and specific motor responses exist comes from studies showing that micro-injection of amphetamine into the ventrolateral striatum, results in oral stereotypies (Kelley et al, 1988; Kelley et al, 1989) while similar injections in several other striatal regions do not (Delfs & Kelley, 1990).

Also on figure 10, next to each synapse, the net resulting effect of D2 stimulation on cAMP activity is indicated. Stimulation of the D2 autoreceptor on terminal DA-I leads to a long-lasting decrease in cAMP activity which in turn reduces the basal level of dopamine activity of DA-I and increases the basal level of acetylcholine activity in A-I.

Stimulation of the D2 auto-receptor on terminal DA-II is somewhat decreased since release of dopamine has been reduced due to the stimulation of M2 receptors by the acetylcholine released from A-I. This might lead to an unchanged or only slightly decreased cAMP activity. Finally, stimulation of M2 receptor on terminal DA-III leads to decreased dopamine release from DA-III (if any is actually released since no glutamate was initially released at this synapse), and thus to decreased stimulation of the D2 autoreceptors and, possibly, to long-lasting increase in cAMP activity. Repetitions of the paired presentation of light and shock result in an enhancement of the above mentioned effects.

A well-known phenomenon of learning is that as acquisition of a given task progresses it becomes more and more difficult to improve on that learning (Rescorla, 1970). This is often illustrated by a negatively accelerated learning curve. This observation can easily be explained by the present model. As previously described, stimulation of the D2 autoreceptors located on the DA-I dopaminergic terminal decreases cAMP activity, decreases dopamine activity, and increases acetylcholine activity. According to the present model, it is stimulation of this autoreceptor that constitutes the key to the more or less permanent changes required for consolidation. However, every time this autoreceptor is stimulated during a training trial, the cAMP activity is further inhibited, which results in ever decreasing dopamine

activity. Less dopamine activity means that less dopamine is available to stimulate the D2 autoreceptor on the next training trial, which translates into a decreasing rate of acquisition.

Figure 11 illustrates the neural processes involved in a retrieval trial during which the CS (light) is presented alone. As before, stimulation of appropriate cortical area the CS (light) leads to the release of glutamate by the cortico-striatal terminal G-I (continuous arrows). Again, glutamate excites both the dopaminergic nigro-striatal terminal DA-I (continuous arrow 1) and the cholinergic A-I interneuron (continuous arrow 2). However, because of the decreased cAMP activity in DA-I, basal acetylcholine activity in A-I is higher than before training while basal dopamine activity is lower. This higher acetylcholine level leads to an increased acetylcholine release (doted arrows) as the result of glutamate stimulation of A-I. This released acetylcholine affects both A-II (doted arrow 1) and A-III (doted arrow 2) interneurons as well as DA-II (doted arrow 3) and DA-III (doted arrow 4) terminals. At the same time, glutamate-produced dopamine release by DA-I (hatched arrows) affects G-I (hatched arrow 1) and A-I (hatched arrow 2), inhibiting them. It also stimulates the D2 autoreceptor on DA-I (hatched arrow 3). Finally, the increased acetylcholine released acts differently on A-II and A-III. At A-II where cAMP activity has

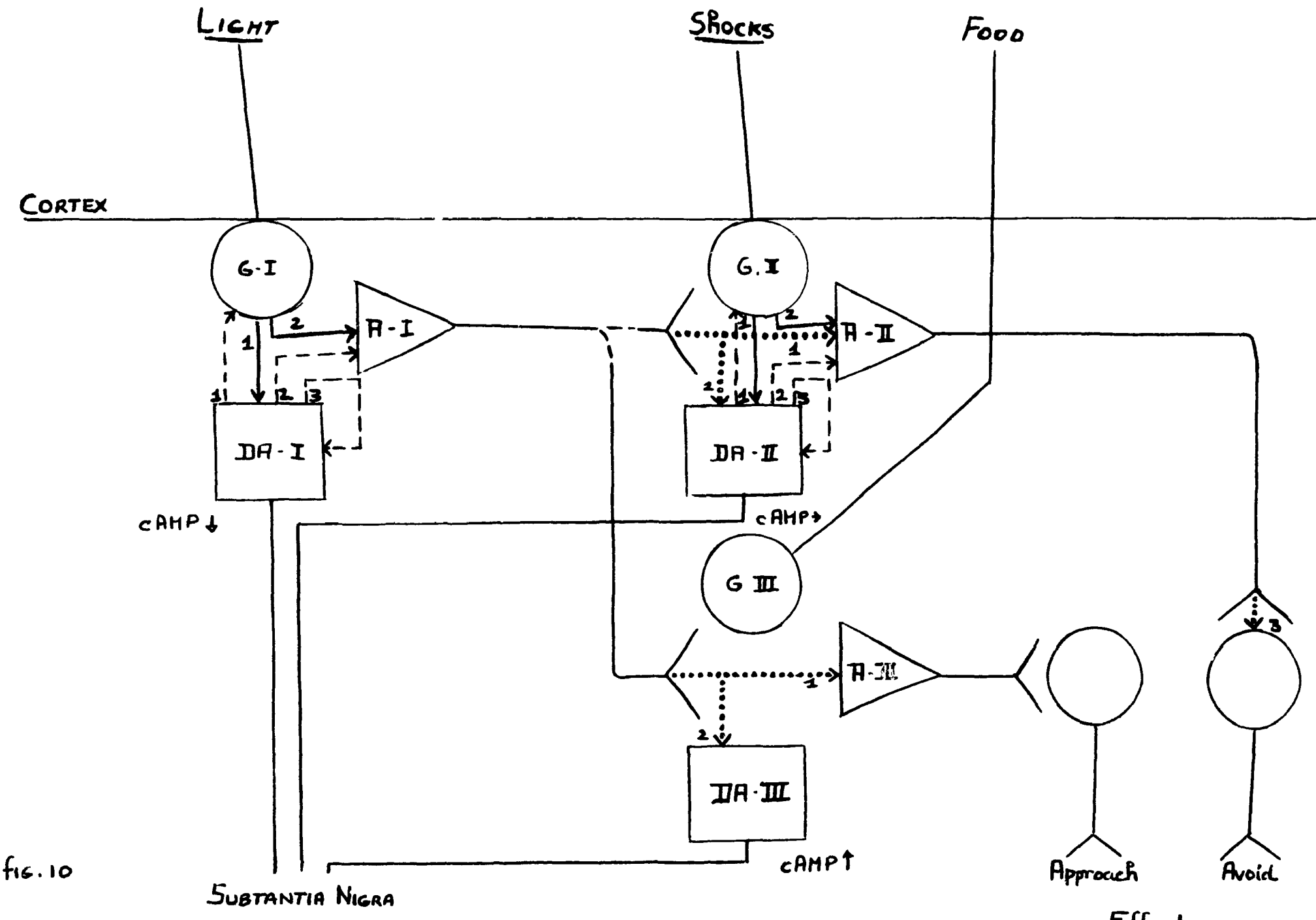
remained normal, the increased release of acetylcholine is sufficient to stimulate the A-II cell causing it to release acetylcholine as if stimulated by glutamate released from G-II. In turn, this acetylcholine stimulates the spiny type II efferent neuron (doted arrow 5). However, at the level of A-III, where cAMP activity has increased gradually during training and therefore increased dopamine basal activity in DA-III and reduced basal acetycholine activity of A-III, even this larger amount of released acetylcholine is not enough to stimulate the A-III interneuron and cause it to release its acetylcholine. Finally, stimulation of the M2 receptor on the DA-II terminal by the acetylcholine released from A-I triggers a mechanism similar to the one that leads to increase cAMP activity in DA-III during training. This gradual increase in cAMP activity builds up every time the CS is presented without the US. It eventually leads to increased dopamine activity and decreased acetylcholine activity. This gradual change might constitute the mechanism of extinction.

Many predictions can be made on the basis of this model; only a few are discussed here. First, if the main role of the glutamatergic cortical input is the transmission of information (stimuli) to the caudate nucleus which then establishes associations, it should be possible to mimic this effect pharmacologically and to replace either of the CS or US by a direct injection of a glutamate agonist into the striatal

area receiving the corresponding cortical fibers. For example, in a modified CER situation, rats could be given an appropriate dose of a glutamate agonist directly into the posteroventral area of striatum just before being placed into the CER box and given foot shock. During the test session, animals would be exposed to either a visual stimulus or an olfactory one. The prediction would be that the rats exposed to the visual stimulus would more inhibited than those exposed to the olfactory stimulus. Second, it should be possible to block acquisition of a modality specific CER by directly injecting a glutamatergic antagonist into the corresponding striatal area. For example, a pre-training direct injection of an appropriate dose of a glutamatergic antagonist into the posteroventral area of the striatum should block the acquisition of a visual CER while sparing the acquisition of an olfactory CER. Finally, predictions about the post-training effect of glutamatergic manipulations are more complex. Most likely, a post-training injection of a glutamatergic agonist into the striatum would disrupt memory consolidation since it would act as a distractor and cause retroactive interference. Such a disrupting effect called retroactive inhibition is well-documented (Underwood, 1957). Following the same logic, a glutamatergic antagonist injected directly into the striatum after training might improve memory by actually blocking or decreasing any possible interference from newly incoming information.

Finally, several elements known to exist in the striatum are intentionally excluded from this model because their possible contributions are yet not well understood. For example, striatal GABA cells, the feedback loop from striatum to substantia nigra, the spiny type I efferents were all left out. The projection from the thalamus to striatum, the function of which is completely unknow, has also been omitted. Eventually all of these must be integrated in any model that will successfully to resolve the mystery of striatal function.

Figure 10. S-R learning model: I. Acquisition and consolidation phases. See conclusion for description.


LIGHT
SHOCKS
FOOD
CORTEX
G-I
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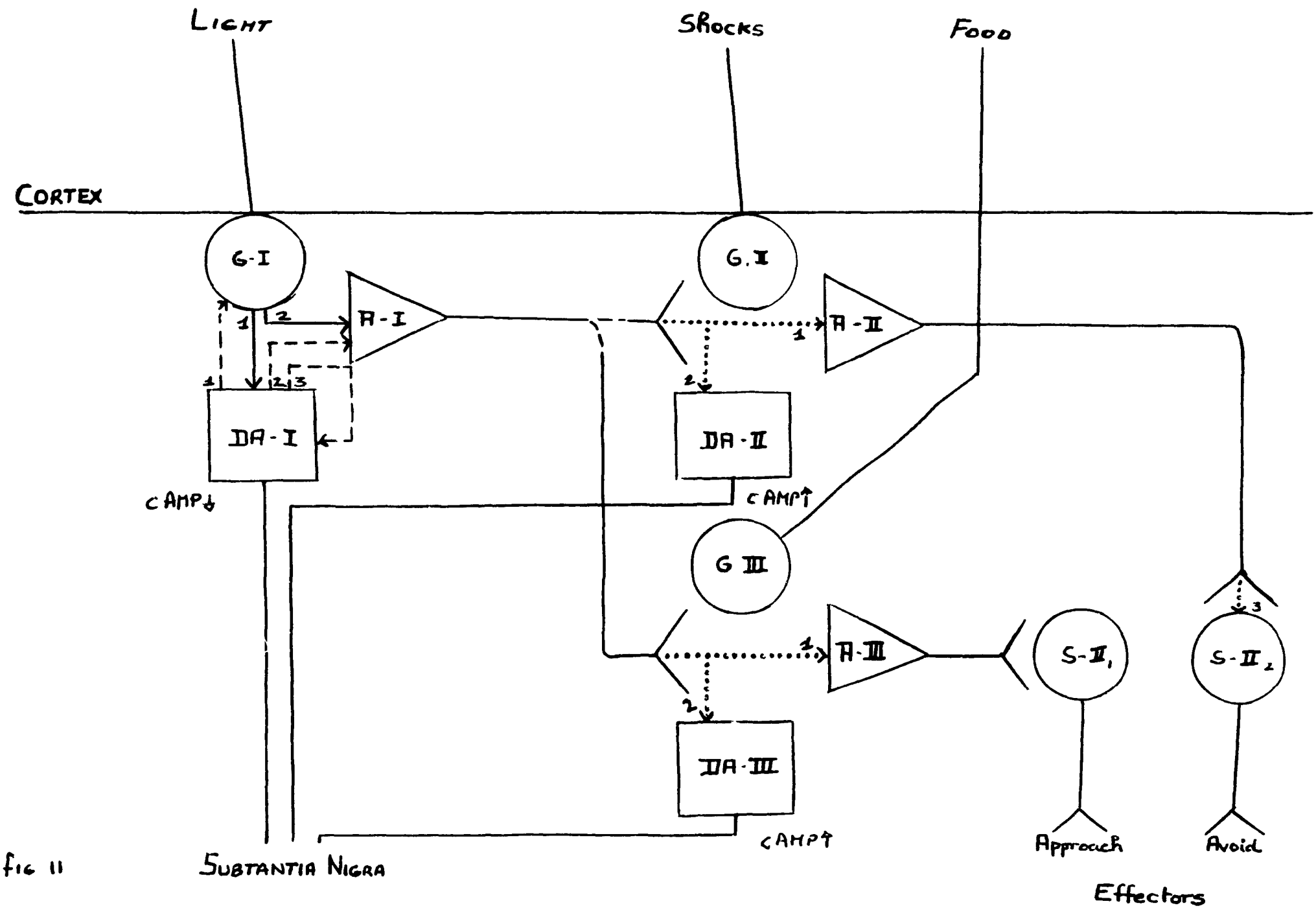
DA-I
DA-II
cAMP↓
cAMP↑
G III
A-III
DA-III
Approach
Avoid
Effectors
SUBTANTIA NIGRA

fig. 10

Figure 11. S-R learning model: II. Retrieval phase. See conclusion for description.


LIGHT
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G III
A-III
DA-III
cAMP↑
S-II1
S-II2
Approach
Avoid
SUBTANTIA NIGRA
Effectors

FIG 11

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