INFORMATION TO USERS

This manuscript has been reproduced from the microfilm master. UMI films the text directly from the original or copy submitted. Thus, some thesis and dissertation copies are in typewriter face, while others may be from any type of computer printer.

The quality of this reproduction is dependent upon the quality of the copy submitted. Broken or indistinct print, colored or poor quality illustrations and photographs, print bleedthrough, substandard margins, and improper alignment can adversely affect reproduction.

In the unlikely event that the author did not send UMI a complete manuscript and there are missing pages, these will be noted. Also, if unauthorized copyright material had to be removed, a note will indicate the deletion.

Oversize materials (e.g., maps, drawings, charts) are reproduced by sectioning the original, beginning at the upper left-hand corner and continuing from left to right in equal sections with small overlaps.

Photographs included in the original manuscript have been reproduced xerographically in this copy. Higher quality 6" x 9" black and white photographic prints are available for any photographs or illustrations appearing in this copy for an additional charge. Contact UMI directly to order.

Bell & Howell Information and Learning
300 North Zeeb Road, Ann Arbor, MI 48106-1346 USA
800-521-0600

NUCLEUS ACCUMBENS DOPAMINE AND INVESTIGATORY BEHAVIOR: MODULATION BY THE VENTRAL SUBICULUM OF THE HIPPOCAMPUS THROUGH THE DOPAMINE CELL BODIES OF THE VENTRAL TEGMENTAL AREA

Mark Legault

A Thesis

in

The Department

of

Psychology

Presented in Partial Fulfillment of the Requirements

for the Degree of Doctor of Philosophy at

Concordia University

Montreal, Quebec, Canada

July 1999

NUCLEUS ACCUMBENS DOPAMINE AND INVESTIGATORY BEHAVIOR: MODULATION BY THE VENTRAL SUBICULUM OF THE HIPPOCAMPUS THROUGH THE DOPAMINE CELL BODIES OF THE VENTRAL TEGMENTAL AREA

Mark Legault, Ph.D.

Concordia University, 1999

ABSTRACT

The nucleus accumbens septi (NAS) receives converging projections from both dopamine (DA) containing neurons of the ventral tegmental area (VTA) and glutamate containing neurons from the ventral subiculum (VS) of the hippocampus. VS projections to the NAS have been suggested to influence investigatory behavior, at least in part, by evoking glutamate-mediated transmitter release from NAS dopaminergic terminals. As the VS is not known to project to the VTA, the possibility that the VS influences dopaminergic transmission at the cell body level has largely been overlooked. In the present thesis, in vivo microdialysis was used to monitor fluctuations in DA release in response to chemical stimulation of the VS by injections of the excitatory amino acid analog N-methyl-D-aspartate (NMDA). Such injections increased investigatory behavior and elevated dopamine in both the DA terminal region of the NAS and the DA cell body region of the VTA. The elevations in VTA DA reflect dendritically released DA and imply an increase in dopaminergic cell firing; this increase was confirmed by single unit recording of identified VTA dopaminergic neurons. VS-evoked elevations in NAS dopamine were blocked by perfusion of the sodium channel blocker tetrodotoxin (TTX) or the ionotropic glutamate receptor antagonist, kynurenic acid (KA) into the VTA. In experiments designed to assess a functional role of VS-mediated elevations in NAS DA, microdialysis was used to monitor elevations in NAS DA evoked by exposure to novel environmental stimuli. Novelty-evoked elevations in NAS DA were abolished by injections of TTX into the VS. Perfusion

of KYN into the VTA also blocked novelty-induced elevations in NAS DA.

The present experiments indicate that the VS modulates NAS and VTA dopamine. The modulation of NAS dopamine is dependent on, and mediated primarily by, increased impulse flow through the VTA. Although the circuitry through which the VS modulates impulse flow through dopaminergic neurons is not known, it appears to involve a glutamatergic link terminating in the VTA. This circuitry is responsive to environmental stimuli and plays a functional role in the modulation of dopaminergic transmission in response to novelty.

Acknowledgements

A doctoral thesis is not often undertaken and completed without the help and contributions of many people. For contributing, in one way or another, directly or indirectly, to the work of thesis I would like to thank the following people.

I thank Dr Roy Wise for teaching me to seek knowledge rather than simply information, and for teaching how to communicate the knowledge that I had acquired. I thank Dr Shimmy Amir for countless thought provoking discussions over morning coffee and Shimmy, along with Dr Jane Stewart, for inspiring the experiments of Chapter 3.

My colleagues and friends, Pat Bauco, Elizabeth Munn, Bill Carlezon, Cathy Marcangione, Demi Rodaros, and Wayne Bowers, who have all, on may occassions, helped provide some insight into the work presented here, or at least a few laughs which were probably more valuable!

Best for last, I thank Martina for sticking by me through it all and having the faith that this would all be worth it in the end. Was it worth it?

I believe over the gates into the School of Graduate Studies a sign should read something like:

"I am the way into the city of woe ...

I was raised here by divine onmipotence,

Premoridal love and ultimate intellect ...

Abandon all hope ye who enter here."

Dante Alighieri

Table of Contents

List of Figures

List of Tables

INTRODUCTION

The nucleus accumbens septi (NAS) is a ventral continuation of the striatum. The striatum has long been thought to be involved in organizing complex behaviors through the motor-related circuitry of the basal ganglia (Wilson, 1914; Nauta, 1986; Alexander & Crutcher, 1990). The NAS, while maintaining its anatomical and functional relationship with the striatum and the basal ganglia, has increasingly come to be regarded as a link between the limbic system and motor system (Nauta and Domesick, 1978, 1986; Heimer & Wilson, 1975; Graybiel, 1976; Mogenson, Jones & Yim, 1980; Chronister & DeFrance, 1981). The NAS receives projections from a wide region of limbic structures and these projections are thought to be involved in attention and investigatory behavior evoked by biologically significant goals, such as novel stimuli, food, water, nesting materials, and sexually receptive mates, or stimuli that signal the availability of such goals (Cador, Robbins, Everitt, Simon, Le Moal & Stinus, 1991; Blackburn, Pfaus, & Phillips, 1992; Robbins & Everitt, 1992). In particular, there is considerable evidence that the hippocampus plays an important role in investigation of novel stimuli (Kimble, 1963; Jarrard, 1968) and that it does so, at least in part, through projections to the NAS (Mogenson & Neilsen, 1984a).

Dysfunction of attention and investigatory processes attributed to the circuitry of the NAS are thought to contribute to the symptomatology of schizophrenia (Carlsson & Carlsson, 1990; Robbins, 1990; Gray, Feldon, Rawlins, Hemsley, & Smith, 1991; Grace, 1993; Jaskiw & Weinberger, 1992; O'Donnell & Grace, 1998). Schizophrenia is a heterogeneous disorder with a number of subtypes but can be characterized by general cognitive and attentional dysfunctions described variously as cognitive fragmentation, sensory overload, or inability to ignore irrelevant stimuli (Snyder, 1972, 1974; Braff, Stone, Callaway, Geyer, Glick, & Bali, 1978; Anscombe, 1987; Hemsely, 1987). Schizophrenics are susceptible to distraction by seemingly irrelevant stimuli and appear

unable to focus attention on relevant aspects of a situation. In schizophrenia, incoming stimuli may be processed as novel and attract attention regardless of whether they are redundant or irrelevant. This destractibility has long since been suggested to underlie some schizophrenic symptoms (Shakow, 1961; Chapman,1966).

The primary inputs to the NAS are dopaminergic projections from the ventral tegmental area (VTA) and glutamatergic projections from various cortical structures. Dopaminergic transmission in the NAS is important for investigatory behavior (Marshall, Richardson, & Teitelbaum, 1974; Fink & Smith, 1980). Dysfunction of dopaminergic transmission may be involved in the pathophysiology of schizophrenia as implied by the efficacy of dopaminergic antagonists in alleviating symptoms in many schizophrenics (Carlsson & Lindqvist, 1963; Snyder, 1972; Creese, Burt, & Snyder, 1976; Seeman, 1987; Grace, Bunney, Moore, & Todd, 1997). However, there is little direct evidence for a dysfunction in dopaminergic transmission in schizophrenia and this has led some researchers to suggest that schizophrenia results from a primary disruption of limbic structures which then leads to a secondary dysfunction in dopaminergic transmission (Weinberger et al., 1988; Robbins, 1990; Gray et al., 1991; Grace, 1990; O'Donnell and Grace, 1998). Two limbic structures that appear to be anatomically and functionally pathological in schizophrenics are the prefrontal cortex (Berman, Zec, & Weinberger, 1986; Weinberger, Bermann & Illowwski, 1988; Jaskiw & Weinberger, 1992) and the hippocampus (Kovelman & Scheibel, 1984; Weinberger et al., 1992; Silbersweig et al., 1995; Weinberger, 1999).

Hippocampal pathology has been suggested by some theorists to be central to both the symptomatology and etiology of schizophrenia (Gray et al., 1991; Jaskiw & Weinberger, 1992; O'Donnell & Grace, 1998; Weinberger, 1999). Dysfunction of hippocampal projections to the NAS has been suggested to disrupt normally adaptive investigation of novel stimuli and this disruption has been suggested to underlie the distractibility of schizophrenics (Weiner, 1990; Gray et al., 1991; Mittleman, LeDuc, &

Whishaw, 1993; O'Donnell & Grace, 1995). Hippocampal pathology has also been suggested to precede and underlie the etiology of prefrontal cortex (PFC) dysfunctions observed in schizophrenics (Jaskiw & Weinberger, 1992; Weinberger et al., 1992; Weinberger, 1999). Thus, the disruptive influences of hippocampal pathology on limbic inputs to the NAS may extend beyond the direct hippocampal-accumbens pathway to include disruption of PFC inputs to the NAS as well.

One way in which the hippocampus may be involved in both adaptive investigatory behavior and in schizophrenia is by influencing dopaminergic transmission in the NAS. Hippocampal lesions have been reported to augment both basal (Lipska, Jaskiw, Chrapusta, Karoum & Weinberger, 1992) and drug-evoked (Wilkinson, Mittleman, Torres, Humby, Hall & Robbins, 1993) dopaminergic transmission in the NAS and to augment the stimulatory effects of dopaminergic agonists on investigatory behaviors (Whishaw & Mittleman, 1991; Mittleman et al., 1993). Interestingly, hippocampal stimulation also augments dopaminergic transmission in the NAS (Legault & Wise, 1995; Blaha, Yang, Floresco, Barr, Phillips, 1997; Brudzynski & Gibson, 1997) and investigatory behavior (MacLean, 1957; Flicker & Geyer, 1982; Mogenson & Neilsen, 1984; Yang & Mogenson, 1987; Brudzynski & Gibson, 1997). Thus the role of the hippocampus in investigatory behavior remains to be fully understood.

Investigatory Behavior

The importance of investigation for adaptive behavior was recognized in the early 1900's by both Ivan Pavlov (1927) and Wallace Craig (1918). Pavlov held that attention, orientation, approach and exploration evoked by a novel stimulus were unconditioned (inherent) investigatory reflexes. If the novel stimulus does not reliably predict any significant event for an animal then the investigatory reflexes habituate; the stimulus looses its ability to attract attention. However, if repeated encounters with the novel stimulus reliably predict an inherently significant event—or in Pavlov's frame of

reference it predicts an unconditioned stimulus (US)— then the association between novel and unconditioned stimuli would be reinforced. When the associations between novel and unconditioned stimuli are reinforced the previously novel stimulus continues to evoke orientation and investigation despite the fact that it is no longer novel. When a previously novel stimulus acquires this ability it is referred to as a conditioned stimulus (CS).

The investigatory reflexes of Pavlov have all the features of appetitive behaviors described by Craig (1918) and later by ethologists (Lorenz, 1950; Tinbergen, 1951) as reflecting motivational processes. Appetitive behaviors were thought to reflect the induction of a "readiness to act" (Craig, 1918) or the energizing of behavior directed towards a biologically significant goal or, in Pavlov's terms, an unconditioned stimulus. Appetitive responses were described as variable sequences of actions that were guided and modified by "special stimuli " (Tinbergen, 1951), an idea reminiscent of Pavlov's conditioned stimuli, that served the function of bringing an animal into contact with an unconditioned stimulus. Once in contact with the US the sequence of actions was terminated with the performance of an unconditioned fixed action pattern or "consummatory act". If a sequence of actions ended with a consummatory act then appetitive behaviors would be evoked on subsequent experiences with similar stimuli, or in Pavlov's terms, investigatory behaviors would be reinforced. In the absence of an appropriate US appetitive behaviors are marked by behavioral arousal and investigatory activity.

Thus, Pavlov's investigatory reflexes or Craig's appetitive behaviors have long been recognized as the fundamental elements of adaptive behaviors. They are central to the approach behaviors described by Schneirla (1959) and the incentive-motivation theory of Bindra (1968). Investigatory behaviors are accepted as a primary component of biologically significant behaviors such as foraging and predation (Craig, 1918; Tinbergen, 1951; Deutch & Howarth, 1963). The brain circuitry involved in unconditioned

investigatory approach, or forward locomotion, appears to overlap substantially with brain circuitry involved in the reinforcement and modulation of adaptive behaviors (Glickman & Schiff, 1967; Wise & Bozarth, 1987).

THE NUCLEUS ACCUMBENS SEPTI

The NAS has long been thought to be involved in attention and investigation of novel and conditioned stimuli (Nauta, 1968; Mogenson et al., 1980; Mogenson, 1987). This idea originated, in part, from the observation that this ventral region of the striatum is preferentially innervated by structures of the limbic cortex whereas the dorsal striatum is preferentially innervated by the neocortex (Nauta, 1968; Graybiel, 1976; Heimer & Wilson, 1975; Nauta & Domesick, 1978; Nauta, 1986; Alhied & Heimer, 1988). Together, the dorsal striatum and the NAS form the major input zone of the basal ganglia (Heimer & Wilson, 1975; Heimer & Van Hoesen, 1979; Nauta, 1986), a collection of ventral forebrain and midbrain nuclei associated with the extrapyramidal control of motor behavior. These nuclei include the striatum, globus pallidus, subthalamic nucleus, substantia nigra, ventromedial and mediodorsal nuclei of the thalamus (Alexander & Crutcher, 1990; Graybiel, 1990; Gerfen, 1992). Yet, just as the NAS is considered a ventral continuation of the caudate, the medial NAS is considered by some to extend from the amygdala (Alhied & Heimer, 1988).

Medium sized spiny neurons (MSNs) comprise over 90% of the striatum; they receive almost all the inputs and give rise to almost all the outputs from these regions (Smith & Bolam, 1990). Just as the medium spiny neurons of the dorsal striatum receive dense inputs from all regions of the neocortex, those of the NAS receive dense inputs from all regions of the limbic cortex (Graybiel, 1976; Nauta, 1986; Alexander & Crutcher, 1990; Phillipson & Griffiths, 1985; McGeorge & Faull, 1989; Brog, Salyapongse, Deutch, & Zahm, 1993). Particularly heavy inputs arise from the prefrontal cortex (PFC; Sesack, Deutch, Roth, & Bunney, 1989; Berendse, Galis-de Gaff, &

Groenewegen, 1992), the basolateral amygdala (Kelley, Domesick, & Nauta, 1982; McDonald, 1991), and hippocampus with particularly dense projections arising from the ventral subiculum (Swanson & Cowan, 1977; Kelley & Domesick, 1982; Groenewegen, Vermeulen-Van der Zee, Te Kortschot, & Witter, 1987). The NAS is also innervated by subcortical limbic-related regions of the thalamus (Wright & Groenewegen, 1995) and the lateral hypothalamus (Brog et al., 1993).

Another set of topographically preferential inputs to the dorsal striatum and the NAS arise from the dopaminergic neurons of the ventral mesencephalon. These dopaminergic neurons form a continuous band which extends outward from the midline of the tegmentum and project forward, through the medial forebrain bundle, to the NAS and striatum in a topographically organized manner; the NAS is innervated by the more medial DA neurons which form the ventral tegmental area (VTA), whereas the caudate is innervated by the laterally extending neurons of the substantia nigra pars compacta (SNc; Dahlstrom & Fuxe, 1964; Fallon & Moore, 1978).

NUCLEUS ACCUMBENS DOPAMINE AND INVESTIGATORY BEHAVIOR

The importance of dopaminergic projections from the VTA to the NAS is firmly established in unconditioned investigatory behavior. Dopaminergic inputs to the striatum were first implicated in the coordination of movement when it became established that degeneration of dopamine containing neurons of the substantia nigra was critical in the pathophysiology of Parkinson's disease (Hornykiewicz, 1963). In Parkinsonian patients the ability to execute coordinated movements can be restored by treatment with the DA precursor L-dihydroxyphenylalanine (L-DOPA). In rats, depletion of striatal dopamine by infusions of the neurotoxin 6-hydroxydopamine (6-OHDA) severely disrupts adaptive behaviors such as locomotion, eating, and drinking; this disruption can also be alleviated by administration of L-DOPA or the direct dopamine agonist apomorphine (Ungerstedt, 1971a, b; Zigmond & Striker, 1972; Fibiger, Zis & McGeer, 1973; Ljungberg &

Ungerstedt, 1976). Shortly after the discovery that depletion of striatal dopamine was associated with behavioral disruptions it was realized that theses disruptions did not simply reflect simple motor impairments but a more subtle impairment in sensorimotor integration (Marshall, Richardson & Teitelbaum, 1974; Carli, Evendon & Robbins, 1985; for review of this issue see White, 1986). For example, 6-OHDA induced depletion of forebrain dopamine does not abolish orientation towards a novel stimulus but accelerates habituation of the orientation reflex and severely reduces approach towards and investigatory contacts with a biologically significant stimuli such as novel stimuli of food (Marshall et al., 1974; Carli, Evendon & Robbins, 1985; Fink & Smith, 1979a, 1980).

Although dopaminergic inputs to the entire striatum are important for the coordination of motor behavior, it is the dopaminergic inputs to the NAS that appear to be most closely involved in the initiation and maintenance of investigatory behaviors. 6-OHDA lesions restricted to the NAS reduce investigatory approach towards biologically significant stimuli such as novel objects and food in rats (Koob, Riley, Smith & Robbins, 1978; Koob, Stinus, & LeMoal, 1981; Kelley & Stinus, 1985; Taghzouti, Simon, Louilot, Herman, & LeMoal, 1985; Pierce, Crawford, Nonneman, Mattingly, & Bardo, 1990). Along the same line, systemic (Bardo, Neisewander & Pierce, 1989; Bardo, Bowling & Pierce, 1990) or intra-NAS (Hooks & Kalivas, 1995) injections of DA antagonists reduce investigatory responses to novel environments without reducing activity in habituated environments. Injections of the GABA agonist, baclofen, into the VTA (which should inhibit VTA neurons) also blocks investigation of novel environments (Hooks & Kalivas, 1995).

In 6-OHDA lesioned rats, investigation of novel stimuli can be reinstated by pretreatment with L-DOPA or the direct DA receptor agonist apomorphine; moreover, this reinstatement can be blocked by pretreatment with the dopamine antagonist, pimozide (Fink & Smith, 1979b, 1980). The reinstatement of investigatory behavior by apomorphine is unique to novel open fields or objects as apomorphine does not render

animals hyperactive in a familiar open field or in response to the presentation of familiar objects (Fink & Smith, 1980). The reinstatement of novelty-specific behavior by apomorphine, and the alleviation of Parkinsonian symptoms by L-DOPA in humans, suggests that while tonic activation of dopamine receptors is required for the execution or coordination of movement the movement is driven or evoked by processes converging on the striatum and NAS from other brain regions.

Although only tonic levels of dopaminergic activity may be necessary for investigatory behaviors, phasic elevations in NAS DA are sufficient to augment investigation of novel stimuli. Direct injections of dopamine or the indirect dopamine agonist amphetamine into the NAS increases investigatory behavior (Pijnenburg & van Rossum, 1973; Creese & Iversen, 1975; Kelly, Seviour & Iversen, 1975). Systemic injections of amphetamine increase investigatory behavior and this increase is abolished by 6-OHDA lesions restricted to the NAS (Kelly & Iversen, 1976).

Investigatory behaviors are increased by pharmacological activation of dopaminergic projections to the NAS. Direct injections of nicotine or the nicotinic receptor agonist cytisine into the dopaminergic cell body region of the VTA increases locomotor activity (Museo & Wise, 1990; Kita, Okamoto & Nakashima, 1992). Direct activation of VTA DA neurons by application of the excitatory amino acid analog N-methyl-D-aspartate (NMDA) increases NAS DA concomitantly with increases in locomotor activity (Westerink, Santiago & deVries, 1992; Wang, O'Connor, Ungerstedt & French, 1994). Inhibiting GABAergic inputs to dopaminergic neurons by intra-VTA injections of opiates also increases locomotor activity (Broekkamp et al., 1976; Joyce & Iversen, 1979; Holmes, Bozarth & Wise, 1983). Injections of the GABA receptor antagonist picrotoxin into the VTA increases locomotion and this increase is blocked by NAS injection of the DA antagonist spiroperidol (Mogenson, Wu, & Manchanda, 1979).

Recent research has demonstrated interactions between the investigatory response evoked by novel stimuli and systemic injections of amphetamine or cocaine. Animals

treated with amphetamine in a novel environment are more active than animals treated with amphetamine in a familiar environment (Badiani, Anagnostaras & Robinson, 1995; Badiani, Browman & Robinson, 1995). This facilitory interaction seems to reflect a drug-induced (and probably dopamine-dependent) augmentation of the novelty-evoked investigatory reflex since unsignalled administration of amphetamine in a habituated environment fails to increase activity (Crombag, Badiani & Robinson, 1996). The potentiative effects of dopaminergic agonists on investigatory locomotion are even more apparent in response to repeated drug treatments. One consequence of repeated intermittent treatments with psychomotor stimulants, opiates, and direct dopamine agonists is a progressive augmentation of drug-evoked behavioral activation, a phenomenon referred to as psychomotor sensitization. In a series of experiments Badiani, Robinson and colleagues have demonstrated that amphetamine- or cocaine-induced sensitization of investigatory behavior is enhanced when the drug is administered for the first time in a novel environment and that same environment is explicitly and exclusively paired with each subsequent amphetamine treatment (Badiani, Browman & Robinson, 1995; Badiani, Anagnostaras & Robinson, 1995). The novelty-enhanced sensitization of investigatory behaviors associated with amphetamine or cocaine administration may involve the establishment of Pavlovian associations between the stimulus properties of a drug (unconditioned stimulus, US) and environmental drug-associated cues (CSs) (Badiani & Stewart, 1993) such that dopaminergic transmission augments and reinforces the investigatory response to novel stimuli.

Investigatory Behaviors are Correlated with Dopaminergic Activation

Dopaminergic neurons are transiently activated in response to presentation of novel stimuli. If a discrete novel stimulus is sufficiently salient to evoke an unconditioned investigatory response (orientation) it will phasically activate midbrain dopamine neurons. This dopaminergic response declines as the investigatory reflex

habituates (Steinfels, Heym, Strecker & Jacobs, 1983; Schultz & Romo, 1990; Ljungberg, Apicella & Schultz, 1992; Horvitz, Stewart & Jacobs, 1997). Dopaminergic neurons are also phasically activated by the unexpected (novel) presentation of reinforcing unconditioned stimuli such as palatable food or fruit juice (Ljungberg et al., 1992; Mirenowicz & Schultz, 1994).

There has been surprisingly little study of the effects of investigatory behavior on in vivo DA release in the NAS. Investigation of novel environments results in a short lasting increase in the dopamine-related electrochemical signal recorded using in vivo voltammetry in the NAS and prefrontal cortex (Rebec, Christensen, Guerra & Bardo, 1997). One recent microdialysis study has shown long-lasting (2 hours) elevations in NAS DA following transfer of animals to a novel cage (Saigusa, Tuinstra, Koshikawa & Cools, 1999). The results of this study contrast with the results of two microdialysis studies from Fibiger and colleagues (Damsma, Pfaus, Wenkstern, Philips & Fibiger, 1992; Pfaus, Damsma Wenkstern & Fibiger, 1995) in which novelty failed to increase NAS DA. In these studies, however, each animal had previously undergone extensive handling and exposure to environments which were similar to the "novel" environment. These treatments may have contributed to habituation of the investigatory response. NAS DA is also elevated in response to a novel palatable food and this elevation habituates with repeated exposures to the food (Bassereo & DiChiara, 1997).

VTA DA neurons and extracellular DA in the NAS, in addition to being activated by novel stimuli, are activated by conditioned stimuli. The electrophysiological studies of Schultz and colleagues have also shown that VTA DA neurons in monkeys fire in response to stimuli that predict the delivery of food. At first, presentation of food that is reliably signaled by a CS food results in the phasic activation of VTA DA neurons upon the delivery of the food. However, with repeated pairing of the signal with the food, the signal assumes the properties of a CS and the dopaminergic response transfers to the signal. Following transfer of the DAergic response to the CS, phasic activation of the DA

neurons is only observed when the CS or food delivery is unpredictable or novel. For example, when food is presented outside of the experimental task (Mirenowicz & Schultz, 1994) or earlier than predicted (Hollerman & Schultz, 1996) it persists in activating DA neurons. Similarly, when monkeys are trained to expect food following a series of signals only the first signal acts as a CS and evokes a DA response; subsequent signals which occur predictably following the presentation of the first signal do not activate DA neurons(Schultz, Apicella & Ljungberg, 1993). Thus predictable, and consequently non-novel, goals fail to activate dopamine neurons.

Studies using in vivo voltammetry consistently report elevations in the DA-related electrochemical signal recorded from NAS electrodes in response to conditioned stimuli that evoke or facilitate investigatory approach behaviors through association with unconditioned stimuli such as food, drink, or injection of self-administered drugs (Phillips, Atkinson, Blackburn & Blaha, 1993; Gratton & Wise, 1994; Kiyatkin & Gratton, 1994; Richardson & Gratton, 1996; Di Ciano, Blaha & Phillips, 1998a). Elevations in the NAS DA-related electrochemical signal have also been reported to correlate with investigatory activity observed when animals are returned to an environment previously paired with amphetamine or cocaine administration (Di Ciano, Blaha & Phillips, 1998b). Data obtained using microdialysis, however, are less consistent than those obtained from voltammetry studies. While some researchers have reported elevations in NAS DA in response to conditioned stimuli associated with a sexual partner (Damsma et al., 1992; Pfaus et al., 1995) others have failed to obtain increases in NAS DA in response to cocaine-related (Kalivas & Duffy, 1990) or food-related (Wilson, Nomikos, Collu & Fibiger, 1995) conditioned stimuli. Bassereo and DiChiara (1997) reported that environments associated with a palatable food failed to elevate NAS DA. The discrepancies between voltammetry and microdialysis studies in obtaining increases in NAS DA in response to conditioned stimuli have not been explained. One possibility is that the dopaminergic response to conditioned stimuli is transient and not detectable

using microdialysis which typically requires sampling times in the range of several minutes.

NAS DA Modulates Behavioral Response to novel and Conditioned Stimuli

Electrophysiological, voltammetric, and microdialysis studies suggest that NAS DA modulates the investigatory response to novel and conditioned stimuli. It has been difficult, however, to establish that conditioned investigatory behaviors are dependent on dopaminergic neurotransmission. Some investigators have reported that investigation evoked by drug-paired stimuli (established by administration of amphetamine or cocaine) is not disrupted by administration of the dopamine antagonist, pimozide (Beninger & Hahn, 1983; Beninger & Herz, 1986). On the other hand, 6-OHDA lesions have been reported to abolish conditioned investigatory responses established by amphetamine treatments (Gold, Swerdlow & Koob, 1988). The most important confound in studying the effects of dopaminergic blockade on conditioned investigation is determining that the primary disruption is not a disruption of the animal's motor capability. One approach that seems to have circumvented this confound is the study of the effects of dopaminergic manipulations on behaviors directed towards CSs. When a CS (such as a light) is established through association with an unconditioned reinforcer (such as food, a sexually receptive mate, or a self-administered drug) it can acquire the ability to establish and maintain the performance of arbitrary behaviors (such as a lever press) if the behavior results in CS presentation (Robbins, 1976). Under these circumstances, the CS is referred to as a conditioned reinforcer.

NAS DA modulates responding for conditioned reinforcers but is not required for the initiation of responding. Infusion of dopamine, D-amphetamine, or selective dopamine antagonists for D1 or D2 receptors directly into the NAS greatly enhances operant behaviors that result in the presentation of conditioned reinforcers (Taylor & Robbins, 1984; Cador, Taylor & Robbins, 1991; Wolterink, Phillips, Cador, Donselaar-

Wolterink, Robbins & Everitt, 1993). The potentiation of responding for CRs is attenuated by systemic or intra-NAS injections of dopamine agonists at doses that do not block the initiation or maintenance of responding for conditioned reinforcers in saline treated animals (Chu & Kelley, 1992; Wolterink et al., 1993). Similarly, 6-OHDA lesions of the NAS abolish amphetamine-induced potentiation of responding for conditioned reinforcers (Taylor & Robbins, 1986). Thus, NAS DA increases the frequency or potentiates the vigor of behaviors directed towards conditioned reinforcers, but other systems seem to be more directly involved in the initiation of these behaviors.

NUCLEUS ACCUMBENS DOPAMINE AND SCHIZOPHRENIA

Dopaminergic neurotransmission in the NAS is thought to be involved in the pathophysiology of schizophrenia. The involvement of dopaminergic dysfunction in this disorder was originally suggested on the basis that dopamine antagonists (neuroleptics) were clinically effective in alleviating schizophrenic symptomatology (Carlsson & Lindqvist, 1963). This finding was soon followed by complimentary reports that dopamine agonists, such as amphetamine or the dopamine precursor, L-DOPA, can induce or exacerbate schizophrenic-like symptoms (Jenkins & Groh, 1970; Angrist, Shopin & Gershon, 1971; Snyder, 1972; Leiberman, Kane & Alvir, 1987). These findings led to the suggestion of hyperdopaminergic function in schizophrenics. There is a strong correlation between the clinical efficacy of neuroleptics and their ability to block the actions of the D2 family of DA receptors (Creese, Burt & Snyder 1976; Seeman, 1987; Grace et al., 1997). VTA DA neurons projecting to the NAS appear to be particularly sensitive to the actions of neuroleptics (Chiodo & Bunney, 1983; White & Wang, 1983; Moghaddam & Bunney, 1990; Grace, 1992; Robertson & Fibiger, 1992). Recent evidence suggests that it is the ability of these drugs to cause depolarization block of VTA DA neurons (by blocking the inhibitory effects of DA on D2 autoreceptors) that strongly correlates with their clinical efficacy. The ability of these drugs to cause

depolarization block in SNc DA neurons correlates with the emergence of extrapyramidal side effects (Grace et al., 1997).

Evidence for dopaminergic dysfunction in schizophrenics does not extend far beyond the efficacy of dopaminergic antagonists to alleviate some schizophrenic symptoms, the correlation of their clinical efficacy with their preferential effects on VTA dopaminergic neurons, and the ability of chronically administered dopaminergic agonists to evoke schizophrenia-like symptoms. There is little direct evidence for primary dopaminergic dysfunction in schizophrenics (Jaskiw & Weinberger, 1992; Carpenter & Buchanan, 1994; O'Donnell & Grace, 1998). Evidence for increased dopamine activity in schizophrenic brain or body fluids is inconsistent (Post, Fink, Carpenter & Goodwin, 1975; Davis, Kahn, Ko & Davidson, 1991; Beuger, van Kammen, Kelley & Yao, 1996), as is evidence for changes in dopamine receptor binding in post-mortem analyses of schizophrenic brains (Hyde, Csanove, Kleinman & Weinberger, 1991; Knable, Hyde, Herman, Carter, Begelow & Kleinman, 1994). Moreover, improvement in schizophrenic symptoms often follows weeks of neuroleptic treatment, and some patients don't respond at all, despite dopamine receptor binding that is confirmed by positron emission tomography (Kane & Leiberman, 1987; Sedvall, 1990).

On the other hand, there is robust evidence for cortical pathology in this disorder particularly in limbic regions that project to the NAS (Jaskiw & Weinberger, 1992; Weinberger, 1999). It has therefore been suggested that disruption of cortical inputs to the NAS could impair attentional filtering and allow unrelated streams of information to intrude on each other and be inappropriately integrated (Swerdlow & Koob, 1987; Weiner, 1990; Gray et al., 1991; Jaskiw & Weinberger, 1992; O'Donnell & Grace, 1998). One possible consequence of this impaired attentional filtering would be that inappropriate, irrelevant, or habituated sensory stimuli evoke investigatory responses (Gray et al., 1991). One mechanisms through which disruption of cortical projections to the NAS might disrupt attentional filtering is by disrupting dopaminergic transmission.

Modulation of NAS Dopamine by Cortical Glutamate

There is increasing evidence that dopaminergic transmission is at least partially modulated by projections from the cortex. Cortical projections to subcortical structures arise from pyramidal neurons which contain the excitatory amino acids glutamate and aspartate as their primary neurotransmitters (Walaas & Fonnum, 1979; Zaczek, Hedreen & Coyle, 1979; Walaas, 1981; Christie, Sikes, Stephenson, Cook & Beart, 1987; Fuller, Russchen & Price, 1987). The neocortex and limbic cortex send dense, presumably glutamatergic, projections to the striatum with particularly heavy projections to the NAS arising from the limbic regions of the ventral subiculum of the hippocampus, the prefrontal cortex (PFC), and the basolateral amygdala. Cortical glutamatergic projections converge on medium spiny neurons of the striatum where their terminals abut with catecholaminergic (presumably dopaminergic) terminals (Pickel, Beckley, Joh & Reis, 1981; Bouyer, Park, Joh & Pickel, 1984; Freund, Powell & Smith, 1984; Totterdell & Smith, 1989; Smith & Bolam, 1990; Sesack & Pickel, 1990, 1992; Johnson, Aylward, Hussain & Totterdell, 1994). The dopaminergic cell body regions of the substantia nigra and VTA each receive glutamatergic inputs from the frontal and prefrontal cortex respectively (Christie, Bridge, James & Beart, 1985; Sesack, Deutch, Roth & Bunney, 1989; Sesack & Pickel, 1990a,1992). Cortical glutamatergic projections to both the dopaminergic cell body regions of the VTA and SN as well as to the dopaminergic terminals in the striatum may each exert important modulatory influences on dopaminergic transmission in the striatum.

Cortical glutamatergic projections to the striatum have been suggested to modulate dopaminergic transmission independently of impulse flow through dopaminergic neurons (Chéramy, Romo, Godeheu, Baruch & Glowinski, 1986; Romo, Chéramy, Godeheu & Glowinski, 1986a,b; Glowinski, Chéramy, Romo & Barbieto, 1988), although this suggestion is currently a topic of controversy. Potential glutamatergic interactions with dopaminergic transmission in the NAS have been the

subject of intense investigation largely for their possible relevance to movement disorders such as Parkinson's disease (Carlsson & Carlsson, 1990; Zigmond, Castro, Keefe, Abercrombie & Sved, 1998), investigatory behaviors (Boldry & Uretsky, 1988; Boldry, Willins, Wallace & Uretsky, 1991; Burns, Robbins & Everitt, 1993; Burns, Arnett, Kelley, Everitt & Robbins, 1996; Wu, Brudzynski & Mogenson, 1993), and schizophrenia (Weinberger et al., 1988; Carlsson & Carlsson, 1990; Robbins, 1990; Gray et al., 1991; Grace, 1991). Evidence that glutamate could evoke transmitter release from dopaminergic terminals independently of impulse flow was first obtained from studies performed using in vitro preparations. When perfused onto to dopaminergic terminals in vitro glutamate is consistently reported to evoke dopamine release and does so when impulse flow in dopaminergic fibers is blocked by coperfusion of tetrodotoxin (TTX) to, or when calcium is removed from the perfusate (Giorguieff, Kemel & Glowinski, 1977; Roberts & Sharif, 1978; Marien, Brien & Jhamandas, 1983; Chéramy et al., 1986; Johnson & Jeng, 1991; Lonart & Zigmond, 1991; Jin, 1997).

In vivo evidence of glutamate-evoked impulse-independent transmitter release from dopaminergic terminals in the striatum was first presented in a series of studies from Glowinski and colleagues (Romo et al., 1986a,b). In these experiments, newly synthesized ^{3}H-labeled dopamine was sampled from the striatal tissue of cats, using the technique of push-pull perfusion, prior to and during activation of glutamatergic projections from the frontal cortex. In order to activate the frontal cortex low doses of GABA (10-5 M) were injected into the ventral thalamus. This dose of GABA activated thalamic neurons (presumably by blocking their inhibitory inputs) which, in turn, provide excitatory inputs to the frontal cortex. GABA injections into the ventral thalamus elevated ^{3}H-dopamine in striatal perfusate. These elevations in striatal ^{3}H-dopamine were accompanied by a decrease the firing rates of substantia nigra dopaminergic neurons persisted following transection of the ascending dopaminergic projections from the substantia nigra to the striatum (Romo et al., 1986a). Thalamus-evoked impulse-

independent elevations in striatal dopamine were eliminated by lesions of the frontal (sensory motor) cortex or by perfusion of glutamate receptor antagonists into the striatum (Romo et al., 1986b). It was therefore suggested that cortical glutamatergic projections to the striatum could directly evoke transmitter release from dopaminergic terminals.

Although investigations subsequent to those of Glowinski and colleagues have continued to provide consistent evidence that application of exogenous glutamate to dopaminergic terminals in vivo elevates extracellular dopamine the functional relevance of this phenomenon has been questioned. It has been widely reported that glutamate infusions into the striatum or NAS elevate extracellular dopamine (Leviel, Gobert, & Buibert, 1990; Shimizu, Duan, & Oomura, 1990; Imperato, Scrocco, Bacchi & Angelucci, 1990; Keefe, Zigmond, & Abercrombie, 1992; Morari, O'Connor, Ungerstedt & Fuxe, 1993) and in many cases (Giorguieff et al., 1977; Lonart & Zigmond, 1991; Westerink, Santiago & deVries, 1992) these elevations have been shown to occur in the presence of TTX (however see Youngren, Daly & Moghaddam, 1993). However, in vivo microdialysis studies have shown that DA release occurs in response to relatively high concentrations of glutamate (greater than 1 mM) whereas lower concentrations fail to increase (Moghaddam, Gruen, Roth, Bunney & Adams, 1990; Youngren et al., 1993) or even decrease (Morari et al., 1996; Taber & Fibiger, 1996) NAS DA. At the concentrations that elevate striatal dopamine, glutamate can induce spreading depression in DA terminal regions (Moghaddam et al., 1990; Svensson, Zhang, Johannessen & Engle, 1994). Moreover, infusion of glutamate antagonists into the NAS increase, rather than decrease, extracellular DA; this suggests that glutamate tonically inhibits DA release (Imperato, Honoré & Jensen, 1990; Keefe et al., 1992; Taber & Fibiger, 1995). Thus some authors have suggested that glutamate-evoked presynaptic dopamine release reflects a pathological processes that is irrelevant to normal brain functioning.

In vivo studies aimed at characterizing the brain circuitry through which cortical glutamatergic projections might modulate striatal dopamine have arisen largely in the

context of the prefrontal cortex. Two reasons for focusing of PFC modulation of NAS dopamine are (1) that the PFC sends glutamatergic inputs to both the VTA and NAS and may thus be capable of modulating dopaminergic transmission both at the level of the dopaminergic terminal and at the level of the dopaminergic cell body, and (2) that the putative dysregulation of NAS dopaminergic transmission in schizophrenics has been suggested to be a downstream effect of PFC dysfunction (Weinberger, Berman & Illowwski, 1988; Robbins, 1990; Grace, 1991). Just as stimulation of the sensorimotor cortex elevates dopamine in the dorsal striatum (Nieoullon, Chéramy & Glowinski, 1978; Taber, Das & Fibiger, 1995) stimulation of the PFC elevates NAS dopamine (Murase, Grenhoff, Chouvet, Gonon & Svensson, 1993; Taber & Fibiger, 1995; You, Tzschentke, Brodin & Wise, 1998). However, recent microdialysis studies have suggested that it is glutamatergic projections to the VTA, rather than to the NAS, that are critical for PFC-evoked elevations in NAS DA. PFC-evoked elevations in NAS DA persist when ionotropic glutamate receptors in the NAS are blocked (Taber & Fibiger, 1995; Karreman & Moghaddam, 1996) suggesting that activation of NAS glutamate receptors does not contribute significantly to PFC-evoked dopamine release. Moreover, PFC-evoked elevations in NAS DA are blocked when impulse flow from dopaminergic neurons is disrupted by perfusion of TTX into the VTA (Karreman & Moghaddam, 1996) indicating that impulse flow through dopaminergic neurons is required for PFC stimulation to elevate NAS dopamine.

There is now considerable evidence that glutamatergic projections from the PFC can increase impulse flow through VTA dopaminergic neurons. Application of ionotropic glutamatergic agonists to the VTA increases the firing rates and evokes burst firing in dopaminergic neurons (Johnson, Seutin & North, 1992; Suaud-Chagny, Chergui, Chouvet & Gonon, 1992; Wang, O'Connor, Ungerstedt & French, 1994) and elevates NAS dopamine (Kalivas, Duffy & Barrow, 1989; Suaud-Chagny et al,. 1992; Wang et al., 1994; Karreman, Westerink & Moghaddam, 1996; Westerink, Kwint & deVries, 1996).

PFC stimulation elevates VTA glutamate (Rossetti, Marcangione & Wise, 1998) and, similar to the effects of exogenous application of glutamatergic agonists, PFC stimulation increases burst-firing in VTA DA neurons (Murase et al., 1993) and elevates NAS dopamine (Taber & Fibiger, 1995; Karreman & Moghaddam, 1996; You et al., 1998). PFC-induced elevations in NAS dopamine, in addition to being blocked by intra-VTA TTX (Karreman & Moghaddam, 1996), are blocked by intra-VTA perfusion of glutamate antagonists (Taber & Fibiger, 1995; Karreman & Moghaddam, 1996; You et al., 1998). Thus, evidence from studies of PFC stimulation suggests that the modulation of NAS DA by cortical glutamate is exerted primarily through activation of impulse flow through dopaminergic neurons at the level of the VTA.

THE HIPPOCAMPUS

Another structure that provides dense glutamatergic inputs to the NAS is the hippocampus. Unlike the PFC, however, the hippocampus does not send known projections to the VTA. The hippocampus is involved some behaviors that have traditionally been regarded as dopamine-mediated. The hippocampus has long been thought to influence goal-directed behavior (Papez, 1937; Jarrard, 1973), exploratory behavior (Kimble, 1963; Jarrard, 1968; O'Keefe & Nadel, 1978; Mogenson, Jones & Yim, 1980), and control of voluntary locomotion (Vanderwolf, 1971; Whishaw, Bland & Vanderwolf, 1972), all of which fall under the rubric of Pavlov's investigatory reflexes (Grastyan, 1959; Kimble, 1968). More recently, the identification of anatomical disruptions in the hippocampi of schizophrenic brains have served to focus attention on this region as a possible source of some aspects of schizophrenic symptomatology (Suddath, Christison, Torrey, Casanova & Weinberger, 1990; Weiner, 1990; Gray et al., 1991; Jaskiw & Weinberger, 1992; O'Donnell & Grace, 1998; Weinberger, 1999). The involvement of the hippocampus in investigatory behavior and schizophrenia has

attracted attention to the possibility that this structure influences dopaminergic transmission in the NAS.

The hippocampus is an anatomically complex structure consisting of several subregions. Although there is no universal agreement on the inclusion or exclusion of subregions as part of the hippocampus it is generally agreed that this structure comprises dentate gyrus, Ammon's horn, the subiculum, and the fimbria-fornix (Witter, 1989; Amaral & Witter, 1989). The hippocampus receives dense inputs from the entorhinal cortex which projects to the dentate gyrus. From the dentate gyrus the intrinsic connectivity of the hippocampus is classically described as the " circuit". Neurons of the dentate gyrus project to pyramidal neurons of Ammon's horn described as CA3 (Cornu Ammonis) which projects, in turn, to pyramidal neurons of CA2 or CA1. These neurons then project to pyramidal neurons of the subiculum which give rise to the primary outputs of the hippocampus (Groenewegen, Vermeulen-van der Zee, Te Kortschot & Witter 1987; Witter, Ostendorf & Groenewegen, 1990).

The complex organization of the hippocampus complicates functional studies of this structure. Some researchers have suggested that the dorsal and ventral regions of the hippocampus serve subtly distinct functions (Hughes, 1965; Jarrard, 1973; Moser, Moser, & Andersen, 1993; Eichenbaum, Otto, & Cohen, 1994). The suggestion of functionally distinct regions within the hippocampus is supported by topographically organized circuitry (Witter et al., 1989). Although, there is little known of which specific regions of the hippocampus may influence investigatory behavior or schizophrenia, recent research has focused on the ventral hippocampus, including both the ventral CA regions and the ventral subiculum (c.f. Lipska et al., 1992; Caine, Geyer & Swerdlow, 1992; Burns et al., 1996). In the following discussion, the term hippocampus will be used to refer to the dorsal and ventral regions of the dentate gyrus, Ammon's horn, and subiculum. However, special attention will be given to the ventral subiculum. This special attention is justified for two reasons; first, the ventral subiculum gives rise to the densest projections from the

hippocampus to the NAS and second, recent behavioral evidence implicates these outputs specifically in investigatory behavior.

Projections from the ventral subiculum to the NAS pass through the fimbria-fornix (Kelley & Domesick, 1982; Groenewegen et al., 1987; Witter et al., 1990; Brog et al., 1993) and terminate largely on dendritic spines of medium spiny neurons (Totterdell & Smith, 1989; Sesack & Pickel, 1990). Neurochemical analysis of limbic projections to the NAS suggests that the excitatory amino acid glutamate is likely the primary neurotransmitter (Walaas & Fonnum, 1979; Zaczeck et al., 1979; Walaas, 1981; Fuller et al., 1987). Electrophysiological data confirm that stimulation of the ventral subiculum or fimbria-fornix evokes excitatory responses in medium spiny neurons of the NAS (Lopes da Silva, Arnolds & Neijt, 1984; Yang & Mogenson, 1984; Boeijinga, Pennartz & Lopes da Silva, 1990) and these responses can be blocked by application of glutamate antagonists onto NAS neurons (Yang & Mogenson, 1984; Pennartz & Kitai, 1991).

The hippocampal inputs to medium spiny neurons (MSNs) of the NAS appear to play an important role in organizing NAS throughput. Approximately 75% of MSNs fire spontaneously and approximately 60% exhibit a bistable membrane potential which oscillates from an extreme hyperpolarized state to a less hyperpolarized state (Yim & Mogenson, 1988; O'Donnell & Grace, 1995). In these neurons the spontaneous activity and the oscillation in membrane potential from the extreme to the less polarized state is controlled by the hippocampus; when impulse flow from subicular projections are blocked by transection of or lidocaine injection into the fimbria-fornix (which through which projections from the ventral subiculum to the NAS pass), medium spiny neurons do not fire spontaneously and they do not exhibit bistable resting potentials, rather they remain in the hyperpolarized resting state (O'Donnell & Grace, 1995). Hippocampal control of the bistable state of MSNs is important for the passage of impulse flow evoked from PFC stimulation to generate action potentials in MSNs. PFC stimulation only generates action potentials when MSNs are in the less polarized resting state. When

impulse flow through the fimbria-fornix is blocked, PFC stimulation evokes excitatory post synaptic potentials but not action potentials.

On the other hand, the hippocampus blocks, rather than permits, the passage of information from the amygdala through the NAS (Mulder, Gijsberti Hodenpijl & Lopes da Silva, 1998). Stimulation of the fimbria-fornix significantly decreases the probability that amygdala stimulation delivered within the following 150 msec will evoke and action potential in MSNs. Moreover, the delivery of tetanizing stimulation to the Fi-Fo causes long-term (up to an hour) inhibition of amygdala-evoked action potential in MSNs. Thus, the hippocampal projections to the NAS have been suggested to "gate" the flow of information from the PFC (O'Donnell & Grace, 1995) and amygdala (Mulder et al., 1998) through the NAS.

Hippocampus & Investigatory Behavior

Neurochemical and electrophysiological studies have shown the hippocampus to be responsive to novel and conditioned stimuli. The activity of hippocampal neurons is increased during exploration of novel environments (Moser, 1995) and is tightly correlated with the presentation of conditioned stimuli that influence behavior (Deadwyler et al., 1979; Weiner & Eichenbaum, 1989). The activity of hippocampal neurons is closely regulated by cholinergic inputs from the basal forebrain (Bland, Andersen & Ganes, 1975; Bland, Colom, Konopacki & Roth, 1988). In vivo neurochemical studies of the hippocampus have provided evidence that cholinergic inputs to the hippocampus are relevant for behavioral arousal and attentional processes associated with novel and conditioned stimuli. Cholinergic input to the hippocampus is phasically increased during investigation of novel environments (Acquas, Wilson & Fibiger, 1996; Theil, Huston &Schwarting, 1998) or novel discrete sensory stimuli such as a light or a tone (Dudar, Whishaw & Szerb, 1979; Inglis & Fibiger, 1995; Acquas et al., 1996). The cholinergic response to a sensory stimulus depends on the significance of

the stimulus; if a tone-light stimulus that initially elevates ACh is not followed by any significant event then elevations in ACh habituate. However, if the tone-light stimulus is established as a CS that signals foot-shock, the elevation in ACh persists (Acquas et al., 1996). Thus the responsiveness of Pavlov's investigatory reflexes to novel and conditioned stimuli is paralleled by the responsiveness of the cholinergic input to the hippocampus.

Activation of the hippocampus (in response to novel and conditioned stimuli) may be involved in the initiation of, rather than simply correlate with, investigatory behavior. Direct electrical stimulation of the hippocampus increases investigatory behavior (McLean, 1957). Microinjections of the cholinergic receptor agonist carbachol into the dentate gyrus or ventral hippocampus also increase investigatory behavior (Grant & Jarrard, 1968; Flicker & Geyer, 1982; Mogenson & Neilson, 1984a). Similarly, stimulation of the ventral subiculum by microinjections of the glutamate receptor analog N-methyl-D-aspartate increase investigatory behavior (Yang & Mogenson, 1987). Investigatory behavior evoked by hippocampal activation and novel stimuli may depend on glutamatergic projections to the NAS. Application of glutamate receptor antagonists to the NAS blocks investigation evoked by novel stimuli (Mogenson & Nielsen, 1984b) or hippocampal injections of carbachol (Mogenson & Neilson 1984a).

Paradoxically, while hippocampal stimulation increases investigatory behavior, so do large hippocampal lesions (Kimble, 1963; Douglas & Isaacson, 1964; Douglas, 1967; Jarrard, 1968; Reinstein, Hannigan, & Isaacson, 1982; Lipska et al., 1992). Large hippocampal lesions also increase responding in situations of partial reinforcement and extinction (Jarrard, 1965, 1973; Gray & McNaughton, 1983; Clark, Feldon & Rawlins, 1992; Schmelzeis & Mittleman, 1996). Hippocampal lesions may also augment or perpetuate responding to conditioned stimuli. For example, hippocampal lesions increase investigatory behavior in environments that have been associated with food (Jarrard, 1976; Devenport, Davenport & Holloway, 1981). Although the effects of stimulation or

lesions of the dorsal hippocampus are similar, stimulation and lesions of the ventral subiculum have opposite effects. Selective lesions of the ventral subiculum, unlike large hippocampal lesions, decrease investigatory behavior evoked by novel stimuli (Burns et al., 1996).

There is increasing evidence that some of the behavioral effects of hippocampal lesions and hippocampal stimulation depend on dopaminergic neurotransmission in the NAS. Increases in investigatory behavior resulting from hippocampal lesions can be blocked by 6-OHDA lesions of the NAS (Emerich & Walsh, 1990) or by treatment with the dopaminergic antagonists haloperidol or clozapine (Lipska & Weinberger, 1994). Investigatory behavior associated with NMDA stimulation of the ventral subiculum is abolished by 6-OHDA lesions of the VTA (Wu & Brudzynski, 1995). Carbachol injections into the ventral hippocampus fail to increase investigatory behavior when dopaminergic transmission is blocked by systemic injections of haloperidol (Brenner & Bardgett, 1998). Thus, a variety of dopaminergic manipulations alter the influence of the hippocampus on investigatory behavior.

Hippocampal Modulation of NAS Dopamine

The precise mechanisms through which the hippocampal glutamate interacts with dopamine to influence investigatory behavior are unclear. One of the most frequently suggested mechanisms through which the hippocampus can influence investigatory behavior in a dopamine-dependent manner is by modulating dopaminergic transmission in the NAS (Lipska et al., 1992; Gray et al., 1991; Grace, 1993; Wu & Brudzynski, 1995; Brudzynski & Gibson, 1997). Historically, evidence implicating the hippocampus in the modulation of NAS DA has been obtained through the demonstration of an augmented response in animals with large hippocampal lesions to the effects of dopaminergic drugs on investigatory behavior. Although the augmented responsivity to dopaminergic drugs provides, at best, indirect evidence that the hippocampus modulates

dopaminergic transmission, lesion studies remain a focus of current research because of their potential relevance to schizophrenia (Lipska et al., 1992; Lipska, Chrapusta, Egan & Weinberger, 1995; Weinberger, 1999).

A link between the hippocampus, attentional filtering, and the NAS has been suggested by the ability of VS projections to the NAS to selectively "gate" information flow through the NAS (see above, O'Donnell & Grace, 1995, 1998; Mulder et al., 1998). Evidence for hippocampal damage in schizophrenics is becoming increasingly robust (Weinberger, 1999) and several authors have noted parallels between the effects of hippocampal lesions in rats and a disruption in investigatory responses in schizophrenics (Weiner, 1990; Gray et al., 1991). An example in this disruption of directing investigatory responses is seen in Pavlovian conditioning. In Pavlovian conditioning, stimuli that have been experienced as inconsequential or irrelevant subsequently serve as poor conditioned stimuli (a phenomenon referred to as latent inhibition; Lubow & Moore, 1959). However, such inconsequential stimuli retain their ability to serve as conditioned stimuli in schizophrenics (Baruch, Hemsley & Gray, 1988; Gray, Pilowsky, Gray & Herman, 1995) and in rats with lesions of either the hippocampus or its inputs from the entorhinal cortex (Akil, Mellgren, Halgren & Frommer, 1969; Kaye & Pearce, 1987; Cassaday, Mitchell, Williams & Gray, 1993; Yee, Rawlins & Feldon, 1995). The ability of previously irrelevant stimuli to serve as CSs in schizophrenics and hippocampally lesioned rats suggests that hippocampal damage disrupts some attentional filtering processes (Gray et al., 1995).

A role for dopaminergic transmission in the persistence of the investigatory response is implied by the ability of dopaminergic antagonists to reduce the ability of irrelevant stimuli to service as CSs in schizophrenics (Gray, Hemsley, & Gray, 1992) and in hippocampal lesioned rats (Tarrasch, Weiner, Rawlins & Feldon, 1992; Yee et al., 1995). Hippocampal damage therefore, has been suggested to alter dopaminergic transmission which then results in indiscriminate investigatory responses, intrusion of

irrelevant stimuli into ongoing cognitive processes, and the fusing of unrelated streams of information (Gray et al., 1991; Jaskiw & Weinberger, 1992; O'Donnell & Grace, 1998).

Hippocampal lesions and NAS DA

In addition to increasing spontaneous locomotion and exploratory behavior, hippocampal lesions augment investigatory behavior enhanced by systemic injections of amphetamine (Lynch, Ballentine & Campbell, 1969; Campbell, Ballentine & Lynch, 1971; Emerich & Walsh, 1990; Whishaw & Mittleman, 1991; Lipska et al., 1992). This enhancement may reflect alterations in either post-synaptic dopamine receptors or alterations in dopaminergic neurons. Hippocampal lesions enhance the investigatory behavior and stereotypy produced by systemic injections (Mittleman, LeDuc & Whishaw, 1993; Lipska & Weinberger, 1993) or intra-NAS injections (Reinstein, Hannigan, & Isaacson, 1982) of direct DA agonists as well as the locomotor suppressive effects of clozapine and haloperidol (Lipska & Weinberger, 1994). Thus, alterations in locomotor activity induced by hippocampal lesions appear to involve lesion-induced alterations in dopaminergic neurotransmission in the NAS.

Neurochemical evidence for altered dopaminergic transmission following hippocampal lesions is less consistent than behavioral evidence. Hippocampal lesions are not associated with greater basal levels of extracellular dopamine; tissue levels of the dopamine metabolite 3-methoxytyramine (assayed post-mortem) are not different from intact animals (Lipska et al., 1995). Using microdialysis, Wilkinson et al (1993) found no differences in basal levels of NAS DA between hippocampal lesioned and intact rats. However, hippocampal lesions appear to augment dopaminergic transmission in response to amphetamine; there is an exaggerated elevation in amphetamine-induced DA release with concomitant potentiation of amphetamine-induced locomotor activity in lesioned rats (Wilkinson et al., 1993). Moreover, aspiration lesions of the hippocampus (Springer & Isaacson, 1982) or excitotoxic lesions of the ventral hippocampus including the VS

(Lipska et al., 1992), but not the dorsal hippocampus (Lipska, Jaskiw, Karoum, Phillips, Kleinman & Weinberger, 1991), have been reported to increase NAS DA turnover assessed using post mortem assay.

Stimulation and NAS DA

The most direct and convincing evidence that the hippocampus can influence dopaminergic transmission comes from studies involving hippocampal stimulation. In a recent microdialysis study, Brudzynski and Gibson (1997) reported that chemical stimulation of the ventral subiculum, by injections of the NMDA, increased NAS dopamine concomitantly with increases in investigatory behavior. Electrical stimulation of the VS has also recently been reported to increase the dopamine-like voltammetry signal recorded from the NAS in anesthetized rats (Blaha, Yang, Floresco, Barr & Phillips, 1997). The most frequently suggested mechanism through which hippocampal stimulation might increase NAS dopamine is by evoking presynatpic transmitter release from dopaminergic terminals (Wu & Brudzynski, 1995; Blaha et al., 1997; Brudzynski & Gibson, 1997). Indeed, Blaha et al., (1997) have reported that elevations in the dopamine-like NAS voltammetry signal evoked by electrical stimulation of the VS are blocked by microinjections of glutamate antagonists into the NAS. These results are consistent with the idea (Romo et al., 1986a,b; Glowinski et al., 1988) that stimulation of cortical glutamatergic projections to the striatum increases dopamine release by actions at the level of the dopaminergic terminal. There remains, however, at least two concerns related to the notion of glutamate-evoked presynaptic dopamine release from striatal terminals. First, the release of dopamine in response to exogenous glutamate has been suggested to result from the induction of a pathological process (such as spreading depression) leading some researchers to question the functional relevance of this phenomenon (Moghaddam et al., 1990; Westerink et al., 1992; Svensson et al., 1994; Taber et al., 1995, 1996). Second, despite several well designed attempts, in vivo

microdialysis studies of PFC-evoked elevations in NAS DA have failed to provide evidence for presynaptic glutamate-mediated dopamine release (Karreman & Moghaddam, 1996; Taber et al., 1995; Taber & Fibiger, 1995). While not yet widely considered in the hippocampal literature, the hypothesis of preysnaptic glutamatergic modulation of NAS DA release has been seriously challenged, as mentioned earlier, in the PFC literature.

The Present Experiments

The present experiments were designed to study the mechanisms through which outputs from the ventral subicular region of the hippocampus modulate investigatory behavior and dopaminergic neurotransmission. Because the hippocampus is not known to innervate the VTA, there has been little attention given to the possibility that the hippocampus might influence NAS DA as does the PFC: through synaptic input to the dopaminergic cell bodies in the VTA. Indeed, electrical stimulation of the ventral subiculum has been reported to evoke brief inhibition followed by prolonged excitation of VTA dopaminergic neurons (Harden & Grace, 1995). The latencies of these responses were sufficiently long to suggest a circuit pathway from the ventral subiculum to the VTA. Thus, the ventral subiculum may exert an important influence on NAS dopamine by modulating impulse flow through VTA dopaminergic neurons.

CHAPTER ONE

Injections of N-methyl-D-aspartate into the ventral hippocampus increase extracellular dopamine in the ventral tegmental area and nucleus accumbens

Legault, M. and Wise, R. A. (1999). Synapse, 31, 241-249

INTRODUCTION

Motivational processes of the limbic system have been suggested to converge on and influence motor processes of the basal ganglia in the nucleus accumbens septi (NAS) (Nauta, Smith, Faull & Domesick, 1978; Nauta, 1986; Mogenson, 1987). The NAS is densely innervated by excitatory, presumably glutamatergic, inputs (Walaas & Fonnum, 1979; Zaczek et al., 1979; Walaas, 1981; Fuller et al., 1987) from cortical and subcortical limbic structures such as the prefrontal cortex, amygdala, and hippocampal formation including Ammon's horn, subiculum, and entorhinal cortex (Swanson & Cowan, 1977; Kelley & Domesick, 1982; Kelley et al., 1982; Groenewegen et al., 1987; Totterdell & Smith, 1989; Meredith & Wouterlood, 1990; Kita & Kitai, 1990; Brog at al., 1993). In addition, the NAS receives dense dopaminergic innervation from the ventral tegmental area (VTA) (Dahlstrom & Fuxe, 1964; Fallon & Moore, 1978). The involvement of NAS dopamine in locomotor behavior and investigatory stereotypies is firmly established. Intra-NAS injections of DA (Pijnenburg & Van Rossum, 1973; Johnson et al., 1996), or the indirect dopamine agonist, amphetamine (Creese & Iversen, 1975) increase locomotor behavior. Blockade of dopaminergic transmission by selective DA antagonists or destruction of dopamine neurons by injection of the selective neurotoxin 6-hydroxydopamine (6-OHDA) reduces exploratory locomotion (Jackson et al., 1975; Fink & Smith, 1980; Taghzouti et al., 1985) as well as amphetamine-induced locomotion (Creese & Iversen, 1975; Fibiger et al., 1973; Fink & Smith, 1979; Kelly & Iversen, 1976; Kelly & Roberts, 1983).

It has long been known that the hippocampus modulates locomotion (Jarrard, 1968; Kimble, 1963) and several lines of evidence suggest that this modulatory action is mediated, at least in part, by glutamatergic projections to NAS. Electrophysiological data confirm that hippocampal stimulation evokes excitatory responses in NAS neurons (Boeijinga et al., 1990; Lopes da Silva et al., 1984; O'Donnell & Grace, 1995) which are blocked by application of glutamate antagonists onto NAS neurons (Pennartz & Kitai, 1991; Yang & Mogenson, 1984). Stimulation of glutamate receptors in the NAS increases locomotor activity. Elevations in locomotor activity can be evoked by direct injections of glutamate or selective agonists for NMDA or AMPA receptors into the NAS (Arnt, 1981; Boldry & Uretsky, 1988; Wu et al., 1993; Johnson et al., 1996). Similarly, hippocampal stimulation (by injection of carbachol into the dentate gyrus or NMDA into the ventral subiculum) increases locomotor activity (Mogenson & Nielsen, 1984; Yang & Mogenson, 1987). Moreover, blockade of glutamate receptors in the NAS abolishes the locomotor response to intra-dentate carbachol (Mogenson & Nielsen, 1984). Hyperlocomotion evoked by either hippocampal stimulation or direct glutamatergic stimulation of the NAS appears to be dopamine dependent. Disruption of dopaminergic neurotransmission in the NAS by 6-OHDA lesions of the VTA abolishes the locomotor response to intra-NAS injections of glutamate agonists (Wu et al., 1993) as does dopamine depletion by pretreatment with α-methyl-p-tyrosine or reserpine (Boldry & Uretsky, 1988; Boldry et al., 1991). The locomotor response to intra-VS NMDA injections is also abolished by 6-OHDA lesions of VTA (Wu & Brudzynski, 1995).

The most frequently suggested mechanism by which glutamatergic projections from the hippocampus may affect locomotor activity in a dopamine-dependent manner is through the presynaptic modulation of dopaminergic neurotransmission in the NAS. It has been suggested that glutamate facilitates or causes dopamine release by an action on dopamine terminals (Chéramy et al., 1986; Romo et al., 1986a,b; Glowinski et al., 1988). Infusion of high concentrations of glutamate (Leviel et al., 1990; Shimizu et al., 1990) or

ionotropic glutamate agonists (Imperato, Scrocco, Bacchi & Angelucci, 1990; Keefe, et al., 1992; Morari et al., 1993; Youngren et al., 1993) into the NAS or dorsal striatum increase extracellular dopamine levels. However, the physiological relevance of glutamate-evoked elevations of extracellular dopamine has recently come into question. Infusion of low concentrations of glutamate (less than 1 mM) into the NAS or dorsal striatum fails to elevate extracellular dopamine in either of these regions (Moghaddam et al., 1990; Taber et al., 1996; Youngren et al., 1993). Only infusions of relatively high concentrations of glutamate into dopamine terminal regions are sufficient to elevate extracellular dopamine and, moreover, such elevations occur concomitantly with electrophysiological indices of spreading depression (Moghaddam et al., 1990; Svensson et al., 1994). Thus, elevations in extracellular dopamine may be secondary to induction of an abnormal physiological state.

Alternately, the hippocampus may modulate locomotion by stimulating dopamine neurons in the VTA. Although there is no known direct projection from the hippocampus to the VTA, electrical stimulation of the ventral subiculum is reported to increase burst firing of VTA dopamine neurons (Harden & Grace, 1995). The latency of this excitatory response suggests a polysynaptic circuit from hippocampus to VTA. The present experiments were conducted to examine the involvement of VTA dopamine in the locomotor response to ventral subiculum injections of NMDA. Initially the locomotor activating effects of NMDA injections into the ventral subiculum were determined across 3 doses of NMDA. Subsequently, in vivo microdialysis was used to estimate extracellular levels of dopamine and its metabolites in the VTA and NAS following NMDA into the ventral subiculum.

MATERIALS and METHODS

Animals and Surgery.

Fifty-eight male Long-Evans rats were used in this study: 17 for VTA microdialysis, 17 for NAS microdialysis, and 24 for locomotor experiments. Each rat weighed 300-350 grams at the time of surgery. The animals were housed in pairs prior to surgery and individually following surgery. The colony room lights were set on a 12-12 hour light-dark cycle; food and water were continuously available.

Each rat was anaesthetized with 60 mg/kg of sodium pentobarbital and given 0.25 mg/kg of atropine to minimize respiratory distress caused by bronchial secretions. For locomotor experiments each rat was implanted with bilateral 22-gauge guide cannulae aimed 1 mm above the ventral subiculum (VS). For microdialysis experiments each animal was implanted with a single 22-gauge VS guide cannula and a single 18-gauge guide cannula aimed either 4 mm above the ipsilateral NAS or 5 mm above the ipsilateral VTA. The respective stereotaxic coordinates for VS and NAS cannulae relative to bregma and ventral to dura were 4.9 mm from the midline, A: -3.0 mm, L: 4.9 mm, V: -7.0 mm and A: +2.4. L: 3.2 mm, V: -3.0 mm according to the atlas of Pellegrino et al., (1979). NAS cannulae were implanted at a 10 degree angle towards the midline in order to avoid penetrating the lateral ventricle. VTA cannulae were implanted with the incisor bar lowered 3.6 mm below the interaural line to allow sufficient separation of VS and VTA cannula for implantation of the VTA dialysis probe. VTA coordinates relative to bregma and dura were A: -5.0 mm, L: 1.1 mm, V: -3.8 mm. VS cannulae were fitted with 28-gauge obturators extending 1 mm beyond the cannula tip. NAS and VTA cannulae were fitted with 25 gauge obturators that were flush with the cannula tip. Animals recovered for a minimum of one week prior to any experimental treatments.

Microdialysis Procedure

Each vertical microdialysis probe consisted of 4 (NAS) or 5 (VTA) mm of protruding dialysis membrane (Hospal AN69) plugged at the tip by epoxy cement and

anchored with epoxy to 22-gauge stainless steel shaft. Fused silica tubing (i.d. = 75 μm, o.d. = 150 μm) was used for both the fluid inlet and outlet of the probe. The fluid inlet terminated at the distal end of the working surface, 0.2 mm from the epoxy-sealed tip of the membrane. The fluid outlet originated at the proximal end of the working surface, immediately inside the stainless steel shaft. For NAS probes the dialysis membrane was sealed with epoxy for a length of 1 mm beyond the shaft leaving a working surface of 3 mm. The VTA probes were sealed for 3 mm beyond the cannula leaving a working surface of 2 mm.

For the insertion of a dialysis probe each animal was lightly anesthetized with 30 mg/kg of sodium pentobarbital (I.P.). A probe was inserted into the guide cannula and cemented into place with acrylic dental cement. Each animal recovered from anesthesia after approximately one hour. Probes were continuously perfused at a rate of 1 μl/minute with artificial extracellular fluid (aCSF) composed of 2.0 mM Sorenson's phosphate buffer containing 145 mM $NaCl_2$, 2.8 mM KCl, 1.2 mM $MgCl_2$, 1.2 mM $CaCl_2$, 150, and 0.2 mM ascorbate, pH 7.3 - 7.4.

Twenty hours after probe implantation, microdialysis sampling began. Dialysate samples were collected every 15 minutes (15 μl) and analyzed for dopamine concentration. First, consecutive samples were collected until a stable baseline dialysate concentration of dopamine was obtained. Baseline concentration was considered to be stable when the dopamine concentrations of five consecutive samples varied by less than 10%. Next, each animal's obturator was removed, the injection cannula was inserted, and a single dose of NMDA was injected. Dialysate samples were then collected for an additional 135 minutes.

Analytical Procedure

Dialysate samples were analyzed using high-performance liquid chromatography (HPLC) with electrochemical detection. Dopamine was isolated by injecting dialysate samples through a reverse-phase column (supelcosil, 3 μm, LC-18, Supelco) via a

Rheodyne injection valve. Dopamine was quantified by an ESA Coulochem II detector (model 5200) and an analytical cell (ESA, model 5011) with two electrodes in series: an oxidizing electrode (+340 mV; 500 nA) and a reducing electrode (-270 mV; 5 nA). The mobile phase for this system consisted of 60 mM NaH_2PO_4, 3.0 mM ascorbate, 15% (v/v) MEOH in nanopure water with 0.035 mM sodium dodecyl sulphate (SDS), 0.1 mM ethyienediaminetetraacetic acid (EDTA) and was adjusted to pH 3.3 - 3.5 with NaOH. The mobile phase was pumped at a rate of 1.4 ml/min by a Waters 510 HPLC pump. A detection limit of 5 fmoles was routinely achieved.

Locomotor Experiments

Locomotor experiments began one week after surgery. On the first day each animal was assigned to a specific box. Each animal was allowed to explore its box for 60 minutes a day for the first three days. On the forth day each animal was injected unilaterally with the NMDA vehicle (aCSF) and placed into its assigned box for 60 minutes. The following day each animal was injected unilaterally (on the same side as the vehicle injection) with its assigned dose of NMDA and placed into its box for 60 minutes.

Locomotor activity was quantified in 20 x 41 cm wooden boxes with clear plastic fronts and wire mesh floors and with photocells and lamps mounted 14 cm from each end. The total number of photobeam interruptions was used as an index of locomotor activity.

Intracranial Injections.

In both locomotor and microdialysis experiments unilateral injections were made to reduce the risk of convulsive seizures and, in locomotor experiments, to avoid any possible confounding effects of asymmetrical injections. Each animal was injected with a predetermined dose (0.074, 0.28, or 0.74 μg) of NMDA. These doses were selected to range around the dose of 0.5 μg that has previously been shown to increase locomotor behavior when injected into the VS (Yang and Mogenson, 1987). Each dose of NMDA

was injected in a volume of 0.5 µl of aCSF. Intracranial injections were made through a 30 gauge stainless steel cannula which extended 1 mm beyond the tip of the guide cannula. The injection cannula was connected to a 1 µl Hamilton syringe via a length of polyethylene tubing (PE20). Injections were made using a syringe pump. The injection time was 46 seconds; the injection cannula was left in place for an additional 60 seconds.

Statistical Analyses

Differences in basal dopamine in both NAS and VTA dialysis experiments were determined using Dose X Baseline sample repeated measures analysis of variance (ANOVA) calculated using the estimates of dopamine (pg) in each 15 µl sample. Each animal's mean baseline was then used to transform its raw scores into percent of baseline scores. Drug effects were determined by single factor ANOVA with time as a repeated measure performed on percent of baseline scores. Significant differences between baseline and post-injection samples were determined using Fisher LSD. The level of significance for ANOVA and post-hoc comparisons was set at $p < 0.05$.

Total photobeam interruptions were taken as an index of locomotor activity. Because were animals were not matched for baseline locomotor activity across groups, difference scores (locomotor score following vehicle injection - locomotor score following NMDA injection) were computed for each animal and subjected to one-way ANOVA with dose as a between subjects measure. The level of significance was set at $p < 0.05$.

RESULTS

Effect of NMDA injections into the VS on extracellular dopamine

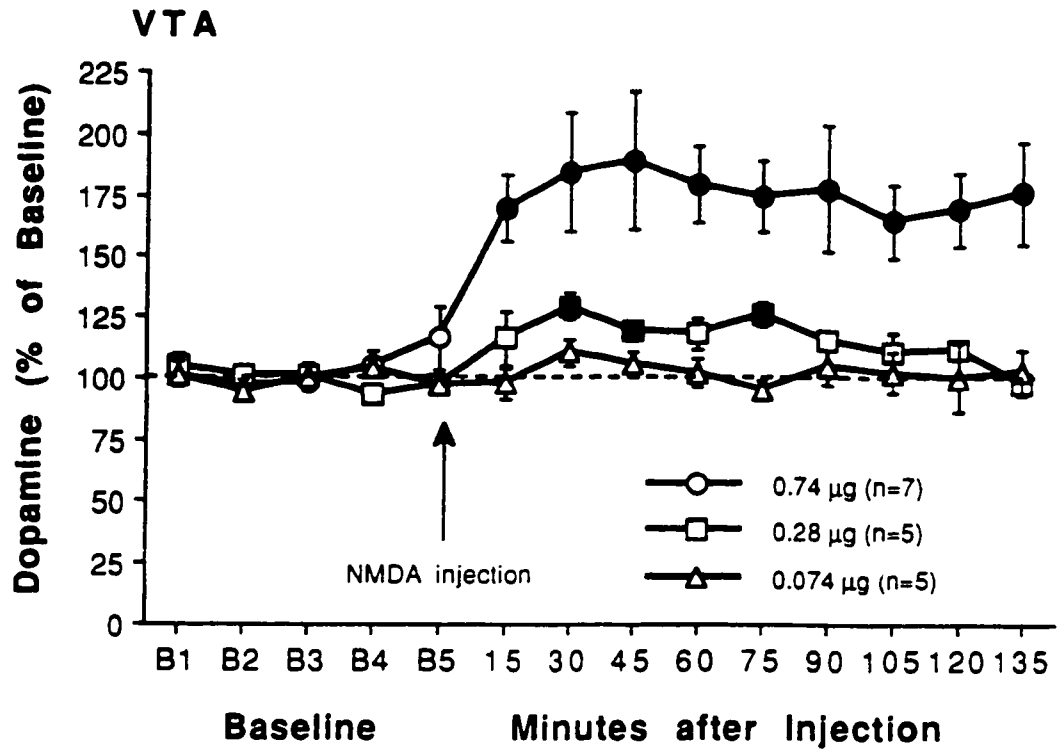
Chemical stimulation of the VS by NMDA resulted in dose-orderly increases in extracellular dopamine and DOPAC in each region (Figures 1 and 2). In the VTA, extracellular dopamine was significantly elevated following intra-VS injection of the two highest doses of NMDA (0.74 μg or 0.28 μg). The lowest dose of NMDA (0.074 μg) produced no reliable effect on VTA dopamine; nonetheless, all doses of intra-VS NMDA resulted in reliable elevations of VTA DOPAC. In the NAS, extracellular dopamine was elevated by each dose of NMDA injected into the VS. Extracellular DOPAC in this region was elevated following injections of the two highest doses of NMDA into the VS, the lowest dose of NMDA failed to evoke reliable elevations of DOPAC in this region.

Following injections of 0.74μg of NMDA dopamine levels rose rapidly and remained elevated throughout the 135 minute sampling period. In each region dopamine concentrations peaked at approximately 180% of baseline (VTA: 189%, NAS: 177%). The time-course of this effect was the same in the two regions: estimates of extracellular dopamine were elevated within 15 minutes from the time of injection and peaked approximately 45 minutes following the injection.

Behavioral Effects of NMDA injections into the VS

In microdialysis experiments, injection of 0.74 μg of NMDA caused considerable behavioral activation characterized by increases in locomotor activity , rearing, sniffing, grooming, and wet-dog shakes whereas the two lower doses of NMDA were without noticeable effect. Following injection of 0.74μg of NMDA, one animal in each of the two dialysis groups displayed convulsions during the sampling period. Convulsions occurred during the second hour following NMDA injections and lasted for less than 5 minutes.

Figure 1. Effect of NMDA injections into the VS on VTA and NAS dopamine (percent of baseline ± SEM). VTA dopamine was elevated by injections of either 0.74 μg [$F(9,54) = 2.421$] or 0.28 μg [$F(9,36) = 2.109$] of NMDA. NAS dopamine was elevated by injection of each dose of NMDA: 0.74 μg, $F(9,54) = 4.118$; 0.28 μg, $F(9,36) = 5.06$; 0.074 μg, $F(9,36) = 3.977$. Filled symbols indicate significant differences between post-injection sample and baseline (Fisher PLSD, $p < 0.05$).


VTA
Dopamine (% of Baseline)
225
200
175
150
125
100
75
50
25
0
NMDA injection
0.74 µg (n=7)
0.28 µg (n=5)
0.074 µg (n=5)
B1 B2 B3 B4 B5 15 30 45 60 75 90 105 120 135
Baseline
Minutes after Injection

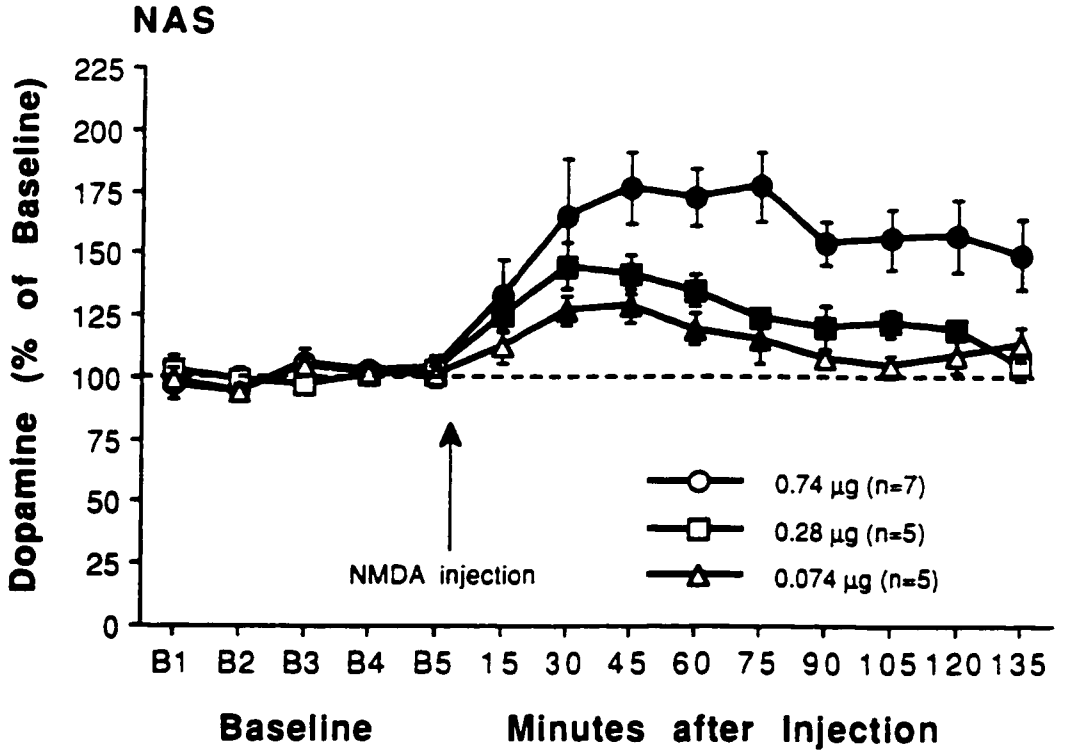
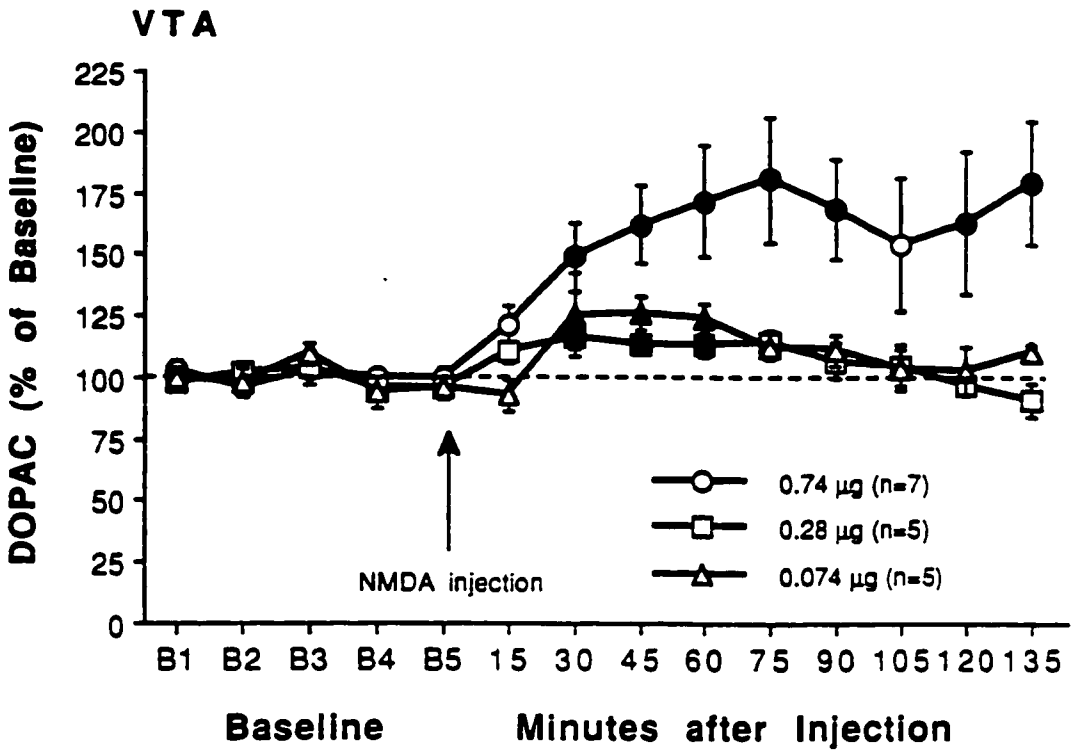
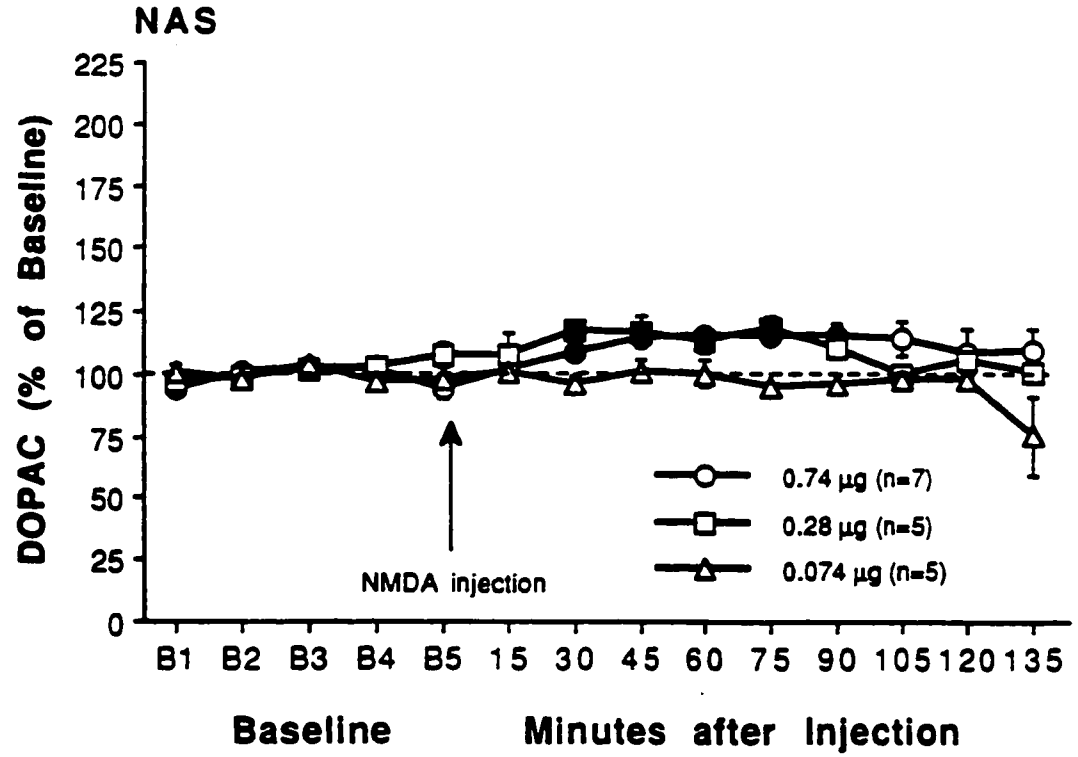

NAS
Dopamine (% of Baseline)
225
200
175
150
125
100
75
50
25
0
NMDA injection
0.74 µg (n=7)
0.28 µg (n=5)
0.074 µg (n=5)
B1 B2 B3 B4 B5 15 30 45 60 75 90 105 120 135
Baseline
Minutes after Injection

Figure 2. Effect of NMDA injections on VTA and NAS DOPAC (percent of baseline ± SEM). VTA DOPAC was elevated by injections of each dose of NMDA: 0.74 μg, $F(9,54) = 4.189$; 0.28μg, $F(9,36) = 6.116$; 0.074μg, $F(9,36) = 3.121$. NAS DOPAC was elevated by injections of either 0.74 μg [$F(9,54) = 2.911$] or 0.28 μg [$F(9,36) = 6.116$] of NMDA. Filled symbols indicate significant differences between post-injection sample and baseline (Fisher PLSD, $p < 0.05$).


VTA
DOPAC (% of Baseline)
225
200
175
150
125
100
75
50
25
0
NMDA injection
0.74 µg (n=7)
0.28 µg (n=5)
0.074 µg (n=5)
B1 B2 B3 B4 B5 15 30 45 60 75 90 105 120 135
Baseline
Minutes after Injection


NAS
DOPAC (% of Baseline)
225
200
175
150
125
100
75
50
25
0
NMDA injection
0.74 µg (n=7)
0.28 µg (n=5)
0.074 µg (n=5)
B1 B2 B3 B4 B5 15 30 45 60 75 90 105 120 135
Baseline
Minutes after Injection

The effects of unilateral injection NMDA into the VS on locomotor activity were quantified in independent groups of animals that did not undergo the microdialysis procedure. In line with observations of animals in microdialysis experiments, only the high dose of NMDA caused significant increases locomotor activity (Figure 3, A). The dose-dependency of this effect is clearly evident from analysis of difference scores (Figure 3, B). Because animals were not matched across groups for baseline locomotor activity, difference scores were calculated for each animal by subtracting photobeam interruptions following vehicle injections from those following NMDA injections. Difference scores for animals injected with 0.74 μg of NMDA were significantly greater than those of animals injected with either of the two lower doses. This increase in activity was evident throughout the entire 60 minute test period.

Three of 24 animals were not included in the locomotor experiment. One animal developed an infection around its cannula assembly and was not tested. Histological analysis revealed blood around the cannula tips of two other animals whose data were not included in subsequent analysis.

Histology

The tips of injection cannulae were located in the ventromedial ventral subiculum dorsal to the entorhinal cortex within the boundaries of the shaded area (Fig. 4). All NAS dialysis probes were located in the medial NAS, between the anterior commisure and lateral ventricle. No probe was found to have penetrated the ventricle or to have fallen lateral to the anterior commisure. VTA probes were located in the lateral portion of the VTA, bordering the substantia nigra pars compacta at the level of the mammillary nucleus. No probes were found to have penetrated the cerebral aqueduct.

Figure 3. Effect of NMDA injection into the VS on locomotor activity. **A:** Locomotor activity (total photobeam interruptions) during the 60 minute period following unilateral vehicle and NMDA injections. Activity following NMDA injections was greater than activity following vehicle injections [Dose x Treatment interaction, $F(2,18) = 19.289$]. Single factor ANOVA revealed that activity evoked by NMDA injection was higher than activity evoked by vehicle injections only in animals treated with the high dose of NMDA [$F(1,6) = 19.88$] (denoted by asterisk). **B:** Difference scores as a function of dose of NMDA. Injection of NMDA increased difference scores [$F(2,19) = 13.404$]. Post-hoc analysis revealed that difference scores for animals treated with the high dose of NMDA were greater than those of animals treated with either of the two lower doses (Asterisk, Fisher PLSD, $p < 0.05$).

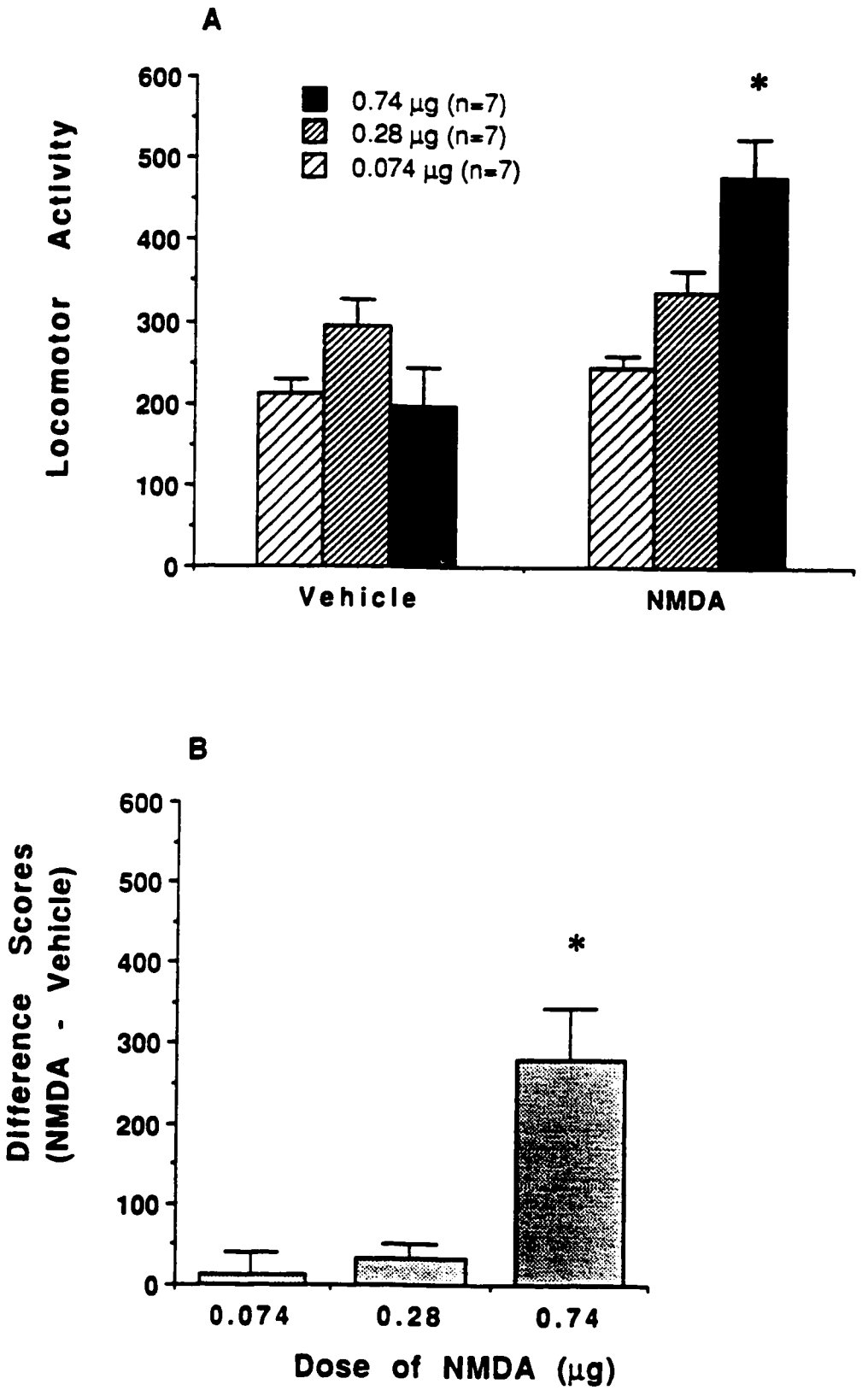
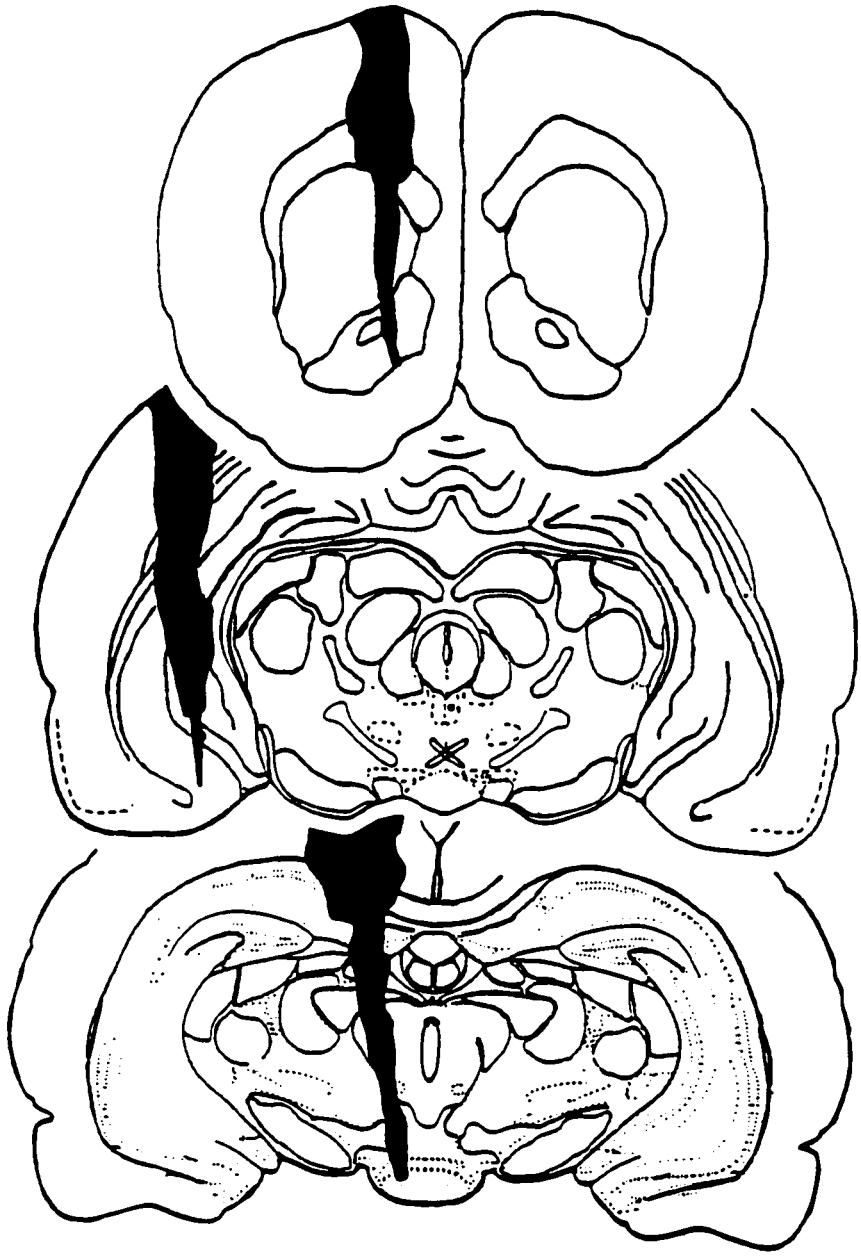

A
Locomotor Activity
600
500
400
300
200
100
0
0.74 µg (n=7)
0.28 µg (n=7)
0.074 µg (n=7)
*
Vehicle
NMDA
B
Difference Scores
(NMDA - Vehicle)
600
500
400
300
200
100
0
*
0.074
0.28
0.74
Dose of NMDA (µg)

Figure 4. Representative placements of a NAS microdialysis probe (top), VS injection cannula (middle) and VTA microdialysis probe (bottom). NAS (3.2 mm anterior to bregma) and VS (3.4 mm posterior to bregma) placements were redrawn from the atlas of Pellegrino et al., 1979. VTA placements (5.0 mm posterior to bregma) were redrawn from the Atlas of Swanson (1992).



DISCUSSION

Chemical stimulation of the VS by unilateral injection of the excitatory amino acid analog NMDA elevated extracellular dopamine and its primary metabolite, DOPAC, ipsilaterally in both dopamine cell body region of the VTA and in the terminal region of the NAS. The finding that intra-VS NMDA injections elevate extracellular dopamine in the NAS concurs with previous findings of elevations in NAS dopamine in response to chemical (Legault et al., 1995; Brudzynski & Gibson, 1997) or electrical (Blaha et al., 1997) stimulation of the VS. The highest dose of NMDA (0.74 μg) also produced reliable increases in locomotor behavior in agreement with previous reports (Yang & Mogenson, 1987; Brudzynski & Gibson, 1997). The present study extends previous findings by establishing that chemical stimulation of the VS elevates somatodendritic dopamine (in the VTA) in addition to synaptic dopamine (in the NAS), and in establishing the dose-orderliness of both VS-evoked elevations in dopamine and locomotor behavior.

Elevations in somatodendritic dopamine and DOPAC in response to chemical stimulation of the VS suggest that efferents of the ventral subiculum can increase the activity of dopamine neurons. While impulse-independent mechanisms might mediate dopamine release from nerve terminals, dendritic release of dopamine most probably reflects the neuronal depolarization associated with action potentials. This interpretation is consistent with several reports that somatodendritic dopamine is elevated by manipulations that increase firing rate or burst-firing of dopamine neurons. For example, direct electrical stimulation of dopamine neurons or electrical stimulation of their afferent fibers, infusion of morphine, or infusion of excitatory amino acids into dopamine cell body regions have all been demonstrated to elevate extracellular dopamine in the cell body regions of the VTA or substantia nigra (Chéramy, Leviel & Glowinski, 1981; Klitenick, DeWitte & Kalivas, 1992; Westerink et al., 1992; Wang et al., 1994; Iravani, Muscat & Kruk, 1996). Preliminary studies have indicated that electrical stimulation of the VS modulates the activity of VTA dopamine neurons (Harden & Grace, 1995). The

elevations in VTA dopamine and DOPAC reported here are consistent with these electrophysiological data and may be considered as a neurochemical reflection of an overall increase in the activity or a shift to burst-firing of dopamine neurons.

There are at least two pathways through which the VS may effect VTA cell firing. One possibility is that the VS modulates outputs of the ventral pallidum by way of the NAS. The ventral pallidum is ideally situated to modulate both dopaminergic neurotransmission and locomotor behavior by way of interconnections with the VTA and mesencephalic nuclei which project to the VTA (Groenewegen & Russchen, 1984; Yang & Mogenson, 1987; Zahm & Brog, 1992). A second possibility is that stimulation of the VS may directly or indirectly activate prefrontal cortex neurons which project to the VTA (Jay & Witter, 1991; Laroche, Jay & Thierry, 1990). The idea that the VS may effect VTA neurons by stimulating the PFC is consistent with evidence that PFC stimulation increases NAS dopamine by increasing impulse flow through the VTA (Karreman & Moghaddam, 1996; Murase et al., 1993; Taber et al., 1995; Taber et al., 1996).

Elevations in VTA dopamine evoked by NMDA injections into the VS indicate that the hippocampus can cause an impulse-dependent elevation of nucleus accumbens dopamine by modulating the activity of VTA dopamine neurons. Nonetheless, in the present study, the two lower doses of NMDA appeared to elevate NAS dopamine by approximately 20% more than VTA dopamine raising the possibility that glutamate released from VS terminals has actions in the NAS that contribute to the net flux in dopamine. One possibility is that glutamatergic projections from the VS to the NAS modulate axon terminal release of dopamine (Blaha et al., 1997; Brudzynski & Gibson, 1997). There is reason to doubt, however, that stimulating discrete glutamatergic inputs to the NAS can produce sufficiently high, potentially pathological (Moghaddam et al., 1990; Svensson et al., 1994), concentrations of glutamate to evoke impulse-independent dopamine release. Chemical or electrical stimulation of the PFC, for example, fails to elevate NAS dopamine levels in the absence of impulse flow through the VTA (Karreman

& Moghaddam, 1996; Taber & Fibiger, 1995) suggesting that glutamate levels in the NAS remain below the concentrations necessary to evoke impulse-independent elevations in dopamine. Likewise, it is improbable that stimulation of the VS in the present study produced high enough concentrations of NAS glutamate to cause impulse-independent elevations in dopamine. The apparent differences between elevations in NAS and VTA dopamine may be a function of several factors unrelated to glutamatergic neurotransmission. First, different lengths of dialysis tubing were used to sample from regions of different sizes and probably different concentrations of extracellular dopamine; second there may be important differences in the ratio of dendritic to axon terminal release; finally, it is possible that microdialysis probes were not placed in the most responsive area in the VTA thus underestimating VS-evoked elevations in dopamine in this region.

The present study identifies the VTA as a possible site through which the VS modulates locomotor behavior. At the highest dose of NMDA tested (0.74 μg) locomotion was increased concurrently with elevations in VTA and NAS dopamine. Injections of this dose of NMDA produced a noticeable increase in locomotion in animals undergoing microdialysis and this increase was quantified and confirmed in independent groups of animals. Elevations in dopamine and locomotor activity both occurred within 15 minutes of the injection. Locomotor activity remained elevated for at least 60 minutes following NMDA injections as did extracellular dopamine in both regions sampled.

It is not clear to what extent increases in locomotor activity are due simply to elevations in NAS dopamine or involve a more complex interaction between dopamine and glutamate on NAS neurons. Clearly, normal dopaminergic neurotransmission is necessary for locomotion induced by injection of NMDA into the VS (Wu & Brudzynski, 1995) or injection of glutamatergic agonists into the NAS (Boldry & Uretsky, 1988; Boldry et al., 1991; Wu et al., 1993). Moreover, increasing dopaminergic neurotransmission in the NAS appears to be sufficient to induce locomotor activity

(Creese & Iversen, 1975; Johnson et al., 1996; Pijnenburg & Van Rossum, 1973) as does stimulation of VTA neurons by infusion of glutamate agonists (Westerink et al., 1996) or disinhibition of VTA dopamine neurons by ventral tegmental opiates (Johnson & North, 1992; Joyce & Iversen, 1979; Kalivas, Widerlov, Stanley, Breese & Prange, 1983; Latimer, Duffy & Kalivas, 1987).

However, glutamatergic inputs to the NAS, particularly those from the ventral subiculum, are necessary for the expression of locomotor activity induced by elevations in NAS dopamine. First, infusions of ionotropic glutamate antagonists into the central NAS reduce exploratory locomotion (Maldonado-Irizarry & Kelley, 1994) and the locomotor response to systemic injections of amphetamine (Burns, Everitt, Kelley & Robbins, 1994) or cocaine (Pulvirenti, Berrier, Kreitfeldt & Koob, 1994). Second, excitotoxic lesions of the hippocampus (but not the basolateral amygdala or prefrontal cortex) abolish the locomotor response to intra-NAS injections of amphetamine (Burns et al., 1993). These data suggest that VS inputs to the NAS play an important function in the expression of exploratory locomotor activity and possibly a more general role in mediating the motivational processes of the NAS.

The elevations in extracellular dopamine and locomotor behavior observed in the present study are presumed to be mediated by NMDA-induced stimulation of VS efferents. Indeed, in vitro application of glutamate or NMDA depolarizes and evokes action potentials in cortical pyramidal and hippocampal neurons (Arvanov & Wang, 1997; Fan & Szerb, 1993; Taube, 1993). However, sufficiently high concentrations of glutamate or NMDA may result in depolarization inactivation of subicular neurons (see for example, Sombati, Coulter & DeLorenzo, 1991) raising the concern that the effects reported in the present study are mediated by inactivation, and not stimulation, of subicular outputs. Although this possibility can not be ruled out it remains unlikely given the concordance between the present results and those of studies demonstrating elevations in NAS dopamine (Blaha et al., 1997) and increased firing of VTA dopamine neurons

(Harden & Grace, 1995) evoked by electrical stimulation of the VS a manipulation that is unlikely to evoke long-term depolarization of subicular outputs. Nonetheless, depolarization inactivation of subicular outputs may explain why intra-VS injections of higher doses of NMDA (2 μg) used in another study (Brudzynski & Gibson, 1997) produced lower elevations in NAS dopamine than those produced by the highest dose (0.74 μg) tested in the present study. However, differences in magnitude of VS-evoked elevations in NAS dopamine might result from any number of differences between these two studies including those related to microdialysis techniques, differences in injection sites, or differences in injection volume and NMDA vehicle (0.2 μl in saline for Brudzynski and Gibson, 0.5 μl in aCSF for the present study).

Dysfunction of the hippocampus and subsequent disruptions in dopaminergic neurotransmission NAS may have functional implications for the pathophysiology of schizophrenia (Grace, 1991, 1993; Mittleman et al., 1993; O'Donnell & Grace, 1995; Weiner & Feldon, 1997). Much interest in this area of research has focused on the idea that dopaminergic neurotransmission in the NAS is regulated or modulated presynaptically by corticostriatal glutamate and that disruption of glutamatergic input to the NAS may underlie disruptions in dopaminergic neurotransmission (Gray et al., 1991; Grace, 1993; Yee et al., 1995). Identification of the circuit elements underlying VS mediated increases in dopaminergic neurotransmission may thus provide insights into the neural processes involved in schizophrenia as well as those involved in exploratory locomotion and other motivated behaviors.

In summary, elevations in VTA dopamine in response to NMDA injections into the VS provide the first neurochemical evidence that the VS modulates the activity of the dopamine neurons in the VTA. While direct effects of NAS glutamate on DA release cannot be ruled out, the present results suggest that indirect effects of VS activation, mediated trans-synaptically through the VTA, underlie both the elevations in NAS dopamine and the increases in locomotor activity that were observed in the present study.

CHAPTER 2

Elevations of Nucleus Accumbens Dopamine by Chemical Stimulation of the Ventral Hippocampus are Mediated Through the Ventral Tegmental Area: Electrophysiological and Dual-Probe Microdialysis Studies

INTRODUCTION

Dopaminergic transmission in the nucleus accumbens septi (NAS) is involved in approach towards and investigation of novel stimuli (Fink & Smith, 1980; Tagzhouti et al., 1985), and is suggested to be involved in reinforcement of approach behaviors (Wise & Bozarth, 1987), compulsive drug self-administration (Wise & Rompré, 1989; Wise, 1996) and the pathophysiological processes of schizophrenia (Snyder, 1972). Both NAS dopamine (DA) and investigatory behavior appear to be influenced by the hippocampus. Stimulation of the hippocampus elevates NAS DA (Blaha et al., 1997; Brudzynski & Gibson, 1997; Legault & Wise, 1999, see Chapter 1) and evokes investigatory behavior (MacLean, 1957; Yang & Mogenson, 1987; Brudzynski & Gibson, 1997; Legault & Wise, 1999) that is abolished by disruption of dopaminergic transmission (Wu & Brudzynski, 1995; Brenner & Bardgett, 1998). Two hypotheses have been offered to account for hippocampal influences on NAS DA. One possibility is that direct glutamatergic projections from the ventral subiculum (VS) of the hippocampus to the NAS (Walaas, 1981; Christie et al., 1987; Fuller et al., 1987; Totterdell & Smith, 1989; Sesack & Pickel, 1990) might evoke glutamate-mediated impulse-independent dopamine release by acting presynaptically on dopaminergic terminals (Romo et al., 1986a,b; Glowinski et al., 1988; Blaha et al., 1997; Brudzynski & Gibson, 1997). A second possibility is that outputs from the VS regulate impulse flow in dopaminergic neurons through polysynaptic projections to the dopaminergic cells of the ventral tegmental area (VTA).

The idea that glutamatergic projections to the NAS might presynaptically evoke DA release has been studied largely in the context of prefrontal cortex (PFC) stimulation. The PFC sends glutamatergic projections to both the NAS (Christie et al., 1987; Fuller et al., 1987; Sesack et al., 1989) and the VTA (Christie et al., 1985; Sesack et al., 1989; Sesack & Pickel. 1990). In the VTA, glutamate increases impulse flow through dopaminergic neurons (Mereu et al., 1991; Johnson et al., 1992). PFC stimulation increases VTA glutamate (Rossetti et al., 1998; You et al., 1998) and also increases impulse flow through dopaminergic neurons (Murase et al., 1993). Thus glutamatergic projections from the PFC could influence NAS DA at both the terminal (NAS) and cell body (VTA) levels. Recent microdialysis studies have demonstrated that it is the glutamatergic projections from the PFC to the dopaminergic cell body region of the VTA, rather than to the terminals in the NAS, that are critical for PFC-evoked elevations in NAS DA. First, PFC-evoked elevations in NAS DA are abolished when dopaminergic impulse flow to the NAS is blocked by perfusion of tetrodotoxin into the VTA (Karremen & Moghaddam, 1996). Second, PFC-evoked elevations in NAS DA are blocked by application of glutamate antagonists to the VTA but not the NAS (Taber & Fibiger, 1995; Karreman & Moghaddam, 1996; You et al., 1998).

While the VS, like the PFC, sends glutamatergic projections to the NAS, the VS, unlike the PFC, is not known to project directly to the VTA. Thus, while the suggestion that a direct projection to the NAS modulates DA release at the level of the DA axon terminals (Blaha et al., 1997; Brudzynski & Gibson, 1997) seems untenable for the reasons listed above, it cannot be argued that the VS directly activates VTA DA neurons. However, we have recently found that NMDA injection into the VS elevates VTA as well as NAS DA (Legault & Wise, 1999). VS-evoked elevations in VTA DA are assumed to reflect dendritic release of DA resulting from VS-evoked increases in dopaminergic impulse flow, and this raises the possibility that the VS can activate VTA dopaminergic neurons trans-synaptically.

The present experiments were designed to determine if synaptic input to the VTA constitutes a critical link in the circuitry by which the hippocampus modulates NAS DA. First, dual-probe microdialysis was used to determine if elevations in NAS DA evoked by intra-VS injections of NMDA are (i) dependent on impulse-flow through the VTA, and (ii) mediated by activation of glutamate receptors in the VTA. In a second experiment, action potentials from VTA DA neurons were recorded in anesthetized rats and firing rates were monitored before, during, and after, NMDA injections into the VS.

MATERIAL AND METHODS

Subjects

Seventy-one male Long-Evans rats (Charles River, St. Constant, Quebec) were used for these experiments. The rats, weighing between 300 and 400 grams at the time of surgery, were housed in pairs prior to and individually following surgery. They were maintained on a 12 hour light/dark cycle. Food and water were available ad libitum.

Microdialysis Studies

Surgery. Twenty-six rats were anesthetized with pentobarbital (60 mg/kg, i.p.) and placed in a stereotaxic frame for simultaneous implantation of unilateral guide cannulae into the NAS and VTA for microdialysis probes and the VS microinjections. In order to maximize the distance between cannulae, NAS and VS cannulae were implanted with the incisor bar set at 5 mm above the interaural line while VTA cannulae were implanted with the incisor bar adjusted to set bregma and lambda at the same horizontal level. Coordinates for NAS cannulae were as follows: 3.2 mm anterior to bregma, 2.4 mm lateral to the saggital suture, and 3.0 mm below dura (NAS cannulae were angled 10 degrees towards the midline to avoid penetrating the lateral ventricle; the vertical coordinate refers to the distance along this vector). Coordinates for VS and VTA cannulae were respectively: AP -3.2 mm, L 4.8 mm, V -6.8 mm; and AP -5.0 mm, L 1.1, V -3.8 mm. Probe cannulae were fitted with obturators that were flush with the cannula tip. Injection cannulae were fitted with obturators that extended 1 mm beyond the cannula tip. Cannula assemblies were secured in place with dental cement and 4 stainless steel screws threaded into the skull. Following recovery from anesthesia each animal was returned to the colony room for at least 7 days before implantation of microdialysis probes.

Microdialysis Procedure. Concentric microdialysis probes were constructed such that a length of dialysis membrane (Hospal AN69; molecular weight cutoff 40 kDA) extended 4 mm (NAS) or 5 mm (VTA) beyond the tip of a 22 gauge stainless steel shaft

which ended flush with the bottom of each guide cannula. Epoxy cement coated the external membrane surface for 1 mm beyond the guide cannula (NAS probes) or 3 mm beyond the guide cannula (VTA probes). Lengths of fused silica tubing (i.d. = 75 μm, o.d. = 150 μm) were used for both the fluid inlet and outlet. The fluid inlet terminated at the distal end of the probe near the membrane tip. The fluid outlet originated just inside the probe shaft. Both the inlet and outlet were glued with epoxy cement to the top of the probe shaft. Microdialysis probes were inserted into the brain at least 18 hours before the beginning of any experiment. Each animal was anesthetized with a low dose of sodium pentobarbital (30 mg/kg, i.p.), probes were inserted and fixed in place with dental cement. Probes were connected to a dual-channel liquid swivel and continuously perfused with a solution of artificial extracellular fluid (aCSF) using a microdialysis pump (Harvard); flow rate was set at 1.0 μl/minute. The aCSF comprised 2.0 mM Sorenson's phosphate buffer containing 145 mM NaCl, 2.8 mM KCl, 1.2 mM $MgCl_2$, 1.2 mM $CaCl_2$, and 0.2 mM ascorbate (pH 7.3 - 7.4).

Microdialysis experiments were designed to determine the effects of intra-VTA dialysis of TTX (1 μM) or Kynurenic acid (KYN, 1 mM) on elevations in NAS DA evoked by intra-VS injections of NMDA. These experiments were carried out over a two-day period. On day 1, either TTX or KYN was infused into the VTA prior to, during, and after injections of NMDA into the VS. NAS dialysate samples were first collected during dialysis of aCSF into the VTA. Consecutive 15 min samples were collected until the DA content (pg) of each of 6 consecutive samples varied by less than 15%. The mean DA content of these 6 samples was defined as baseline. The VTA perfusate (aCSF) was then replaced with either KYN or TTX, and 20 minutes were then allowed for flow rates to stabilize prior to collection of the next sample. Following this stabilization period, either 4 (KYN test) or 6 (TTX test) consecutive samples were then collected from the NAS probe. NMDA (0.74 μg in 0.5 μl, injected in 1 min.) or vehicle (aCSF) was then injected into the VS and NAS dialysate samples were collected for 2

hours. Finally, 2 hours after the NMDA injection, KYN or TTX solutions were replaced with aCSF. Animals that had received intra-VS NMDA injections on Day 1 were tested again on Day 2. On this day, both NAS and VTA probes were perfused with aCSF. Baseline samples from the NAS were collected as described above; NMDA was then injected into the VS and NAS dialysate samples were collected for 2 hours. This test allowed us to confirm the effectiveness of the site of injection into the VS.

Analytical Procedure. Dialysate samples were analyzed on-line for dopamine content by HPLC with electrochemical detection. Dopamine was isolated using a reverse-phase column (Supelco, supelcosil, 3 mm, LC-18) and quantified using an ESA Coulochem II detector (model 5200) and an analytical cell (ESA model 5011) with two electrodes in series. The potential of the first (oxidizing) electrode was set at 340 mV (500 nA) and second electrode (reduction) was set at -270 mV (5 nA). The mobile phase (in deionized water) consisted of 60 mM NaH_2PO_4, 3.0 mM ascorbate, 15% v/v MEOH, 0.035mM sodium dodecyl sulphate (SDS), 0.1 mM ethylenediaminetetraacetic acid (EDTA) with a pH adjusted to 3.5 using NaOH. The detection threshold for DA was at least 0.5 pg.

Single Unit Recording of VTA DA Neurons

Forty-five rats were used for electrophysiological experiments. Each animal was anesthetized with urethane (1.2 g/kg, i.p.) and mounted in a stereotaxic frame. The surface of the skull was exposed and a 22 gauge guide cannula was implanted into the VS at the coordinates previously mentioned. The cannula was secured with wax to 2 stainless-steel screws threaded into the skull. A 28 gauge injection cannula containing an NMDA solution was inserted into the guide cannula and left in place for the remainder of the experiment. The incisor bar was then lowered to set bregma and lambda to same the horizontal plane. The bone and dura above the VTA ipsilateral to the VS injection cannula were removed. A glass micropipette (1-2 μm tip diameter; impedance 2-7 MΩ at 1000 Hz) filled with pontamine skye blue (0.2% w/v) was lowered into the VTA by

hydraulic microdrive. Dopamine neuron action potentials were identified according to classical criteria of Bunney and Grace (1978): (i) initially positive-going bi- or triphasic action potentials with a large second negative segment and a duration longer than 2.5 ms (ii) slow, irregular basal firing rate (1 to 8 Hz); (iii) location in the VTA. Dopamine action potentials were isolated from noise using the Cluster Cutting module of the Discovery software package (dataWave Technologies, CO, USA). Once a dopaminergic neuron was identified and isolated, baseline firing was recorded for at least 5 minutes. Either NMDA or aCSF was then injected into the VS and action potentials were recorded for another 15 minutes. In 4 cases no injection was made and the cell was recorded for at least 30 minutes to determine the magnitude of firing rate variation over time.

Drugs and Intracranial Injections

NMDA was dissolved in aCSF at a concentration of 1.48 μg/μl and 0.5 μl of this solution was injected centrally, at a flow rate of 1 μl/min through a 28 gauge injection cannula. This dose of NMDA was chosen on the basis of a previous study showing that it increases both DA in the ipsilateral NAS and VTA DA and locomotor activity in awake freely moving rats (Legault and Wise, 1999). Solutions of KYN and TTX were mixed fresh in aCSF and sonicated for at least 20 minutes immediately prior to perfusion through microdialysis probes. The concentration of kynurenic acid (1 mM) was chosen of the basis of a previous study showing that intra-VTA application of this concentration via dialysis blocks elevations in NAS DA evoked by stimulation of the PFC (You et al., 1999). The concentration of TTX (1 μM) was chosen because it is on the lower end of the range of concentrations that reduce NAS DA when perfused either into the NAS (Westerink et al., 1987) or VTA (Taber et al., 1995; Karreman and Moghaddam, 1996)

Data Analysis

For analysis of data from electrophysiological experiments, peri-event time histograms (PETH) with 10s bins were generated off-line. For each cell, mean firing rates were calculated for the 5 minute pre-injection period and for each of the 5 minute periods that

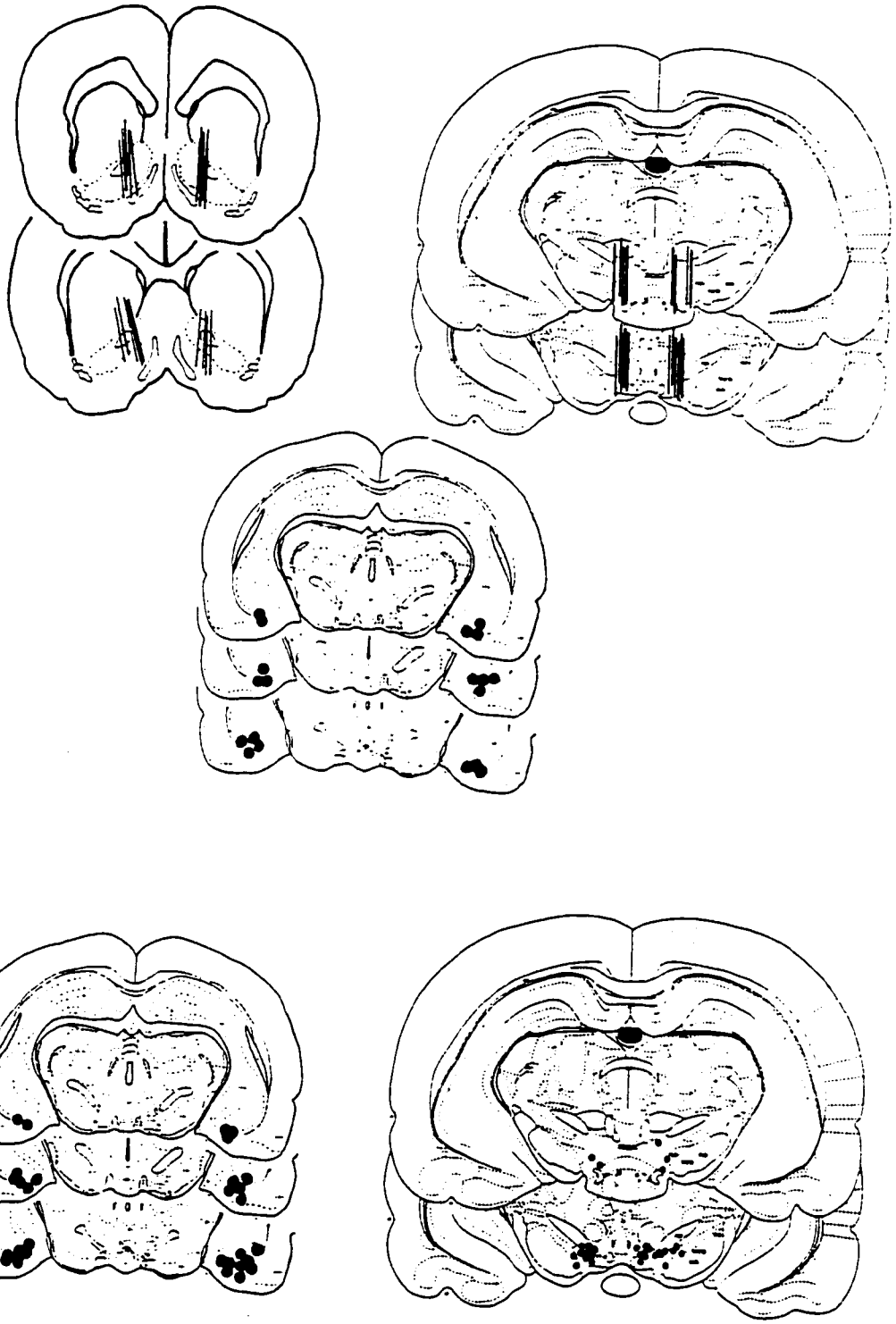
followed. The 5 minute pre-injection firing rate was taken as baseline. Post-injection values were then expressed as percent of baseline firing rate. A cell was considered to have changed its firing rate if there was a minimum of 10% difference from baseline in at least 2 of the 3 post-injection periods.

For microdialysis experiments, basal DA was estimated by calculating the mean DA content (pg) in the 6 dialysate samples collected prior to experimental treatments. Each animal's mean baseline was then used to convert the DA content of each of its samples into a percent of baseline value. Treatment effects between groups were determined using two-way repeated measures ANOVA with Time as a repeated measure and post-hoc comparisons were made using Student's t test. Within-groups treatment effects were analyzed using one-way repeated measures ANOVA with Time as a repeated measure. Post-hoc comparisons between baseline and treatment effects were made using Fischer's least significant difference test (LSD) with the level of statistical significance was set at $p < 0.05$.

Histology

At the end of electrophysiological experiments the recording site was marked with Pontamine Skye Blue by passing a 20 μA cathodal current through the glass micropipette for 25 minutes. Each deeply anesthetized animal was then decapitated and the brain was removed and stored in a 10% formalin solution. At the end of microdialysis experiments, each rat was deeply anesthetized by injection of sodium pentobarbital (60 mg/kg) and transcardially perfused with normal saline followed by a10% formalin solution. All brains were stored in 10% formalin for at least one week and subsequently sliced in 20 μm sections with a microtome; recording, microdialysis, and injection sites were localized by examination under low magnification in a light microscope. The locations of microdialysis membranes, VS injection cannulae, and recording pipette tips are represented in Figure 5.

Figure 5. Representation of the locations of dialysis membranes, recording pipette tips, and injection cannula tips. *Top*. Locations of dialysis membranes and VS-injection sites. For the sake of clarity all dialysis and injection sites for animals treated with intra-VTA KYN are represented in the left hemisphere and all sites for animals treated with intra-VTA TTX are represented in the right hemisphere. *Bottom*. Locations of single unit recording sites and VS injection sites. For cells that increased firing when NMDA was injected into the VS, the injection and recording sites are represented on the left hemisphere. Cells for which NMDA decreased or caused no net effect in firing rate over the 15 minute session the injection and recording site are represented in the right hemisphere. For clarity, the location of VS injection and VTA recording sites are not represented to control cells.. Diagrams of the NAS and VS were reproduced from the atlas of Pellegrino, Pellegrino, and Cushman (1979). NAS: 3.0 and 3.2 mm anterior from bregma. VS: 3.0 mm, 3.2 mm and 3.4 mm posterior from bregma. Diagrams of the VTA were reproduced from the atlas of Swanson (1992). VTA: 4.8 and 5.3 mm posterior from bregma



RESULTS

Effect of TTX Perfusion into the VTA

Perfusion of TTX (1μM) through VTA microdialysis probes decreased NAS DA in all animals. During application of TTX to the VTA, NAS DA levels decreased steadily until, by the 5th post-TTX sample, DA was reduced to below 20% of baseline. DA levels remained below 20% of baseline throughout the remainder of the TTX infusion. In animals that were to receive NMDA injections into the VS, the mean baseline value of NAS DA was 0.57 (±0.038) pg/μl and was decreased to a minimum of 0.074 pg/μl, while in animals that were to receive aCSF injections the mean baseline value of 6.48 (±0.057) pg/μl was decreased to a minimum of 0.097 pg/μl.

Perfusion of TTX into the VTA, thus, prevented the elevations in NAS DA induced (Day 2 tests, below, shown in Figure 8) by NMDA injections into the VS (Figure 6). During TTX infusions, there were no detectable differences in NAS DA levels between animals that received intra-VS NMDA or intra-VS aCSF injections. Thus, at no point following NMDA injections (administered 90 minutes after the initiation of TTX perfusion) was NAS DA greater than 20% of baseline.

Effect of KYN perfusion into the VTA

Perfusion of KYN through VTA microdialysis probes prevented the elevation of NAS DA by intra-VS NMDA injections (Figure 7). In animals that received NMDA injections, the mean basal value of NAS DA was 0.48 (±0.027) pg/μl whereas animals that received aCSF the mean basal value was 0.52 (±0.016) pg/μl. At no point following NMDA injections (administered 60 minutes after the initiation of KYN perfusion into the VTA) were NAS DA levels different from baseline. In animals that received aCSF injections during KYN perfusion there was a small but reliable decrease in NAS DA. There was no difference in NAS DA between animals receiving KA+VS NMDA injections and those receiving KA+aCSF (Treatment: $F_{1,17} = 5.246$; $p > 0.05$).

Figure 6. Effect of NMDA injections into the VS on nucleus accumbens dopamine (mean % of baseline ± SEM) during TTX perfusion into the VTA. Microdialysis samples were collected every 15 minutes. Intra-VTA TTX perfusion was initiated following the collection of 6 baseline samples. NMDA (0. 74 μg) or aCSF was injected into the ipsilateral VS 90 minutes after the initiation of TTX perfusion. TTX decreased NAS DA [$F(8, 19) = 122.0$; $p = 0.0001$]. Either NMDA or aCSF was injected into the VS 90 minutes after the initiation of TTX perfusion (after sample 12). NMDA had no effect on NAS DA; there was no difference NAS DA between animals injected with NMDA or aCSF [$F(1,19) = 1.35$; $p = 0.1604$] nor was there a difference between the sample collected immediately prior the NMDA injection and any subsequent sample (Fisher LSD, $p > 0.05$). Filled symbols indicate significant differences from baseline (Fisher LSD, $p < 0.05$).

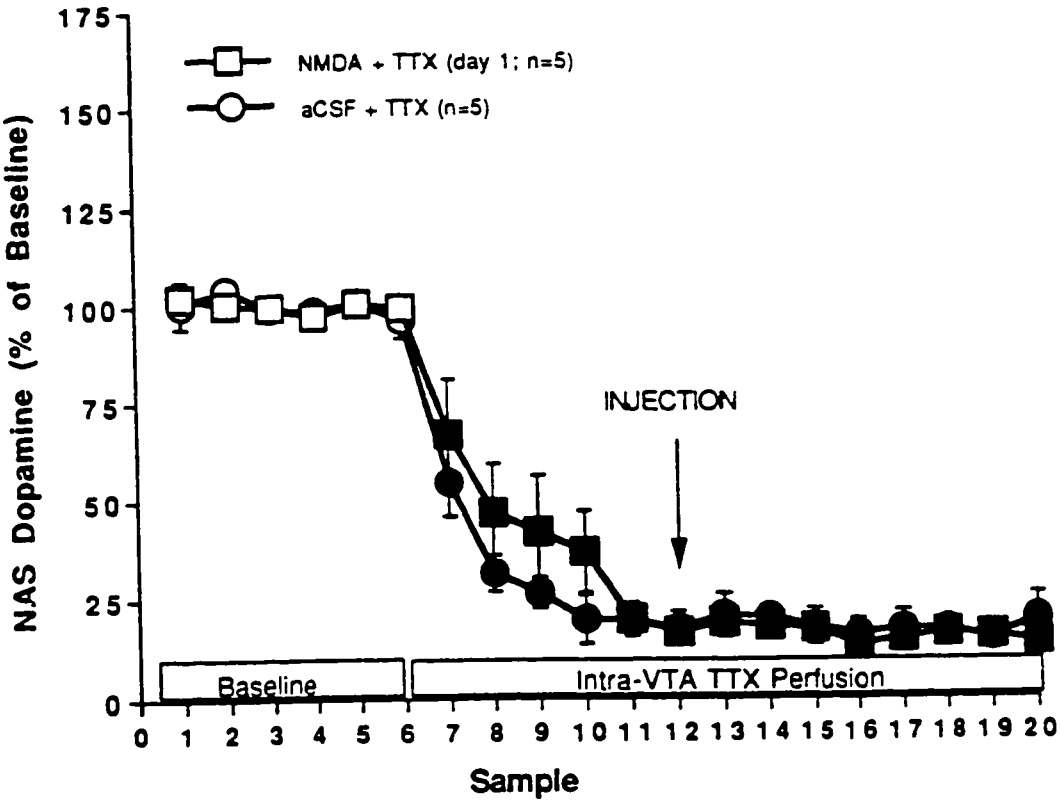
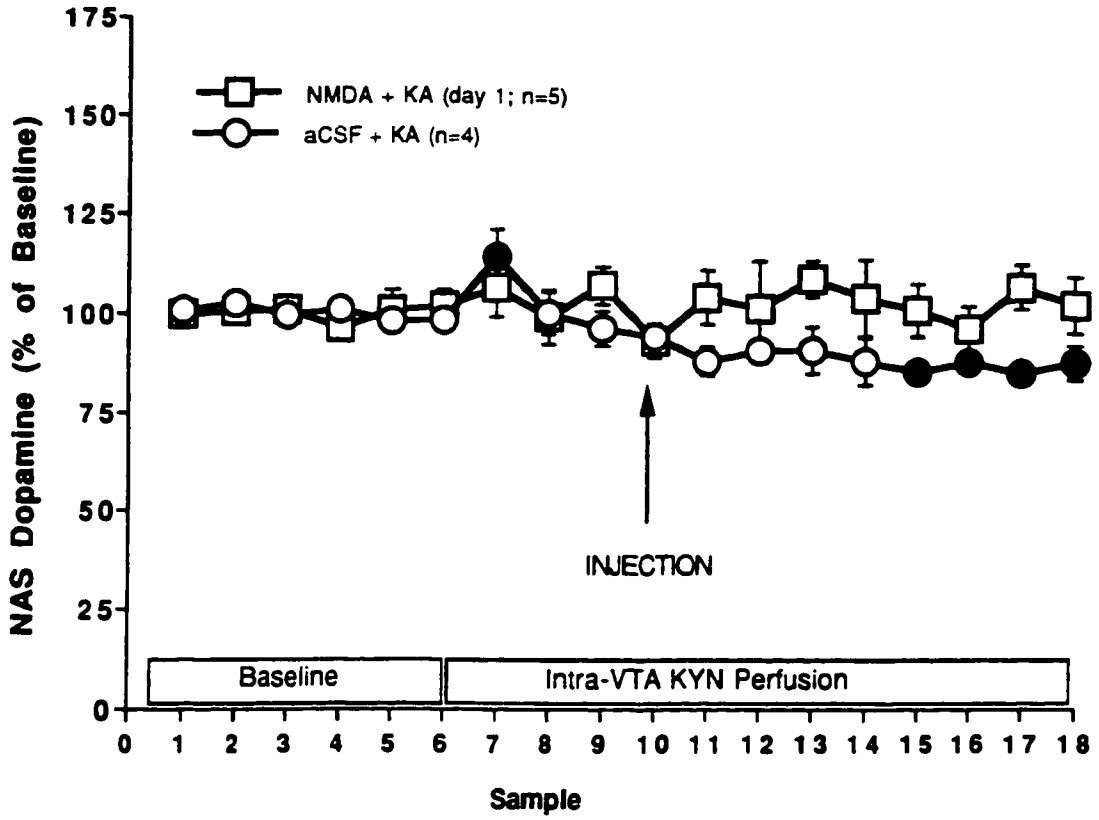

NMDA + TTX (day 1; n=5)
aCSF + TTX (n=5)
NAS Dopamine (% of Baseline)
175
150
125
100
75
50
25
0
INJECTION
Baseline
Intra-VTA TTX Perfusion
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
Sample

Figure 7. Effect of NMDA injections into the VS on nucleus accumbens dopamine (mean % of baseline ± SEM) during perfusion of KYN into the VTA. Microdialysis samples were collected every 15 minutes. Intra-VTA KYN perfusion was initiated following the collection of 6 baseline samples. NMDA (0.74 μg) or aCSF was injected into the VS 60 minutes after the initiation of KYN perfusion (after the 10th sample). NMDA had no effect on NAS DA; there was no difference between baseline and post-NMDA samples [$F(4,17) = 0.478$; $p = 0.9181$]. KYN caused a slight decrease in NAS DA in animals injected with aCSF [$F(3,17) = 3.996$; $p = 0.006$]. Filled symbols indicate significant differences from baseline (Fisher LSD, $p < 0.05$).


NMDA + KA (day 1; n=5)
aCSF + KA (n=4)
NAS Dopamine (% of Baseline)
175
150
125
100
75
50
25
0
INJECTION
Baseline
Intra-VTA KYN Perfusion
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18
Sample

Confirmation of VS-Evoked Elevations in NAS DA (Day 2 test)

NMDA injections on Day 2, during perfusion of aCSF into the VTA, increased NAS DA (Figure 8). Baseline dopamine values for animals that had received TTX or KYN on Day 1 were 0.57 (±0.036) or 0.65 (±0.024) pg/μl respectively. Following NMDA injections, NAS DA in animals treated on Day 1 with TTX or KYN peaked at 152% and 160% of baseline (or 0.867 pg/μl and 1.4 pg/μl) respectively. DA levels peaked approximately 45 minutes after the NMDA injection and had almost returned to basal levels 2 hours later. The Day 2 test thus confirmed, for each animal's data that were included in the Day 1 analyses, that NMDA was accurately injected into the VS.

For 4 animals (2 each from the VTA-TTX and VTA-KA experiments) the effectiveness of VS injection sites could not be confirmed by a Day 2 test because NAS microdialysis probes broke between Day 1 and Day 2. For each of these animals NMDA injections failed to elevate NAS DA on Day 1. Histological examination revealed that the injection cannula of each of these animals was placed in the VS. Nonetheless, the Day 1 data from these animals was not included in the statistical analyses. Data from an additional 3 animals that received VTA-KA and NMDA injections were also excluded. For one animal the VTA microdialysis probe was anterior to the VTA; in this animal KYN infusion failed to block NMDA induced elevations in NAS dopamine. For the other 2 animals, NMDA injections on both Day 1 and Day 2 failed to elevate NAS DA. Histological analysis revealed that injection cannula were placed anterior to the VS bordering the posterior basolateral amygdala (data not shown).

Single Unit Recording of VTA Dopaminergic Neurons

Injection of 0.74 μg of NMDA into the VS increased the firing rates of 45% (14/31), decreased the firing rates of 13% (4/31), and failed to produce sustained alterations in the firing rates of 42% (13/31) of VTA DA neurons (Figures 9 and 10). There were no differences in baseline firing rates between cells that increased, decreased, or were not effected by NMDA injections (Table 1). A total of 35 cells were recorded following

Figure 8. Effect of intra-VS NMDA injections on nucleus accumbens dopamine (mean % of baseline ± SEM) on DAY 2. Microdialysis samples were collected (from the same probe used on DAY 1) every 15 minutes. Following the collection of 6 baseline samples, NMDA was injected into the VS. NMDA elevated DA levels both in animals that had received intra-VTA TTX or KYN on DAY 1. For animals that had received TTX on DAY 1 $F(4,13) = 8.65$; $p = 0.0001$ and for animals that had received KYN on DAY 1 $F(4,13) = 8.36$; $p = 0.0001$.

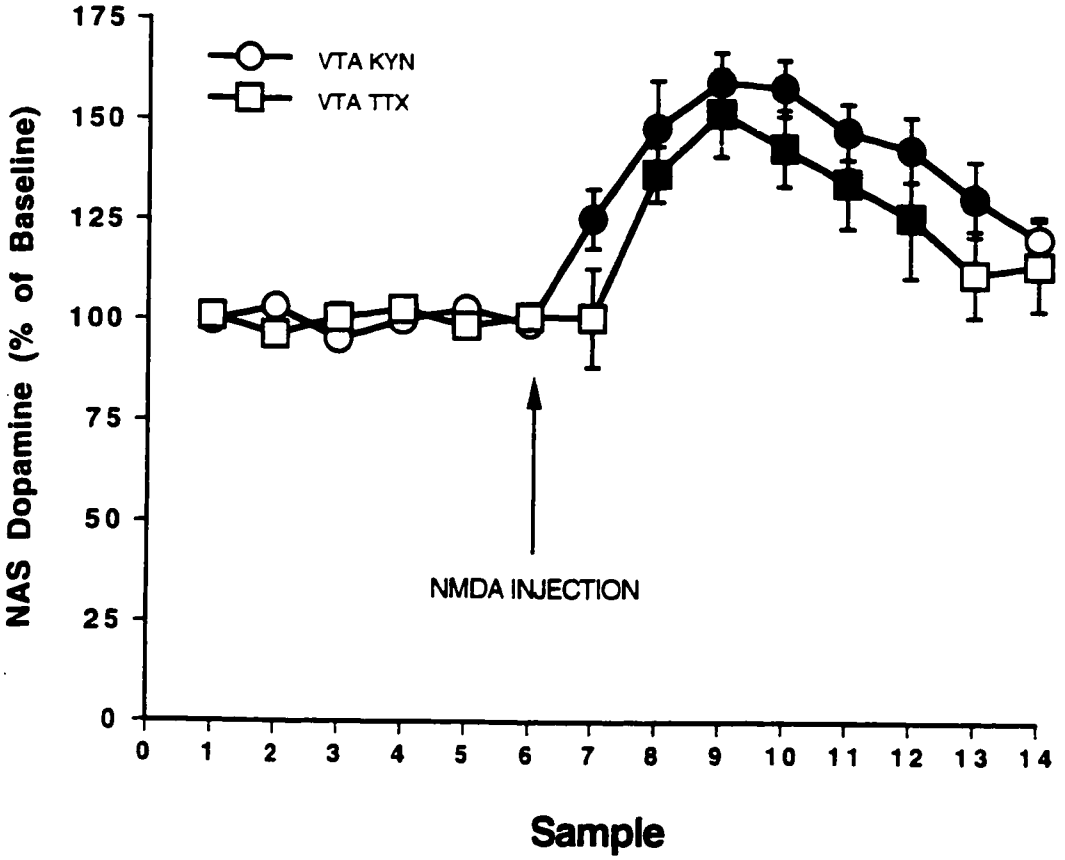

VTA KYN
VTA TTX
NAS Dopamine (% of Baseline)
175
150
125
100
75
50
25
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14
Sample
NMDA INJECTION

Figure 9. Peri-event time histograms from 4 individual VTA dopaminergic neurons recorded for 5 minutes prior to and for 15 minutes following injection of NMDA or aCSF into the VS. NMDA typically caused a brief inhibition in the firing rates of dopaminergic neurons followed by either (A) and increase in firing rate, (B) a decrease in firing rate, or (C) no effect when averaged over 15 minutes. Injections of aCSF (D) produced no effects in any dopaminergic neurons.

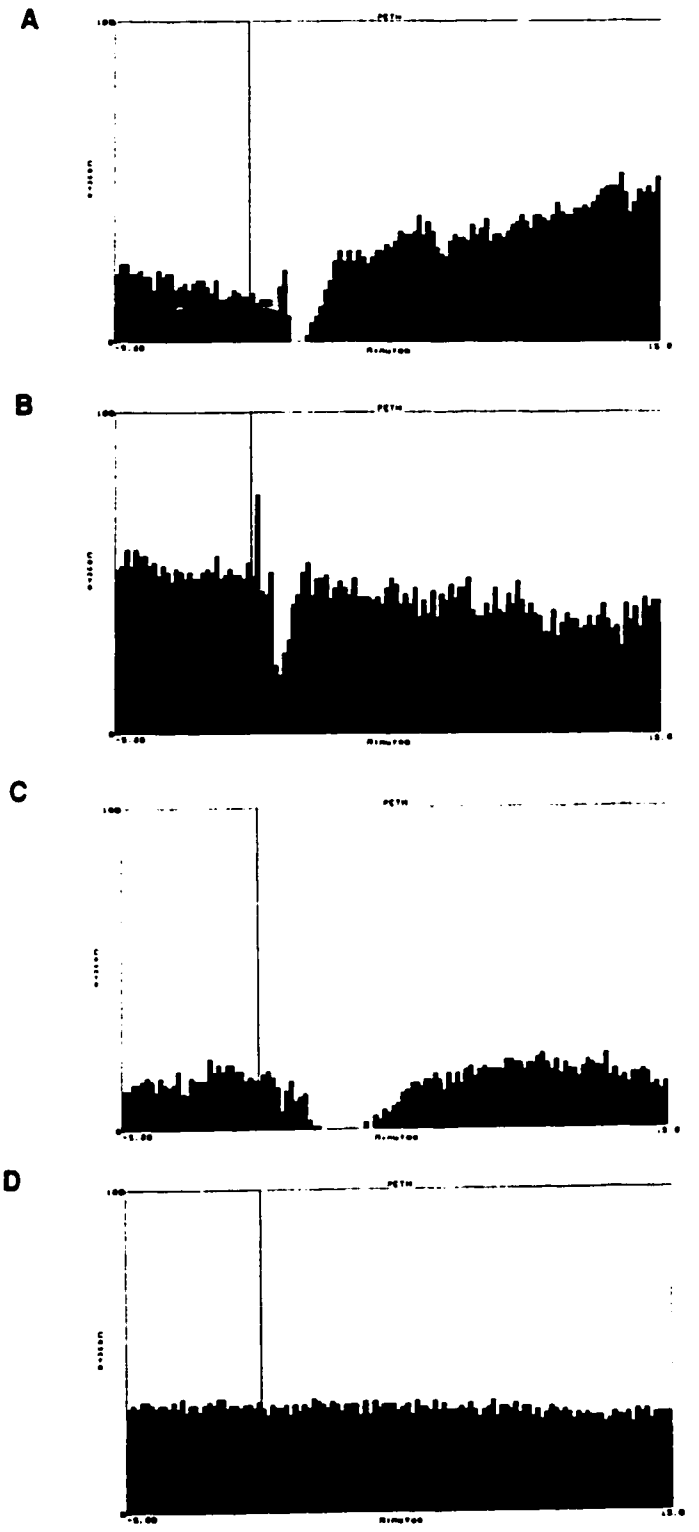

A
B
C
D

Figure 10. Mean firing rates of dopaminergic neurons (expressed as % of baseline firing rate) during each of the 5 minute post-injection intervals.

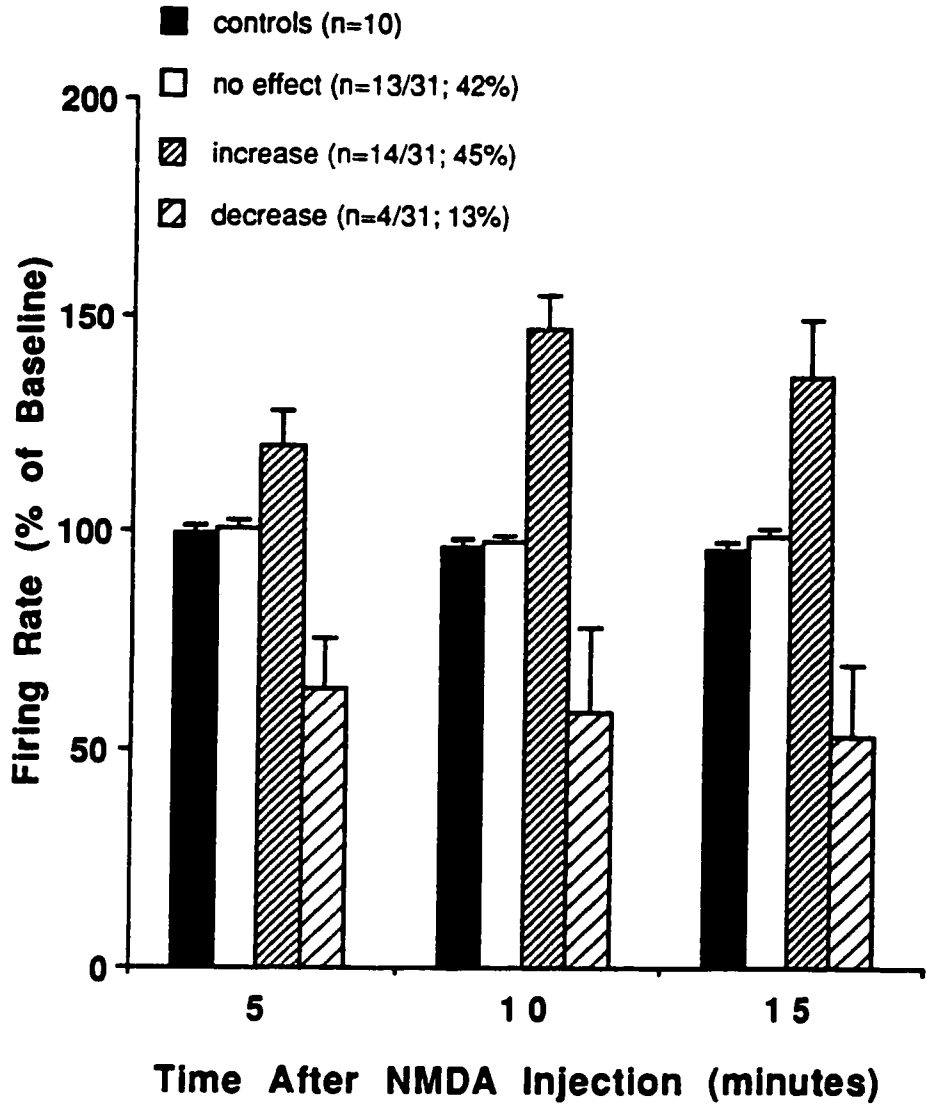

controls (n=10)
no effect (n=13/31; 42%)
increase (n=14/31; 45%)
decrease (n=4/31; 13%)
200
150
100
50
0
Firing Rate (% of Baseline)
5
10
15
Time After NMDA Injection (minutes)

TABLE 1

MEAN FIRING RATES, Hz (SEM), OF VTA DA NEURONS PRIOR TO AND FOLLOWING NMDA INJECITONS INTO THE VS

	BASELINE	5 MINUTES	10 MINUTES	15 MINUTES
Increase	3.36 (0.48)	4.06 (0.59)	4.74 (0.63)	4.34 (0.50)
Decrease	3.47 (0.68)	2.59 (0.74)	2.67 (0.92)	2.36 (0.78)
No Effect	3.96 (0.53)	4.01 (0.54)	3.93 (0.53)	3.93 (0.52)
Controls	4.4 (0.47)	4.35 (0.45)	4.27 (0.45)	4.27 (0.44)

NMDA injections into the VS. Only data from cells that were recorded for at least 15 minutes after NMDA injections were included in statistical analyses for changes in firing rate. This criterion was set in order for electrophysiological data to coincide with the timing of the first microdialysis sample collected after NMDA injections in the present and in previous experiments (Legault and Wise, 1999). Complete data sets were obtained from 26 cells. For the other 9 cells, the firing rates became erratic, action potentials distorted, and the cells were lost before the 15 minute post-injection period was completed. However, for 5 of these cells, action potentials were recorded for at least 10 minutes after NMDA injections. The effects of NMDA on the firing rates of these cells are included in the descriptive statistics (total of 31 cells).

Of the 14 cells that increased firing, 10 were recorded for the entire 15 minute session without incident. For these 10 cells the mean firing rate over the 15 minute session was increased to 156% (±15.0) of baseline (Time: $F_{9,27} = 4.257$; $p=0.0138$). The mean firing rates of these cells at each of the 3 post-injection intervals (5 minutes each) was greater than those of control cells (Treatment x Time interaction: $F_{3,51} = 14.3$, $p = 0.0001$; Fisher LSD $p < 0.05$). For 3 cells that increased firing rate after NMDA injections, the dopamine agonists quinpirole (200 µg/kg, i.p.) was injected 10 minutes after NMDA. Within 10 minutes of the quinpirole injection there was a gradual decrease in firing rate characteristic of dopaminergic neurons (data not shown). Finally, NMDA appeared to stimulate one cell into depolarization block; within 5 minutes of the NMDA injection there was a rapid increase in this cell's firing rate (from 4.7 Hz to approximately 15 Hz) followed by complete suppression of activity. Quinpirole (200 µg/kg, i.p.) was injected 10 minutes after NMDA and within 5 minutes firing was reinstated. The mean firing rate in the first 5 minutes after the reinstatement firing was 160% of baseline and gradually declined over the next 10 minutes (data not shown).

For the four cells in which NMDA decreased firing by greater than 10% of baseline rate, the mean firing rate over the 15 minutes session was 59% (sem: ±8.9%) of

baseline. Decreases in firing rates were sustained throughout the recording session, however they did not attain statistical significance (main effect of Time; $F = 3.11$, $p = 0.81$), likely due to the small sample size (n=4). For the 13 cells in which intra-VS NMDA injections evoked less than 10% changes in firing rate the mean firing rate was 99.6% (sem: ±0.92%) of baseline. The firing rates of cells recorded following intra-VS injection of aCSF were not different from those of cells recorded without injections; data from these control groups were pooled. Over the 15 minute session the mean firing of control cells was 96.6% of baseline. Within each of the three 5 minute periods the firing rate of no single control cell differed from its baseline firing rate by more than 10%. Nonetheless, relative to baseline, there was a statistically reliable decrease in the firing rates of control cells over the recording period with a mean decrease to 96% of baseline [$F(3,24) = 2.97$, $p < 0.05$).

NMDA often caused complex, multiphasic changes in the firing patterns of some VTA DA neurons. Often, NMDA injections resulted in a biphasic response; there was an initial inhibition followed by a return to basal firing rate or a sustained increase in firing rate. In 3 cells, NMDA injections produced triphasic effects, with either increases or decreases in firing rate occurring between changes in the opposite direction. Thus, although NMDA failed to cause uniform sustained changes in the mean firing rates of many (42%) of neurons recorded for 15 minutes these neurons were not necessarily unresponsive to NMDA.

DISCUSSION

The present study confirms that chemical stimulation of the VS elevates NAS DA (Legault et al., 1995; Brudzynski & Gibson, 1997; Legault & Wise, 1999). The present results add to evidence that the hippocampus can modulate dopaminergic transmission by demonstrating that VS stimulation can increase impulse flow through VTA dopaminergic neurons and by demonstrating that impulse flow through VTA dopaminergic neurons is critical for VS stimulation to increase NAS DA. Intra-VS injections of NMDA failed to increase NAS DA when impulse flow through dopaminergic neurons was disrupted by perfusion of TTX into the VTA (on Day 1) but increased NAS DA during perfusion of aCSF the VTA (on Day 2). VS-evoked elevations in NAS DA were comparable in both magnitude and duration as we have previously reported (Legault and Wise, 1999).

Electrophysiological recordings confirmed that injections of NMDA into the VS increases the firing rates of at least a sub-population of identified VTA dopaminergic neurons. The firing rates of almost 50% of dopaminergic neurons were elevated by NMDA injections. These elevations were sustained for a minimum of 15 minutes, a time during which the same dose of NMDA increases locomotor activity and elevates both NAS and VTA DA collected from microdialysis samples in freely moving rats (Legault & Wise, 1999). In addition to monotonic increases in the firing rates of dopaminergic neurons, NMDA injections into the VS frequently caused a transient initial inhibition in firing rates and less frequently caused multiphasic alternations between increases and decreases in firing rates. These multiphasic effects of VS stimulation on dopaminergic neurons are consistent with the effects of electrical stimulation of the VS which has been reported to cause brief inhibition followed by a long-latency increase in the burst-firing of VTA dopaminergic neurons (Harden & Grace, 1995). The complex responses of dopaminergic neurons to VS stimulation suggest that VS can modulate both inhibitory and excitatory inputs to VTA DA neurons. Modulation of both inhibitory and excitatory inputs to the VTA may account for the failure to obtain increases in the firing rates in

some of the neurons recorded. Convergence of offsetting inputs to a recorded neuron may have resulted in no net increase or decrease in the firing rate. Misalignment of the VS injection site with respect to VS outputs that converge on the recorded neuron might also account for some of the variability in NMDA-induced responses; it is possible that had dopaminergic neurons been recorded for longer periods, the NMDA would have spread into a region of the VS that gave rise to outputs that ultimately converged on and stimulated the recorded neuron. Nonetheless, it is clear from the present electrophysiological study and a previous microdialysis study (Legault & Wise, 1999) that NMDA injections into the VS have a net excitatory effect on dopaminergic transmission, increasing dopaminergic cell firing and increasing both somatodendritic and terminal DA release.

The importance of increased impulse flow through dopaminergic neurons for elevations of NAS DA induced by stimulation of the ventral subiculum was demonstrated by the effects of TTX perfusion into the VTA. Perfusion of TTX into the VTA reduced dopamine in the NAS to approximately 20% of basal levels and prevented the elevations in NAS DA normally evoked by stimulation of the VS. The reduction in NAS DA during perfusion of TTX into the VTA is in agreement with previous reports that basal extracellular DA in the striatum or NAS depends on the conduction of impulses through voltage-gated sodium channels from dopaminergic cell bodies and along the dopaminergic axons ascending the medial forebrain bundle (Robertson et al., 1991; Keefe et al., 1992; Morari et al., 1992; Taber et al., 1995; Karreman and Moghaddam, 1996). The failure of VS stimulation to elevate NAS DA during blockade of impulse flow through VTA dopaminergic neurons suggests that the hippocampus influences dopaminergic transmission primarily by increasing impulse flow through dopaminergic neurons rather than by evoking glutamate-mediated impulse-independent dopamine release from terminals in the NAS.

An alternative to the suggestion that NMDA injections into the VS elevate NAS DA by causing glutamate-induced impulse-independent DA release (Brudzynski and Gibson, 1997) is that a basal levels of dopaminergic impulse flow are required for glutamate, within the physiological range of concentrations, to presynaptically induce transmitter release from dopaminergic terminals (c.f. Grace, 1995). This possibility was addressed by experiments in which KYN was perfused into the VTA during NMDA injections into the VS. Blockade of ionotropic glutamate receptors on dopaminergic cell bodies by application of KYN does not, like TTX, abolish impulse-flow through dopaminergic neurons but shifts impulse activity from burst-firing to pacemaker-like firing (Grenhoff et al., 1988; Charlety et al., 1991). Thus, during perfusion of KYN into the VTA extracellular DA in the NAS was slightly reduced, by approximately 15%. These results are consistent with previous reports that blockade of ionotropic glutamate receptors in the VTA causes small reductions in NAS DA (Taber et al., 1995; Karreman & Moghaddam, 1996). Nonetheless, if glutamate could act on dopaminergic terminals to augment impulse-dependent transmitter release then stimulation of subiculoaccumbens projections should still have elevated NAS DA. Nonetheless, perfusion of KYN into the VTA completely abolished NMDA-induced elevations in NAS DA.

The present experiments support the conclusion that the primary mechanism through which VS-stimulation elevates NAS DA is by increasing impulse flow through VTA dopaminergic neurons. In apparent discrepancy with these results are those of Blaha et al (1997) who reported that the electrical stimulation of the VS elevated the dopamine-like voltammetric signal recorded from the NAS, and that these elevations were blocked by injections of glutamate receptor antagonists into the NAS. On the basis of their results, Blaha et al (1997) concluded that VS-evoked elevations in NAS dopamine were mediated by glutamatergic actions on dopaminergic terminals. The only indication that stimulation of subiculo-accumbens glutamatergic inputs to the NAS might augment DA release was that NAS DA was not decreased in NMDA injected animals as

it was in control animals receiving KYN. However the difference in NAS DA between NMDA-injected and aCSF-injected animals was small and not statistically significant. Thus, although the present studies cannot rule out the possibility of glutamate-mediated transmitter release from dopaminergic terminals, they do suggested that the influence of such a phenomenon in VS-evoked elevations in NAS dopamine is minimal and bellow the threshold of detection by microdialysis. Indeed, for exogenously applied glutamate to evoke impulse-independent elevations in NAS DA into a range detectable by microdialysis high concentrations (greater than 1 mM) are required (Moghaddam et al., 1990; Keefe et al., 1992; Westerink et al., 1992) and such concentrations appear to evoke DA release by causing spreading depression (Moghaddam et al., 1990; Svensson et al., 1994).

Although the circuitry through which VS stimulation activates VTA DA neurons remains to be determined, the experiments involving intra-VTA perfusion of KYN suggest a glutamatergic link terminating in the VTA. One possible circuit involves projections from the hippocampus to the PFC (Swanson, 1981; Jay & Witter, 1991). Electrical stimulation of the VS evokes excitatory responses in PFC neurons (Laroche et al., 1990; Jay et al., 1995) and at least some VS-activated PFC neurons project to the VTA (Jay et al., 1995). Injections of NMDA into the VS induce FOS in the PFC (Klarner, Koch & Schnitzler, 1998) suggesting that the PFC is activated by conditions similar to those used in the present study. The PFC provides well-characterized glutamatergic inputs to the VTA (Sesack & Pickel, 1992; Rossetti et al., 1998). Stimulation of glutamate receptors on DA neurons evokes excitatory postsynaptic potentials and cell firing (Mereu et al., 1991; Johnson et al., 1992; Suaud-Chagny et al., 1992) and increases NAS DA (Kalivas et al., 1989; Suaud-Chagny et al., 1992; Karreman et al., 1996; Westerink et al., 1996). Moreover, the microdialysis and electrophysiological data reported in the present study parallel those from studies of PFC-evoked elevations in NAS DA. Activation of the PFC elevates NAS and striatal DA and,

as was the case with the present experiments involving VS stimulation, elevations in NAS DA evoked by PFC stimulation are blocked by intra-VTA perfusion of TTX (Karreman & Moghaddam, 1996) or of glutamate antagonists (Taber et al., 1995; Karreman & Moghaddam, 1996; You et al., 1998). The similar characteristic of PFC and VS-evoked elevations in NAS DA would be expected if such a common circuit were involved.

Another possibility is that activation of outputs from the VS disinhibits VTA dopaminergic neurons. Midbrain dopaminergic neurons receive inhibitory GABAergic inputs from the ventral pallidum (Gerfen, 1992) and these neurons are inhibited by stimulation of the VS (Yang and Mogenson, 1987). Thus, activation of the VS could reduce inhibitory GABAergic inputs to the VTA. Blockade of $GABA_A$ receptors in the VTA increases NAS DA (Westerink et al., 1996). Since both the firing rates of VTA dopaminergic neurons (Grenhoff et al., 1988; Charlety et al., 1991) and NAS DA (Taber et al., 1995; Karreman & Moghaddam, 1996) seem to be tonically regulated by glutamatergic inputs, disruption of inhibitory GABAergic inputs may have resulted unmasking of glutamate-mediated activation of these neurons.

Subiculo-accumbens glutamate has been suggested to influence goal-directed behaviors by interactions with dopaminergic inputs to the NAS (Yang & Mogenson, 1987; Burns et al., 1993; Burns et al., 1996; Hitchcott & Phillips, 1997). Dysfunctional interactions between these two inputs to the NAS have been suggested to be important in the pathophysiology of schizophrenia (Gray et al., 1991; O'Donnell & Grace, 1998). Until recently, the study of interactions between hippocampal outputs and NAS DA has focused primarily on the direct hippocampal projection to the NAS. This focus has been based largely on the hypothesis that glutamate augments or induces transmitter release from dopaminergic terminals in this region. The results of the present study, in contrast, indicate that the VTA is an important site through which outputs from the VS ultimately modulate NAS DA by modulating mesolimbic impulse flow.

CHAPTER 3

Novelty-Evoked Elevations in Nucleus Accumbens Dopamine: Dependence on Impulse Flow from the Ventral Subiculum and Glutamatergic Neurotransmission in the Ventral Tegmental Area.

Introduction

The nucleus accumbens septi (NAS) receives converging inputs from dopaminergic neurons of the ventral tegmental area (VTA; Dahlstrom & Fuxe, 1964; Fallon & Moore, 1978) and from the putatively glutamatergic neurons from limbic structures such as the hippocampus, amygdala, and prefrontal cortex (Walaas, 1981; Christie et al., 1987; Fuller et al., 1987). There is considerable evidence that these inputs modulate the investigatory locomotion that was considered an unconditioned reflex by Pavlov (1927), was viewed as a fundamental element of adaptive behavior (Pavlov, 1927; Schneirla, 1957; Glickman & Schiff, 1967), and was suggested to reflect motivational (Craig, 1918; Bindra, 1968; Mogenson et al., 1980; Robbins & Everitt, 1992) or reward (Wise & Bozarth, 1987) processes. The dopaminergic inputs to the NAS are an established link in the circuitry modulating investigatory behavior; intra-NAS injections of dopamine or the indirect dopaminergic agonist amphetamine facilitates investigatory behavior (Creese & Iversen, 1975; Pijnenburg & Van Rossum, 1973; Pijnenburg et al., 1976). Amphetamine-facilitated investigation (Kelly et al., 1975; Kelly & Iversen, 1976; Joyce and Iversen, 1984) as well as investigation evoked by novel stimuli or food (Koob et al., 1978; Koob, Stinus & LeMoal, 1981; Tagzhouti et al., 1985; Kelley & Stinus, 1985) are abolished by 6-hydroxydopamine lesions of the NAS. Dopaminergic neurons projecting to the NAS are activated by salient novel stimuli (Ljungberg et al., 1992; Horvitz et al., 1997) and NAS dopamine is increased during investigation of novel environments (Rebec et al., 1997; Saigusa et al., 1999).

The glutamatergic inputs from the hippocampus to the NAS are thought to form another link in the circuitry modulating investigatory behavior (Mogenson & Neilsen, 1984a; Yang & Mogenson, 1987; Burns et al., 1996). Although the NAS receives inputs from throughout the hippocampus, the densest inputs arise from the ventral subiculum (VS; Kelley & Domesick, 1982; Groenewegen et al., 1987; Meredith et al., 1990; Sesack & Pickle, 1990). Microinjections of N-methyl-D-aspartate (NMDA) or carbachol into the region of the ventral subiculum increases investigatory behavior (Yang & Mogenson, 1987; Brenner & Bardgett, 1998) and hippocampal-induced investigation is blocked by injections of glutamate antagonists into the NAS (Mogenson & Neilsen, 1984a). Excitotoxic lesions restricted to the ventral subiculum abolish investigation of novel environments (Burns et al., 1996) as do injections of glutamate antagonists into the NAS (Mogenson & Neilsen, 1984b; Maldonado-Irizarry & Kelley, 1995).

Investigatory behavior induced by hippocampal stimulation is abolished by 6-OHDA lesions of the VTA (Wu & Brudzynski, 1995) or systemic administration of dopamine antagonists (Brenner & Bardgett, 1998). The most direct hypothesis accounting for hippocampal-induced dopamine-dependent investigation is that hippocampal stimulation increases NAS dopamine. Indeed, stimulation of the VS elevates NAS dopamine concomitantly with investigatory behavior (Brudzynski & Gibson, 1997; Legault & Wise, 1999). However, the mechanisms through which VS stimulation elevates NAS dopamine are not known. One suggestion (Blaha et al., 1997; Brudzynski & Gibson, 1997) is that glutamate released from VS inputs in the NAS evokes impulse-independent transmitter release through actions on dopaminergic terminals (Romo et al., 1986a,b; Glowinski et al., 1988). Alternately, VS stimulation may elevate NAS dopamine by increasing impulse flow through VTA dopaminergic neurons; although the VS is not known to project to the VTA, VS stimulation activates VTA dopaminergic neurons (Harden & Grace, 1995; Legault et al., 1998, Chapter 2 of present thesis) and, consistent with activation of dopaminergic cell bodies, causes

somatodendritic dopamine release in the VTA (Legault & Wise, 1999, Chapter 1 of present thesis). Moreover, elevations in NAS dopamine evoked by VS stimulation are blocked by perfusion of either tetrodotoxin or the glutamate receptor antagonist kynurenic acid into the VTA (Legault et al., 1998), thus, the VTA appears to be a critical link in the circuitry through which the VS elevates NAS dopamine.

Although direct hippocampal stimulation facilitates investigatory behavior and increases NAS dopamine, it is not yet established that these effects reflect the activation of a circuitry responsive to environmental stimuli. The present experiments were designed to determine if impulse flow from the ventral subiculum mediates novelty-evoked elevations in NAS dopamine. Moreover, to examine the neurochemical mechanisms through which the hippocampus might modulate this response, glutamatergic transmission in the VTA was blocked by perfusion of the glutamate receptor antagonist kynurenic acid into the VTA. If the hippocampus increases NAS dopamine by evoking glutamate-mediated transmitter release from dopaminergic terminals then this effect would persist during blockade of VTA glutamate. If, however, the hippocampus increases NAS dopamine primarily through glutamate-mediated actions in the VTA, then kynurenic acid perfusion should block novelty-evoked elevations in NAS dopamine.

METHODS

Animals and Surgery

Sixty male Long-Evans rats (each weighing 325-400g at the time of surgery) were used for the present experiments. Rats were maintained on a 12 hour light-dark cycle; food and water were continuously available. For surgical implantation of guide cannulae each rat was anesthetized with sodium pentobarbital (60 mg/kg, i.p.) and given atropine (0.25 mg/kg, s.c.) to minimize respiratory congestion caused by bronchial secretions. Each rat was implanted with a single 18 gauge stainless steel cannula to guide a microdialysis probe into the NAS. Each cannula terminated 4 mm above the NAS. With the incisor bar elevated 5 mm above the intra-aural line the stereotaxic coordinates were 2.4 mm anterior to bregma, 3.2 mm from the midline, and 3.0 mm below dura (cannula were angled 10 degrees towards the midline in order to avoid penetrating the lateral ventricle). From these rats, each of 24 was also implanted with an 18 gauge microdialysis probe cannula terminating 5 mm above the VTA either ipsilateral (12 rats) or contralateral (12 rats) to the NAS cannula. In order to maximize the distance between NAS and VTA cannulae, each VTA cannula was implanted with the animal's head adjusted so bregma and lambda were on the same horizontal plane. The stereotaxic coordinates for VTA cannulae were 5.0 mm posterior to bregma, 1.1 mm from the midline, 3.8 mm from the skull. Each of these cannulae (NAS and VTA) was fitted with a stainless steel obturator that terminated flush with the bottom of the guide cannula, thus, each microdialysis probe was inserted into undisturbed tissue. Each of the 30 remaining rats was implanted with a single 22 gauge cannula aimed at the ventral subiculum either ipsilateral (18 rats) or contralateral (12 rats) to the NAS cannula. The stereotaxic coordinates, with the head elevated 5 mm above the intra-aural line were 3.0 mm posterior to bregma, 4.8 mm from the midline, 6.5 mm below dura. All cannulae were held in place by acrylic dental cement which adhered to 4 screws threaded into the skull. Each animal was then allowed to wake up from the anesthesia and then returned to its home cage.

APPARATUS

Experimental Chambers

Each rat was tested in an octagonal Plexiglas chamber (42 cm x 39 cm x 33.5 cm). In order to minimize illumination and distraction by extraneous stimuli the chamber walls were covered with heavy paper and the lids were closed except for a 15 cm diameter hole in the middle. Each box was equipped with four pairs of photobeam emitters and receivers. One emitter and one receiver was place on very second of the eight walls with its accompanying emitter or receiver on the opposite wall, thus, every second wall was equipped with one emitter and one receiver. Each chamber could be divided into two sections by an opaque barrier. The barrier was placed at the juncture between the 3 frontmost walls and the 5 back walls. Thus, the area of the front section was slightly less than one third the area of the back section. The larger back section was used as a novel environment to evoke investigation. In order to maximize the salience of the novel environment, several small objects (e.g.. glass bottle, rubber stopper, test-tube tray) were placed randomly on the floor of the back chamber.

Microdialysis Probes

The microdialysis probes were of concentric design and have described in detail elsewhere (Legault & Wise, 1999). Each probe was constructed such that a length of dialysis membrane (Hospal, molecular weight cutoff 40 kDA) protruded 4 (NAS) or 5 (VTA) mm from the end of the guide cannula. For NAS probes, the membrane was sealed with epoxy for a length of 1 mm beyond the cannula leaving a 3 mm exposed surface. For VTA probes, the membrane was sealed with epoxy for 3 mm beyond the cannula leaving a 2 mm exposed surface. Fused silica (i.d. = 75 μm, o.d. = 150 μm) was used for both the fluid inlet and fluid outlet.

PROCEDURE

General Procedure

Each rat was allowed at least 7 days to recover from surgery prior to implantation of microdialysis probes. Each microdialysis probe was connected to a dual-channel liquid swivel and was continuously perfused at a rate of 1.0 µl/min with a solution of artificial cerebrospinal fluid (aCSF; comprised 2.0 mM Sorenson's phosphate buffer containing 145 mM NaCl, 2.8 mM KCl, 1.2 mM $MgCl_2$, 1.2 mM $CaCl_2$, and 0.2 mM ascorbate, pH 7.3 - 7.4) for at least 2 hours prior to implantation. For implantation of microdialysis probes each rat was lightly anesthetized with 30 mg/kg sodium pentobarbital (i.p.). Probes were inserted and fixed permanently in place with dental cement. Each rat that was to be tested for fluctuations in NAS DA during investigation of novel stimuli was then placed in the front section of a test chamber with the barrier in place. Each rat that was not tested for investigation of novel stimuli (habituation groups) was place in a chamber without a barrier.

Each rat habituated to its environment for a minimum of 18 hours after probe implantation. Following this habituation period, perfusate samples were collected every 15 minutes from the NAS and were analyzed on-line for DA content. The first 6 consecutive samples in which the DA content varied from each other by less than 10% were defined as baseline. Following the establishment of a stable dopamine baseline, each rat was tested according to its preassigned treatment in one of the following experiments.

(1) Novelty (n=12). For 6 animals the barrier was removed and each rat was permitted to investigate the novel cage section. NAS dialysate samples were collected every 15 minutes for 120 minutes (2 hours). For another 6 animals, that had habituated to the chamber without a barrier, microdialysis samples were collected every 15 minutes for 2 hours.

(2) Tetrodotoxin (TTX) injections into the VS (n=24). Following the collection of baseline samples each of 12 rats was injected with TTX (0.16 ng) into the VS either ipsilateral or contralateral to the dialyzed NAS. Six rats from each of the ipsilateral and contralateral groups were tested for dopaminergic responses to novel stimuli. For these rats, the barrier was removed 30 minutes after the TTX injection. The remaining rats were tested entirely in undivided chambers. Dialysate samples were collected for 150 minutes after the TTX injection (2 hours after removal of the barrier).

(3) Kynurenic acid (KYN) perfusion into the VTA (n=24). Each of 12 rats was perfused with KYN (1.0 mM) through a microdialysis probe aimed at the VTA either ipsilateral or contralateral to the dialyzed NAS. Six rats from each group were tested in response to novel stimuli. For these rats, the barrier was removed 60 minutes after the initiation of KYN perfusion. Dialysate samples were collected for 180 minutes following the initiation of KYN perfusion.

Analytical Procedure

Dialysate samples were analyzed for DA content using HPLC with electrochemical detection. DA was separated from the dialysate by injecting samples through a reverse-phase column (supelcosil, 3 μm, LC-18, Supelco). DA was quantified by an ESA Coulochem detector (5200) and an analytical cell (ESA, model 5011) with two electrodes in series. The first electrode (oxidation) was set to 340 mV and the second (reduction) electrode was set to -270 mV. The mobile phase for this system consisted of 60 mM NaH_2PO_4, 3.0 mM ascorbate, 15% (v/v) MEOH with 0.035 mM sodium dodecyl sulphate (SDS), 0.1 mM ethylenediaminetetraacetic acid (EDTA), pH adjusted to 3.5 with NaOH.

Histology

At the end of an experiment, each animal was removed from its chamber, anesthetized with sodium pentobarbital 120 mg/kg and transcardially perfused with 0.9% NaCl followed by a 10% formalin solution. Each brain was stored in 10% formalin for at least 1 week and then sliced into 40 μm sections on a cryostat. Sections were mounted onto

microscope slides. Probe and cannula placements were determined by low magnification light microscopy.

DOSE DETERMINATION AND INTRACRANIAL INJECTIONS

TTX (Sigma) was mixed in aCSF and sonicated for at least 20 minutes prior to injection. Immediately following removal of the obturator from the VS cannula a 28 gauge injection cannula was inserted and TTX, in a volume of 0.5 µl, was injected over a period of 60 seconds. The injection cannula was left in place for 2 minutes and the obturator was replaced.

The dose of TTX was chosen based on the results of a pilot experiment involving 6 rats. Each of two rats were tested for novelty-evoked elevations in NAS DA following intra-VS injection on one of three doses of TTX. Initially a dose of 0.16 ng/0.5 µl was tested because this concentration (1.0 µM) has previously been shown to effectively block impulse flow from the VTA as determined by reduction in NAS DA to near undetectable levels (Westerink et al., 1992; Legault et al., 1998). In addition, a dose 10-fold higher and a dose 10-fold lower were also tested. The lowest dose to TTX was ineffective at blocking novelty-evoked elevations in NAS DA whereas the highest dose produced a significant decrease in NAS DA and ataxia (data not shown). Thus, for the present experiments a dose of 0.16 ng was used.

KYN was mixed in aCSF and sonicated for at least 20 minutes immediately prior to perfusion into the VTA. The concentration of KYN was the same as that used in previous studies from this lab (You et al., 1998; Legault et al., 1998). When perfused into the VTA this dose of KYN effectively blocks elevations in NAS DA evoked by chemical stimulation of the VS or electrical stimulation of the prefrontal cortex.

STATISTICAL ANALYSES

NAS DA is represented as percent of baseline ± SEM. For each rat, the mean DA content of the 6 baseline samples was first calculated. Then, this mean was used to convert the DA content in each of that rats samples into a percent of baseline. Treatment effects were determined by ANOVA with consecutive microdialysis samples used as a repeated measure (Sample). Significant main effects were further analyzed by simple ANOVA followed by Fisher LSD ($p > 0.05$).

Activity scores were calculated as the number of times a rat sequentially interrupted 2 photobeams following removal of the barrier or for the last 2 hours of dialysis in animals tested in the open chambers. Activity counts were grouped into 15 minute bins so as to correspond with the timing of microdialysis samples. Treatment effects were determined by ANOVA with Time as a repeated measure.

RESULTS

Investigatory Behavior Evoked by Novel Stimuli

The profile of locomotor activity was similar for all animals exposed to novel stimuli, regardless of their experimental treatment (Figure 11). Within the first 15 minutes following removal of the barrier locomotor activity (assessed by photobeam interruptions) was highest. Locomotor activity decreased monotonically and was at the level of habituated animals by 90 minutes after the barrier was removed. The locomotor activity of animals that remained in a habituated environment was low and did not change over the 2 hour experimental session; these animals were generally quietly at rest.

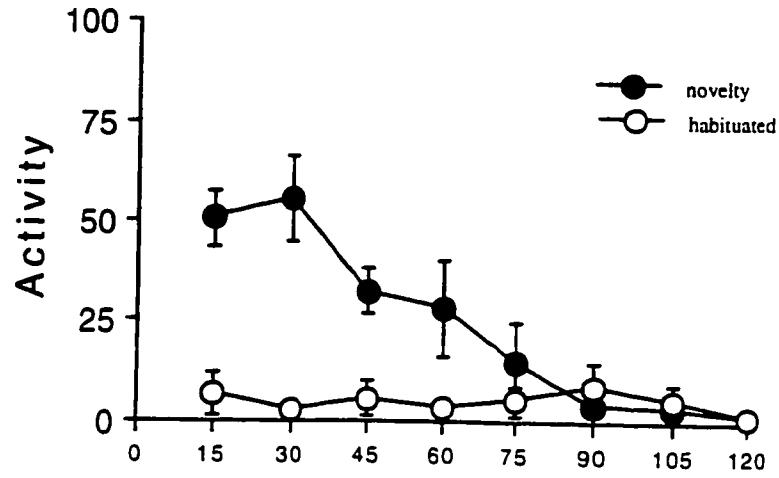
Novelty-Evoked Elevations in NAS DA

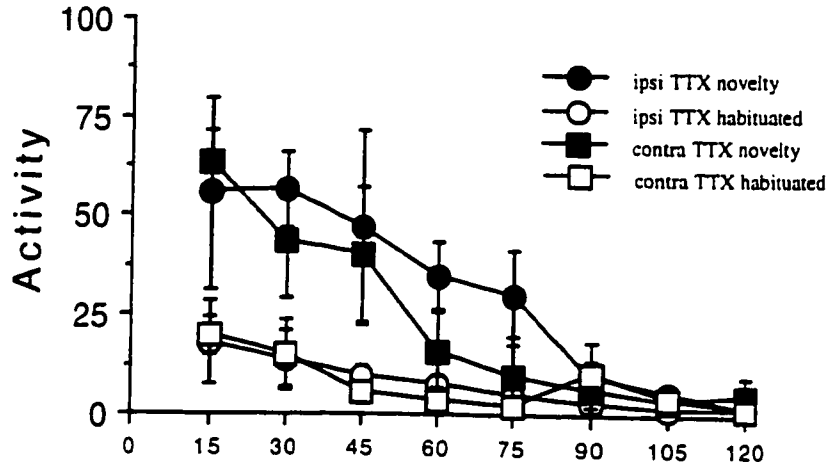
Exposure to novel stimuli elevated NAS DA (Figure 12). Significant elevations in dopamine were obtained in the first microdialysis sample, collected 15 minutes after the barrier was removed. NAS DA peaked at 141% of baseline in the sample collected 30 minutes after the barrier was removed and remained elevated (with respect to base line values) for the entire 2 hour session. There was no change in NAS DA sampled from animals in the habituated environment.

Effect of intra-VS TTX

Following injection of TTX into the VS ipsilateral to the dialyzed NAS exposure to the novelty stimuli failed to increase NAS DA (Figures 13 and 14). In these animals NAS DA did not differ from basal levels in any sample collected following the TTX injection. In contrast, exposure the novel stimuli increased NAS DA in animals that received injections of TTX into the contralateral VS. In these animals, removal of the barrier was associated with an increase in NAS DA to a maximum of 125% of baseline within 30 to 45 minutes followed by a return to basal levels within approximately 90 minutes. Differences in NAS DA between animals injected with TTX into the ipsilateral or contralateral VS were statistically significant for animals exposed to novelty [Effect of Side: $F(1,150) = 7.913$, $p = 0.0184$]

Figure 11. Activity scores (sequential interruption of 2 photobeams) in animals exposed to novel stimuli and in animals exposed to habituated stimuli. *Top*: Activity scores in animals during microdialysis but receiving no experimental treatment. Animals exposed to novel stimuli were more active than those exposed to habituated stimuli [$F(1,10) = 9.971$, $p = 0.0102$]. *Middle*: Activity scores of animals that received microinjection of TTX into the VS. Animals exposed to novel stimuli were more active than those exposed to habituated stimuli [$F(1,22) = 7.414$, $p = 0.0124$]. *Bottom*: Activity scores of animals that received intra-VTA perfusion of kynurenic acid. Animals exposed to novel stimuli were more active than those exposed to habituated stimuli [$F(1,22) = 23.189$, $p = 0.0001$].


100
75
50
25
0
Activity
0
15
30
45
60
75
90
105
120
novelty
habituated


100
75
50
25
0
Activity
0
15
30
45
60
75
90
105
120
ipsi TTX novelty
ipsi TTX habituated
contra TTX novelty
contra TTX habituated

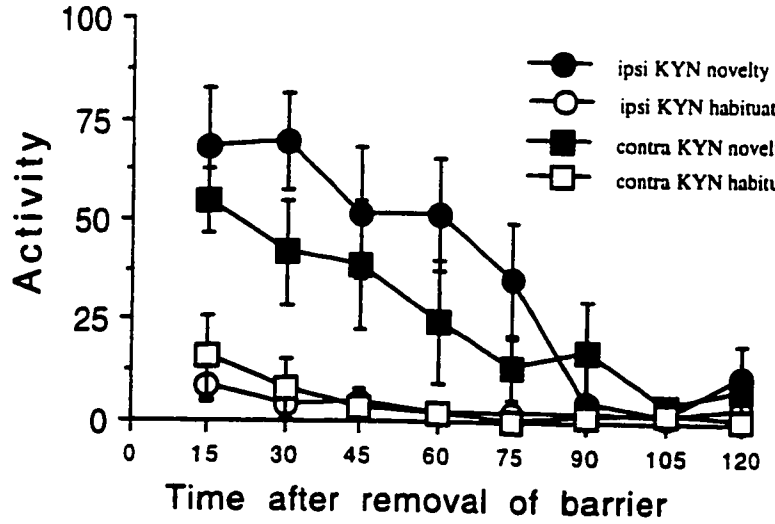

100
75
50
25
0
Activity
0
15
30
45
60
75
90
105
120
Time after removal of barrier
ipsi KYN novelty
ipsi KYN habituated
contra KYN novelty
contra KYN habituated

Figure 12. Effects of exposure to novel or habituated stimuli on NAS dopamine. Microdialysis samples were collected every 15 minutes. For animals exposed to novel stimuli, following the collection of 6 baseline samples the barrier was removed from the test chamber (vertical line) and samples were collected for 120 minutes. For animals exposed to habituated stimuli, samples were collected for 120 minutes following the last baseline sample. Exposure to novel stimuli elevated NAS dopamine [$F(5,13) = 8.994$, $p < 0.0001$]. NAS dopamine in animals exposed only to habituated stimuli did not change [$F(5,13) = 1.38$, $p < 0.2345$]. Filled symbols represent significant differences from baseline (Fisher LSD).

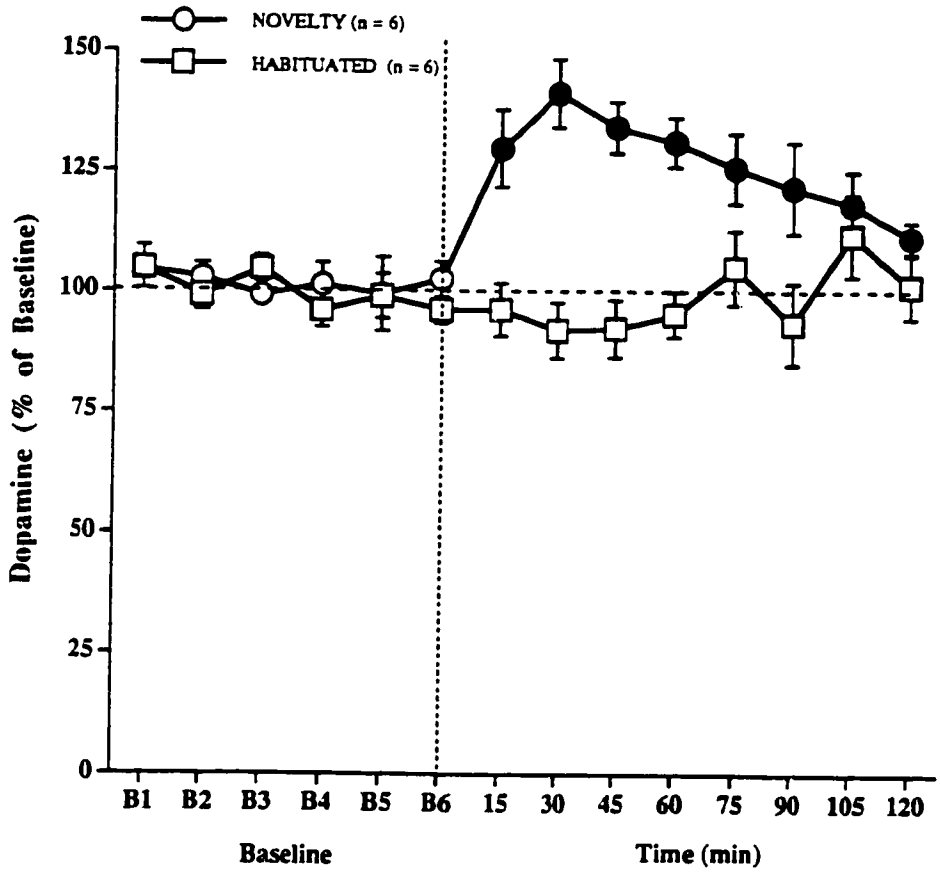

NOVELTY (n = 6)
HABITUATED (n = 6)
Dopamine (% of Baseline)
150
125
100
75
50
25
0
B1
B2
B3
B4
B5
B6
15
30
45
60
75
90
105
120
Baseline
Time (min)

Figure 13. Effect of TTX injections into the ventral subiculum (VS) on NAS dopamine during exposure to novel stimuli. Microdialysis samples were collected every 15 minutes. Following the collection of baseline samples, TTX was injected into either the ipsilateral or contralateral VS and 2 more samples were collected (denoted as TTX on the figure). The barrier was then removed (vertical line) and samples were collected for another 120 minutes. Following TTX injections into the ipsilateral VS there was no increase in NAS dopamine in response to novel stimuli [$F(5,15) = 0.229$, $p = 0.9781$] but following injections of TTX into the contralateral VS, novel stimuli evoked significant elevations in NAS dopamine [$F(5,15) = 5.55$, $p = 0.0001$].

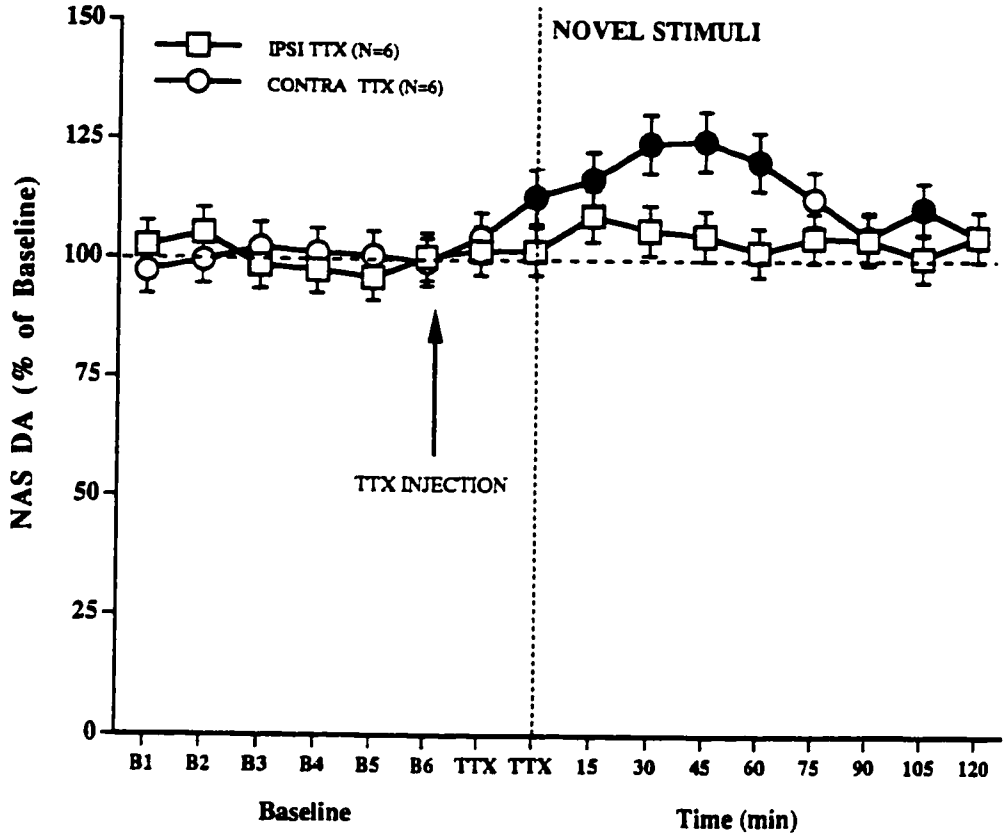
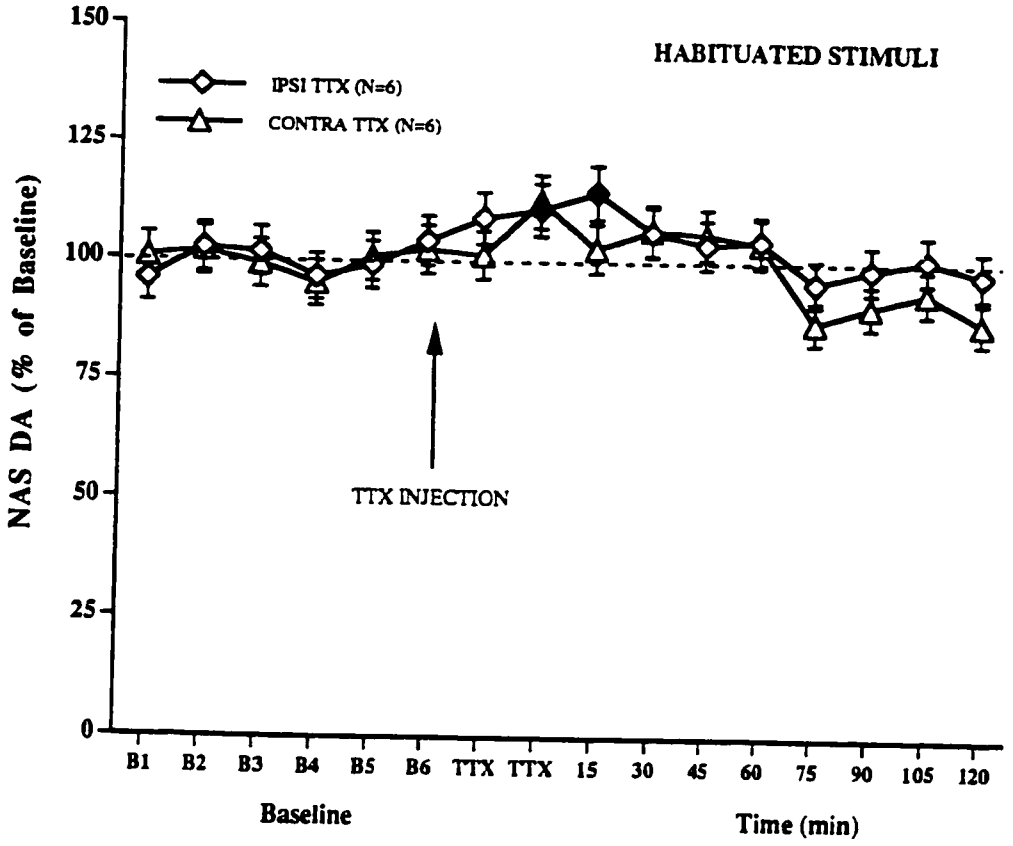

150
125
100
75
50
25
0
NAS DA (% of Baseline)
IPSI TTX (N=6)
CONTRA TTX (N=6)
NOVEL STIMULI
TTX INJECTION
B1
B2
B3
B4
B5
B6
TTX
TTX
15
30
45
60
75
90
105
120
Baseline
Time (min)

Figure 14. Effect of TTX injections into the ventral subiculum (VS) on NAS dopamine during exposure to habituated stimuli. Microdialysis samples were collected every 15 minutes. Following the collection of baseline samples, TTX was injected into either the ipsilateral or contralateral VS and 2 more samples were collected (denoted as TTX on the figure). Samples were then collected for an additional 120 minutes. There was a significant main effect when TTX was injected into the ipsilateral VS [$F(5,15) = 2.818$, $p = 0.0075$]. There was no effect when injected into the contralateral VS [$F(5,15) = 2.12$, $p = 0.339$]. Filled symbols represent significant differences from baseline.


HABITUATED STIMULI
IPSI TTX (N=6)
CONTRA TTX (N=6)
NAS DA (% of Baseline)
150
125
100
75
50
25
0
TTX INJECTION
B1
B2
B3
B4
B5
B6
TTX
TTX
15
30
45
60
75
90
105
120
Baseline
Time (min)

Injections of TTX into the ipsilateral VS of habituated rats were associated with a slight and short lasting increase in NAS DA which was evident before, and lasted for only 1 sample, after the barrier was removed. In this group of animals, NAS DA was increased to a maximum of 115% of baseline 45 minutes after the TTX injection and within returned to basal levels 60 minutes of the injection. Injections of TTX into the contralateral VS did not produce any significant changes in NAS DA.

Effect of intra-VTA kynurenic acid on NAS DA

Perfusion of the ionotropic glutamate antagonist KYN into the VTA blocked novelty-evoked elevations in NAS DA (Figures 15,16). During intra-VTA perfusion of KYN, NAS DA did not differ from baseline either within the period intervening the onset of KYN and removal of the barrier or following removal of the barrier. During perfusion of KYN into the contralateral VTA, exposing the animals to the novel stimuli significantly elevated NAS DA. Elevations in NAS DA peaked at 127% of baseline 30 to 45 minutes after removal of the barrier and returned to basal levels within 90 minutes. NAS DA was significantly different between animals perfused with KYN into the ipsilateral or contralateral VTA [Effect of Side: $F(1,170) = 4.924$, $p = 0.0500$). Perfusion of KYN into either the ipsilateral or contralateral VTA produced no effect on NAS DA in animals tested in a habituated environment.

Histology

The placements of microdialysis membranes and injection cannulae were similar to those represented in Figure 4 and Figure 5. All NAS probes were located in the medial NAS between the midline and not extending laterally beyond the anterior commisure. Microdialysis probes aimed at the VTA (KYN acid perfusion) were located in the anterior VTA. Injection sites in the VS (TTX) were similar to NMDA injection sites of Chapters 1 and 2. No subjects were excluded on the basis of histological analysis.

Figure 15. Effect of KYN perfusion into the ventral tegmental area (VTA) on NAS dopamine during exposure to novel stimuli. Microdialysis samples were collected every 15 minutes. Following the collection of 6 baseline samples, kynurenic acid perfusion into the VTA was initiated (samples prefixed by K on figure). One hour later, the barrier was removed (vertical line) exposing animals to novel stimuli. Samples were collected for another 120 minutes. Perfusion of KYN into the ipsilateral VTA blocked novelty-evoked elevations in NAS dopamine [$F(5, 17) = 1.235$, $p = 0.2816$]. Novel stimuli still elevated NAS dopamine when KYN was perfused into the contralateral VTA [$F(5,17) = 4.492$, 0.0001].

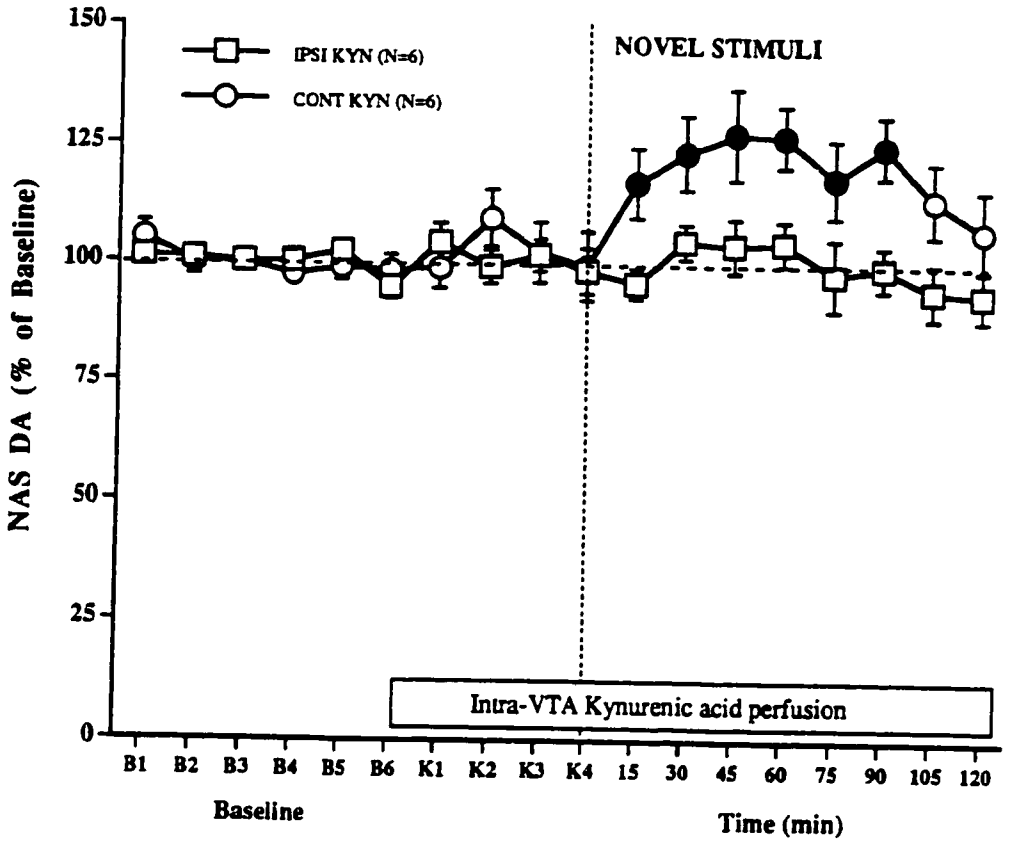
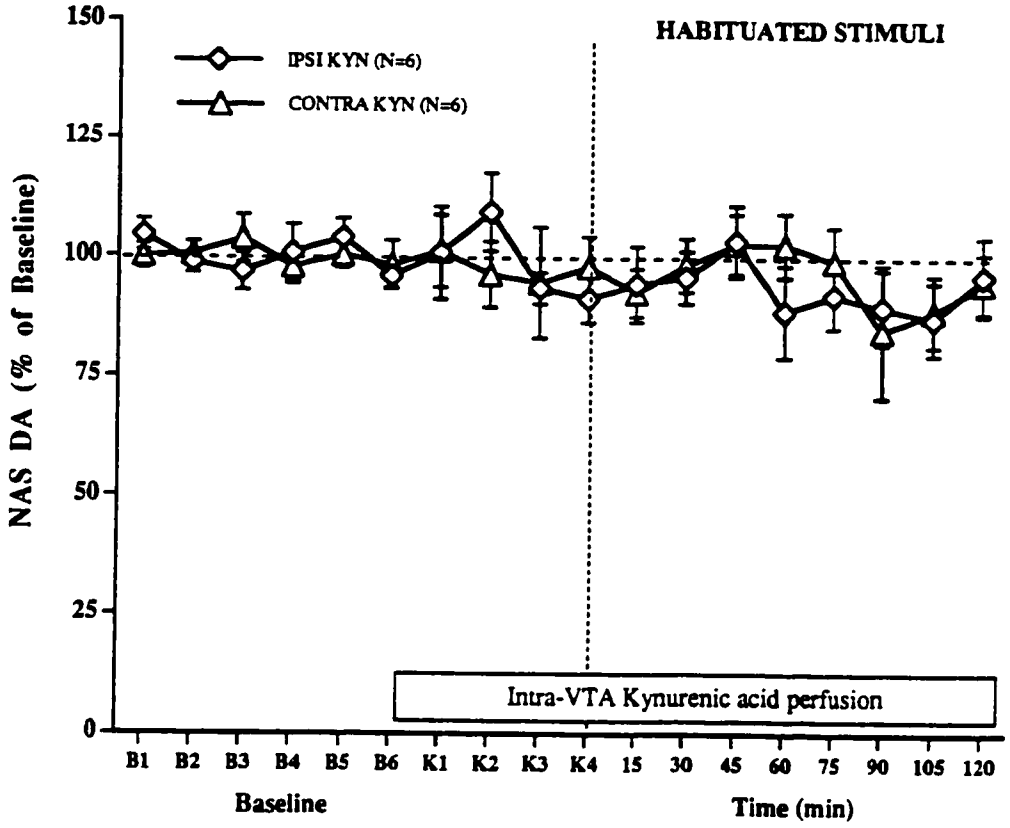

150
125
100
75
50
25
0
NAS DA (% of Baseline)
IPSI KYN (N=6)
CONT KYN (N=6)
NOVEL STIMULI
Intra-VTA Kynurenic acid perfusion
B1 B2 B3 B4 B5 B6 K1 K2 K3 K4 15 30 45 60 75 90 105 120
Baseline
Time (min)

Figure 16. Effect of KYN perfusion into the ventral tegmental area (VTA) on NAS dopamine during exposure to habituated stimuli. Microdialysis samples were collected every 15 minutes. Following the collection of 6 baseline samples, kynurenic acid perfusion into the VTA was initiated (samples prefixed by K on figure). In concordance with animals exposed to novel stimuli, "kynurenic acid" samples were collected for one hour; samples were then collected for an additional 120 minutes. During exposure to habituated stimuli perfusion of KYN had no effect on NAS dopamine when perfused into either the ipsilateral [$F(5,17) = 1.112$, $p = 0.3679$] or contralateral [$F(5,17) = 0.7610$, $p = 0.6868$) VTA.


HABITUATED STIMULI
IPSI KYN (N=6)
CONTRA KYN (N=6)
NAS DA (% of Baseline)
150
125
100
75
50
25
0
Intra-VTA Kynurenic acid perfusion
B1 B2 B3 B4 B5 B6 K1 K2 K3 K4 15 30 45 60 75 90 105 120
Baseline
Time (min)

DISCUSSION

The present results confirm recent reports that investigation of novel environments elevates nucleus accumbens dopamine (Rebec et al., 1997; Saigusa et al., 1999) and compliment electrophysiological reports that salient novel stimuli increase impulse flow through dopaminergic neurons (Ljungberg et al., 1992; Horvitz et al., 1997; Schultz, 1998) which likely elevates NAS dopamine. Until recently, much of the evidence linking elevations NAS dopamine with increased investigatory behavior has been obtained in the context of the locomotor stimulating properties of indirect dopaminergic agonists such as amphetamine, cocaine, or opiates (Joyce & Iversen, 1979; Creese & Iversen, 1975; Kelly et al., 1975). Such drugs can evoke dramatic elevations in NAS dopamine, sometimes to greater than 5 times basal levels (or 500% increases), in association with their behaviorally relevant actions (Robinson et al., 1988; Kuczenski & Segal, 1989; Kalivas & Duffy, 1990; Wise et al., 1995; Wise et al., 1995). In comparison to the elevations in NAS dopamine evoked by such drugs, the elevations in NAS dopamine associated with investigation of novel environmental stimuli appear unremarkable. In the present study, novel stimuli elevated NAS dopamine to less than two-times basal levels (to approximately 130% of baseline). Although modest, these elevations were reliable and are comparable in magnitude to those of a recent microdialysis study in which novel stimuli were also reported to elevate NAS dopamine (Saigusa et al., 1999). Moreover, the magnitude of novelty-evoked elevations in NAS dopamine is comparable to the magnitude of elevations evoked by other naturally occurring biologically significant stimuli such as food (Hernandez & Hoebel, 1988; Radhakishun et al., 1988; Wilson et al., 1995; Bassereo & DiChiara, 1997; Taber & Fibiger, 1998) or a sexually receptive mate (Damsma et al., 1992; Pfaus et al., 1995). NAS dopamine has been suggested to facilitate investigatory behavior by modulating the motivational impact of environmental stimuli (Wise & Bozarth, 1987; Robbins & Everitt, 1992; Blackburn, Pfaus & Phillips, 1992; Berridge & Robinson, 1998). Inasmuch as elevations in NAS dopamine are a reflection

of the motivational impact of environmental stimuli the present results suggest similar impact evoked by exposure to novel stimuli, food, and sexual partners.

The involvement of projections from the VS in novelty-evoked elevations in NAS dopamine are reflected in the effects of TTX injections. Unilateral injections of TTX, into the VS ipsilateral to the dialyzed NAS, abolished novelty-evoked elevations in dopamine. The present results, therefore, represent the first demonstration that the VS mediates elevations in NAS dopamine through a circuitry responsive to environmental stimuli. Furthermore, within this circuitry, elevations in NAS dopamine are mediated by processes occurring downstream from novelty-evoked activation of the VS. These results are line with reports that direct chemical stimulation of the ventral subiculum increases NAS dopamine concomitantly with investigatory behavior (Brudzynksi & Gibson, 1997; Legault & Wise, 1999). Although the activity of ventral subiculum neurons was not directly measured in the present study, there is sufficient evidence from other studies to suggest that novel stimuli activate the hippocampus. For instance, excitatory cholinergic transmission in the hippocampus (Dudar et al., 1979; Inglis & Fibiger, 1995; Acquas et al., 1996; Theil et al., 1998) and the activity of hippocampal neurons (Moser, 1995; Xu et al., 1998) are increased during investigation of novel stimuli.

The mechanisms through which activation of the ventral subiculum increase NAS dopamine are not known. One mechanism that has been suggested is that glutamate released from ventral subiculum projections to the NAS evoke impulse-independent dopamine release from dopaminergic terminals (Romo et al., 1986; Glowinski et al., 1988; Blaha et al., 1997; Brudzynksi & Gibson, 1997). In support of this suggestion, electrical stimulation of the ventral subiculum is reported to elevate the dopamine-like voltammetry signal recorded from the NAS and these elevations are blocked by intra-NAS injections of glutamate receptor antagonists (Blaha et al., 1997) suggesting a glutamate-mediated mechanism within the NAS.

On the other hand, recent microdialysis and electrophysiological studies have demonstrated an excitatory influence of the ventral subiculum on VTA dopaminergic neurons; stimulation of the ventral subiculum activates VTA dopaminergic neurons (Harden & Grace, 1995; Legault et al., 1998) and, consistent with increased impulse flow through dopaminergic neurons, increases somatodendritic dopamine release in the VTA (Legault & Wise, 1999). Elevations in NAS dopamine associated with stimulation of the ventral subiculum are abolished by blockade of impulse flow through dopaminergic axons (by perfusion of TTX) or blockade of ionotropic glutamate receptors (by perfusion of KYN) into the VTA (Legault et al., 1998). Together, the results of these electrophysiological and microdialysis studies suggest that ventral subiculum stimulation increases NAS dopamine primarily by increasing impulse flow through VTA dopaminergic neurons; the circuitry through which the ventral subiculum does so likely involves an excitatory glutamatergic projection to the VTA.

On the basis of these results, it was of interest to determine the effects of kynurenic acid perfusion into the VTA on novelty-evoked, ventral subiculum-dependent, elevations in NAS dopamine. Parallel to the blockade of elevations in NAS dopamine induced by ventral subiculum stimulation (Legault et al., 1998), elevations in NAS dopamine evoked by novel stimuli were abolished by intra-VTA kynurenic acid. Although these results do not preclude the possibility that direct glutamatergic projections from the ventral subiculum to the NAS can evoke or augment dopamine release, they do suggest that glutamatergic inputs to the dopaminergic cell body region are primarily responsible for novelty-evoked elevations in NAS dopamine. These results add to a growing body evidence that glutamate actions in the VTA directly mediate elevations in NAS dopamine associated with appetitive stimuli such as food (Taber & Fibiger, 1997; Westerink, Kwint & deVries, 1997) or electrical stimulation of the prefrontal cortex (You et al., 1998).

TTX injections into the ventral subiculum (ipsilateral to the dialyzed NAS) at a dose that blocked novelty-evoked elevations in NAS dopamine did not disrupt basal dopamine levels. Thus, it does not appear that outputs from this region exert a simple tonic excitatory effect on extracellular dopamine. These results are in agreement with a recent electrophysiological study in which TTX injections into the ventral subiculum were reported to have no effect on the firing rates of VTA dopaminergic neurons or the number of identifiable spontaneously active dopaminergic neurons (Todd & Grace, 1998). Nonetheless, some studies have reported behavioral, pharmacological, and neurochemical changes suggestive of alterations in dopaminergic transmission that emerge days or weeks following lesions of the hippocampus (Reinstein et al., 1981; Springer & Isaacson, 1982; Lipska et al., 1992, 1993; Wilkinson et al., 1993). The protracted time course of hippocampal lesion-induced changes in dopaminergic transmission likely reflects interactions between hippocampal and dopaminergic systems that are more complex than disruption of simple tonic influence on dopamine release.

Ventral subiculum-mediated elevations in NAS dopamine appear not to be a simple correlate of investigatory behavior but a critical neurochemical mechanism through which novel stimuli evoke investigatory behavior; disruption of dopaminergic transmission abolishes investigatory behavior associated with hippocampal stimulation (Wu & Brudzynski, 1995; Brenner & Bardgett, 1998). However, in the present study, unilateral injections of TTX into the ventral subiculum failed to abolish investigatory behavior while blocking elevations in the NAS ipsilateral to the TTX-injected ventral subiculum. These results are likely accounted for by the fact that unilateral TTX injections did not appear to disrupt neurotransmission in the contralateral NAS. Although bilateral depletion of striatal dopamine, by 6-OHDA injections, can severely reduce investigatory behavior such injections do not abolish orientation or investigatory approach but accelerate habituation (Marshall et al., 1974; Carli et al., 1985; Fink & Smith, 1980; Kelley & Stinus, 1985). On the other hand, stimulation of dopaminergic

transmission in the absence of any environmental stimulation (by unsignalled intravenous injection of amphetamine) does not increase investigatory behavior while still significantly elevating NAS dopamine (Badiani et al., 1998). Thus, NAS dopamine appears to augment, rather than initiate, investigatory behavior. The neurochemical inputs to the NAS responsible for initiating investigatory behavior appear to be glutamatergic and arise from the ventral subiculum. Direct glutamatergic stimulation of the NAS facilitates investigatory behavior and this effect is blocked by disruption of dopaminergic transmission (Boldry & Uretsky, 1988; Boldry et al., 1991; Wu et al., 1993). Lesions of the ventral subiculum reduce investigation of novel environments (Burns et al., 1996) and investigatory behaviors facilitated by intra-NAS injections of amphetamine (Burns et al., 1993). However, lesions of the prefrontal cortex or basolateral amygdala, which also send glutamatergic projections to the NAS, fail to disrupt investigatory behavior (Burns et al., 1993; Burns et al., 1996). Thus, glutamatergic projections to the NAS specifically from the ventral subiculum appear to interact with NAS dopamine to modulate investigatory behavior.

Although the ventral subiculum is not known to project to the VTA, stimulation of the ventral subiculum activates VTA dopaminergic neurons (Harden & Grace, 1995; Legault et al., 1998). The activation VTA dopaminergic neurons by the ventral subiculum may account for some of the electrophysiological responses of dopaminergic neurons to novel stimuli. The activity of dopaminergic neurons is increased by novel stimuli and the unsignalled delivery of appetitive stimuli, is not altered by the signaled delivery of appetitive stimuli, and is depressed when signaled appetitive stimuli are withheld (Schultz, 1998). The present results, and those demonstrating activation of dopaminergic neurons in response to ventral subiculum stimulation (Harden & Grace, 1995; Legault et al., 1998), suggest that the hippocampus mediates at least phasic activation of dopaminergic neurons in response to novel stimuli.

GENERAL DISCUSSION

The aim of the present thesis was to examine the mechanisms through which the ventral subiculum influences dopaminergic transmission in the NAS and the relevance of this influence to investigatory behavior. From the present experiments it can concluded that the ventral subiculum influences both NAS and VTA dopamine and that the primary mechanism through which it does so is by altering impulse flow through VTA dopaminergic neurons. Although the circuitry through which the ventral subiculum influences dopaminergic neurons remains undetermined it likely involves a glutamatergic link terminating in the VTA. This circuitry is responsive to novel stimuli and plays a pivotal role in unconditioned increases in dopaminergic transmission evoked by novel stimuli. Activation of this circuitry, by either direct chemical stimulation or by exposure to novel stimuli, appears to play an important role in investigatory behavior.

Investigatory behavior depends in large part on hippocampal function and (Jarrard, 1968; Kimble, 1973; O'Keefe and Nadel, 1978; Mogenson and Neilsen, 1984) and the influence of hippocampal function on dopaminergic transmission (Wu and Brudzynksi, 1995; Brenner and Bardgett, 1998). The experiments of Chapter 1 (in which the VS was activated by NMDA) and the experiments of Chapter 3 (in which animals were exposed to novel stimuli) strengthen the evidence linking hippocampal activation, investigatory behavior, and NAS dopamine. The results of Chapter 1 are in agreement with reports that direct chemical or electrical stimulation of the hippocampus elevates extracellular dopamine in the NAS (Blaha et al., 1997; Brudzynski and Gibson, 1997; Boulenguez et al., 1998) and, by doing so, facilitates investigatory behavior (McLean, 1957; Flicker and Geyer, 1982; Mogenson and Neilsen, 1984a; Yang and Mogenson, 1987; Brenner and Bardgett, 1998). In Chapter 3, exposure to novel stimuli was presumed to naturally activate the hippocampus. Although there was no direct measure of hippocampal activation in the present experiments, exposure to novel stimuli has been shown to activate hippocampal neurons (Moser, 1995; Xu et al., 1998) and increase

cholinergic transmission in the hippocampus (Inglis and Fibiger, ; Acquas et al., 1996 ; Thiel et al., 1998). That novelty-evoked elevations in NAS dopamine are mediated by activation of the hippocampus is reflected in the effects of TTX injections into the ventral subiculum. Collectively, the experiments of Chapters 1 and 3 indicate that increases in impulse flow from the ventral subiculum can facilitate investigatory behavior, are sufficient to elevate NAS dopamine, and are necessary for novel stimuli to elevate NAS dopamine.

HIPPOCAMPAL MODULATION OF DA

Modulation of Impulse Flow Through the VTA

Collectively the experiments of the present thesis identify the VTA as a critical link in the brain circuitry through which activation of the ventral subiculum increases dopaminergic transmission. The experiments of chapters 1 and 2 demonstrate that stimulation of the ventral subiculum increases impulse flow through a sub-population of VTA dopaminergic neurons causing release of somatodendritic dopamine associated with increased impulse flow through dopaminergic neurons, and indicate further that impulse flow through the VTA is necessary for ventral subicular stimulation to evoke detectable elevation in NAS dopamine. Although these experiments cannot rule out the possibility that glutamate acts directly on dopaminergic terminals in the NAS and contribute to VS-mediated elevations in NAS dopamine by evoking impulse-independent transmitter release they do support the conclusion that any impulse-independent contribution is minimal. Microdialysis studies have shown that extracellular dopamine in the striatum can be reduced to below 20% of basal levels by perfusion of TTX into the region of the dopaminergic cell bodies or the medial forebrain bundle through which dopaminergic axons ascend to the striatum (Chapter 2 of present thesis). Thus, at least 80% of basal extracellular dopamine detected by microdialysis is impulse-dependent. It can be concluded therefore, that if activation of hippocampal projections to the NAS does cause

glutamate-mediated impulse-independent dopamine release this action is not likely to contribute more than 20% to basal extracellular dopamine. This conclusion parallels those reported in several studies of prefrontal cortex modulation of dopamine release in the NAS.

There are at least two reasons for which this conclusion might have been unexpected in the case of the ventral subiculum. First, glutamatergic projections from the ventral subiculum are not known to innervate the VTA. Second, electrical stimulation of the ventral subiculum has been reported elevate the dopamine-like voltammetry signal recorded from the NAS and these elevations were reported to be blocked by injections of glutamate receptor antagonists into the NAS (Blaha et al., 1997). Indeed, the intra-VTA microdialysis experiments of Chapter 1 were undertaken with the expectation that stimulation of the ventral subiculum would elevate NAS but not VTA dopamine. A dissociation between elevations in NAS and VTA dopamine would have provided initial evidence that ventral subiculum stimulation could elevate NAS dopamine in the absence of changes in impulse activity through dopaminergic cell bodies. The conclusion that ventral subicular evoked elevations in NAS dopamine are primarily, if not exclusively, dependent on impulse flow through the VTA leaves two critical issues unresolved: one, is the discrepancy between the conclusions drawn from the present experiments and those of Blaha et al. (1997) who concluded that stimulation of the ventral subiculum elevated NAS dopamine by glutamate-mediated actions on dopaminergic terminals, while the other is the circuitry through which the ventral subiculum ultimately influences VTA dopaminergic neurons.

One possible resolution of the discrepancy between conclusions supported by the present thesis and those of Blaha is that hippocampal stimulation does cause glutamate-mediated dopamine release, but that microdialysis is not sensitive enough to detect it. Another possibility is that glutamatergic projections from the ventral subiculum can influence VTA dopaminergic neurons indirectly through the activation of NAS outputs.

Stimulation of the ventral subiculum or its projections through the fimbria-fornix have established excitatory effects on NAS neurons (Lopes da Silva et al., 1984; Yang and Mogenson, 1984; O'Donnell and Grace, 1995). Activation of the NAS can increase the firing of dopaminergic neurons (Grace and Bunney, 1985), presumably because GABAergic projections from the NAS inhibit GABAergic inputs to, and thus disinhibit, dopaminergic neurons (Grace and Bunney, 1985; Tepper, Martin, and Anderson, 1995). Preliminary evidence in support of this possibility has recently been reported in abstract form (Todd and Grace, 1998); injections kynurenic acid into the NAS blocked the activation of VTA dopaminergic neurons evoked by NMDA injections into the ventral subicular stimulation.

Possible Circuitry

There are several possible circuits through which projections from the ventral subiculum could ultimately influence glutamatergic projections to the VTA. Already discussed in some detail (see Discussion of Chapter 2) is a circuit involving a link between the ventral subiculum and the VTA originating in the prefrontal cortex. Electrophysiological experiments have confirmed that stimulation of the hippocampus activates prefrontal cortex neurons that project to the VTA (Jay et al., 1995). The neurochemical and electrophysiological parallels between elevations in dopaminergic transmission evoked by stimulation of either the ventral subiculum or prefrontal cortex makes the idea of a prefrontal cortex link a primary avenue for future study. The first studies along such a line might be designed to determine if TTX and kynurenic acid perfusion into the PFC abolish the elevations in NAS dopamine evoked by hippocampal stimulation.

The ventral subiculum may also influence glutamatergic (as well as cholinergic) inputs to the VTA arising from the mesencephalic pedunculopontine nucleus (PPN) and laterodorsal tegmental nucleus (LDTg). These nuclei send both cholinergic and

glutamatergic projections to the dopaminergic cell body regions of the substantia nigra and VTA (Sugimoto and Hattori, 1984; Lavoie and Parent, 1994; Oakman et al., 1995). Activation of these nuclei evokes excitatory responses in dopaminergic neurons (Futami, Takakusaki, and Kitai, 1995) and elevates NAS dopamine (Klitenick and Kalivas, 1994). The most likely circuit through which the ventral subiculum can influence projections from the PPN and LDTg is through the NAS. The NAS gives rise to inhibitory GABAergic projections to the ventral pallidum (Nauta et al., 1978; Groenewegen and Russchen, 1984; Heimer et al., 1991; Berendse et al., 1992; Lynd-Balta and Haber, 1994). Some neurons of the ventral pallidum project to the pedunculopontine or laterodorsal tegmental nuclei (Swanson et al., 1984; Yang and Mogenson, 1987). Electrical stimulation of the ventral subiculum inhibits ventral pallidal neurons that project to the PPN and LDTg (Yang and Mogenson, 1987) may disinhibit projections from the PPN and LDTg to the VTA.

IMPLICATIONS

Dopaminergic neurons of the VTA and SN are selectively activated by novel stimuli, reinforcing stimuli, and conditioned stimuli (Schultz, 1998). The responses of dopaminergic neurons are complex; dopaminergic neurons are activated by novel stimuli that evoke orientation and by the unsignalled presentation of reinforcers or conditioned stimuli. However, dopaminergic neurons are unresponsive to reinforcers or conditioned stimuli that have been signaled by other stimuli, and their activity is depressed when conditioned stimuli are not followed by a reinforcer. The present thesis provides evidence that these responses are at least partially mediated by the hippocampus. The most obvious suggestion is that novel stimuli activate dopaminergic neurons via the hippocampus. The net effect of hippocampal activation (by either direct NMDA injections or by activation of sensory inputs by exposure to novel environmental stimuli) is a sustained activation of dopaminergic transmission. Nonetheless, the precise role of

the hippocampus in novelty-evoked activation of dopaminergic neurons must be tempered by evidence from the present and previous (Harden and Grace, 1995) electrophysiological studies demonstrating phasic (and sometimes sustained) inhibition of dopaminergic neurons in response to stimulation of the ventral subiculum. Studies aimed at determining the effects of TTX injections into the ventral subiculum on novelty-evoked activation of dopaminergic neurons may help clarify the role of the hippocampus in these dopaminergic responses.

Hippocampal influences of dopaminergic transmission have become a focus of research into the pathophysiology of schizophrenia. Based on the clinical efficacy of neuroleptics in the treatment of schizophrenia, this disorder has traditionally been suggested to result from hyperdopaminergic transmission. Hippocampal dysfunction has been suggested to contribute to the etiology and symptomatology of schizophrenia by increasing dopaminergic transmission (Gray et al., 1991; Jaskiw and Weinberger, 1992; Grace, 1993; O'Donnell and Grace, 1998; Weinberger, 1999). Until recently, however, there has been only indirect evidence that the hippocampus influences dopaminergic transmission. The results of the present thesis provide direct evidence that impulse flow from the hippocampus exerts an excitatory influence on dopaminergic transmission, by a circuitry linking the ventral subiculum to the VTA, and that this influence is exerted in response to environmental stimuli. Dysfunctional activation of dopaminergic transmission by the ventral subiculum, therefore, offers a potential mechanism for hippocampal-mediated dopaminergic pathology in schizophrenia.

In summary, the experiments of the present thesis provide evidence that projections from the ventral subiculum of the hippocampus can exert a phasic excitatory influence over dopaminergic transmission in the NAS and VTA. This influence is due primarily to actions in the dopaminergic cell body region of the VTA and can be evoked by environmental stimuli.

References

Ackil, J., Mellgren, R. L., Halgren, C., & Frommer, S. P. (1969). Effects of CS exposure on avoidance learning in rats with hippocampal lesions. Journal of Comparative and Physiological Psychology, 69, 739-747.

Acquas, E., Wilson, C., & Fibiger, H. C. (1996). Conditioned and unconditioned stimuli increase frontal cortical and hippocampal acetylcholine release: effects of novelty, habituation, and fear. Journal of Neuroscience, 16, 3089-3096.

Alexander, G., & Crutcher, M. (1990). Functional architecture of basal ganglia circuits: neural substrates of parallel processing. Trends in Neuroscience, 13, 366-371.

Alheid, G. F., & Heimer, L. (1988). New perspectives in basal forebrain organization of special relevance for neuropsychiatric disorders: the striatopallidal, amygdaloid, and corticopetal components of substantia innominata. Neuroscience, 27, 1-39.

Amaral, D. G., & Witter, M. P. (1989). The three-dimensional organization of the hippocampal formation: A review of anatomical data. Neuroscience, 31, 571-591.

Angrist, B., Shopin, B., & Gershon, S. (1971). Comparative psychotomimetic effects of stereoisomers of amphetamine. Nature, 234, 152-153.

Anscombe, F. (1987). The disorder of consciousness in schizophrenia. Schizophrenia Bulletin, 2, 241-260.

Apicella, P., Ljungberg, T., Scarnati, E., & Schultz, W. (1991). Responses to reward in monkey dorsal and ventral striatum. Experimental Brain Research, 85, 491-500.

Arnt, J. (1981). Hyperactivity following injections of a glutamate agonist and 6,7-ADTN into rat nucleus accumbens and its inhibition by THIP. Life Sciences, 28, 1597-1603.

Arvanov, V. L., & Y., W. R. (1997). NMDA-induced response in pyramidal neurons of the rat medial prefrontal cortex slices consists of NMDA and non-NMDA components. Brain Research, 768, (1-2), 361-364.

Badiani, A., & Stewart, J. (1993). Tolerance and sensitization to the behavioral effects of drugs. Behavioural Pharmacology, 4, 289-312.

Badiani, A., Anagnostaras, A. G., & Robinson, T. E. (1995). The development of sensitization to the psychomotor stimulant effects of amphetamine is enhanced in a novel environment. Psychopharmacology, 117, 443-452.

Badiani, A., Browman, K. E. & Robinson, T. E. (1995). Influence of novel versus home environments on sensitization to the psychomotor stimulant effects of cocaine and amphetamine. Brain Research, 674, 291-298.

Badiani, A., Oates, M. M., Day, H. E. W., Watson, S. J., Akil, H., & Robinson, T. E. (1998). Amphetamine-induced behavior, dopamine release, and c-fos mRNA expression: Modulation by environmental novelty. Journal of Neuroscience, 18 (24), 10579-10593.

Bardgett, M. E., Jackson, J. L., Taylor, G. T., & Csernansky, J. G. (1995). Kainic acid decreases hippocampal neuronal number and increases dopamine receptor binding in the nucleus accumbens: An animal model of schizophrenia. Behavioural Brain Research, 70, 153-164.

Bardo, M. T., Neisewander, J. L., & Pierce, R. C. (1989). Novelty-induced place preference behavior in rats: Effects of opiate and dopaminergic drugs. Pharmacology, Biochemistry, and Behavior, 32, 683-689.

Bardo, M. T., Bowling, S. L., & Pierce, R. C. (1990). Changes in locomotion and dopamine neurotransmission following amphetamine, haloperidol, and exposure to novel environmental stimuli. Psychopharmacology, 101, 338-343.

Baruch, I., Hemsley, D. R., & Gray, J. A. (1988). Differential performance of acute and chronic schizophrenics in a latent inhibition task. Journal of Nervous and Mental Disease, 176, 598-606.

Bassereo, V., & Di Chiara, G. (1997). Differential influence of associative and nonassociative learning mechanisms on the responsiveness of prefrontal and accumbal dopamine transmission to food stimuli in rats fed ad libitum. Journal of Neuroscience, 17 (2), 851-861.

Beninger, R. J., & Hahn, B. L. (1983). Pimozide blocks establishment but not expression of amphetamine-produced environment-specific conditioning. Science, 220, 1304-1306.

Beninger, R. J., & Herz, R. S. (1986). Pimozide blocks establishment but not expression of cocaine-produced environment-specific conditioning. Life Science, 38, 1425-1431.

Berendse, H. W., Galis-de-Graaf, Y., & Groenewegen, H. J. (1992). Topographical organization and relationship with ventral striatal compartments of prefrontal corticostriatal projections in the rat. Journal of Comparative Neurology, 316, 314-347.

Berman, K. F., Zec, R. F., & Weinberger, D. R. (1986). Physiologic dysfunction of dorsolateral prefrontal cortex in schizophrenia: II. Role of neuroleptic treatment, attention, and mental effort. Archives of General Psychiatry, 43, 126-135.

Berridge, K. C., & Robinson, T. E. (1998). What is the role of dopamine in reward: hedonic impact, reward, learning, or incentive salience. Brain Research Reviews, 28, 309-369.

Beuger, M., van Kammen, D. P., Kelley, M. E., & Yao, J. (1996). Dopamine turnover in schizophrenia before and after haloperidol withdrawal: CSF, plasma, and urine studies. Neuropsychopharmacology, 15, 75-86.

Bindra, D. (1968). Drive and incentive-motivation. Psychological Review, 75, 1-22.

Blackburn, J. R., Pfaus, J. G., & Phillips, A. G. (1992). Dopamine functions in appetitive and defensive behaviours. Progress in Neurobiology, 39, 247-279.

Bland, B. H., Andersen, P., & Ganes, T. (1975). Two generators of hippocampal theta activity in rabbits. Experimental Brain Research, 94, 199-218.

Bland, B. H., Colom, L. V., Konopacki, J., & Roth, S. H. (1988). Intracellular records of carbachol-induced theta rhythm in hippocampal slices. Brain Research, 447, 364-368.

Boejinga, P. H., Pennartz, C. M. A., & Lopes da Silva, F. H. (1990). Paired-pulse facilitation in the nucleus accumbens following stimulation of the subicular inputs in the rat. Neuroscience, 35, 301-311.

Boldry, R. C., & Uretsky, N. J. (1988). The importance of dopaminergic neurotransmission in the hypermotility response produced by the administration of N-methyl-d-aspartic acid into the nucleus accumbens. Neuropharmacology, 27, 569-577.

Boldry, R. C., Willins, D. L., Wallace, L. J., & Uretsky, N. J. (1991). The role of endogenous dopamine in the hypermotility response to intra-accumbens AMPA. Brain Research, 559, 100-108.

Bouyer, J. J., Park, D. H., Joh, T. H., & Pickel, V. M. (1984). Chemical and structural analysis of the relation between cortical inputs and tyrosine hydroxylase-containing terminals rat neostriatum. Brain Research, 302, 267-275.

Braff, D., Stone, C., Callaway, E., Geyer, M. A., Glick, I. & Bali, L. (1978). Prestimulus effects on human startle reflex in normals and schizophrenics. Psychophysiology, 15, 339-343.

Brenner, D. M., & Bardgett, M. E. (1998). Haloperidol blocks increased locomotor activity elicited by carbachol infusion into the ventral hippocampal formation. Pharmacology, Biochemistry, and Behavior, 60, (3), 759-764.

Broekkamp, C. L. E., Van den Boggard, A. J. J., Heijnen, H. J., Rops, R. H., Cools, A. R. & Van Rossum, J. M. (1976). Separation of inhibiting and stimulating effects of morphine on self-stimulation behavior by intracerebral microinjections. European Journal of Pharmacology, 36, 443-446.

Brog, J. S., Salyaspongse, A., Deutch, A. Y., & Zahm, D. S. (1993). The pattern of afferent innervation of the core and shell in the "accumbens" part of the rat ventral striatum: Immunohistochemical detection of retrogradely transported fluoro-Gold. Journal of Comparative Neurology, 338, 255-278.

Brudzynski, S. M., & Gibson, C. J. (1997). Release of dopamine in the nucleus accumbens caused by stimulation of the subiculum in freely moving rats. Brain Research Bulletin, 42, (4), 303-308.

Bunney, B. S., & Grace, A. A. (1978). Acute and Chronic haloperidol treatment: Comparison of effects on nigral dopaminergic cell activity. Life Sciences, 23, 1715-1728.

Burns, L. H., Robbins, T. W., & Everitt, B. J. (1993). Differential effects of excitotoxic lesions of the basolateral amygdala, ventral subiculum and medial prefrontal cortex on responding with conditioned reinforcement and locomotor activity potentiated by intra-accumbens infusions of D-amphetamine. Behavioral Brain Research, 55, 167-183.

Burns, L. H., Everitt, B. J., Kelley, A. E., & Robbins, T. W. (1994). Glutamate-dopamine interactions in the ventral striatum: Role in locomotor activity and responding with conditioned reinforcement. Psychopharmacology, 115, 516-528.

Burns, L. H., Annett, L., Kelley, A. E., Everitt, B. J., & Robbins, T. W. (1996). Effects of lesions to amygdala, ventral subiculum, medial prefrontal cortex, and nucleus accumbens on the reaction to novelty: Implications for limbic striatal interactions. Behavioral Neuroscience, 110, (1), 60-73.

Cador, M., Robbins, T. W., Everitt, B. J., Simon, H., Le Moal, M. & Stinus, L. (1991). Limbic-striatal interactions in reward-related processes: Modulation by the dopaminergic system. In, P. Wilner, J. Scheel-Kruger (Eds.), The Mesolimbic Dopamine System: From Motivation to Action, pp. 225-250, Wiley, New York.

Cador, M., Taylor, J. R., & Robbins, T. W. (1991). Potentiation of the effects of reward-related stimuli by dopaminergic-dependent mechanisms in the nucleus accumbens. Psychopharmacology, 104, 377-385.

Caine, S. B., Geyer, M. A. & Swerdlow, N. R. (1992). Hippocampal modulation of acoustic startle and prepulse inhibition in the rat. Pharmacology, Biochemistry, and Behavior, 43, 1201-1208.

Campbell, B. A., Ballantine, P. & Lynch, G. (1971). Hippocampal control of behavioral arousal: Duration of lesion effects and possible interactions with recovery after frontal cortical damage. Experimental Neurology, 33, 159-170.

Carli, M., Evendon, J. L., & Robbins, T. W. (1985). Depletion of unilateral striatal dopamine impairs initiation of contraleteral actions and not sensory attention. Nature, 313, 679-682.

Carlsson, M. & Carlsson, A. (1990). Interactions between glutamatergic and monoaminergic systems within the basal ganglia - Implications for schizophrenia and Parkinson's disease. Trends in Neuroscience, 13, (7), 272276.

Carlsson, A., & Lindqvist, M. (1963). Effect of chlorpromazine or haloperidol on formation of 3-methoxytyramine and normetanephrine in mouse brain. Acta Pharmacologica et Toxicologica, 20, 140-144.

Carpenter, W. T., & Buchanan, R. W. (1994). Schizophrenia. New England Journal of Medicine, 330, 681-690.

Carr, D. B., & Sesack, S. R. (1996). Hippocampal afferents to the rat prefrontal cortex: synaptic targets and relation to dopamine terminals. Journal of Comparative Neurology, 369, (1), 1-15.

Chapman, J. (1966). The early symptoms of schizophrenia. British Journal of Psychiatry, 112, 225-251.

Charlety, P., Grenhoff, J., Chergui, K., De la Chapelle, B., Buda, M., Svensson, T., & Chouvet, G. (1991). Burst firing of mesencephalic dopamine neurons is inhibited by somatodendritic application of kynurenate. Acta Physiologica Scandinavica, 142, (1), 105-112.

Chéramy, A., Leviel, V., & Glowinski, J. (1981). Dendritic release of dopamine in the substantia nigra. Nature, 289, 537-542.

Chéramy, A., Romo, R., Godeheu, G., Baruch, P., & Glowinski, J. (1986). In Vivo presynaptic control of dopamine release in the cat caudate nucleus II. Facilitory or inhibitory influence of L-glutamate. Neuroscience, 19, (4), 1081-1090.

Christie, M. J., Bridge, S., James, L. B., & Beart, P. M. (1985). Excitotoxin lesions suggest an aspartatergic projection from rat medial prefrontal cortex to ventral tegmental area. Brain Research, 333, 169-172.

Chiodo, L. A., & Bunney, B. S. (1983). Typical and atypical neuroleptics: differential effects of chronic administration on the activity of A9 and A10 midbrain dopaminergic neurons. Journal of Neuroscience, 3, (4), 1607-1619.

Christie, M. J.. Sikes, R. W., Stephenson, J. A., Cook, C. J., & Beart, P. M. (1987). Excitatory amino acid projections to the nucleus accumbens septi in the rat: a retrograde transport study using D [^{3}H] aspartate and [^{3}H] GABA. Neuroscience, 22, 425-440.

Chronister, R. B., & DeFrance, J. F. (1981). Nucleus accumbens in historical perspective. In, R. B. Chronister and J. F. DeFrance (Eds.), The Neurobiology of the Nucleus Accumbens, pp 1-6. Haer Institute for Electrophysiological Research, Maine.

Chu, B., & Kelley, A. E. (1992). Potentiation of reward-related responding by psychostimulant infusion into nucleus accumbens: role of dopamine receptor subtypes. Psychobiology, 20, 153-162.

Clark, A. J ., Feldon, J., & Rawlins, J. N. (1992). Aspiration lesions of rat ventral hippocampus disinhibit responding in conditioned suppression or extinction, but spare latent inhibition and the partial reinforcement extinction effect. Neuroscience, 48, 821-829.

Clow, D. W., & Jhamandas, K. (1989). Characterization of L-glutamate action on the release of endogenous dopamine from the rat caudate-putamen. Journal of Pharmacology and Experimental Therapeutics, 248, 722-728.

Craig, W. (1918). Appetites and Aversions as constituents of instincts. Biological Bulletin, 2, 91-107.

Creese, I., & Iversen, S. D. (1975). The pharmacological and anatomical substrates of the amphetamine response in the rat. Brain Research, 83, 419-436.

Creese, I., Burt, D. R., & Snyder, S. H. (1976). Dopamine receptor binding predicts clinical and pharmacological potencies of antischizophrenic drugs. Science, 192, 596-598.

Crombag, H. S., Badiani, A., & Robinson, T. E. (1996). Signaled versus unsignalled intravenous amphetamine: large differences in the acute psychomotor response and sensitization. Brain Research, 722, 227-231.

Dahlstrom, A., & Fuxe, K. (1964). Evidence for the existence of monoamine-containing neurons in the central nervous system: I. Demonstration of monoamines in the cell bodies of brain stem neurons. Acta Physiologica Scandinavica, 62, 1-55.

Damsma, G., Pfaus, J. G., Wenkstern, D., Phillips, A. G., & Fibiger, H. C. (1992). Sexual behavior increases dopamine transmission in the nucleus accumbens and striatum of male rats: comparison with novelty and locomotion. Behavioral Neuroscience, 106, 181-191.

Day, J., Damsma, G., & Fibiger, H. C. (1991). Cholinergic activity in the rat hippocampus, cortex, and striatum correlates with locomotor activity: An in vivo microdialysis study. Pharmacology, Biochemistry, and Behavior, 38, 723-729.

De France, J., Marchand, J., Sikes, R., Chronister, R., & Hubbard, J. (1985). Characterization of fimbria input to nucleus accumbens. Journal of Neurophysiology, 54, 1553-1567.

Deadwyler, S. A., West, M., & Lynch, G. (1979). Activity of dentate granule cells during learning: Differentiation of perforant path input. Brain Research, 169, 29-43.

Deutsch, J. A., & Howarth, C. I. (1963). Some tests of a theory of intracranial self-stimulation. Psychological Review, 70, 444-460.

Devenport, L. D., Devenport, J. A., & Holloway, F. A. (1981). Stereotypy: Modulation by the hippocampus. Science, 212, 1288-1289.

Di Ciano, P., Blaha, C.D., & Phillips, A. G. (1998a). Conditioned changes in dopamine oxidation currents in the nucleus accumbens of rats by stimuli paired with self-administration or yoked-administration of d-amphetamine. European Journal of Neuroscience, 10, 1121-1127.

Di Ciano, P., Blaha, C.D., & Phillips, A. G. (1998b). The relationship between dopamine oxidation currents in the nucleus accumbens and conditioned increases in motor activity in rats following repeated administration of d-amphetamine or cocaine. European Journal of Neuroscience, 10, 1113-1120.

Douglas, R. J., & Isaacson, R. L. (1964). Hippocampal lesions and activity. Psychonomic Science, 1, 187-188.

Douglas, R. J. (1967). The hippocampus and behavior. Psychological Bulletin, 67, 416-442.

Dudar, J. D., Whishaw, I. Q., & Szerb, J. C. (1979). Release of acetylcholine from the hippocampus of freely moving rats during sensory stimulation and running. Neuropharmacology, 18, 673-679.

Dugast, C., Suaud-Chagnay, M. F., & Gonon, F. (1994). Continuos in vivo monitoring of evoked dopamine release in the rat nucleus accumbens by amperometry. Neuroscience, 62, (3), 647-654.

Eichenbaum, H., Otto, T., & Cohen, N. J. (1994). Two functional components of the hippocampal memory system. Behavioural and Brain Sciences, 17, 449-518.

Emerich, D. F., & Walsh, T. J. (1990). Hyperactivity following intradentate injection of colchicine: A role for dopamine systems in the nucleus accumbens. Pharmacology, Biochemistry, and Behavior, 37, 149-154.

Fallon, J. H., & Moore, R. Y. (1978). Catecholamine innervation of the basal forebrain. IV. Topography of the dopamine projections to the basal forebrain and neostriatum. Journal of Comparative Neurology, 180, 353-368.

Fan, P., & Szerb, J. C. (1993). Effects of ammonium ions on synaptic transmission and on responses to quisqualate and N-methyl-D-aspartate in hippocampal CA1 pyramidal neurons in vitro. Brain Research, 632, 225-231.

Evenden, J. L., & Carli, M. (1985). The effects of 6-hydroxydopamine lesions of the nucleus accumbens and caudate nucleus of rats on feeding in a novel environment. Behavioural Brain Research, 1, 63-70.

Fibiger, H. C., Zis, A. P., & McGeer, E. G. (1973). Feeding and drinking deficits after 6-hydroxydopamine administration in the rat: similarities to the lateral hypothalamic syndrome. Brain Research, 55, 135-148.

Fink, J. S., & Smith, G. P. (1979a). Decreased locomotion and investigatory exploration after denervation of catecholamine terminal fields in the forebrain of rats. Journal of Comparative and Physiological Psychology, 93, 34-65.

Fink, J. S., & Smith, G. P. (1979b). L-Dopa repairs deficit in locomotor and investigatory exploration produced by denervation of catecholamine terminal fields in the forebrain of rats. Journal of Comparative and Physiological Psychology, 93, 66-73.

Fink, J. S., & Smith, G. P. (1980). Mesolimbicortical dopamine terminal fields are necessary for normal locomotor and investigatory exploration in rats. Brain Research, 199, 359-384.

Flicker, C., & Geyer, M. A. (1982). Behavior during hippocampal microinfusions. II. Muscarinic locomotor activation. Brain Research Reviews, 4, 105-127.

Freund, T. F., Powell, J. F., & Smith, D. (1984). Tyrosine hydroxylase-immunoreactive boutons in synaptic contact with identified striatonigral neurons, with particular reference to dendritic spines. Neuroscience, 13, 1189-1215.

Fuller, T., Russchen, F., & Price, J. (1987). Sources of presumptive glutamatergic/aspartergic afferents to the rat ventral striatopallidal region. Journal of Comparative Neurology, 258, 317-338.

Gerfen, C. R. (1992). The neostriatal mosaic: Multiple levels of compartmental organization. Trends in Neuroscience, 15, 133-139.

Giorguieff, M. F., Kemel, M. L., & Glowinski, J. (1977). Presynaptic effect of L-glutamic acid on dopamine release in rat striatal slices. Neuroscience Letters, 6, 77-78.

Glickman, S. E., & Schiff, B. B. (1967). A biological theory of reinforcement. Psychological Review, 74, (2), 81-109.

Glowinski, J., Chéramy, A., Romo, R., & Barbieto, L. (1988). Presynaptic regulation of dopaminergic transmission in the striatum. Cellular and Molecular Neurobiology, 8, 7-17.

Gold, L. H., Swerdlow, N. R., & Koob, G. F. (1988). The role of mesolimbic dopamine in conditioned locomotion produced by amphetamine. Behavioral Neuroscience, 102, 544-552.

Grace, A. A. (1991). Phasic versus tonic dopamine release and the modulation of dopamine system responsivity: a hypothesis for the etiology of schizophrenia. Neuroscience, 41, (1), 1-24.

Grace, A. A. (1992). The depolarization block hypothesis of neuroleptic action: implications for the etiology and treatment of schizophrenia. Journal of Neural Transmission [Suppl], 36, 91-131.

Grace, A. A. (1993). Cortical regulation of subcortical dopamine systems and its possible relevance to schizophrenia. Journal of Neural Transmission [GenSect], 91, 111-134.

Grace, A. A. (1995). The tonic/phasic model of dopamine system regulation: its relevance for understanding how stimulant abuse can alter basal ganglia function. Drug and Alcohol Dependence, 37, 111-129.

Grace, A. A., & Bunney, B. S. (1985). Opposing effects of striatonigral feedback pathways on midbrain dopamine cell activity. Brain Research, 333, 271-284.

Grace, A. A., Bunney, B. S., Moore, H., & Todd, C. L. (1997). Dopamine-cell depolarization block as a model for the therapeutic actions of antipsychotic drugs. Trends in Neuroscience, 20, 31-37.

Grant, L. E. & Jarrard, L. E. (1968). Functional dissociation within hippocampus. Brain Research, 10, 392-401.

Grastyan, E. (1959). The hippocampus and higher nervous activity. In, M. A. B. Brazier (Ed.), The central nervous system and behavior. New York, Josia Macy Foundation.

Gratton, A. & Wise, R. A. (1994). Drug- and behavior-associated changes in dopamine-related electrochemical signals during intravenous cocaine self-administration. Journal of Neuroscience, 14, (7), 4130-4146.

Gray, J. A., Feldon, J., Rawlins, J. N. P., Hemsely, D. R. & Smith, A. D. (1991). The neuropsychology of schizophrenia. Behavioral and Brain Sciences, 14, (1), 1-84.

Gray, J. A. & McNaughton, N. (1983). Comparison between the behavioral effects of septal and hippocampal lesions: A review. Neuroscience and Biobehaivoral Reviews, 7, 119-188.

Gray, J. A., Joseph, M. H., Hemsley, D. R., Young, A. M. J., Warburton, E. C., Boulengez, P., Grigoryan, G. A., Peter, S. L., Rawlins, J. N. P., Taib, C.-T., Yee, B. K., Cassaday, H., Wiener, I., Gal, G., Gusak, O., Joel, D., Shadach, E., Shalev, U., Tarrasch, R. & Feldon, J. (1995). The role of mesolimbic dopaminergic and retrohippocampal afferents to the nucleus accumbens in latent inhibition: implications for schizophrenia. Behavioural Brain Research, 71, 19-31.

Gray, N. S., Pilowsky, L. S., Gray, J. A. & Kerwin, R. W. (1995). Latent inhibition in drug-naive schizophrenics: relationship to duration of illness and dopamine D2 binding using SPET. Schizophrenia Research, 17, 95-107.

Graybiel, A. M. (1976). Input-Output anatomy of the basal ganglia. In: Symposium Lecture, Proceedings of the Society for Neuroscience, Toronto, Canada.

Graybiel, A. M. (1990). Neurotransmitters and neuromodulators in the basal ganglia. Trends in Neuroscience, 13, (7), 244-253.

Grenhoff, J., Tung, C. & Svensson, T. (1988). The excitatory amino acid antagonist kynurenate induces pacemaker-like firing of dopamine neurons in rat ventral tegmental area in vivo. Acta Physiologica Scandinavica, 134, (4), 567-568.

Groenewegen, H. J. & Russchen, F. T. (1984). Organization of the efferent projections of the nucleus accumbens to pallidal, hypothalamic, and mesencephalic structures: a tracing and immunohistochemical study in the cat. Journal of Comparative Neurology, 223, 347-367.

Groenewegen, H. J., Vermeulen-Van der Zee, E., Te Kortschot, A. & Witter, M. P. (1987). Organization of the projections from the subiculum to the ventral striatum of the rat. A study using anterograde transport of phaseolus vulgaris leucoagglutinin. Neuroscience, 23, 103-120.

Harden, D. G. & Grace, A. A. (1995). Hippocampal activation suppresses VTA dopamine cell firing: A potential role For hippocampal regulation of phasic DA release. Society for Neuroscience Abstract, 21, 1660.

Heimer, L. & Wilson, R. D. (1975). The subcortical projections of the allocortex. Similarities in the neural associations of the hippocampus, the pririform cortex, and the neocortex. In: Santini (ed.), Golgi Centennial Symposium: Perspectives in Neurology (pp. 177-193). Raven Press, New York.

Heimer, L. & Van Hoesen, G. (1979). The ventral striatum. In I. Divac and R. G. E. Oberg (Eds.), The neostriatum, Pergamon Press, New York, pp. 147-158.

Hemsley, D. R. (1987). An experimental psychological model for schizophrenia. In: H. Hafner, W.F. Gattaz & W. Janzavik (Eds.), Search for the Causes of Schizophrenia, Springer Verlag.

Hernandez, L. & Hoebel, B. G. (1988). Feeding and hypothalamic stimulation increase dopamine turnover in the accumbens. Physiology and Behavior, 44, 599-606.

Hitchcott, P. K. & Phillips, G. D. (1997). Amygdala and hippocampus control dissociable aspects of drug-associated conditioned rewards. Psychopharmacology, 131, 187-195.

Hollerman, J. R. & Schultz, W. (1996). Activity of dopamine neurons in learning a familiar task context. Society for Neuroscience Abstract, 22, 1388.

Holmes, L. J., Bozarth, M. A. & Wise, R. A. (1983). Circling from intracranial morphine applied to the ventral tegmental area in rats. Brain Research Bulletin, 11, 295-298.

Hooks, M. S. & Kalivas, P. W. (1995). The role of mesoaccumbens-pallidal circuitry in novelty-induced behavioral activation. Neuroscience, 64, 3 587-597.

Hornykiewicz, O. (1963). Die topsche localisation das verhalten von noradrenalin und dopamin (3-hydroytyramin) in der substantia nigra des normalen und Parkinson-kranken menschen. Wiener Klinische Wochenschrift, 57, 309-312.

Horvitz, J. C., Stewart, T. & Jacobs, B. L. (1997). Burst activity of ventral tegmental dopamine neurons is elicited by sensory stimuli in the awake cat. Brain Research, 759, 251-258.

Hughes, K. R. (1965). Dorsal and ventral hippocampus lesions and maze learning: influence of peroperative environment. Canadian Journal of Psychology, 19, 325-332.

Hyde, T., Csanove, M., Kleinman, J. E. & Weinberger, D. R. (1991). Neuroanatomical and neurochemical pathology in schizophrenia. In A. Tasman (Ed.): American Psychiatric Press Review of Psychiatry, vol 10, pp 7-23. APPA Press, Washington DC.

Imperato, A., Scrocco, M. G., Bacchi, S. & Angelucci, L. (1990). NMDA receptors and in vivo dopamine release in the nucleus accumbens and caudatus. European Journal of Pharmacology, 187, 555-556.

Imperato, A., Honoré, T. & Jensen, L. (1990). Dopamine release in the nucleus caudatus and in the nucleus accumbens is under glutamatergic control through non-NMDA receptors: a study in freely-moving rats. Brain Research, 530, 223-228.

Inglis, F. M., Day, J. C. & Fibiger, H. C. (1994). Enhanced acetylcholine release in hippocampus and cortex during the anticipation and consumption of a platable meal. Neuroscience, 62, (4), 1049-1056.

Inglis, F. M. & Fibiger, H. C. (1995). Increases in hippocampal and frontal cortical acetylcholine release associated with presentation of sensory stimuli. Neuroscience, 66, (1), 81-86.

Iravani, M. M., Muscat, R. & Kruk, Z. L. (1996). Comparison of somatodendritic and axon terminal dopamine release in the ventral tegmental area and the nucleus accumbens. Neuroscience, 70, (4), 1025-1037.

Jackson, D. M., Anden, N. & Dahlstrom, A. (1975). A functional effect of dopamine in the nucleus accumbens and in some other dopamine-rich parts of the rat brain. Psychopharmacology, 45, 139-149.

Jarrard, L. E. (1965). Hippocampal ablation and operant behavior in the rat. Psychonomic Science, 2, 115-118.

Jarrard, L. E. (1973). The hippocampus and motivation. Psychological Bulletin, 79, (1), 1-12.

Jarrard, L. E. (1968). Behavior of hippocampal lesioned rats in home cage and novel situations. Physiology and Behavior, 3, 65-70.

Jarrard, L. E. (1976). Anatomical and behavioral analysis of hippocampal cell fields in rats. Journal of Comparative and Physiological Psychology, 90, 1035-1050.

Jaskiw, G. E. & Weinberger, D. R. (1992). Dopamine and schizophrenia -- a cortically corrective approach. Seminars in the Neurosciences, 4, 179-188.

Jay, T. M. & Witter, M. P. (1991). Distribution of hippocampal CA1 and subicular efferents in the prefrontal cortex of the rat studied by means of anterograde transport of phaseolus vulgaris-leucoagglutinin. Journal of Comparative Neurology, 313, 574-586.

Jay, T. M., Glowinski, J. & Thierry, A. M. (1995). Inhibition of hippocampoprefrontal cortex excitatory responses by the mesocortical DA system. Neuroreport, 6, (14), 1845-1848.

Jenkins, R. B. & Groh, R. H. (1970). Mental symptoms in Parkinsonian patients treated with L-DOPA. Lancet, II, 177-179.

Jin, S. (1997). AMPA- and kainate-receptors differentially mediate excitatory amino acid-induced dopamine and acetylcholine release from rat striatal slices. Neuropharmacology, 36, (11-12), 1503-1510.

Johnson, K. M. & Jeng, Y.-J. (1991). Pharmacological evidence for N-methyl-D-aspartate receptors on nigrostriatal dopaminergic terminals. Canadian Journal of Physiology and Pharmacology, 69, 1416-1421.

Johnson, S. W., Seutin, V. & North, R. A. (1992). Burst firing in dopamine neurons induced by N-methyl-D-aspartate: role of electrogenic sodium pump. Science, 258, 665-667.

Johnson, S. W. & North, R. A. (1992). Opioids excite dopamine neurons by hyperpolarization of local interneurons. Journal of Neuroscience, 12, 483-488.

Johnson, L. R., Aylward, R. L. M., Hussain, Z. & Totterdell, S. (1994). Input from the amygdala to the rat nucleus accumbens: its relationship with tyrosine hydroxylase immunoreactivity and identified neurons. Neuroscience, 61, (4), 851-865.

Johnson, K., Chruchill, L., Klitenick, M. A., Hooks, M. S. & Kalivas, P. W. (1996). Involvement of the ventral tegmental area in locomotion elicited from the nucleus accumbens of ventral pallidum. Journal of Pharmacology and Experimental Therapeutics, 277, 1122-1131.

Joyce, E. M. & Iversen, S. D. (1979). The effect of morphine applied locally to mesencephalic dopamine cell bodies on spontaneous motor activity in the rat. Neuroscience Letters, 14, 207-212.

Kalivas, P. W., Widerlov, E., Stanley, D., Breese, G. & Prange, A. J. J. (1983). Enkephalin action on the mesolimbic system: A dopamine-dependent and a dopamine-independent increase in locomotor activity. Journal of Pharmacology and Experimental Therapeutics, 227, 229-237.

Kalivas, P. W., Duffy, P. & Barrow, J. (1989). Regulation of the mesocorticolimbic dopamine system by glutamic acid receptor subtypes. Journal of Pharmacology and Experimental Therapeutics, 251, 378-387.

Kalivas, P. W. & Duffy, P. (1990). The effect of acute and daily cocaine treatment on extracellular dopamine in the nucleus accumbens. Synapse, 5, 48-58.

Kane, J. M. & Leiberman, J. (1987). Maintenance pharmacotherapy in schizophrenia. In: H. Y. Meltzer (Ed.), Psychopharmacology, the Third Generation of Progress: the Emergence of Molecular Biology and Biological Psychiatry, pp 1103-1109. Raven Press, New York.

Karreman, M., Westerink, B. & Moghaddam, B. (1996). Excitatory amino acid receptors in the ventral tegmental area regulate dopamine release in the striatum. Journal of Neurochemistry, 67, 601-607.

Karreman, M. & Moghaddam, B. (1996). The prefrontal cortex controls release of dopamine in the medial striatum: An effect mediated by the ventral tegmental area. Journal of Neurochemistry, 66, (2), 589-598.

Keefe, K., Zigmond, M. & Abercrombie, E. (1992). Extracellular dopamine in striatum: Influence of nerve impulse activity in medial forebrain bundle and local glutamatergic input. Neuroscience, 47, (2), 325-332.

Kelley, A. E. & Domesick, V. B. (1982). The distribution of the projection from the hippocampal formation to the nucleus accumbens in the rat: An anterograde- and retrograde-horseradish peroxidase study. Neuroscience, 7, (12), 2321-2335.

Kelley, A. E., Domesick, V. B. & Nauta, W. J. H. (1982). The amygdalostriatal projection in the rat - an anatomical study by anterograde and retrograde tracing methods. Neuroscience, 7, 615-6630.

Kelley, A. E. & Stinus, L. (1985). Disappearance of hoarding behavior and 6-hydroxydopamine lesions of the mesolimbic dopamine neurons and its reinstatement with L-DOPA. Behavioural Neuroscience, 99, 531-545.

Kelly, P. H., Seviour, P. W. & Iversen, S. D. (1975). Amphetamine and apomorphine responses in the rat following 6-OHDA lesions of the nucleus accumbens septi and corpus striatum. Brain Research, 94, 507-522.

Kelly, P. H. & Iversen, S. D. (1976). Selective 6-OHDA induced destruction of mesolimbic dopamine neurons: Abolition of psychostimulant-induced locomotor activity in rats. European Journal of Pharmacology, 40, 45-56.

Kelly, P. H. & Roberts, D. C. S. (1983). Effects of amphetamine and apomorphine on locomotor activity after 6-OHDA and electrolytic lesions of the nucleus accumbens. Pharmacology Biochemistry and Behavior, 19, 137-143.

Kimble, D. P. (1968). Hippocampus and internal inhibition. Psychological Bulletin, 70, (5), 285-295.

Kimble, D. P. (1963). The effects of bilateral hippocampal lesions in rats. Journal of Comparative and Physiological Psychology, 56, (1), 273-283.

Kita, H. & Kitai, S. T. (1990). Amygdaloid projections of the frontal cortex and striatum. Journal of Comparative Neurology, 298, 40-49.

Kita, T., Okamoto, M. & Nakashima, T. (1992). Nicotine-induced sensitization to ambulatory stimulant effect produced by daily administration into the ventral tegmental area and the nucleus accumbens. Life Sciences, 50, 583-590.

Kiyatkin, E. A. & Gratton, A. (1994). Electrochemical monitoring of extracellular dopamine in nucleus accumbens of rats lever-pressing for food. Brain Research, 652, 225-234.

Klarner, A., Koch, M. & Schnitzler, H.-U. (1998). Induction of FOS-protein in the forebrain and disruption of sensorimotor gating following N-methyl-D-aspartate infusion into the ventral hippocampus of the rat. Neuroscience, 84, (2), 443-452.

Klitenick, M. A., DeWitte, P. & Kalivas, P. W. (1992). Regulation of somatodendritic dopamine release in the ventral tegmental area by opioids and GABA: An in vivo microdialysis study. Journal of Neuroscience, 12, 2623-2632.

Klitenick, M. A. & Kalivas, P. W. (1994). Behavioral and neurochemical studies of opioid effects in the pedunculopontine nucleus and mediodorsal thalamus. Journal of Pharmacology and Experimental Therapeutics, 269, 437-448.

Knable, M. B., Hyde, T. M., Herman, M. M., Carter, J. M., Begelow, L. & Kleinman, J. E. (1994). Quantitative autoradiography of dopamine-D1 receptors, D2 receptors, and dopamine uptake sites in postmortem striatal specimens from schizophrenic patients. Biological Psychiatry, 36, 827-835.

Koob, G. F., Riley, S. J., Smith, S. C. & Robbins, T. W. (1978). Effects of 6-hydroxydopamine lesions of the nucleus accumbens septi and olfactory tubercle on feeding, locomotor activity, and amphetamine anorexia. Journal of Comparative and Physiological Psychology, 92, 917-927.

Koob, G. F., Stinus, L. & Le Moal, M. (1981). Hyperactivity and hypoactivity produced by lesions to the mesolimbic dopamine system. Behavioural Brain Research, 3, 341-359.

Kovelman, J. A. & Scheibel, A. B. (1984). A neurohistological correlate of schizophrenia. Biological Psychiatry, 19, 160-1617.

Kuczenski, R. & Segal, D. (1989). Concomitant characterization of behavioral and striatal neurotransmitter response to amphetamine using in vivo microdialysis. Journal of Neuroscience, 9, 2051-2065.

Laroche, S., Jay, T. M. & Thierry, A. M. (1990). Long-term potentiation in the prefrontal cortex following stimulation of the hippocampal CA1/subicular region. Neuroscience Letters, 114, 184-190.

Latimer, L. G., Duffy, P. & Kalivas, P. W. (1987). Mu opioid receptor involvement in enkephalin activation of dopamine neurons in the ventral tegmental area. Journal of Pharmacology and Experimental Therapeutics, 241, 328-337.

Legault, M., Rossetti, Z. & Wise, R. A. (1995). The effect of NMDA injections into the ventral subiculum on nucleus accumbens dopamine. Society for Neuroscience Abstract, 21, 368.

Legault, M. & Wise, R. A. (1999). Injections of N-methyl-D-aspartate into the ventral hippocampus increase extracellular dopamine in the ventral tegmental area and nucleus accumbens. Synapse, 31, 241-249.

Legault, M., Rompré, P.-P. & Wise, R. A. (1998). Stimulation of the ventral subiculum elevates nucleus accumbens dopamine by increasing impulse-flow through the ventral tegmental area. Society for Neuroscience Abstracts, 24, 937.

Leiberman, J. A., Kane, J. M. & Alvir, J. (1987). Provocative tests with psychostimulant drugs in schizophrenia. Psychopharmacology, 91, 415-433.

Leviel, V., Gobert, A. & Guibert, B. (1990). The glutamate-mediated release of dopamine in the rat striatum: further characterization of the dual excitatory-inhibitory function. Neuroscience, 39, (2), 305-312.

Lipska, B. K., Jaskiw, G. E., Karoum, F., Phillips, I., Kleinman, J. E. & Weinberger, D. R. (1991). Dorsal hippocampal lesion does not affect dopaminergic indicies in the basal ganglia. Pharmacology, Biochemistry, and Behavior, 40, 181-184.

Lipska, B. K., Jaskiw, G. E., Chrapusta, S., Karoum, F. & Weinberger, D. R. (1992). Ibotenic acid lesion of the ventral hippocampus differentially affects dopamine and its metabolites in the nucleus accumbens and prefrontal cortex in the rat. Brain Research, 55, 1-6.

Lipska, B. K. & Weinberger, D. R. (1993). Delayed effects of neonatal hippocampal damage on haloperidol-induced catalepsy and apomorphine-induced stereotypic behaviors in the rat. Developmental Brain Research, 75, 213-222.

Lipska, B. K. & Weinberger, D. R. (1994). Subchronic treatment with haloperidol or clozapine in rats with neonatal excitotoxic hippocampal damage. Neuropsychopharmacology, 10, 199-205.

Lipska, B. K., Chrapusta, S. J., Egan, M. F. & Weinberger, D. R. (1995). Neonatal excitotoxic ventral hippocampal damage alters dopamine response to mild repeated stress and to chronic haloperidol. Synapse, 20, 125-130.

Lipska, B. K., al-Amin, H. A. & Weinberger, D. R. (1998). Excitotoxic lesion of the rat medial prefrontal cortex. Effects on abnormal behaviors associated with neonatal hippocampal damage. Neuropsychopharmacology, 19, 451-464.

Ljungberg, T. & Ungerstedt, U. (1976). Reinstatement of eating by dopamine agonists in aphagic dopamine denervated rats. Physiology and Behavior, 16, (3), 277-283.

Ljungberg, T., Apicella, P. & Schultz, W. (1992). Responses of monkey dopamine neurons during learning of behavioral reactions. Journal of Neurophysiology, 67, 145-163.

Lonart, G. & Zigmond, M. (1991). High glutamate concentrations evoke Ca++-independent dopamine release from striatal slices: A possible role of reverse dopamine transport. Journal of Pharmacology and Experimental Therapeutics, 256, (3), 1132-1138.

Lopes da Silva, F. H., Arnolds, D. E. A. T. & Neijt, H. C. (1984). A functional link between the limbic cortex and ventral striatum: Physiology of the subiculum accumbens pathway. Experimental Brain Research, 55, 205-214.

Lorenz, K. (1950). An energy model of instinctive actions. Symposia of the society for experimental biology. Cambridge University Press.

Lubow, R. E. & Moore, A. U. (1959). Latent inhibition: the effect of non-reinforced pre-exposure to the conditioned stimulus. Journal of Comparative and Physiological Psychology, 52, 415-419.

Lynch, G., Ballentine, P. & Campbell, B. A. (1969). Potentiation of behavioural arousal following cortical damage and subsequent recovery. Experimental Neurology, 23, 195-206.

Lynch, G., Ballentine, P. & Campbell, B. A. (1971). Differential rates of recovery following neuronal frontal cortical lesions in rats. Physiology and Behavior, 7, 737-741.

Lynd-Balta, E. & Haber, S. E. (1994). Primate striatonigral projections: a comparison of the sensorimotor-related striatum and the ventral striatum. Journal of Comparative Neurology, 345, 562-578.

Kalivas, P. W., Widerlov, E., Stanley, D., Breese, G. & Prange, A. J. J. (1983). Enkephalin action on the mesolimbic system: A dopamine-dependent and a dopamine-independent increase in locomotor activity. Journal of Pharmacology and Experimental Therapeutics, 227, 229-237.

Kalivas, P. W., Duffy, P. & Barrow, J. (1989). Regulation of the mesocorticolimbic dopamine system by glutamic acid receptor subtypes. Journal of Pharmacology and Experimental Therapeutics, 251, 378-387.

Kalivas, P. W. & Duffy, P. (1990). The effect of acute and daily cocaine treatment on extracellular dopamine in the nucleus accumbens. Synapse, 5, 48-58.

Kane, J. M. & Leiberman, J. (1987). Maintenance pharmacotherapy in schizophrenia. In: H. Y. Meltzer (Ed.), Psychopharmacology, the Third Generation of Progress: the Emergence of Molecular Biology and Biological Psychiatry, pp 1103-1109. Raven Press, New York.

Karreman, M., Westerink, B. & Moghaddam, B. (1996). Excitatory amino acid receptors in the ventral tegmental area regulate dopamine release in the striatum. Journal of Neurochemistry, 67, 601-607.

Karreman, M. & Moghaddam, B. (1996). The prefrontal cortex controls release of dopamine in the medial striatum: An effect mediated by the ventral tegmental area. Journal of Neurochemistry, 66, (2), 589-598.

Keefe, K., Zigmond, M. & Abercrombie, E. (1992). Extracellular dopamine in striatum: Influence of nerve impulse activity in medial forebrain bundle and local glutamatergic input. Neuroscience, 47, (2), 325-332.

Kelley, A. E. & Domesick, V. B. (1982). The distribution of the projection from the hippocampal formation to the nucleus accumbens in the rat: An anterograde- and retrograde-horseradish peroxidase study. Neuroscience, 7, (12), 2321-2335.

Kelley, A. E., Domesick, V. B. & Nauta, W. J. H. (1982). The amygdalostriatal projection in the rat - an anatomical study by anterograde and retrograde tracing methods. Neuroscience, 7, 615-6630.

Kelley, A. E. & Stinus, L. (1985). Disappearance of hoarding behavior and 6-hydroxydopamine lesions of the mesolimbic dopamine neurons and its reinstatement with L-DOPA. Behavioural Neuroscience, 99, 531-545.

Kelly, P. H., Seviour, P. W. & Iversen, S. D. (1975). Amphetamine and apomorphine responses in the rat following 6-OHDA lesions of the nucleus accumbens septi and corpus striatum. Brain Research, 94, 507-522.

Kelly, P. H. & Iversen, S. D. (1976). Selective 6-OHDA induced destruction of mesolimbic dopamine neurons: Abolition of psychostimulant-induced locomotor activity in rats. European Journal of Pharmacology, 40, 45-56.

Kelly, P. H. & Roberts, D. C. S. (1983). Effects of amphetamine and apomorphine on locomotor activity after 6-OHDA and electrolytic lesions of the nucleus accumbens. Pharmacology Biochemistry and Behavior, 19, 137-143.

Kimble, D. P. (1968). Hippocampus and internal inhibition. Psychological Bulletin, 70, (5), 285-295.

Kimble, D. P. (1963). The effects of bilateral hippocampal lesions in rats. Journal of Comparative and Physiological Psychology, 56, (1), 273-283.

Kita, H. & Kitai, S. T. (1990). Amygdaloid projections of the frontal cortex and striatum. Journal of Comparative Neurology, 298, 40-49.

Kiyatkin, E. A. & Gratton, A. (1994). Electrochemical monitoring of extracellular dopamine in nucleus accumbens of rats lever-pressing for food. Brain Research, 652, 225-234.

Klarner, A., Koch, M. & Schnitzler, H.-U. (1998). Induction of FOS-protein in the forebrain and disruption of sensorimotor gating following N-methyl-D-aspartate infusion into the ventral hippocampus of the rat. Neuroscience, 84, (2), 443-452.

Klitenick, M. A., DeWitte, P. & Kalivas, P. W. (1992). Regulation of somatodendritic dopamine release in the ventral tegmental area by opioids and GABA: An in vivo microdialysis study. Journal of Neuroscience, 12, 2623-2632.

Klitenick, M. A. & Kalivas, P. W. (1994). Behavioral and neurochemical studies of opioid effects in the pedunculopontine nucleus and mediodorsal thalamus. Journal of Pharmacology and Experimental Therapeutics, 269, 437-448.

Knable, M. B., Hyde, T. M., Herman, M. M., Carter, J. M., Begelow, L. & Kleinman, J. E. (1994). Quantitative autoradiography of dopamine-D1 receptors, D2 receptors, and dopamine uptake sites in postmortem striatal specimens from schizophrenic patients. Biological Psychiatry, 36, 827-835.

Koob, G. F., Riley, S. J., Smith, S. C. & Robbins, T. W. (1978). Effects of 6-hydroxydopamine lesions of the nucleus accumbens septi and olfactory tubercle on feeding, locomotor activity, and amphetamine anorexia. Journal of Comparative and Physiological Psychology, 92, 917-927.

Koob, G. F., Stinus, L. & Le Moal, M. (1981). Hyperactivity and hypoactivity produced by lesions to the mesolimbic dopamine system. Behavioural Brain Research, 3, 341-359.

Kovelman, J. A. & Scheibel, A. B. (1984). A neurohistological correlate of schizophrenia. Biological Psychiatry, 19, 160-1617.

Kuczenski, R. & Segal, D. (1989). Concomitant characterization of behavioral and striatal neurotransmitter response to amphetamine using in vivo microdialysis. Journal of Neuroscience, 9, 2051-2065.

Laroche, S., Jay, T. M. & Thierry, A. M. (1990). Long-term potentiation in the prefrontal cortex following stimulation of the hippocampal CA1/subicular region. Neuroscience Letters, 114, 184-190.

Latimer, L. G., Duffy, P. & Kalivas, P. W. (1987). Mu opioid receptor involvement in enkephalin activation of dopamine neurons in the ventral tegmental area. Journal of Pharmacology and Experimental Therapeutics, 241, 328-337.

Legault, M., Rossetti, Z. & Wise, R. A. (1995). The effect of NMDA injections into the ventral subiculum on nucleus accumbens dopamine. Society for Neuroscience Abstract, 21, 368.

Legault, M. & Wise, R. A. (1999). Injections of N-methyl-D-aspartate into the ventral hippocampus increase extracellular dopamine in the ventral tegmental area and nucleus accumbens. Synapse, 31, 241-249.

Legault, M., Rompré, P.-P. & Wise, R. A. (1998). Stimulation of the ventral subiculum elevates nucleus accumbens dopamine by increasing impulse-flow through the ventral tegmental area. Society for Neuroscience Abstracts, 24, 937.

Leiberman, J. A., Kane, J. M. & Alvir, J. (1987). Provocative tests with psychostimulant drugs in schizophrenia. Psychopharmacology, 91, 415-433.

Leviel, V., Gobert, A. & Guibert, B. (1990). The glutamate-mediated release of dopamine in the rat striatum: further characterization of the dual excitatory-inhibitory function. Neuroscience, 39, (2), 305-312.

Lipska, B. K., Jaskiw, G. E., Karoum, F., Phillips, I., Kleinman, J. E. & Weinberger, D. R. (1991). Dorsal hippocampal lesion does not affect dopaminergic indicies in the basal ganglia. Pharmacology, Biochemistry, and Behavior, 40, 181-184.

Lipska, B. K., Jaskiw, G. E., Chrapusta, S., Karoum, F. & Weinberger, D. R. (1992). Ibotenic acid lesion of the ventral hippocampus differentially affects dopamine and its metabolites in the nucleus accumbens and prefrontal cortex in the rat. Brain Research, 55, 1-6.

Lipska, B. K. & Weinberger, D. R. (1993). Delayed effects of neonatal hippocampal damage on haloperidol-induced catalepsy and apomorphine-induced stereotypic behaviors in the rat. Developmental Brain Research, 75, 213-222.

Lipska, B. K. & Weinberger, D. R. (1994). Subchronic treatment with haloperidol or clozapine in rats with neonatal excitotoxic hippocampal damage. Neuropsychopharmacology, 10, 199-205.

Lipska, B. K., Chrapusta, S. J., Egan, M. F. & Weinberger, D. R. (1995). Neonatal excitotoxic ventral hippocampal damage alters dopamine response to mild repeated stress and to chronic haloperidol. Synapse, 20, 125-130.

Lipska, B. K., al-Amin, H. A. & Weinberger, D. R. (1998). Excitotoxic lesion of the rat medial prefrontal cortex. Effects on abnormal behaviors associated with neonatal hippocampal damage. Neuropsychopharmacology, 19, 451-464.

Ljungberg, T. & Ungerstedt, U. (1976). Reinstatement of eating by dopamine agonists in aphagic dopamine denervated rats. Physiology and Behavior, 16, (3), 277-283.

Ljungberg, T., Apicella, P. & Schultz, W. (1992). Responses of monkey dopamine neurons during learning of behavioral reactions. Journal of Neurophysiology, 67, 145-163.

Lonart, G. & Zigmond, M. (1991). High glutamate concentrations evoke Ca++-independent dopamine release from striatal slices: A possible role of reverse dopamine transport. Journal of Pharmacology and Experimental Therapeutics, 256, (3), 1132-1138.

Lopes da Silva, F. H., Arnolds, D. E. A. T. & Neijt, H. C. (1984). A functional link between the limbic cortex and ventral striatum: Physiology of the subiculum accumbens pathway. Experimental Brain Research, 55, 205-214.

Lorenz, K. (1950). An energy model of instinctive actions. Symposia of the society for experimental biology. Cambridge University Press.

Lubow, R. E. & Moore, A. U. (1959). Latent inhibition: the effect of non-reinforced pre-exposure to the conditioned stimulus. Journal of Comparative and Physiological Psychology, 52, 415-419.

Lynch, G., Ballentine, P. & Campbell, B. A. (1969). Potentiation of behavioural arousal following cortical damage and subsequent recovery. Experimental Neurology, 23, 195-206.

Lynd-Balta, E. & Haber, S. E. (1994). Primate striatonigral projections: a comparison of the sensorimotor-related striatum and the ventral striatum. Journal of Comparative Neurology, 345, 562-578.

MacLean, P. D. (1957). Chemical and electrical stimulation of hippocampus in unrestrained animals. II. Behavioral findings. Archives of Neurology and Psychiatry, 78, 128-142.

Maldonado-Irizarry, C. S. & Kelley, A. E. (1995). Excitatory amino acid receptors within nucleus accumbens subregions differentially mediate spatial learning in the rat. Behavioural Pharmacology, 6, 527-539.

Marien, M., Brien, J. & Jhamandas, K. (1983). Regional release of [3H]dopamine from rat brain in vitro: effects of opiates on release induced by potassium, nicotine, and L-glutamic acid. Canadian Journal of Physiology and Pharmacology, 61, 43-60.

Marshall, J. F., Richardson, J. S. & Teitelbaum, P. (1974). Nigrostriatal bundle damage and the lateral hypothalamic syndrome. Journal of Comparative and Physiological Psychology, 87, 808-830.

McDonald, A. J. (1991). Topographical organization of amygdaloid projections to the caudatoputamen, nucleus accumbens, and related striatal-like areas of the rat brain. Neuroscience, 44, (1), 15-33.

McGeorge, A. J. & Faull, R. L. M. (1989). The organization of the projections from the cerebral cortex to the striatum in the rat. Neuroscience, 29, (3), 503-537.

Meredith, G. E., Wouterlood, F. G. & Pattisleanno, A. (1990). Hippocampal fibers make synaptic contacts with glutamate decarboxylase-immunoreactive neurons in the rat nucleus accumbens. Brain Research, 513, 329-334.

Mereu, G., Costa, E., Armstrong, D. M. & Vicini, S. (1991). Glutamate receptor subtypes mediate excitatory synaptic currents of dopamine neurons in midbrain slices. Journal of Neuroscience, 11, 1359-1366.

Mirenowicz, J. & Schultz, W. (1994). Importance of unpredictedness for reward responses in primate dopamine neurons. Journal of Neurophysiology, 72, 1024-1027.

Mittleman, G., LeDuc, P. A. & Whishaw, I. Q. (1993). The role of D1 and D2 receptors in the heightened locomotion induced by direct and indirect dopamine agonists in rats with hippocampal damage: an animal model of schizophrenia. Behavioural Brain Research, 55, 253-267.

Mogenson, G. J., Wu, M. & Manchanda, S. K. (1979). Locomotor activity initiated by microinfusions of picrotoxin into the ventral tegmental area. Brain Research, 161, 311-319.

Mogenson, G. J., Jones, D. L. & Yim, C. Y. (1980). From motivation to action: Functional interface between the limbic system and the motor system. Progress in Neurobiology, 14, 69-97.

Mogenson, G. J., Swanson, L. W. & Wu, M. (1983). Neural projections from nucleus accumbens to globus pallidus, substantia innominata, and lateral preoptic-lateral

hypothalamic area; an anatomical and electrophysiological investigation in the rat. Journal of Neuroscience, 3, (1), 189-202.

Mogenson, G. J. & Nielsen, M. A. (1984a). A study of the contribution of hippocampal-accumbens-subpallidal projections to locomotor activity. Behavioral Neural Biology, 42, 38-51.

Mogenson, G. J. & Nielsen, M. (19984b). Neurophamacological evidence to suggest that the nucleus accumbens and subpallidal region contribute to exploratory locomotion. Behavioral and Neural Biology, 42, 52-60.

Moghaddam, B., Gruen, R., Roth, R., Bunney, B. & Adams, R. (1990). Effect of L-glutamate on the release of striatal dopamine: in vivo dialysis and electrochemical studies. Brain Research, 518, 55-60.

Moghaddam, B. & Bunney, B. S. (1990). Acute effects of typical and atypical antipsychotic drugs on the release of dopamine from prefrontal cortex, nucleus accumbens, and striatum of the rat: an in vivo microdialysis study. Journal of Neurochemistry, 54, 1755-1760.

Morari, M., O'Connor, W. T., Ungerstedt, U. & Fuxe, K. (1993). N-methyl-D-aspartic acid differentially regulates extracellular dopamine, GABA, and glutamate levels in the dorsolateral neostriatum of the halothane-anesthetized rat: an in vivo microdialysis study. Journal of Neurochemistry, 60, 1884-1893.

Morari, M., O'Connor, W., Ungerstedt, U., Bianchi, C. & Fuxe, K. (1996b). Functional neuroanatomy of the nigrostriatal and striatonigral pathways as studied with dual probe

microdialysis in the awake rat - II. Evidence for striatal N-methyl-D-aspartate receptor regulation of striatonigral GABAergic transmission and motor function. Neuroscience, 72, (1), 89-97.

Moser, E., Moser, M.-B. & Andersen, P. (1993). Spatial learning impairment parallels the magnitude of dorsal hippocampal lesions, but is hardly present following ventral lesions. Journal of Neuroscience, 13, 3916-3925.

Moser, E. (1995). Learning-related changes in hippocampal field potentials. Behavioural Brain Research, 71, 11-18.

Mulder, A. B., Gijsberti Hodenpijl, M. & Silva, L. d. (1998). Electrophysiology of the hippocampal and amygdaloid projections to the nucleus accumbens of the rat: Convergence, segregation, and interaction of inputs. Journal of Neuroscience, 18, (13), 5095-5102.

Murase, S., Grenhoff, J., Chouvet, G., Gonon, F. G. & Svensson, T. H. (1993). Prefrontal cortex regulates burst firing and transmitter release in rat mesolimbic dopamine neurons studied in vivo. Neuroscience Letters, 157, 53-56.

Museo, E. & Wise, R. A. (1990). Locomotion induced by ventral tegmental microinjections of a nicotinic agonist. Pharmacology Biochemistry and Behavior, 35, 735-737.

Nauta, W. J. H. & Domesick, V. B. (1978). Crossroads of limbic and striatal circuitry: Hypothalamo-nigral connections. In. K. E. Livingston and O. Hornykiewicz (Eds.), Limbic Mechanisms, Plenum, New York.

Nauta, W. J. H., Smith, G. P., Faull, R. L. M. & Domesick, V. B. (1978). Efferent connections and nigral afferents of the nucleus accumbens septi in the rat. Neuroscience, 3, 385-401.

Nauta, H. J. W. (1986). The relationship of the basal ganglia to the limbic system. In P.J. Vinken, G. W. Bruyn, and H. L. Klawans (Eds.), Handbook of clinical neurology, vol 5 (49): Extrapyramidal disorders. Elsevier Science.

Nelson, M. D., Saykin, A. J., Flashman, L. A. & Riordan, H. J. (1998). Hippocampal volume reduction in schizophrenia as assessed by magnetic resonance imaging: a meta-analytic study. Archives of General Psychiatry, 55, 433-440.

Nieoullon, A., Chéramy, A. & Glowinski, J. (1978). Release of dopamine evoked by electrical stimulation of the motor and visual areas of the cerebral cortex in both caudate nuclei and in the substantia nigra. Brain Research, 145, 69-83.

O'Donnell, P. & Grace, A. A. (1995). Synaptic interactions among excitatory afferents to nucleus accumbens neurons: Hippocampal gating of prefrontal cortical input. Journal of Neuroscience, 15, (5), 3622-3639.

O'Keefe, J. & Nadel, L. (1978). The Hippocampus as a Cognitive Map. Clarendon, Oxford.,

Oakman, S. A., Faris, P. L., Kerr, P. E., Cozzari, C. & Hartman, B. K. (1995). Distribution of pontomesencephalic cholinergic neurons projecting to substantia nigra

differs significantly from those projecting to ventral tegmental area. Journal of Neuroscience, 15, 5859-5869.

Papez, J. W. A. (1937). A proposed mechanism of emotion. Archives of Neurology and Psychiatry, 38, 725-743.

Pavlov, I. P. (1927). Conditioned Reflexes. Oxford University press, Oxford.,

Pennartz, C. M. A. & Kitai, S. T. (1991). Hippocampal inputs to identified neurons in an in vitro slice preparation of the rat nucleus accumbens: Evidence for feed-forward inhibition. Journal of Neuroscience, 11, 2838-2847.

Pfaus, J. G., Damsma, G., Wenkstern, D. & Fibiger, H. C. (1995). Sexual activity increases dopamine transmission in the nucleus accumbens and striatum of female rats. Brain Research, 693, 21-30.

Phillips, A. G., Atkinson, L. J., Blackburn, J. R. & Blaha, C. D. (1993). Increased extracellular dopamine in the nucleus accumbens of the rat elicited by a conditioned stimulus for food: an electrochemical study. Canadian Journal of Physiology and Pharmacology, 71, 387-393.

Phillipson, O. T. & Griffiths, A. C. (1985). The topographic order of inputs to nucleus accumbens in the rat. Neuroscience, 16, (2), 275-296.

Pickel, V. M., Beckley, S. C., Joh, T. H. & Reis, D. J. (1981). Ultrastructural immunocytochemical localization of tyrosine hydroxylase in the neostriatum. Brain Research, 225, 373-385.

Pierce, R. C., Crawford, C. A., Nonneman, A. J., Mattingly, B. A. & Bardo, M. T. (1990). Effect of forebrain dopamine depletion on novelty-induced place preference behavior in rats. Pharmacology, Biochemistry, and Behavior, 36, 321-325.

Pijnenburg, A. J. J. & van Rossum, J. M. (1973). Stimulation of locomotor activity following injection of dopamine into the nucleus accumbens. Journal of Pharmacy and Pharmacology, 25, 1003-1005.

Post, R. M., Fink, E., Carpenter, W. T. & Goodwin, F. K. (1975). Cerebrospinal fluid amine metabolites in acute schizophrenia. Archives of General Psychiatry, 32, 1063-1069.

Pulvirenti, L., Berrier, R., Kreitfeldt, M. & Koob, G. F. (1994). Modulation of locomotor activity by NMDA receptors in the nucleus accumbens core and shell regions of the rat. Brain Research, 664, 231-236.

Radhakishun, F. S., Van Ree, J. M. & Westerink, B. H. C. (1988). Scheduled eating increases dopamine release in the nucleus accumbens of food-deprived rats as assessed with on-line brain microdialysis. Neuroscience Letters, 85, 351-356.

Rebec, G. V., Christensen, J. R., Guerra, C. & Bardo, M. T. (1997). Regional and temporal differences in real-time dopamine efflux in the nucleus accumbens during free-choice novelty. Brain Research, 21, 61-67.

Reinstein, D. K., Hannigan, J. H. J. & Isaacson, R. L. (1982). Time course of certain behavioral changes after hippocampal damage and their alteration by dopaminergic

intervention into nucleus accumbens. Pharmacology, Biochemistry, and Behavior, 17, 193-202.

Richardson, N. R. & Gratton, A. (1996). Behavior-relevant changes in nucleus accumbens dopamine transmission elicited by food reinforcement: an electrochemical study in rat. Journal of Neuroscience, 16, 8160-8169.

Robbins, T. W. (1976). Relationship between reward-enhancing and stereotypical effects of psychomotor stimulant drugs. Nature, 264, 57-59.

Robbins, T. W. (1990). The case for frontostriatal dysfunction in schizophrenia. Schizophrenia Bulletin, 16, 391-402.

Robbins, T. W. & Everitt, B. J. (1992). Functions of dopamine in the dorsal and ventral striatum. Seminars in the Neurosciences, 4, 119-127.

Roberts, P. J. & Sharif, N. A. (1978). Effects of L-glutamate and related amino acids upon the release of [3H]dopamine from rat striatal slices. Brain Research, 157, 391-395.

Roberts, P. J. & Anderson, S. D. (1979). Stimulatory effect of L-glutamate and related amino acids on [3H]dopamine release from rat striatum: an in vitro model for glutamate actions. Journal of Neurochemistry, 32, 1539-1545.

Robinson, T. E., Jurson, P. A., Bennet, J. A. & Bentgen, K. M. (1988). Persistent sensitization of dopamine neurotransmission in ventral striatum (nucleus accumbens) produced by prior experience with (+)-amphetamine: a microdialysis study in freely moving rats. Brain Research, 462, 211-222.

Romo, R., Chéramy, A., Godeheu, G. & Glowinski, J. (1986a). In vivo presynaptic control of dopamine release in the cat caudate nucleus I. Opposite changes in neuronal activity and release evoked from thalamic motor nuclei. Neuroscience, 19, (4), 1067-1079.

Romo, R., Chéramy, A., Godeheu, G. & Glowisnki, J. (1986b). In vivo presynaptic control of dopamine release in the cat caudate nucleus III. Further evidence for the implication of corticostriatal glutamatergic neurons. Neuroscience, 19, (4), 1091-1099.

Romo, R., Scarnati, E. & Schultz, W. (1992). Role of primate basal ganglia and frontal cortex in the internal generation of movements: comparisons in striatal neurons activated during stimulus-induced movement initiation and execution. Experimental Brain Research, 91, 385-395.

Rossetti, Z., L., Marcangione, C. & Wise, R., A. (1998). Increase of extracellular glutamate and expression of Fos-like immunoreactivity in the ventral tegmental area in response to electrical stimulation of the prefrontal cortex. Journal of Neurochemistry, 70, (4), 1503-1511.

Saigusa, T., Tuinstra, T., Koshikawa, N. & Cools, A. R. (1999). High and low responders to novelty: effects of a catecholamine synthesis inhibitor on novelty-induced changes in behaviour and release of accumbal dopamine. Neuroscience, 88, (4), 1153-1163.

Schmelzeis, M. C. & Mittleman, G. (1996). The hippocampus and reward: Effects of hippocampal lesions on progressive-ratio responding. Behavioural Neuroscience, 110, 1049-1066.

Schneirla, T. C. (1959). An evolutionary and developmental theory of biphasic processes underlying approach and withdrawal. In M. R. Jones (ed.), Nebraska symposium on motivation. pp. 1-42. University of Nebraska Press, Lincoln, Na.

Schultz, W. & Romo, R. (1990). Dopamine neurons of the monkey midbrain: Contingencies of responses to stimuli eliciting immediate behavioral reactions. Journal of Neurophysiology, 63, 607-624.

Schultz, W., Apicella, P. & Ljungberg, T. (1993). Responses of monkey dopamine neurons to reward and conditioned stimuli during successive steps of learning a delayed response task. Journal of Neuroscience, 13, 900-913.

Schultz, W. (1998). Predictive reward signal of dopamine neurons. Journal of Neurophysiology, 80, 1-27.

Sedvall, G. (1990). PET imaging of dopamine receptors in human basal ganglia: relevance to mental illness. Trends in Neuroscience, 13, 302-308.

Seeman, P. (1987). Dopamine receptors and the dopamine hypothesis of schizophrenia. Synapse, 1, 133-152.

Sesack, S. R., Deutch, A. Y., Roth, R. H. & Bunney, B. S. (1989). Topographical organization of the efferent projections of the medial prefrontal cortex in the rat: an

anterograde tract-tracing study with phaseolus vulgaris leucoagglutinin. Journal of Neural Transmission, 290, 213-242.

Sesack, S. R. & Pickel, V. M. (1990a). Prefrontal cortical efferents in the rat synapse on unlabelled neuronal targets of catecholamine terminals in the nucleus accumbens septi and on dopamine neurons in the ventral tegmental area. Brain Research, 506, 166-168.

Sesack, S. R. & Pickel, V. M. (1990b). In the rat medial nucleus accumbens, hippocampal and catecholaminergic terminals converge on spiny neurons and are in apposition to each other. Brain Research, 527, 266-279.

Shakow, D. (1961). Segmental set: A theory of the formal psychological deficit in schizophrenia. Archives of General Psychiatry, 6, 1-17.

Shimizu, N., Duan, S. M. & Oomura, Y. (1990). Glutamate modulates dopamine release in the striatum as measured by brain microdialysis. Brain Research Bulletin, 25, 99-102.

Silbersweig, D. A., Stern, E., Frith, C., Cahill, A., Holmes, A., Grootoon, S., Seaward, J., McKenna, P., Chua, S. E., Schnorr, L., Jones, T. & Frackowiak, R. S. J. (1995). A functional neuroanatomy of hallucinations in schizophrenia. Nature, 378, 176-176.

Smith, A. D. & Bolam, J. P. (1990). The neural network of the basal ganglia as revealed by the study of synaptic connections of identified neurones. Trends in Neuroscience, 13, 259265.

Snyder, S. H. (1972). Catecholamines in the brain as mediators of amphetamine psychosis. Archives of General Psychiatry, 27, 169-179.

Snyder, S. H. (1974). Madness and the Brain. McGraw-Hill, New York.

Sombati, S., Coulter, D. A. & DeLorenzo, R. J. (1991). Neurotoxic activation of glutamate receptors induces an extended neuronal depolarization in cultured hippocampal neurons. Brain Research, 566, ((1-2)), 316-319.

Springer, J. E. & Isaacson, R. L. (1982). Catecholamine alterations in basal ganglia after hippocampal lesions. Brain Research, 252, 185-188.

Steinfels, G. F., Heym, J., Strecker, R. E. & Jacobs, B. L. (1983). Behavioral correlates of dopaminergic unit activity in freely moving cats. Brain Research, 258, 217-228.

Suaud-Chagny, M. F., Chergui, K., Chouvet, G. & Gonon, F. (1992). Relationship between dopamine release in the rat nucleus accumbens and the discharge activity of dopaminergic neurons during local in vivo application of amino acids in the ventral tegmental area. Neuroscience, 49, (1), 63-72.

Suddath, R. L., Christison, G. W., Torrey, E. F., Casanova, M. F. & Weinberger, D. R. (1990). Anatomical abnormalities in the brains of monozygotic twins discordant for schizophrenia. New England Journal of Medicine, 322, 789-794.

Sugimoto, T. & Hattori, T. (1984). Organization and efferent projections of nucleus tegmenti pedunculopontinus pars compacta with special reference to its cholinergic aspects. Neuroscience, 11, (4), 931-946.

Svensson, T. H., Zhang, J., Johannessen, K. & Engle, J. A. (1994). Effect of local infusion of glutamate analogues into the nucleus accumbens of rats: an electrochemical and behavioural study. Brain Research, 643, (155-161),

Swanson, L. W. & Cowan, W. M. (1977). An autoradiographic study of the organization of the efferent connections of the hippocampal formation in the rat. Journal of Comparative Neurology, 172, 49-84.

Swanson, L. W. (1981). A direct projection from Ammon's horn to prefrontal cortex in the rat. Brain Research, 217, 150-154.

Swanson, L. W., Mogenson, G. J., Gerfen, C. R. & Robinson, P. (1984). Evidence for a projection from the lateral preoptic area and substantia innominata to the mesencephalic locomotor region in the rat. Brain Research, 295, 161-178.

Swerdlow, N. R. & Koob, G. F. (1987). Dopamine, schizophrenia, Mania, and depression: Toward a unified hypothesis of cortico-striato-pallido-thalamic function. Behavioural Brain Sciences, 10, 197-245.

Taber, M. T. & Fibiger, H. C. (1993). Electrical stimulation of the medial prefrontal cortex increases dopamine release in the striatum. Neuropsychopharmacology, 9, (4), 271-275.

Taber, M. T. & Fibiger, H. C. (1995). Electrical stimulation of the prefrontal cortex increases dopamine release in the nucleus accumbens of the rat: Modulation by metabotropic glutamate receptors. Journal of Neuroscience, 15, (5), 3896-3904.

Taber, M. T., Das, S. & Fibiger, H. C. (1995). Cortical regulation of subcortical dopamine release: Mediation via the ventral tegmental area. Journal of Neurochemistry, 65, (3), 1407-1410.

Taber, M. T., Baker, G. B. & Fibiger, H. C. (1996). Glutamate receptor agonists decrease extracellular dopamine in the rat nucleus accumbens in vivo. Synapse, 24, 165-172.

Taber, M. T. & Fibiger, H. C. (1997). Feeding-evoked dopamine release in the nucleus accumbens: Regulation by glutamatergic mechanisms. Neuroscience, 76, (4), 1105-1112.

Taghzouti, K., Louilot, S., Herman, J. P., LeMoal, M. & Simon, H. (1985). Alternation behavior, spatial discrimination and reversal disturbances following 6-hydroxydopamine lesions in the nucleus accumbens of the rat. Behavior and Neural Biology, 44, 354-363.

Tarrasch, R., Weiner, I., Rawlins, J. N. P. & Feldon, J. (1992). Disruption of latent inhibition by interrupting the subicular input to nucleus accumbens and its antagonism by haloperidol. Psychopharmacology, 6, 111.

Taylor, J. R. & Robbins, T., W. (1984). Enhanced behavioural control by conditioned reinforcers following microinjections of d-amphetamine into the nucleus accumbens. Psychopharmacology, 84, 405-412.

Taylor, J. R. & Robbins, T. W. (1986). 6-Hydroxydopamine lesions of the nucleus accumbens, but not of the caudate nucleus, attenuate enhanced responding with reward-related stimuli produced by intra-accumbens d-amphetamine. Psychopharmacology, 90, 390-397.

Tepper, J. M., Martin, L. P. & Anderson, D. R. (1995). GABA-A receptor-mediated inhibition of rat substantia nigra dopaminergic neurons by pars reticulata projection neurons. Journal of Neuroscience, 15, 3092-3103.

Thiel, C. M., Huston, J. P. & Schwarting, R. K. W. (1998). Hippocampal acetylcholine and habituation learning. Neuroscience, 85, (4), 1253-1262.

Tinbergen, N. (1951). Hierarchical organization of instinctive actions. In. D. Bindra and J. Stewart (Eds.), Motivation. 1966, pp. 29-35. Penguin, Baltimore.

Todd, C. L. & Grace, A. A. (1998). Modulation of ventral tegmental area dopamine cell activity by the ventral subiculum. Society for Neuroscience Abstracts, 24, 1642.

Totterdell, S. & Smith, A. D. (1989). Convergence of hippocampal and dopaminergic input onto identified neurons in the nucleus accumbens of the rat. Journal of Chemical Neuroanatomy, 2, 285-298.

Tsai, C. T., Mogenson, G. J., Wu, M. & Yang, C. R. (1989). A comparison of the effects of electrical stimulation of the amygdala and hippocampus on subpallidal output neurons to the pedunculopontine nucleus. Brain Research, 494, 22-29.

Ungerstedt, U. (1971a). Adipsia and aphagia after 6-hydroxydopamine induced degeneration of the nigro-striatal dopamine system in the rat brain. Acta Physiologica Scandinavica, 82 (Suppl 367), 95-122.

Ungerstedt, U. (1971b). Postsynaptic supersensitivity after 6-hydroxydopamine induced degeneration of the nigro-striatal dopamine system. Acta Physiologica Scandinavica, 82 (Suppl. 367), 69-93.

Vanderwolf, C. H. (1971). Limbic-diencephalic mechanisms of voluntary movement. Psychological Review, 78, 83-113.

Walaas, I. & Fonnum, F. (1979). The effects of surgical and chemical lesions of neurotransmitter candidates on the nucleus accumbens. Neuroscience, 4, (1), 209-216.

Walaas, I. (1981). Biochemical evidence for overlapping neocortical and allocortical glutamate projections to the nucleus accumbens and rostral caudatoputamen. Neuroscience, 6, (3), 399-405.

Wang, T. & French, E. D. (1993). L-Glutamate excitation of A10 dopamine neurons is preferentially mediated by activation of NMDA receptors: extra and intracellular electrophysiological studies in brain slices. Brain Research, 627, 299-306.

Wang, T. & French, E. D. (1993). Electrophysiological evidence for the existence of NMDA and non-NMDA receptors on rat ventral tegmental dopamine neurons. Synapse, (13), 270-277.

Wang, T., O'Connor, W. T., Ungerstedt, U. & French, E. D. (1994). N-methyl-D-aspartic acid biphasically regulates the biochemical and electrophysiological response of A10 dopamine neurons in the ventral tegmental area: in vivo microdialysis and in vitro electrophysiological studies. Brain Research, 666, 255-262.

Weinberger, D. R., Berman, K. F. & Illowwsky, B. P. (1988). Physiological dysfunction of dorsolateral prefrontal cortex in schizophrenia. iii. A new cohort and evidence for a monoaminergic mechanism. Archives of General Psychiatry, 49, 609-615.

Weinberger, D. R. (1999). Cell biology of the hippocampal formation in schizophrenia. Biological Psychiatry, 45, 395-402.

Weiner, I. (1990). Neural substrates of latent inhibition: the switching model. Psychological Bulletin, 108, 442-461.

Weissenborn, R. & Winn, P. (1992). Regulatory behavior, exploration, and locomotion following NMDA or 6-OHDA lesions in the rat nucleus accumbens. Behavioural Brain Research, 51, 127-137.

Westerink, B. H. C., Tuntler, J., Damsma, G., Rollema, H. & deVries, J. B. (1987). The use of tetrodotoxin for the characterization of drug-enhanced dopamine release in conscious rats studied by brain dialysis. Naunyn-Schmiedeberg's Archives of Pharmacolgy, 336, 502-507.

Westerink, B., Santiago, M. & deVries, J. (1992). The release of dopamine form nerve terminals and dendrites of nigrostriatal neurons induced by excitatory amino acids in the conscious rat. Naunyn-Schmiedeberg's Archives of Pharmacology, 345, 523-529.

Westerink, B., Kwint, H.-F. & deVries, J. (1996). The pharmacology of mesolimbic dopamine neurons: A dual probe microdialysis study in the ventral tegmental area and nucleus accumbens of the rat brain. Journal of Neuroscience, 16, (8), 2605-2611.

Westerink, B. C., Kwint, H. F. & de Vries, J. B. (1997). Eating-induced dopamine release from mesolimbic neurons is mediated by NMDA receptors in the ventral tegmental area: a dual-probe microdialysis study. Journal of Neurochemistry, 69, 66-668.

Whishaw, I., Q., Bland, B. H. & Vanderwolf, C. H. (1972). Hippocampal activity, behavior, self-stimulation, and heart rate during electrical stimulation of the lateral hypothalamus. Journal of Comparative and Physiological Psychology, 79, 115-127.

Whishaw, I. Q. & Mittleman, G. (1991). Hippocampal modulation of nucleus accumbens: Behavioral evidence from amphetamine-induced activity profiles. Behavioral and Neural Biology, 55, 289-306.

White, F. J. & Wang, R. Y. (1983). Differential effects of classical and atypical antipsychotic drugs on A9 and A10 dopamine neurons. Science, 221, 1054-1057.

White, N. M. (1986). Control of sensorimotor function by dopaminergic nigrostriatal neurons: Influence on eating and drinking. Neuroscience and Biobehavioral Reviews, 10, 15-36.

Wilkinson, L. S., Mittleman, G., Torres, E., Humby, T., Hall, F. S. & Robbins, T. W. (1993). Enhancement of amphetamine-induced locomotor activity and dopamine release in nucleus accumbens following excitotoxic lesions of the hippocampus. Behavioural Brain Research, (55), 143-150.

Wilson, S. A. K. (1914). An experimental research into the anatomy and physiology of the corpus striatum. Brain, 36, 427-492.

Wilson, C., Nomikos, G. C., Collu, M. & Fibiger, H. C. (1995). Dopaminergic correlates of motivated behavior: Importance of drive. Journal of Neuroscience, 15, (7), 5169-5178.

Wise, R. A. & Bozarth, M. A. (1987). A psychomotor stimulant theory of addiction. Psychological Review, 94, 469-492.

Wise, R. A. & Rompré, P.-P. (1989). Brain dopamine and reward. Annual Review of Psychology, 40, 191-225.

Wise, R. A., Newton, P., Leeb, K., Burnette, B., Pocock, D. & Justice, J. B. J. (1995). Fluctuations in nucleus accumbens dopamine concentration during intravenous cocaine self-administration in rats. Psychopharmacology, 120, 10-20.

Wise, R. A., Leone, P., Rivest, R. & Leeb, K. (1995). Elevations of nucleus accumbens dopamine and DOPAC levels during intravenous heroin self-administration. Synapse, 21, 140-148.

Wise, R. A. (1996). Neurobiology of addiction. Current Opinions in Neurobiology, 6, 243-251.

Witter, M. P. (1989). Connectivity of the rat hippocampus. In, V. Chan-Palay & C. Kohler (Eds.), The hippocampus - New vistas, pp 53-69, Alan R Liss, inc.

Witter, M. P., Ostendorf, R. H. & Groenewegen, H. J. (1990). Heterogeneity in the dorsal subiculum of the rat: Distinct neuronal zones project to different cortical and subcortical targets. European Journal of Neuroscience, 2, 718-725.

Wolterink, G., Phillips, G., Cador, M., Donselaar-Wolterink, I., Robbins, T. W. & Everitt, B. J. (1993). Relative roles of ventral striatal D1 and D2 doapmine receptors in responding with conditioned reinforcement. Psychopharmacology, 110, 355-364.

Wright, C. I. & Groenewegen, H. J. (1995). Patterns of convergence and segregation in the medial nucleus accumbens of the rat: Relationships of prefrontal cortical, midline thalamic, and basal amygdaloid afferents. Journal of Comparative Neurology, 361, 383-403.

Wu, M., Brudzynski, S. M. & Mogenson, G. J. (1993). Functional interaction of dopamine and glutamate in the nucleus accumbens in the regulation of locomotion. Canadian Journal of Physiology & Pharmacology, 71, 407-413.

Wu, M. & Brudzynski, S. M. (1995). Mesolimbic dopamine terminals and locomotor activity induced from the subiculum. Neuroreport, 6, 1601-1604.

Xu, L., Anwyl, R. & Rowan, M. J. (1998). Spatial exploration induces a persistent reversal of long-term potentiation in rat hippocampus. Science, 394, 891-894.

Yang, C. R. & Mogenson, G. J. (1984). Electrophysiological response of neurons in the nucleus accumbens to hippocampal stimulation and the attenuation of the excitatory response by the mesolimbic dopaminergic system. Brain Research, 324, 69-84.

Yang, C. R. & Mogenson, G. J. (1987). Hippocampal signal transmission to the pedunculopontine nucleus and its regulation by dopamine D2 receptors in the nucleus accumbens: An electrophysiological and behavioral study. Neuroscience, 23, (3), 1041-1055.

Yee, B. K., Rawlins, J. N. P. & Feldon, J. (1995). Latent inhibition in rats is abolished by NMDA-induced neuronal loss in the retrophippocampal region, but this lesion effect can be prevented by systemic haloperidol treatment. Behavioural Neuroscience, 109, 227-240.

Yim, C. Y. & Mogenson, G. J. (1980). Effect of picrotoxin and nipecotic acid on inhibitory response of dopaminergic neurons in the ventral tegmental area to stimulation of the nucleus accumbens. Brain Research, 199, 466-472.

You, Z.-B., Tzschentke, T. M., Brodin, E. & Wise, R. A. (1998). Electrical stimulation of the prefrontal cortex increases cholecystokinin, glutamate, and dopamine release in the nucleus accumbens: an in vivo microdialysis study in freely moving rats. Journal of Neuroscience, 18, (16), 6492-6500.

Youngren, K. D., Daly, D. A. & Moghaddam, B. (1993). Distinct actions of endogenous excitatory amino acids on the outflow of dopamine in the nucleus accumbens. Journal of Pharmacology and Experimental Therapeutics, 264, 289-293.

Zaczek, R., Hedreen, J. C. & Coyle, J. T. (1979). Evidence for a hippocampal-septal glutamatergic pathway in the rat. Experimental Neurology, 65, 145-156.

Zigmond, M. J. & Striker, E. M. (1972). Deficits in feeding behavior after intra-ventricular injection of 6-hydroxydopamine in rats. Science, 177, 1211-1212.

Zigmond, M. J., Castro, S. L., Keefe, K. A., Abercrombie, E. D. & Sved, A. F. (1998). Role of excitatory amino acids in the regulation of dopamine synthesis and release in the neostriatum. Amino Acids, 14, 57-62.