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Mesolimbic Contribution to Dopamine-Dependent Circling Behavior

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A Thesis

in

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ABSTRACT

Mesolimbic Contribution to Dopamine-Dependent Circling Behavior

Lois Meryl Colle Ph.D.
Concordia University, 1989

Animals with unilateral lesions of the telencephalic dopamine pathways circle when given psychomotor stimulant drugs. The dominant "two component" hypothesis attributes the directional bias of the animals to asymmetric activation of the nigrostriatal division of the dopamine system, but the mesolimbic division is also asymmetrically activated in these studies. The present experiments were designed to determine if asymmetric activation restricted to the mesolimbic division of the system might not itself induce some degree of directional bias in stimulant-induced locomotion.

Experiments 1 and 2 were designed to determine if animals would circle in response to amphetamine and apomorphine following 6-hydroxydopamine (6-OHDA) lesions (Experiment 1) or electrolytic lesions (Experiment 2). The lesions were aimed at the A10 (mesolimbic) cell region and the A9 (nigrostriatal) cell region. Animals with 6-OHDA or electrolytic lesions of the A10 area circled following amphetamine and apomorphine injection. Amphetamine affected A10- and A9-lesioned animals similarly following each lesion, but apomorphine affected A10- and A9-lesioned animals differently. The results of Experiments 1 and 2 suggest that asymmetrical activation of the A10 system is sufficient to cause circling

and that, under some conditions, circling following asymmetrical A10 activation differs from the circling following asymmetrical A9 activation.

Since it could be argued that circling following lesions of the A10 cell region was due to degeneration of A10 cells that send axons to the striatum, Experiment 3 was designed to determine if animals would circle in response to amphetamine and apomorphine following electrolytic lesions restricted to the nucleus accumbens (NAS), a terminal region of the A10 system. Animals with lesions restricted to the NAS circled in response to amphetamine suggesting, again, that asymmetrical activation of the A10 system results in circling.

Experiment 4 was also designed to determine whether asymmetrical activation of the A10 system would result in circling, however, in this case, the system was unilaterally activated by microinjections into the NAS. Unilateral microinjections of *d*-amphetamine into the NAS caused circling; injections of *l*-amphetamine were less effective, ruling out non-specific effects of pH, osmolarity and the like.

The present experiments suggest that asymmetrical activation of the mesolimbic division of the telencephalic dopamine system is a sufficient condition for circling behavior.

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Finally, and most importantly, I would like to thank Roy Wise. Roy was an excellent supervisor, giving me the freedom to explore in the lab while gently challenging my ideas and endeavours. Roy had faith in my scientific ability, and devoted a good deal of his time helping me develop into a scientist. For this I will be eternally grateful.

DEDICATION

I dedicate this thesis to the late Larry Holmes. Larry was responsible for getting me involved in research 10 years ago; we worked together as undergraduate and graduate students. Larry always challenged my ideas and provided me with hours of stimulating conversation. When Larry found out that my thesis was on circling behavior, he laughed and said that it was destiny that I follow in his footsteps. Thank you Larry.

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Historical Perspective

In 1873 Ferrier reported that unilateral electrical stimulation of the corpus striatum caused animals to turn the head away from the stimulated side toward the tail (Pycock, 1980). Since that time there have been numerous reports that asymmetrical, directionally-biased movements can be evoked by asymmetric activation of several areas within the central nervous system, ranging from the caudal brainstem to the rostral forebrain. The type of directionally biased movements evoked at these different sites varies. In some cases asymmetric activation causes only head turning and lateral bending along the longitudinal axis of the spine, but in others it causes animals to locomote in circles. This latter behavior is generally referred to as either turning, circling or rotation. Since the mechanisms of movement within the central nervous system are hierarchically organized, it makes sense that stimulation at different levels of the brain may induce directionally biased movements that are qualitatively different.

Although asymmetric activation in a number of central sites induces circling, researchers within the last two decades have focussed their attention on the basal ganglia. The initiation and control of movement are major functions of the basal ganglia. By using circling as a behavioral index of basal ganglia activation, researchers have advanced our understanding of the neurophysiology and neuropharmacology

of basal ganglia function. This information has been applied to the understanding of several neurological movement disorders reflecting dysfunction within the basal ganglia (Pycock, 1980).

Of the movement disorders associated with the basal ganglia, Parkinson's disease has received the most attention. Parkinson's disease is generally associated with a bilateral loss of dopaminergic cells within the basal ganglia (Hornykiewicz, 1979), though there are documented cases of hemi-Parkinsonism, where there is only a unilateral loss of dopaminergic cells (Bracha, Shults, Glick and Kleinman, 1987). The symptoms of Parkinson's disease include akinesia, rigidity, tremor and, in some cases, loss of motivation (Hornykiewicz, 1979; Sacks, 1983). Bilateral damage to dopamine-containing cells in animals causes some symptoms of Parkinson's disease; unilateral damage causes some of the symptoms of hemi-Parkinsonism. Because some of the symptoms of Parkinson's disease can be produced in lesioned animals, researchers have studied the lesioned rat as an animal model for Parkinson's disease. In particular, circling behavior, which occurs following unilateral lesions of the dopamine system, has been widely used by behavioral pharmacologists as an animal model to screen for potential anti-Parkinsonian drugs. The validity of using circling behavior as a model of Parkinson's disease was recently confirmed by Bracha et al (1987) who observed that hemi-Parkinsonian patients have a tendency to walk in circles.

The directionally biased movements that occur following unilateral dopamine lesions are generally assumed to result from asymmetric activation of the nigrostriatal dopaminergic pathway. When the dopamine system is unilaterally lesioned, dopaminergic activation is restricted to one side of the brain; when the intact side is activated the animals circle toward the lesioned side. In most studies where nigrostriatal lesions are intended, however, the damage is not restricted to the nigrostriatal system. Indeed, lesions of the nigrostriatal system usually cause a unilateral reduction in the dopaminergic activity of the adjacent mesolimbic system, but it is rarely considered that the asymmetric activation of this system can induce directionally biased movements. The dominant theory of dopamine-dependent circling is that the direction of circling is totally determined by postural asymmetries resulting from nigrostriatal damage; in this view the mesolimbic system is important for forward locomotion--seen as determining the rate of circling--but not for postural asymmetry--seen as determining the direction of circling (Moore and Kelly, 1977; Pycock and Marsden, 1978). The purpose of the experiments presented in this thesis was to re-examine the role of the mesolimbic system in circling behavior.

Defining circling behavior

The term "circling" is generally used to describe movements that result in the completion of a full 360° turn. Circling behavior can take qualitatively different forms. In

one form of circling, the animal displays a tight curvature along the spine, with head, neck and trunk bent; in this case circling occurs because the animal uses the hindlimb contralateral to the stimulated hemisphere as a pivot point and moves both forelimbs laterally with a paddling motion (Kilpatrick, 1986). With this form of circling, it appears as though the postural bias is induced by the internal state of the animal, and the animal appears driven into circles. When engaged in this type of circling the animal can turn up to 30 times per minute, and is frequently unresponsive to changes in environmental stimuli (Kilpatrick, 1986; Pycock, 1980). In another form of circling behavior, there may be little or no curvature along the spine; circling occurs because the animal makes asymmetric limb movements. Sometimes these asymmetric movements result in small diameter circles no greater than the length of the longitudinal axis of the rat's body and other times these movements result in large diameter circles (Kilpatrick, 1986). In some of these cases the asymmetric limb movements appear to be induced by the internal state of the animal, but in other cases, the asymmetric limb movements are induced by constraints within the testing environment (Holmes, Bozarth and Wise, 1983; Holmes and Wise, 1985a; Wise and Holmes,1986), instead of by some internal program. In some types of circling that are induced by environmental constraints, asymmetric limb movements occur only when an animal reaches a corner in the testing environment; animals circle many times in a small

enclosure and few times in a large enclosure (Holmes et al., 1983; Holmes and Wise, 1985a; Wise and Holmes,1986).

Until recently, most investigators focussed their attention on the rate and direction of circling, while the phenomenological aspects, such as the type of limb movements, were largely ignored. However, it has become increasingly apparent that investigation of the phenomenological aspect of circling may provide clues as to the potentially subtle functions served by different neurochemical systems in circling behavior. Indeed, there are now reasons to suspect that the type of circling induced by manipulation of non-dopaminergic systems may be different from that induced by manipulation of the dopamine system (Holmes and Wise, 1985a; Kilpatrick, 1986; Roffman, Bernard, Dawson, Sobiski and Shelens,1978; Wise and Holmes,1986). Briefly, it appears that asymmetrical activation of the dopamine system can cause a systematic tendency to turn preferentially toward the least activated side even under conditions where the animal is capable of locomotion in a straight line (Holmes and Wise, 1985a; Kilpatrick, 1986; Roffman et al.,1978; Ungerstedt, 1971b; Ungerstedt and Arbuthnott,1970; Vaccarino and Franklin, 1982; Vaccarino and Franklin, 1984). This contrasts with the pronounced postural asymmetry that generally accompanies circling induced by asymmetrical activation of non-dopaminergic pathways; in most cases of non-dopaminergic circling it is less clear that

animals are capable of locomotion in a straight line (Kilpatrick, 1986).

DOPAMINE-DEPENDENT CIRCLING BEHAVIOR

Hemispheric imbalance of dopaminergic activity within the basal ganglia is associated with asymmetric circling behavior, generally toward the hemisphere with less dopamine. The first report suggesting that a dopamine-containing region may be involved in circling behavior came in 1873, when David Ferrier showed that unilateral stimulation of the striatum caused animals to deviate toward the unstimulated side (Pycock, 1980). At the time it was not known that the striatum was rich in dopamine. The first study directly implicating the dopaminergic pathways in certain types of circling behavior was published in 1966 (Anden, Dahlstrom, Fuxe and Larson, 1966).

Anatomy of the Dopamine Pathways

The dopamine fiber systems have conventionally been divided into three major groups, a nigrostriatal system (Lindvall and Bjorkland, 1974; Ungerstedt, 1971a), a mesolimbic system (Lindvall and Bjorkland, 1974; Ungerstedt, 1971a), and a mesocortical system (Berger, Thierry, Tassin and Moyne, 1976; Lindvall and Bjorkland, 1974; Thierry, Blanc, Sobel, Stinus and Glowinski, 1973). The mesencephalon contains dopamine cell bodies that give rise to each of these fiber systems. The dopamine-containing cells of the substantia nigra, located laterally in the mesencephalon, are found in a layer that forms the dorsal surface of the nucleus,

the substantia nigra pars compacta (SNpc). Most of the fibers from these cells project to the ipsilateral striatum; however, some of these fibers bifurcate and project to the contralateral striatum (Pritzel, Sarter, Morgan and Huston, 1983). There are also some fibers that project only to the contralateral striatum (Altar, Neve, Loughlin, Marshall and Fallon, 1983; Fass and Butcher, 1981; Jaeger, Joh and Reis, 1983; Pritzel et al., 1983). It has been estimated that five to ten percent of dopamine cells project to the contralateral striatum (Pritzel et al., 1983). A small number of dopamine-containing fibers from the SNpc, project to cortical and limbic regions as well (Fallon and Moore, 1978). Some of these neurons innervate only cortical regions and some innervate only limbic regions, while others have axon collaterals that innervate both limbic and cortical structures (Fallon, 1981).

The dopamine-containing cells of the ventral tegmental area (VTA) are medial to and continuous with the SNpc; they extend medially from the medial boundary of the substantia nigra all the way to the midline. Most of these cells send fibers that project to limbic areas, including the nucleus accumbens, the olfactory tubercle, the lateral septum, the amygdala, the habenula and the bed nucleus of the stria terminalis (Fallon and Moore, 1978). Other cells send fibers to parts of the frontal, entorhinal and cingulate cortices (Berger et al., 1976; Fallon and Moore, 1978; Thierry et al., 1973). There is also a small number of dopamine-containing fibers from the VTA that project to the striatum. Although the cells

originating in the VTA project to limbic, cortical and striatal areas, these cells, unlike those of the SNpc, do not send axon collaterals that innervate more than one forebrain region (Bannon and Roth, 1983; Fallon, 1981; Fallon and Loughlin, 1982; Loughlin and Fallon,1984).

The role of the nigrostriatal system

Lesion studies. The first indication that asymmetrical activation of the dopamine-containing cells of the nigrostriatal system could result in circling behavior came from lesion studies. Anden et al. (1966) were the first to show that electrolytic lesions that caused a unilateral depletion of caudate dopamine caused animals to turn their head and tail toward the lesioned side. Injections of l-DOPA, a dopamine precursor, increased the degree of turning of the head and tail toward the lesioned side and resulted in circling toward the lesioned side (ipsiversive circling). These authors suggested that the drug-induced circling was due to asymmetrical activation of dopamine within the caudate.

Since the time of Anden's demonstration that electrolytic lesions induced circling, and that drugs which enhance dopaminergic activity increased the rate of the circling, investigators have used more specific lesioning techniques to study the role of the dopamine system in circling behavior. This was made possible by using the neurotoxin 6-hydroxydopamine (6-OHDA) which destroys catecholamine-containing neurons (Ungerstedt, 1968) but causes little damage to non-catecholaminergic neurons; unilateral

injections of 6-OHDA into the ascending dopamine systems can cause reductions in dopamine concentrations in the ipsilateral hemisphere at doses that do not cause substantial reductions in other neurotransmitter concentrations (Ungerstedt,1968). Ungerstedt and Arbuthnott (1970) were the first to unilaterally inject 6-OHDA into the SNpc to determine whether it caused animals to circle. They observed that animals immediately circled toward the lesioned side following the SNpc injection of 6-OHDA; this lesion-induced asymmetry in spontaneous activity dissipated within a few days. If the animals were disturbed by handling or a change in environment, however, they once again began to turn toward the lesioned side (Ungerstedt,1971b; Ungerstedt and Arbuthnott, 1970). The circling induced by the lesion was presumed to reflect an imbalance in dopaminergic activity occurring as a consequence of the lesion, with animals circling away from the side with the more spontaneously active dopamine system. Spontaneous circling, occurring as a consequence of a unilateral SNpc 6-OHDA injection, has since been confirmed in other reports (Costall, Marsden, Naylor and Pycock, 1976; Iwamoto, Loh and Way, 1976).

In most lesion studies of circling behavior, the dopamine system is pharmacologically activated several days following the 6-OHDA injection. Amphetamine and apomorphine have been the most extensively used dopaminergic drugs in the circling paradigm. Amphetamine increases synaptic concentrations of dopamine, inhibits reuptake and inhibits the

enzyme monoamine oxidase which inactivates dopamine (Heikkila, Orlansky, Mytilineou and Cohen, 1975). Apomorphine binds to dopamine receptors; at low doses apomorphine preferentially acts at presynaptic dopamine receptors (autoreceptors) and at high doses it also acts at postsynaptic receptors (Carlsson, 1975). Other dopaminergic drugs, including l-DOPA, bromocriptine, amantadine and ergometrine have also been routinely tested.

Ungerstedt and Arbuthnott (1970) tested their animals in a hemispheric bowl to measure the speed of drug-induced circling following unilateral SNpc injections of 6-OHDA. They used the hemispheric bowl because they found the behavior of their lesioned animals variable when tested in an open field. In the open field each animal was easily distracted by its surrounding and the circling curve was uneven. When the animals were tested in the bowls following amphetamine injection, they were minimally distracted by their environment and circled toward the lesioned side for hours. Ungerstedt and Arbuthnott (1970) suggested that amphetamine caused circling because nerve terminals on the lesioned side had degenerated and only the intact dopamine system was activated by amphetamine. Thus amphetamine presumably enhanced the lesion-induced imbalance between the innervated and the denervated caudate nucleus. Many studies have since confirmed that amphetamine induces circling toward the lesioned side, whether following unilateral 6-OHDA injection into the SNpc or following electrolytic lesions of the SNpc; 6-

OHDA injections or electrolytic lesions at the level of the SNpc or at the level of the caudate are equally effective (Arbuthnott and Crow, 1971; Christie and Crow, 1971; Costall et al., 1976; Dunnett, Bjorkland, Stenevi and Iversen, 1981; Dunnett, Bjorkland, Schmidt, Stenevi and Iversen,1983; Kelly, 1975; Kelly and Moore, 1976; Kelly and Moore, 1977; Pycock and Marsden, 1978; Robinson and Becker, 1983; Von Voightlander and Moore, 1973).

In animals with unilateral lesions of the nigrostriatal system, the degree of circling induced by amphetamine is reported to be related to the degree of dopamine release caused by amphetamine injection and to the degree of nigrostriatal damage. By making use of the intracerebral dialysis technique, Zetterstrom, Herrera-Marschitz and Ungerstedt (1986) reported that amphetamine caused a dose-dependent increase in dopamine release in the caudate on the unlesioned side but not on the lesioned side, and that the time course change in the total amount of dopamine released in the intact caudate correlated with the rate of amphetamine-induced ipsiversive circling. In their study animals had lesions that caused a greater than 95% depletion of caudate dopamine on the lesioned side. In a more recent study, Robinson and Whishaw (1988) failed to observe an obvious relationship between the amount of dopamine released in the intact caudate and rate of amphetamine-induced ipsiversive circling in animals with lesions that caused a greater than 95% depletion of caudate dopamine on the lesioned side.

Robinson and Whishaw (1988), however, only tested one dose of amphetamine, and it is possible that they might have observed a relationship between the degree of dopamine release and the rate of circling had they tested more doses. Ungerstedt (1971b) reported that animals with extensive denervation of the caudate turned quickly whereas those with partial denervation turned slowly following a high dose of amphetamine. In the study by Robinson and Whishaw (1988), animals with extensive lesions did not circle more in response to amphetamine than animals with partial lesions. It is likely that Robinson and Whishaw failed to see a relationship between lesion size and the rate of circling because they tested their animals several weeks following the lesion, at a time when a substantial amount of recovery had probably occurred.

The effects of apomorphine are more complex than the effects of amphetamine. Apomorphine induces circling either away from or toward the lesioned side, depending on the location of the lesion and the type of lesion. Following extensive unilateral 6-OHDA lesions of the SNpc or the caudate, apomorphine causes animals to circle away from the lesioned side (Anlezark, Pycock and Meldrum, 1976; Costall et al., 1976; Dunnett and Iversen, 1982; Kelly,1975; Kelly and Moore, 1976; Starr and Summerhayes,1982; Ungerstedt, 1971c; Von Voightlander and Moore, 1973). Ungerstedt (1971c) was the first to hypothesize that animals circle away from the lesioned side following apomorphine because the denervated

caudate becomes supersensitive to dopamine and dopamine agonists following these lesions. He reasoned that animals would circle away from the lesioned side if the lesioned caudate were more sensitive than the intact caudate to apomorphine. It is now well documented that extensive denervation of the nigrostriatal system does increase the sensitivity of the denervated caudate by increasing the number of postsynaptic dopamine receptors in the caudate (Creese, Burt and Snyder, 1977). It is presumed that the increase in the number of receptors occurs as a compensatory response to a lesion-induced reduction in dopamine levels. Indeed, Ungerstedt and Marshall (1975) estimated that the denervated caudate is approximately forty times more sensitive to the effects of apomorphine than the innervated caudate. Independent support for the increased responsivity of the denervated caudate came from the observation that dopamine injected into the denervated caudate caused more circling away from the lesioned side than dopamine injected into the non-denervated caudate (Costall, Naylor and Pycock 1976; Setler, Malesky, McDevitt and Turner, 1978; Ungerstedt, Ljungberg and Schultz, 1978). When the intrinsic cells of the caudate--those on which the dopamine receptors reside--are damaged by electrolytic lesions (Costall et al., 1976; Ungerstedt, 1971c) apomorphine loses the ability to induce contraversive circling behavior. Dopamine receptor blockers also block the ability of apomorphine to induce circling in 6-OHDA injected animals (Pycock, Donaldson and Marsden, 1975;

Christie and Crow, 1973; Von Voigtlander and Moore, 1973; Nakura, Engel and Goldstein, 1978). Therefore, it is generally accepted that apomorphine induces contraversive circling following 6-OHDA injections into the SNpc or the caudate by activating a greater number of receptors in the lesioned caudate.

When the caudate or SNpc is destroyed by electrolytic lesions, apomorphine causes animals to circle towa d the lesioned side, rather than away from the lesioned side as is the case following 6-OHDA lesions. Electrolytic lesions of the caudate damage the intrinsic cells of the caudate--those on which the dopamine receptors reside--and presumably cause circling toward the lesioned side because the intact caudate has more receptors available for activation by apomorphine; this activation in the intact caudate drives the animal toward the lesioned side.

Apomorphine-induced circling toward the lesioned side following electrolytic lesions of the SNpc has been more difficult to explain. That animals with electrolytic lesions of the SNpc circle toward the lesioned side is surprising when you consider that some studies report that the degree of caudate dopamine depletion induced by an electrolytic lesion is comparable to the degree of caudate dopamine depletion induced by a 6-OHDA lesion (Costall et al., 1976; Hodge and Butcher, 1979; Iwamoto et al.,1976; Schwartz, Gunn, Sharp and Evarts,1976). There are several lines of evidence suggesting that apomorphine causes ipsiversive circling following

electrolytic lesions of the SNpc by more effectively activating the caudate on the unlesioned side than the caudate on the lesioned side. First, the ipsiversive circling induced by apomorphine is blocked if a lesion is placed in the caudate contralateral to the lesioned SNpc (Costall et al., 1976); a contralateral caudate lesion does not affect the rate of apomorphine-induced contraversive circling in animals with 6-OHDA lesions of the SNpc (Costall, Fortune, Naylor and Nohria, 1979; Marshall and Ungerstedt, 1977). Second, caudate dopamine injections that elicit asymmetrical movements prior to a SNpc electrolytic lesion fail to do so following the lesion; higher doses of dopamine are necessary to induce asymmetrical movements after the lesion (Costall et al., 1976). Dopamine injections into the caudate on the unlesioned side still induce asymmetrical movements at the same doses (Costall et al., 1976). Third, the dose of apomorphine required to induce circling toward the lesioned side following electrolytic lesions is approximately twenty-fold higher than the dose required to induce circling away from the lesioned side following 6-OHDA lesions (Costall et al., 1976). Lower doses are presumed more effective following SNpc 6-OHDA lesions because of an increase in the number of caudate dopamine receptors on the lesioned side. Higher doses are presumably necessary following electrolytic lesions of the SNpc because these lesions do not result in a change in receptor sensitivity in the caudate on the lesioned side (Costall et al., 1976) and therefore apomorphine induces

circling by activating normally sensitive receptors in the caudate on the unlesioned side. It is presently not clear why the caudate ipsilateral to an electrolytic lesion does not become supersensitive following extensive electrolytic lesions of the SNpc. One possibility is that electrolytic lesions of the SNpc damage a non-dopaminergic nigrostriatal pathway that is necessary for normal receptor activity (Costall et al., 1976). This pathway would be spared following 6-OHDA lesions.

In addition to the direction of circling, the type of circling induced by apomorphine, in most cases, differs from the type of circling induced by amphetamine following unilateral 6-OHDA lesions of the SNpc. Following apomorphine injection, animals display a pronounced lateral bending along the longitudinal axis of the body, with the body curved away from the lesioned side. When these animals circle, the hindlimb ipsilateral to the side of the lesion is used as a pivot point (Ziegler and Szechtman, 1988) and both forelimbs step laterally with a paddling motion (Kilpatrick, 1986). The hindlimb contralateral to the side of the lesion generally steps backward. Occasionally, the twisting of the body toward the unlesioned side is so vigorous that animals will flip over (Ungerstedt, 1971c). On the other hand, following most doses of amphetamine animals are rarely posturally asymmetric and generally step equally with the hindlimbs (Ungerstedt and Arbuthnott, 1970; Ziegler and Szechtman, 1988).

It is presently not clear why the type of circling induced by amphetamine and apomorphine differs. The differences in the type of circling induced by amphetamine and apomorphine may be partly due to differences in the degree of locomotion and stereotypy caused by the doses of these drugs that are usually tested. Let us first consider the case of amphetamine. In most studies, low to moderate doses (0.5 mg/kg-2.0 mg/kg) of amphetamine are used to induce circling; when these doses are used circling occurs in the absence of obvious postural asymmetry (Ziegler and Szechtman, 1988; Steiner, Bonatz, Huston and Schwarting, 1988). In unlesioned animals, these doses of amphetamine are known to cause an increase in forward locomotion (Kelly, Seviour and Iversen, 1975; Sharp, Zetterstrom, Ljungberg and Ungerstedt, 1987). When high doses of amphetamine (5.0 mg/kg and above) are used to induce circling, the circling is characterized by postural asymmetry (Costall et al., 1976). In unlesioned rats, these doses are known to induce stereotypy rather than forward locomotion (Kelly et al.,1975; Sharp et al., 1986). Now let us consider the case of apomorphine-induced circling. In most studies, the dose of apomorphine (1.0-2.0 mg/kg) injected is within the dose range known to induce stereotypy, rather than forward locomotion, in unlesioned rats (Kelly et al., 1975). There are some studies where lower doses of apomorphine (below 1.0 mg/kg) have been tested, doses known to increase locomotor activity in unlesioned animals, but the circling in these animals is still characterized by pronounced postural

asymmetry and stereotypy. That lower doses of apomorphine cause this type of circling is not surprising when you consider that apomorphine presumably causes circling in these rats by activating the denervated caudate. Since the denervated caudate is estimated to be approximately 40 times more sensitive to the effects of apomorphine (Ungerstedt and Marshall, 1975), even very low doses would likely induce stereotypy. Although it appears that stereotypy- inducing doses of apomorphine and amphetamine result in circling characterized by postural asymmetry, more research is needed to determine the nature of the relationship between stereotypy and postural asymmetry.

It has been suggested that differences in the type of circling induced by amphetamine and apomorphine are due to differences in the degree of dopaminergic activation (Ungerstedt,1971b,1971c). Ungerstedt (1971b,1971c) originally suggested that amphetamine and apomorphine induce circling by activating equivalent circuits on opposite sides of the brain; in the case of amphetamine-induced circling the intact caudate drives the animal and in the case of apomorphine-induced circling the dopamine-denervated caudate drives the animal. According to Ungerstedt's conceptualization, the type of circling induced by amphetamine should be the same as the type of circling induced by apomorphine, particularly if the same degree of caudate activation occurs following each drug.

In addition to amphetamine and apomorphine, other dopaminergic drugs induce circling following unilateral lesions of the nigrostriatal system. Drugs that act to increase synaptic dopamine concentrations cause circling toward the lesioned side. These drugs include methylamphetamine (Christie and Crow, 1971), ephedrine (Christie and Crow, 1971; Boulu, Rapin, Lebas and Jaquet, 1972), methylphenidate (Christie and Crow, 1971; Von Voigtlander and Moore, 1973), nomifensine (Costall and Naylor, 1977; Pycock, Milson, Tarsy and Marsden, 1976) and amantadine (Ungerstedt, Avemo, Avemo, Ljungberg and Ranje, 1973; Von Voigtlander and Moore, 1973). Dopaminergic receptor agonists cause circling away from the lesioned side. These drugs include N-propyl-norapomorphine (Costall, Naylor and Neumeyer, 1975; Mendez, Cotzias, Fihn and Dahl, 1975; Neumeyer, Dafeldecker, Costall and Naylor, 1977), diacetylapomorphine (Baldessarini, Walton and Borgman, 1976), piribedel (Costall and Naylor, 1974a) L-DOPA (Mendez et al., 1975; Pycock and Marsden, 1978; Ungerstedt, 1971c) and bromocriptine (Corrodi, Fuxe, Hokfelt, Lidbrink and Ungerstedt, 1973).

Unilateral stimulation studies. Electrical stimulation along different parts of the ascending nigrostriatal pathway induces circling behavior. Electrical stimulation at the level of the dopamine-containing SN cells sometimes induces circling toward the stimulated side and sometimes induces circling away from the stimulated side (Arbuthnott, Crow, Fuxe and Ungerstedt, 1970; Arbuthnott and Crow, 1971;

Arbuthnott and Ungerstedt, 1975; Gratton and Wise, 1984; Roffman et al., 1978; Vaccarino and Franklin, 1982). It is presently not clear why electrical stimulation induces ipsiversive circling in some cases and contraversive circling in other cases. Vaccarino and Franklin (1982) suggested that the direction of circling was dependent upon the stimulation site within the SN; they found ipsiversive circling from far lateral stimulation sites within the SNpc and contraversive circling from medial stimulation sites within the SNpc. Gratton and Wise (1984), however, found that the direction of circling induced by electrical stimulation of the SNpc bore no relationship to the medial-lateral location of the electrode site; some animals circled ipsiversively and others circled contraversively following electrical stimulation of the medial SNpc and some animals circled ipsiversively and others circled contraversively following electrical stimulation of the lateral SNpc. Gratton and Wise (1984) suggested that the direction of circling may be more related to the stimulation parameters (pulse frequency) used at each site than to the exact site of the stimulation as suggested by Vaccarino and Franklin (1982).

In several of the studies where contraversive circling has been reported following SNpc electrical stimulation, it appears that the contraversive circling is dopamine-dependent; stimulation within the SNpc in these studies is accompanied by the release of dopamine in the caudate (Arbuthnott and Crow, 1971; Von Voightlander and Moore, 1971) and can be blocked by pretreatment with dopamine receptor blockers

(Arbuthnott and Ungerstedt, 1975; Roffman et al., 1978; Vaccarino and Franklin, 1982) or by lesions of the nigrostriatal system (Arbuthnott and Crow, 1971). Electrical stimulation in the nigral region can elicit circling that resembles forward locomotion with a bias to one side (Vaccarino and Franklin, 1982) or circling that is characterized by a tight lateral curving of the spine, in which case animals make small circles in the center of the test box (Roffman et al., 1978). These differences in the type of circling may reflect differences in the degree of dopaminergic activation caused by the stimulation. Both types of circling are blocked by dopamine receptor blockers (Roffman et al., 1978; Vaccarino and Franklin, 1982).

Electrical stimulation of the medial forebrain bundle (Arbuthnott and Crow, 1971; Arbuthnott and Ungerstedt, 1975; Casteneda, Robinson and Becker, 1985) induces circling away from the side of the stimulation. Circling induced by medial forebrain bundle electrical stimulation is usually attributed to nigrostriatal activation since 6-OHDA lesions of the nigrostriatal system (Castaneda et al.,1985), or pretreatment with dopamine receptor blockers (Roffman et al., 1978) block the circling. Unilateral medial forebrain bundle stimulation elicits circling that resembles forward locomotion with a directional bias; there is little lateral bending along the longitudinal axis of the animal's body when circling (Pycock, 1980; Roffman et al., 1978). Electrical stimulation in the

caudate also induces circling away from the stimulated side (Zimmerberg and Glick, 1974).

Unilateral microinjections of drugs that cause dopaminergic activation induce either circling or lateral bending along the longitudinal axis of the body. Injections of dopamine into the caudate generally cause animals to curve the body away from the injected side without circling, but sometimes they cause animals to circle (Costall and Naylor, 1974b; Setler et al., 1978; Ungerstedt, Butcher, Butcher, Anden and Fuxe, 1969). In the first study of this type, Ungerstedt et al. (1969) reported that a large unilateral dopamine injection into the caudate caused animals to bend the longitudinal axis of the body away from the injected side with adducted limbs on the contralateral side and abducted limbs on the ipsilateral side. These animals did not forward locomote unless their tails were pinched; when activated by tail pinching these animals circled away from the injected side (Ungerstedt et al., 1969).

Intra-caudate injections of amphetamine (Joyce, Davis and Van Hartesveldt, 1981; Joyce and Van Hartesveldt, 1984; Wolfson and Brown, 1983) and apomorphine (Herrera-Marschitz, Forster and Ungerstedt, 1985; Starr and Summerhayes, 1982) cause circling away from the injected side. The amount of circling induced by either amphetamine or apomorphine appears to be related to the location of the injection site within the caudate; injections into the anterior dorsal region of the caudate are generally more effective than

injections into the posterior ventral region (Herrera-Marschitz et al., 1985; Joyce, Davis and Van Hartesveldt, 1981; Starr and Summerhayes, 1982; Wolfson and Brown, 1983). These observations have led some researchers to conclude that only some regions of the caudate are involved in amphetamine- and apomorphine-induced circling behavior (heterogeneously organized) (Joyce et al., 1981; Herrera-Marschitz et al., 1985). That only some regions of the caudate are involved in amphetamine- and apomorphine-induced circling behavior had been suggested previously by Dunnett and his colleagues (Dunnett et al.,1981). Dunnett et al. (1981) reported that amphetamine-induced circling in animals with unilateral nigrostriatal lesions was attenuated when fetal dopamine cells were placed into the dorsal caudate, but not when they were placed into the ventral caudate.

Unilateral microinjections into the SNpc also cause circling. When morphine, which increases the firing rate of dopaminergic cells (Matthews and German,1984), is injected into the SNpc region, animals circle away from the injected side (Holmes and Wise, 1985a; Iwamoto and Way, 1977). Vaccarino and Franklin (1984) reported that the effects of microinjections of other dopaminergic drugs into the SNpc are dependent upon the injection site within the SNpc. They observed that injections of the dopamine antagonist alpha-flupenthixol into the lateral SNpc caused ipsiversive circling while injections into the medial SNpc caused contraversive circling. In addition, they reported that apomorphine causes

circling when injected into the medial SNpc, but not when injected into the lateral SNpc.

Summary of the studies. In summary, there is an abundance of evidence suggesting that asymmetrical activation of the nigrostriatal system causes circling behavior. This evidence derives from lesion as well as electrical and chemical stimulation studies. In most of the studies reviewed above, it was generally assumed that an imbalance in striatal dopamine activity caused the animals to circle toward the side with less dopaminergic activity; in these studies, the potential contribution of the ascending mesolimbic system to circling behavior was largely ignored. Nevertheless, close examination of these studies reveals that asymmetric activation of the mesolimbic system may have contributed to the circling behavior. For example, in most of the lesion studies, the 6-OHDA injections which resulted in caudate dopamine depletion also resulted in nucleus accumbens and the olfactory tubercle dopamine depletion (Anden et al., 1966; Costall et al., 1976; Mendez et al., 1975; Ungerstedt, 1971b; Ungerstedt and Arbuthnott, 1970; Von Voightlander and Moore, 1973). Similarly, while it was assumed that electrical stimulation along the MFB induced circling by activating the nigrostriatal system (Castaneda et al., 1985) it is likely that electrical stimulation along the MFB also activated the mesolimbic dopamine system (Mogenson and Wu, 1982). In addition, it is likely that electrical stimulation within the SNpc activated dopaminergic cells that project from the SNpc to limbic

regions. Even in the case of drug-induced circling following microinjections into the substantia nigra, it is possible that the circling was partly due to drug diffusion to the adjacent ventral tegmental area, or to activation of SNpc dopamine cells that project to limbic regions.

The role of the mesolimbic system

It is only more recently that attention has been directed toward the role of the mesolimbic system in circling behavior. The generally accepted 'two-component' hypothesis of circling behavior states that activation of the mesolimbic system--regardless of side--determines the rate of locomotion, while an imbalance in activation in the nigrostriatal system determines the direction of this activity (Kelly and Moore, 1977; Moore and Kelly, 1977; Pycock and Marsden, 1978). The data that led to this view and more recent data that appear to challenge this view will be reviewed below.

Lesion studies. It was research on the locomotor-stimulating effects of amphetamine and apomorphine that prompted the investigation of the mesolimbic system in circling behavior. By 1975, there were several reports that suggested that dopamine agonists produced their locomotor stimulating effects by activating dopaminergic neurons and their post-synaptic receptors within the nucleus accumbens. First, it was reported that dopamine or dopamine agonist injections directly into the nucleus accumbens caused animals to locomote (Pijnenburg and Van Rossum, 1973; Pijnenburg, Honig, van der Heyden and Van Rossum, 1976); pretreatment

with dopamine receptor blockers prevented the increase in locomotion (Pijnenburg et al.,1976). In addition, there were reports that the locomotor-stimulating effect of amphetamine was attenuated by injections of dopamine receptor blockers into the nucleus accumbens (Pijnenburg, Honig and Van Rossum, 1975) or by bilateral denervation of the nucleus accumbens (Kelly et al., 1975). Finally, bilateral denervation of the nucleus accumbens increased the locomotor stimulating effect of apomorphine (Kelly et al., 1975), presumably due to the enhanced effectiveness of this drug in the supersensitive nucleus accumbens.

It was consideration of the data presented above that led Kelly (1975) to investigate the role of the mesolimbic system in circling behavior. He reasoned that if amphetamine and apomorphine increased locomotion by bilaterally activating the nucleus accumbens, unilateral activation of the accumbens should result in unilaterally activated locomotion and cause circling; he predicted that animals with unilateral lesions of the nucleus accumbens would circle toward the lesioned side following amphetamine and away from the lesioned side following apomorphine. Kelly (1975) found that a high dose of amphetamine induced only weak circling several weeks following unilateral 6-OHDA injections into the nucleus accumbens. This circling which was toward the lesioned side, reached a peak of approximately 2 turns per minute. This same dose of amphetamine caused pronounced circling several weeks following unilateral 6-OHDA injections into the caudate;

animals with caudate lesions circled toward the lesioned side with a peak rate of approximately 16 turns per minute. Following apomorphine injection, only rats with caudate lesions circled away from the lesioned side.

On the basis of these data Kelly (1975) concluded that unilateral lesions of the nucleus accumbens are not sufficient to cause circling following dopamine agonists. Close examination of Kelly's data suggests, however, that they may not be conclusive because of the location of his lesion and the doses of dopamine agonists that he tested. First, Kelly's 6-OHDA injection site was in the anterior part of the nucleus accumbens. This raises the possibility that amphetamine-induced activation of spared dopamine-containing terminals within the posterior nucleus accumbens was sufficient to prevent circling. Indeed, the spared terminals in the posterior accumbens might have increased their release of dopamine in response to the loss of the anterior nucleus accumbens terminals (Hefti, Enz and Melamed, 1985; Robinson and Whishaw, 1988).

Second, Kelly (1975) tested his animals with a high dose of amphetamine, a dose known to induce pronounced stereotypy (Kelly et al., 1975); high doses of amphetamine generally cause only a short-lasting increase in locomotor activity, presumably because an animal's ability to locomote is interfered with by the onset of stereotypy (Sharp et al.,1987). In this regard, it is important to note that amphetamine's stereotypy inducing effects are presumably mediated through

release of dopamine within the caudate (Kelly et al., 1975); even though this dose of amphetamine increases dopamine release within the accumbens, it also increases dopamine release within the caudate (Sharp et al., 1987) and the stereotypy induced by the latter effect is expressed at the expense of the locomotion induced by the former effect (Sharp et al., 1987). In Kelly's study, amphetamine-induced circling in the animals with nucleus accumbens lesions peaked after 10 minutes and then dropped down to zero; this drop in circling activity corresponds to the time at which this dose of amphetamine generally induces stereotypy (Fog, 1972; Randrup and Munkvad, 1970; Sharp et al., 1987). Others have also reported that the onset of stereotypy induced by high doses of dopamine agonists may be incompatible with drug-induced circling (Ungerstedt, 1971b; Ungerstedt and Arbuthnott, 1970). Thus, had Kelly tested his animals with a lower dose of amphetamine, a dose known to increase locomotion without inducing much stereotypy, animals might have circled following the unilateral accumbens lesions. The failure to observe apomorphine-induced circling may also be attributable to the high dose of apomorphine (10 mg) that he administered, a dose known to induce intense stereotypy (Kelly et al., 1975). Curiously, in his paper Kelly (1975) mentioned that high doses of amphetamine and apomorphine induce stereotypy and suppress locomotion, but he did not consider that these doses may have reduced the circling rate in his animals with accumbens lesions.

Costall et al. (1976) also investigated the role of the mesolimbic system in drug-induced circling behavior. In their study they injected 6-OHDA into the ventral tegmental area (VTA) and into the nucleus accumbens. Animals that received unilateral VTA 6-OHDA injections circled toward the lesioned side spontaneously and following moderate doses of amphetamine (2.5 mg) and apomorphine (0.5 mg). These animals, however, only circled when tested one and three days following the lesion; by the fifth day following the lesion they no longer circled. Animals with unilateral lesions of the nucleus accumbens did not circle at any time following the lesion. On the basis of these observations, Costall et al. (1976) concluded that a unilateral lesion of the mesolimbic system is unable to generate circling behavior. The fact that circling did not last more than several test days is not surprising when you consider that the lesions of the VTA caused mesolimbic dopamine levels on the lesioned side to drop to 46 percent while lesions of the nucleus accumbens caused mesolimbic dopamine levels on the lesioned side to drop to 63 percent of the mesolimbic dopamine level in the intact side. Since these lesions were not extensive, it is likely that the spared neurons compensated for the asymmetry (Robinson and Whishaw, 1988). It is well documented that behavioral recovery occurs following incomplete lesions of the dopaminergic system (Marshall, 1984). Before suggesting that unilateral mesolimbic activation does not cause circling, Costall et al. (1976) should have looked for drug-induced

circling in animals that had larger levels of mesolimbic dopamine depletion.

In summary, both Kelly (1975) and Costall et al. (1976), on the basis of the studies cited above, concluded that unilateral denervation of the mesolimbic system does not result in drug induced circling. Further work on the role of the mesolimbic system in circling behavior did, however, suggest that this dopamine system did have a critical role in drug-induced circling.

Kelly and Moore (1977) were the first to suggest that the mesolimbic system had a role in drug-induced circling. They examined the effects of bilateral 6-OHDA lesions of the nucleus accumbens on drug-induced circling in rats with unilateral nigrostriatal lesions. They reported that bilateral lesions of the nucleus accumbens blocked amphetamine-induced circling and potentiated apomorphine-induced circling in animals with unilateral nigrostriatal lesions. These observations suggested to Kelly and Moore (1977) that the activity at mesolimbic dopamine receptors influenced circling behavior.

Moore and Kelly (1977) proposed a model in an attempt to describe the interaction of the mesolimbic and nigrostriatal dopamine systems in drug-induced circling behavior. According to their model, the direction of circling is determined by striatal activation and the rate of circling is determined by nucleus accumbens activation. More specifically, they proposed that the direction of circling is

determined by a signal representing the difference in the activity of dopamine receptors in the right and left caudate nuclei. The resultant caudate output is then conducted to an amplifier. The gain of the amplifier was proposed to be a function of the activity at dopamine receptors in the nucleus accumbens. Therefore, the rate of circling, according to Moore's and Kelly's (1977) model, is a function of the amplifier output. According to this model, animals with unilateral nigrostriatal lesions and bilateral nucleus accumbens lesions (Kelly and Moore, 1977) did not circle following amphetamine because there was less dopamine for amphetamine to release onto nucleus accumbens dopamine receptors, resulting in a low amplifier gain. On the other hand, apomorphine-induced circling was presumably potentiated because apomorphine activated supersensitive dopamine receptors in the nucleus accumbens, resulting in a high amplifier gain.

A similar conclusion regarding the role of the nucleus accumbens in circling behavior was independently arrived at by Pycock and Marsden (1978). In their experiment, circling behavior was assessed following bilateral medial forebrain bundle lesions; one lesion caused only limbic dopamine depletion and the other lesion caused both limbic and caudate dopamine depletion. The result was animals with bilateral limbic dopamine depletion and unilateral caudate dopamine depletion. These animals did not circle following amphetamine injection but did circle following apomorphine injection. Pycock and Marsden (1978) attributed apomorphine-induced

circling in these animals to the activation of bilateral supersensitive limbic dopamine receptors and unilateral supersensitive caudate receptors. In a second experiment, animals with unilateral caudate depletion received bilateral electrolytic lesions of the nucleus accumbens; these animals failed to circle in response to either apomorphine or amphetamine. In addition, these animals did not display any postural asymmetry.

The interpretation of Pycock and Marsden (1978) was that circling in animals consists of two components, a caudate imbalance causing a postural asymmetry (lateral bending along the longitudinal axis of the spine) and stimulation of mesolimbic dopamine providing a locomotor activation. According to this view, unilateral activation of the caudate induces a postural asymmetry that determines the direction of circling if it occurs; the actual occurrence of circling, however, depends on the locomotion that results from mesolimbic activation. They did suggest, however, that the limbic and caudate components may not be entirely independent of each other; this was suggested on the basis of their finding that animals with bilateral lesions of the accumbens and unilateral lesions of the caudate were not posturally asymmetric.

The idea that the caudate controls posture, hence giving the direction to circling animals, while the nucleus accumbens controls activity, hence contributing to the rate of locomotion, whether it be in a straight or a circular path, has been widely

accepted even though there are more recent data suggesting that this 'two-component' model cannot account for all kinds of dopamine mediated circling behavior. This two-component view is challenged by data suggesting that the role of the caudate is not restricted to a directional role. Animals circle following unilateral injections of dopamine agonists into the caudate even though the drug does not diffuse to the accumbens to stimulate locomotor activity (Herrera-Marschitz et al., 1985; Joyce and Van Hartesveldt, 1984; Wolfson and Brown, 1983). This suggests that unilateral activation within the caudate alone can drive an animal forward to induce circling. This view is also challenged by recent data from electrical and pharmacological stimulation studies suggesting that unilateral activation of the mesolimbic system may not only increase locomotion, but may induce a directional bias.

Unilateral stimulation studies. Circling behavior has been reported following either unilateral electrical or chemical stimulation of the mesolimbic system. Unilateral electrical stimulation of the VTA caused animals to circle away from the stimulated side (Roffman et al., 1978); the circling behavior was blocked by pretreatment with dopamine receptor blockers (Roffman et al., 1978). Similarly, unilateral pharmacological stimulation of the VTA with drugs that unilaterally increase mesolimbic dopaminergic activity induces circling. When neurotensin (Holmes and Wise, 1985b), morphine (Holmes et al., 1983; Holmes and Wise, 1985a; Wise and Holmes, 1986) or [d-pen2,D-Pen5] enkephalin (Jenck, Bozarth and Wise, 1988)

were unilaterally injected into the VTA, animals circled away from the injected side; circling induced by each of these drugs was prevented by pretreatment with dopamine receptor blockers. The type of circling induced by unilateral microinjections of morphine into the VTA was not characterized by pronounced postural asymmetry; instead, the animals followed the perimeter of the testing environment with the side of the body ipsilateral to the stimulation next to the environment's walls (Wise and Holmes, 1986). The animals did not bend the longitudinal axis of the spine laterally unless they reached a corner.

Although the electrical and pharmacological stimulation studies suggest that unilateral activation of the mesolimbic system may cause circling, they are not conclusive. First, in the case of VTA electrical stimulation, it is possible that the activation of non-dopaminergic cells caused the circling; even though neuroleptics blocked the electrically-induced circling (Roffman et al., 1978), it is possible that they did so by debilitating the animals in some general way. Second, in the case of VTA pharmacological stimulation, it is possible that the circling was partly caused by diffusion of the drug to the substantia nigra. Finally, since some VTA cells send projections to the caudate (Fallon and Moore, 1978), it is possible that the circling caused by either electrical or pharmacological stimulation of the VTA was caused by unilateral activation of the caudate.

THE PRESENT EXPERIMENTS

The purpose of the present series of experiments was to further investigate the role of the mesolimbic system in circling behavior. The 'two-component' view of circling (Pycock and Marsden, 1978) suggests that mesolimbic activation causes the locomotor component of circling but does not cause any directional bias; it also suggests that caudate activation causes the directional bias of circling but does not cause the locomotor component. As stated above, the role attributed to the caudate in this view has been questioned on the basis of the findings that unilateral activation of the caudate alone can cause circling (Herrera-Marschitz et al., 1985; Joyce and Van Hartesveldt, 1984; Wolfson and Brown, 1983); these data suggest that mesolimbic activation is not necessary to drive the animal forward. The present studies were conducted to determine whether unilateral activation of the mesolimbic system would result in drug-induced circling behavior.

EXPERIMENT 1:

6-OHDA LESIONS OF A9 AND A10

The purpose of the first experiment was to determine whether amphetamine- and apomorphine-treated animals circle following unilateral 6-OHDA lesions to the A10 area. For purposes of comparison, animals with unilateral 6-OHDA lesions to the A9 area were tested with amphetamine and apomorphine. Animals with unilateral 6-OHDA lesions of either the A9 or the A10 cell region were tested with amphetamine and apomorphine for several weeks following the lesion. The rate of circling as well as the type of circling was observed. While it is well established that animals with A9 area lesions circle following amphetamine and apomorphine injections, previous studies have failed to observe circling in animals with A10 area lesions.

METHOD

Subjects

Twenty male Long-Evans rats, weighing 300-325 grams at the time of surgery, were subjects. They were housed individually with 24-hour access to food and water. Animal room lighting was maintained on a normal twelve hour light-dark cycle.

Lesions

Each animal was given a unilateral infusion of 6-OHDA (8μg in 4μl of 0.9% saline and 0.1% ascorbic acid) under pentobarbital anesthesia (15 mg/kg Somnotol) following pretreatment with desmethylimipramine (25 mg/kg) and

pargyline (50 mg/kg). Doses of 6-OHDA are expressed as the weight of the base. The neurotoxin was injected through a stereotaxically lowered 28 gauge cannula at a rate of 0.4µl/60 seconds. Following the infusion, the cannula was left in place for 4 minutes. The deGroot coordinates for A10 region injector cannulae were 4.0 mm posterior to bregma, 0.5 mm lateral to the midsagittal suture, and 8.5 mm ventral to the dural surface. Half of the rats received the injection in the left hemisphere and half of the rats received the injection in the right hemisphere. The deGroot coordinates for A9 region injector cannulae were 3.6 mm posterior to bregma, 2.1 mm lateral to the midsagittal suture and 8.2 mm ventral to the dural surface. Half of the rats received the injection in the left hemisphere and half of the rats received the injection in the right hemisphere.

Test drugs

Amphetamine sulfate was dissolved in physiological saline and injected intraperitoneally. Apomorphine hydrochloride, dissolved by warming it in physiological saline, was administered subcutaneously. In each case, the dosage was 1.25 mg/kg injected in a volume of 1 ml/kg.

Apparatus

The animals were tested for circling in two settings. The rate of circling was determined in circular plastic test chambers (28 cm in diameter) with flat bottom bases. A velcro harness, wrapped around the rat's rib cage, was attached by a flexible cable to a microswitch device for

counting left and right turns. Circling in one direction closed one microswitch without affecting the other; circling in the opposite direction closed the second microswitch without affecting the first. Full circles were required for a count in either direction. Counts were recorded by a microprocessor at 5-minute intervals. The phenomenology of circling--the stepping patterns and spine-curvature--was determined in an open field that measured 75 cm by 75 cm with 30 cm walls. Behavior was videotaped from a camera vertically overhead for subsequent analysis.

Procedure

Pre-lesion testing. Prior to lesioning, each animal was placed into a test chamber and the numbers of circles toward the left and right were recorded over a 15-min period. Each animal was then removed from the test chamber, injected with 1.25 mg/kg of amphetamine and placed back into the test chamber where the numbers of circles toward the left and toward the right were recorded for an additional 60-min. This test was done to determine whether individual animals had consistent circling biases prior to the lesion.

Post-lesion testing. Each animal was tested with amphetamine 1, 3, 7, 14 and 28 days following the lesioning and with apomorphine 16 days following the lesioning. On each of these test days, each animal was first placed into a test chamber and the numbers of circles to the left and to the right were recorded for a 15-min period. The animal was then injected with either amphetamine (1.25 mg/kg) or apomorphine

(1.25 mg/kg) and placed back into the test chamber; the numbers of circles in each direction were recorded for a 60-min period.

The phenomenology of amphetamine- and apomorphine-induced behavior were each assessed three weeks following the lesion. For this assessment, each animal was tested with amphetamine on one day and with apomorphine on another; the tests were 2 days apart and the order of testing was counterbalanced. Fifteen minutes after injection, each animal was placed into the open field and observed for a 5-min period. The open field behavior was analyzed from videotapes according to (1) the direction of circling (2) the size of the circles (3) the type of stepping movements made while circling (4) the degree of postural asymmetry accompanying the circling and (5) the animal's responsiveness to a food pellet or a thin metal spatula (approximately 15-cm long) brought toward the snout of the animal while it was moving.

Histology

For visualization of central catecholamine-containing neurons, animals were treated with glyoxylic acid following a modification of the method of Battenberg and Bloom (1975). The animals were anesthetized with chloryl hydrate (400 mg/kg) and perfused rapidly with an ice-cold phosphate-buffered Ringers solution containing 0.5% paraformaldehyde and 2% glyoxylic acid. The brains were quickly removed, frozen in crushed dry ice, and stored in a cryostat at -22°C. Twenty-micron coronal sections were cut and thawed onto

chilled glass slides which were immersed in a chilled (2-4°C) bath of 2% glyoxylic acid and 7% sucrose for 2-5 minutes, dried in a warm air stream and then incubated in a covered glass slide container at 80°C for 10 minutes. The sections were examined in a Zeiss fluorescence microscope using epi-illumination with 355-425 nm excitation and 460 nm barrier filters.

The extent of cell loss following the 6-OHDA lesion was estimated by comparing the density of the cells between the lesioned and intact sides. The extent of terminal region loss was estimated by comparing the density of terminals between the lesioned and intact sides. This method provided a crude estimate of the region of dopamine cell-body and terminal loss.

Statistical Analysis

One-way repeated measures analyses of variance were conducted on the net number of circles across days of testing. The net number of circles was obtained by subtracting the number of circles away from the lesioned side from the number of circles toward the lesioned side; thus a positive number indicated a greater number of circles toward the lesioned side and a negative number indicated a greater number of circles away from the lesioned side. The net number of circles prior to the lesion was compared by post-hoc tests to the net number of circles following the lesion.

RESULTS

Histochemical data

A10 lesions. The VTA on the lesioned sides of animals with A10 lesions was devoid of fluorescent A10 cells in all cases. In some rats the degeneration was restricted to A10 cells but in other rats adjacent A9 cells had also degenerated. The degree of A9 cell degeneration after A10 lesions varied; in some rats only the most medial A9 cells degenerated while in others some lateral A9 cells also degenerated. In the most extensive cases only far-lateral A9 cells were detectable. There was less fluorescence in the nucleus accumbens, olfactory tubercle, septum, and parts of the caudate on the lesioned side than on the non-lesioned side. No attempt was made to quantify this decrease since the decrease in fluorescence intensity is, at best, only a crude index of terminal loss.

A9 lesions. The SN on the lesioned sides of A9 lesioned rats varied in the degree of A9 cell degeneration. In some rats only the far-lateral A9 cells degenerated while in others both medial and lateral A9 cells degenerated. In some rats with both medial and lateral A9 degeneration, lateral A10 cells also degenerated. In no animal was the A10 region completely devoid of fluorescence following an A9 lesion. The dopamine-containing terminal regions in the caudate and nucleus accumbens on the lesioned side showed less fluorescence than those on the non-lesioned side.

The rate of circling

A10 lesions. Following A10 lesions animals increased the rate of circling toward the lesioned side under drug-free

conditions and in response to amphetamine and apomorphine. Under drug-free conditions, the increase in circling toward the lesioned side ($F(5,45)=3.84$, $p<.05$) was most pronounced on the first test day following the lesion and gradually decreased through weeks of testing (Fig. 1); the rate of circling toward the unlesioned side was the same prior to and following the lesion. Following amphetamine injections, the increase in the rate of circling toward the lesioned side ($F(5,45)=2.53$, $p<.05$) was most pronounced on test days 1, 7 and 14 (Fig. 2). Generally, the lesions had little effect on the rate of circling toward the unlesioned side, though animals circled more toward this side on the first test day than they did on any other test day. Following apomorphine injection, animals circled toward the lesioned (Tukey, $p< .05$). Before the lesion, under drug-free conditions and following amphetamine injection, some rats circled preferentially toward the right, some circled preferentially to the left, and others circled equally to the left and the right. Following the lesion each animal circled preferentially toward the lesioned side, including those with pre-lesion biases away from the lesioned side.

Variations in dopamine fluorescence did not predict differences in the degree of the lesion-induced circling bias following the lesion. Animals with degeneration restricted to the A10 cell region circled preferentially toward the lesioned side to the same degree as did animals with A10 lesions that encroached well into the A9 region.

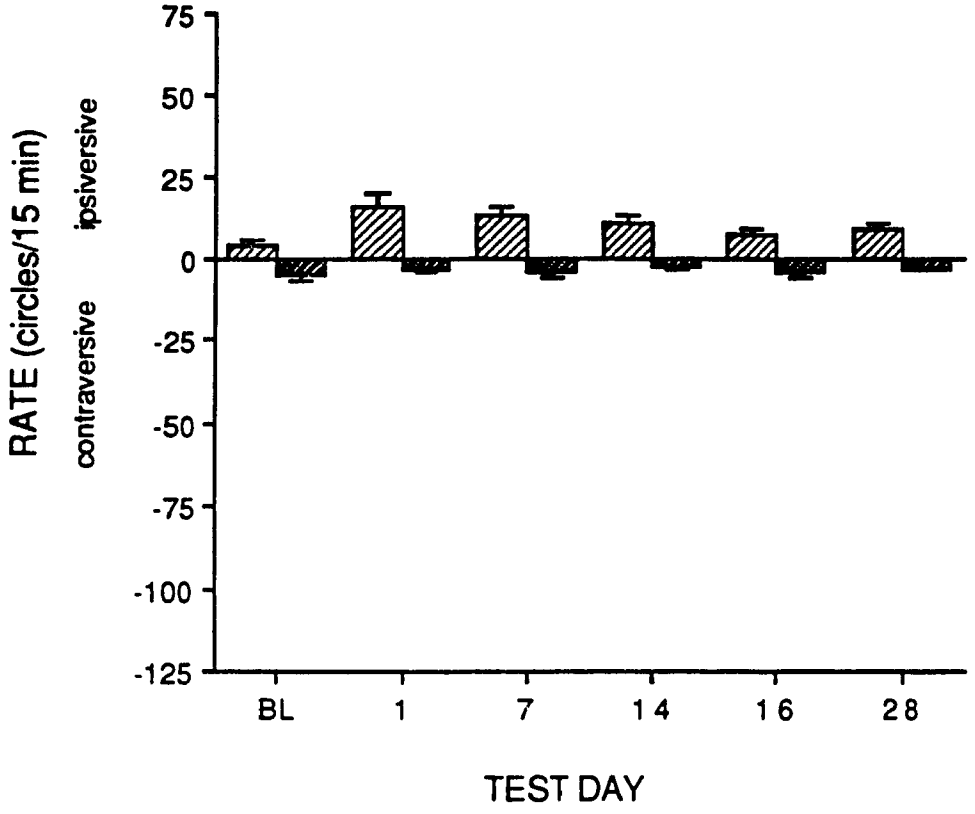

Figure 1. Rates of spontaneous circling in animals with unilateral 6-OHDA lesions of VTA. Baseline (BL) rates were determined on the day before the 6-OHDA injections.

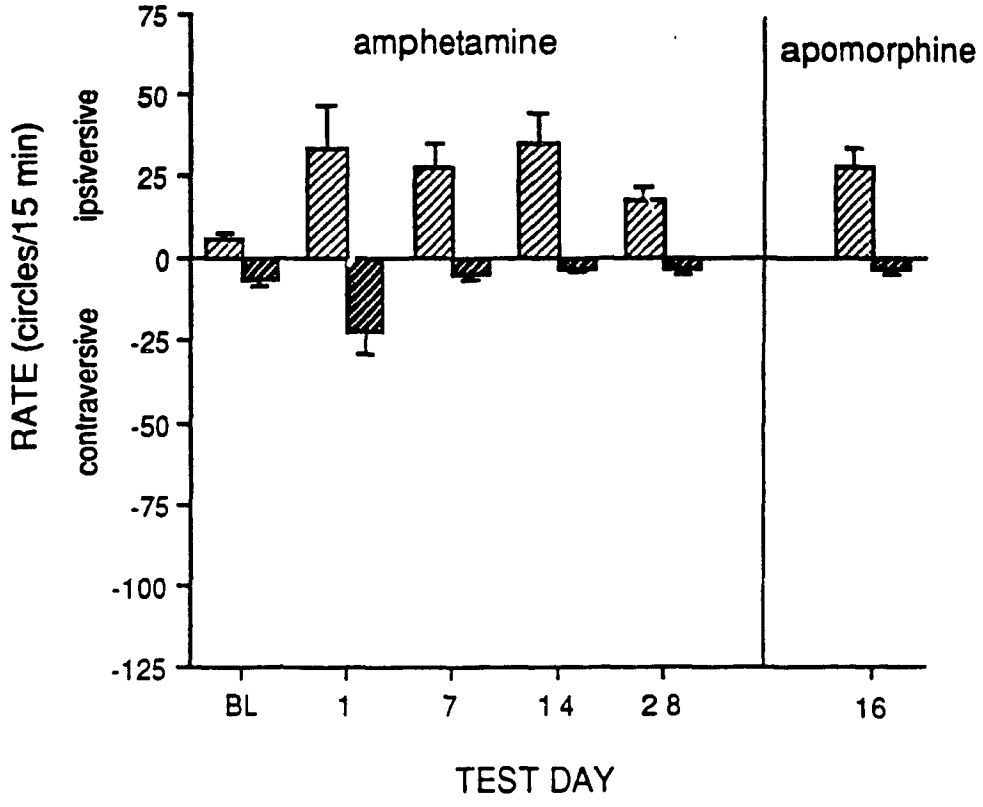

Figure 2. Rates of amphetamine-induced and apomorphine-induced circling in animals with unilateral 6-OHDA lesions of VTA. Baseline (BL) rates were determined on the day before the 6-OHDA injections.

A9 lesions. Following the A9 area lesions, animals increased the rate of circling toward the lesioned side under drug-free conditions and in response to amphetamine; these lesioned animals increased the rate of circling toward the unlesioned side in response to apomorphine. Under drug-free conditions the rate of circling toward the lesioned side increased from the first test day onward (Fig. 3) while the rate of circling toward the unlesioned side was the same prior to and following the lesion ($F(5,45)=2.74$, $p<.05$); this lesion-induced bias following A9 area lesions occurred in the same direction to the bias induced by A10 area lesions. On the first test day, amphetamine-treated animals increased the rate of circling toward the unlesioned side but did not change the rate of circling toward the lesioned side (Fig. 4). On all subsequent test days, however, amphetamine-treated animals reliably increased ($F(5,45)=14.96$, $p<.05$) the rate of circling toward the lesioned side (Fig. 4); on these days the rate of circling toward the unlesioned side was not different from pre-lesion values. Following apomorphine injection, these A9-lesioned rats increased the rate of circling toward the unlesioned side and decreased the rate of circling toward the lesioned side; this contrasts with A10-lesioned rats that increased their rate of circling toward the lesioned side following apomorphine injection. Prior to lesioning, under drug-free conditions and following amphetamine injection, some rats with A9 area lesions circled preferentially toward the right, some circled preferentially to the left, and others circled

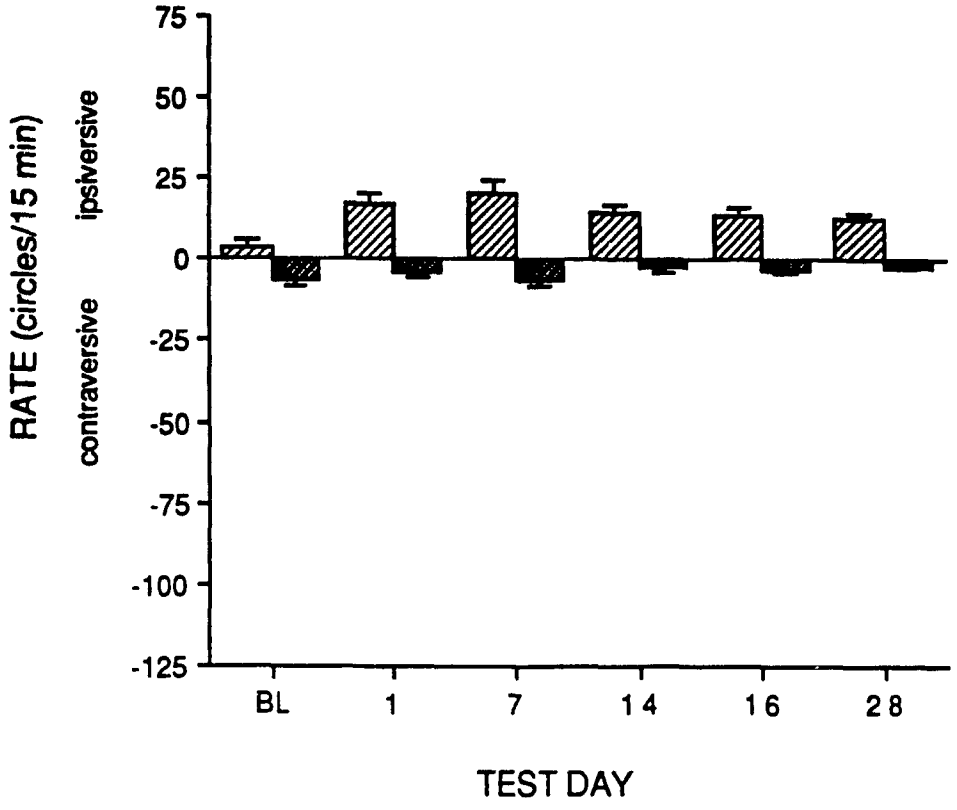

Figure 3. Rates of spontaneous circling in animals with unilateral 6-OHDA lesions of SN. Baseline (BL) rates were determined on the day before the 6-OHDA injections.

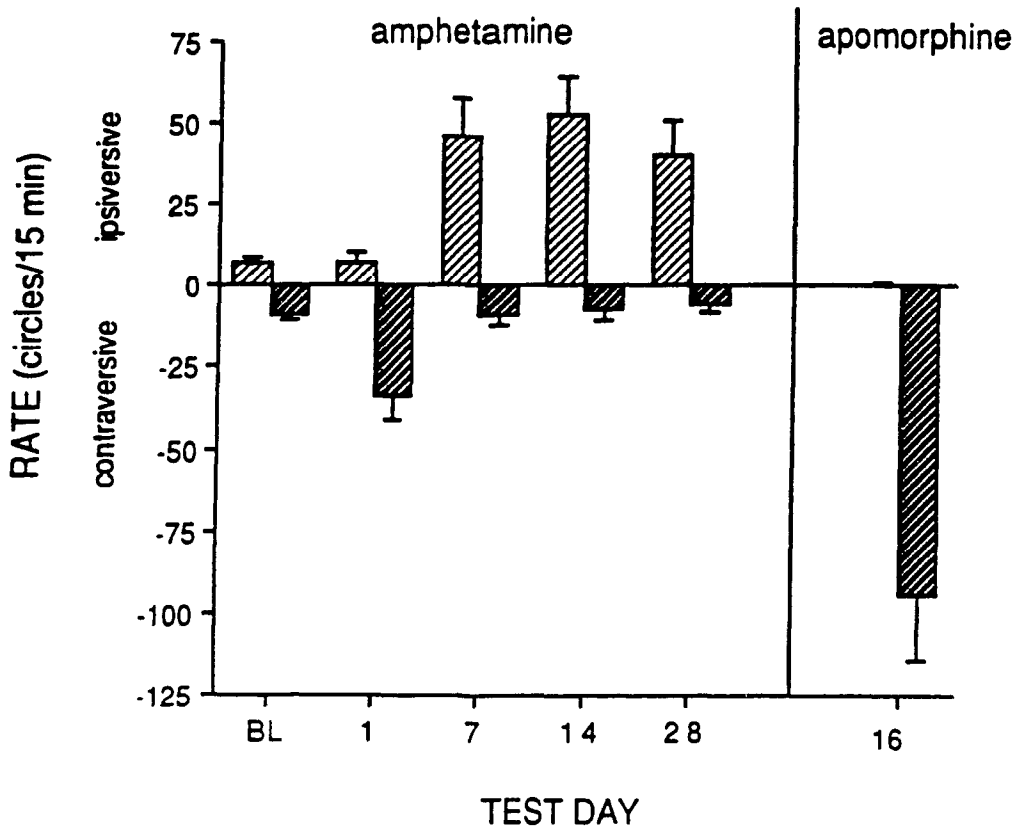

Figure 4. Rates of amphetamine-induced and apomorphine-induced circling in animals with unilateral 6-OHDA lesions of SN. Baseline (BL) rates were determined on the day before the 6-OHDA injections.

equally to the left and the right. Regardless of the bias prior to the lesion, each animal circled preferentially toward the lesioned side following the lesion.

Variations in dopamine fluorescence predicted differences in the degree of the lesion-induced circling bias following the lesion. Animals with cell degeneration of both A9 and A10 circled toward the lesioned side to a greater degree than did animals with cell degeneration restricted to the far lateral part of A9. This contrasts with animals with A10 lesions where the degree of the lesion-induced circling bias was not obviously related to the degree of cell degeneration.

Open field observations

A10 area lesions. Following amphetamine injection in the open field, each animal with an A10 area lesion moved preferentially toward the lesioned side. Eight of ten animals moved close to the open field walls with the flank of the body contralateral to the lesioned side next to the open field wall. These animals turned toward the lesioned side only when they came to a corner. While moving close to the wall the limbs stepped with equal frequency and the longitudinal axis of the body was straight. Since each animal moved along the perimeter of the open field, the size of the circles made by each animal was as large as the open field. The other 2 animals remained in the center of the open field, circling preferentially toward the lesioned side. When these animals circled, the spine was bent and the two forepaws stepped laterally as well as posteriorly. When these animals circled

toward the lesioned side the spine was bent toward that side and when they circled toward the unlesioned side the spine was bent toward that side; while there was no chronic curvature of the spine in either case, each of these animals circled more frequently toward the lesioned side than the unlesioned side. In these animals, the diameter of each circle was greater than would have been predicted on the basis of the curvature of the spine; each circle was approximately twice the length of each rat's body. The manner in which the hindpaws moved could not be observed from the top-view videotapes. All amphetamine-treated A10-lesioned animals sniffed and explored the food pellet or the small metal spatula when either was placed close to the snout.

Variations in dopamine fluorescence did not predict differences in the type of amphetamine-induced circling observed. Animals that made small diameter circles in the center of the open field appeared to have the same degree of A10 cell degeneration as animals that locomoted next to the open field walls.

Following apomorphine injection each A10-lesioned rat locomoted back and forth next to an open field wall; even animals that circled in the center of the open field following amphetamine injection locomoted next to the wall following apomorphine. While moving close to the wall each animal kept the longitudinal axis of its body straight and the limbs stepped with equal frequency. Each of these rats moved its head from side to side and intensely sniffed as it moved along the open

field wall. When the animal reached a corner, it reversed direction and continued to move along the same wall. Each animal stopped moving to sniff the spatula or food pellet placed near its snout. Overall, animals moved substantially less following apomorphine injection than following amphetamine injection in the open field.

A9 area lesions. Following amphetamine injection in the open field, each A9-lesioned rat turned preferentially toward the lesioned side. Seven of ten animals kept the flank of the body contralateral to the lesion next to the open field walls; this resulted in turning toward the lesioned side when an animal came to a corner. Each animal stepped equally with its limbs and the longitudinal axis of the body was straight until a corner was reached. Since each animal moved along the perimeter of the open field, the size of the circles was as large as the open field.

The remaining three A9-lesioned rats moved in circles in the center of the open field. When circling, the spine bent toward the side and the two forepaws stepped laterally as well as posteriorly. The lateral forepaw movements drew the animal into a route with a smaller radius than that of the curve of the spine. The diameter of these circles was roughly the length of the animal's body. When these animals circled toward the lesioned side the spine was bent toward that side and when they circled toward the unlesioned side the spine was bent toward that side; approximately 3 out of 4 of these circles were toward the lesioned side. In these animals it

appeared as though the asymmetrical paw movements preceded the curvature of the spine, rather than the other way around.

All of the A9 lesioned animals, regardless of whether they circled around the perimeter or in the center of the open field, were responsive to changes in the environment following amphetamine injection. Each animal stopped moving and sniffed the food pellet and spatula when they were placed toward the snout of the rat. Each animal demonstrated the ability to turn in either direction.

In summary, the type of circling observed in animals with lesions of the A9 area following amphetamine was similar to that observed in animals with lesions of the A10 area. Following either lesion, most animals locomoted along the perimeter of the open field; in these cases the size of the circles was the size of the open field. The animals that circled in the center of the open field differed from each other in terms of the degree of circling and the diameter of the circles; animals with A9 area lesions circled more frequently and made smaller diameter circles than animals with A10 area lesions. All of these animals showed the capacity to turn either way.

The type of circling induced by apomorphine could not be predicted by the type of circling induced by amphetamine; animals that made small diameter circles following amphetamine responded to apomorphine in the same way as animals that locomoted along the perimeter of the open field. Following apomorphine injection eight animals with A9 area

lesions restricted their movement to one region of the open field and made small diameter circles. Each of these animals curved its spine so sharply that its head almost touched the base of its tail. The forepaws stepped either sideways or forward while the hindpaw on the side opposite to the lesion stepped predominantly backwards. The hindpaw on the lesioned side stepped the least; generally, this paw remained in a relatively fixed position on the open field floor and moved only to complete a circle that was initiated by the movement of the other three paws. When all paws were moving, the result was small diameter circles, about the length of the animal's curved body, directed toward the unlesioned side. When circling, these animals responded minimally to environmental stimuli. If an open field wall was in the path of a circling animal, it pushed up against the wall until it completed the circle; the animal did not adjust its stance to avoid the wall. Similarly, if a food pellet or a small metal spatula was placed toward the snout of the rat, it briefly sniffed it then continued circling. These eight rats had large lesions with degeneration of all of A9 and, in several cases, partial degeneration of A10.

The remaining two animals explored the entire open field and circled toward the unlesioned side. When circling, the forepaws stepped either sideways or forward while the hindpaw on the side of the lesion stepped forward. When these three paws moved at the same time the rat turned 180°. The hindpaw on the side opposite to the lesion, which was always

the last to be moved, then stepped forward resulting in the completion of a circle. The diameter of the resulting circle was approximately twice the length of each rat's body. Each rat only curved its spine when it was circling; more frequently, the spine was straight and the rat's limbs stepped equally. These two rats sniffed the food pellet and the spatula when they were placed near the snout. These rats had small lesions, restricted to the lateral portion of the A9 cell group; the response of these rats to amphetamine was not predictably different from the rats with much larger lesions.

In summary, the type of apomorphine-induced circling observed in animals with lesions of the A9 area was very different from that observed in animals with lesions of the A10 area. Following apomorphine injection, most rats with A9 area lesions moved in one circumscribed region of the open field, circled very tightly, and failed to respond to environmental stimuli. In contrast, all rats with A10 area lesions explored the entire open field, circled loosely, and responded to environmental stimuli following apomorphine injection.

DISCUSSION

Animals with lesions of either the A10 or the A9 dopamine cell group circled under no-drug conditions and following amphetamine and apomorphine injection. Since, in the case of animals with lesions of the A10 area, A10 cells and their fibers degenerated on the lesioned side, circling in these rats prior to and following drug injection is assumed to have

resulted from asymmetric activation of the A10 system. Since, in the case of animals with lesions of the A9 area, A9 cells and their fibers degenerated on the lesioned side, circling in these rats prior to and following drug injection is assumed to have resulted from asymmetric activation of the A9 system.

That circling can be a consequence of lesions restricted to the A10 dopamine cell group is a new finding and one that raises questions for the generally accepted 'two-component' hypothesis of circling that states that activation of the mesolimbic system--regardless of side--determines the degree of locomotion, while an imbalance in activation of the nigrostriatal system determines the direction of this activity. According to this view, unilateral or bilateral activation of the mesolimbic system drives the animal forward while unilateral activation of the nigrostriatal system steers the animal away from the activated side (Moore and Kelly, 1977; Pycock and Marsden, 1978). The data presented here suggest that activation of the mesolimbic system not only determines the degree of locomotion, but can also bias the direction of locomotion.

The circling observed following A10 lesions in the present study is consistent with the observations of others that animals circle following treatments that unilaterally increase mesolimbic dopamine activity; following ventral tegmental microinjections of morphine, [d-pen2,D-Pen5] enkephalin or neurotensin animals circle away from the injected side

(Holmes and Wise, 1985a; Holmes and Wise, 1985b; Jenck et al.,1988). In each of these cases, the circling results because the animals locomote with a directional preference, rather than resulting from forced asymmetric movements. Animals also circle following unilateral nucleus accumbens injections of apomorphine (Starr and Summerhayes,1982; Messier,1989, personal communication).

Although A9 and A10 lesions each altered the animals so that they circled more in one direction than the other, there were some differences in the effects of amphetamine and apomorphine injection following these lesions. Amphetamine injections on the first test day increased the general activity of A10-lesioned animals but did not result in circling whereas animals with A9 area lesions circled toward the unlesioned side. Circling toward the unlesioned side shortly following A9 area lesions is assumed to be due to degeneration-induced release of dopamine from storage pools of lesioned neurons, which reaches its peak one day following the lesion and is complete by three days following the lesion (Ungerstedt, 1971b). It is not clear why animals with A10 area lesions did not circle preferentially toward the unlesioned side at this time. Even in individual cases where animals circled toward the unlesioned side more than the lesioned side, there was still a substantial number of circles directed toward the lesioned side, far more than the number of circles directed toward this side prior to the lesion and far more than the number of circles directed toward this side by any animal with

an A9 area lesion on this day. However, these animals did circle more toward the unlesioned side on this test day than on any other test day following amphetamine injection, suggesting that amphetamine increased the degeneration-induced release of dopamine on the lesioned side on this day. One possibility is that the time course of degeneration-induced release following lesions of the A10 system differs from that following lesions of the A9 system; if this were the case, animals with A10 area lesions might have circled away from the lesioned side if first tested several hours following the lesion.

Following the initial difference in the direction of circling following amphetamine injection, the circling was quantitatively and qualitatively similar in the A9- and A10-lesioned animals. The rates of circling were not obviously different during subsequent tests and the stepping patterns observed following amphetamine injection were similar. In addition, none of the animals were consistently posturally asymmetric following amphetamine injections.

The most surprising finding in the present study was that A10-lesioned animals circled toward the lesioned side following apomorphine injection but that A9-lesioned animals circled away from the lesioned side following apomorphine injection. It is well established that animals with A9 lesions that result in at least an 85 percent reduction in striatal dopamine release circle away from the lesioned side following apomorphine (Hefti et al., 1980; Kozlowski Sawyer and

Marshall, 1980; Ungestedt, 1971). Since there is an increase in the number of dopamine receptors on the denervated side (Creese et al., 1977), apomorphine causes greater activation of that side and results in circling away from that side (Hefti et al., 1980; Ungerstedt, 1971; Ungerstedt and Marshall, 1975). If we restrict ourselves to currently accepted models of circling behavior--that animals turn away from the side with greater dopaminergic activation--we would have to speculate that animals with A10 lesions circled toward the lesioned side following apomorphine because apomorphine activated more dopamine receptors on the unlesioned side. This is puzzling since the lesions should have been extensive enough to induce receptor up-regulation in the nucleus accumbens (Staunton, Magistretti, Koob, Shoemaker and Bloom, 1982); A10 lesions induced by smaller doses of 6-OHDA than that used here have been reported to increase apomorphine's locomotor stimulating effects presumably due to activation of up-regulated dopamine receptors within the nucleus accumbens (Kelly et al., 1975). Thus animals in this study should have circled away from the lesioned side upon apomorphine administration, because apomorphine should have more effectively activated the supersensitive lesioned side. It may be the case that apomorphine interacts differently with a unilaterally lesioned A10 system than it does with a unilaterally lesioned A9 system or a bilaterally lesioned A10 system, but this remains to be tested. Such a thing could occur as a consequence of a change in the activity of pathways that cross from the

lesioned A10 region to the contralateral dopamine-containing terminal regions (Altar et al., 1983; Fass and Butcher, 1981; Jaeger et al., 1983; Pritzel et al., 1983).

As well as circling in different directions following apomorphine injection, the type of circling observed in the A9- and A10-lesioned animals differed following apomorphine injection. During the open field test, following apomorphine injection, each A10-lesioned animal forward locomoted next to the open field wall; most A9-lesioned animals remained in one region of the open field and pivoted. It is unclear why animals with A10 lesions respond differently to apomorphine than animals with A9 lesions. One clue to the difference in the type of circling may be found by examining the types of behaviors that unlesioned animals generally display following the dose of apomorphine used in this study (1.25 mg/kg). This high dose of apomorphine generally causes animals to display a composite of stereotyped behaviors, including repetitive head and limb movements, biting, pivoting and sniffing (Kelly et al., 1975; Szechtman, Ornstein, Teitelbaum and Golani, 1985). In addition, Szechtman et al. (1985) reported that these stereotyped behaviors unfold in a relatively fixed sequence; following 1.25 mg/kg of apomorphine, forward walking yields first to circling, then to revolving, then to tight pivoting and finally to side-to-side movements of the forequarters around relatively stationary hindquarters. The behavior of the A10-lesioned rats did not follow this progression following apomorphine injection; the forward walking did not yield to

circling, revolving or pivoting during the test period. Even when these animals were observed 30 minutes following injection, they were still walking forward. Generally, the forward walking seen following apomorphine injection only lasts several minutes (Szechtman et al., 1985). That A10-lesioned animals did not show the progression from forward walking to intense stereotypy (pivoting) suggests that this dose of apomorphine might be less effective in A10-lesioned rats than it is in unlesioned rats. If we accept that dopamine receptors within the caudate mediate at least some of apomorphine's stereotypy-inducing effects (Kelly et al., 1975), it could be argued that the A10 lesions, in some way, caused the caudate to become less responsive to apomorphine, perhaps by causing a down-regulation of caudate dopamine receptors. It has been suggested that unilateral 6-OHDA lesions of the A9 region can cause a down-regulation of dopamine receptors in the intact striatum (Costall, Kelly and Naylor, 1983), but it is not known whether lesions restricted to the A10 region could induce a bilateral down-regulation of caudate dopamine receptors.

The behavior of the A9-lesioned rats did progress from forward walking to pivoting. At the time that these animals were observed in the open field, pivoting dominated. Apomorphine generally induces pivoting in unlesioned animals, at the time interval following injection (15-20-min) that the A9-lesioned animals in the present study were observed (Szechtman et al., 1985). The lateralized nature of the

pivoting observed in the A9-lesioned animals can be attributed to apomorphine's activation of the greater number of dopamine receptors in the caudate on the lesioned side; since the lesioned side would have been preferentially activated, pivoting behavior should be expected to be primarily directed toward the unlesioned side. Whereas in unlesioned animals there does not appear to be a relationship between which hind leg is used as a pivot (for postural support) and the direction of circling induced by apomorphine injection (Szechtman and Pisa, 1986), in animals with A9 lesions the hindpaw on the lesioned side was always used as a pivot and circling was always directed toward the unlesioned side. Although apomorphine can induce circling in unlesioned animals, the rate of circling is substantially lower than that induced following A9 lesions.

One last topic that deserves discussion, even though it does not bear on the differences induced by A9 and A10 lesions, relates to the differences in the types of circling observed following amphetamine and apomorphine injection in A9-lesioned animals. It is possible that these differences result from the fact that apomorphine has been found to be more potent and efficacious than amphetamine in inducing stereotypy, particularly at the dose (1.25 mg/kg) used in the present study (Feigenbaum, Yanai, Blass, Moon and Klawans, 1982). If these differences in the types of circling are secondary to differences in the effectiveness of these drugs, then doses of amphetamine that are known to induce

stereotypy should induce circling that is phenomenologically similar to the type of circling reported here following apomorphine. Similarly, lower doses of apomorphine--known to consistently increase locomotion-- should induce circling that is phenomenologically similar to the type of circling reported here following amphetamine. Consistent with this possibility are reports of others that animals with A9 area lesions make lateralized movements and pivot following high, stereotypy-inducing (5.0 mg/kg and above) doses of amphetamine (Costall et al., 1976; Kelly, 1975; Ungerstedt and Arbuthnott, 1970). The exact nature of the relationship between circling and stereoypy-inducing doses of dopamine agonists remains to be determined.

EXPERIMENT 2:

ELECTROLYTIC LESIONS OF A9 AND A10

Experiment 1 showed that animals with unilateral 6-OHDA lesions of the A10 dopamine-containing cell group circled following amphetamine and apomorphine injection. Since the A10 6-OHDA lesions caused some damage to A9 dopamine-containing cells in most cases, it could be argued that the circling that occurred following injection of these drugs resulted from asymmetrical activation of the A9 system. The main purpose of the present experiment was to determine whether amphetamine- and apomorphine-treated animals circle following small, unilateral, electrolytic lesions restricted to the A10 region. Electrolytic lesions are anatomically specific and the boundaries of this type of lesion are easier to define than the boundaries of a 6-OHDA lesion. Another purpose of the present experiment was to begin to explore more fully the influence of the environment on the behavior of the animals. In animals presumed to have asymmetrical activation of the A10 system, Wise and Holmes (1986) found that the direction of circling was not a fixed consequence of which hemisphere had the stronger dopaminergic activation; in their experiment the direction of circling changed as a function of changes in environmental contingencies. Zeigler and Szechtman (1988), however, subsequently reported that the circling caused by amphetamine in A9-lesioned rats was not controlled by environmental contingencies; these animals were presumed to have

asymmetric activation of the A9 system, suggesting that the circling that occurs following amphetamine injections in animals with A9 area lesions may be a fixed consequence of which hemisphere has the stronger dopaminergic activation. Thus, the data of Wise and Holmes (1986), along with those of Zeigler and Szechtman (1988), suggest that the type of circling observed following asymmetric activation of the A10 system may be subtly different from the type of circling observed following asymmetric activation of the A9 system. A third purpose of the present experiment was to determine whether the patterns of circling seen in Experiment 1 were typical of the drugs tested or were unique to the particular doses chosen.

METHOD

Subjects

Twenty male Long-Evans rats, weighing 350-400 grams at the time of surgery, were subjects. They were housed individually with 24 hour access to food and water with room lighting maintained on a twelve hour light-dark cycle.

Lesions

Under sodium pentobarbital anesthesia (60 mg) a unilateral monopolar 254 µm stainless steel lesioning electrode, insulated with varnish except at the cross-section of the tip, was lowered into each rat. The deGroot coordinates for A10 lesions (n=10) were 4.0 mm posterior to bregma, 0.5 mm lateral to the midsagittal suture, and 8.5 mm ventral to the

dural surface. The deGroot coordinates for A9 lesions (n=10) were 3.6 mm posterior to bregma, 2.1 mm lateral to the midsagittal suture, and 8.2 mm ventral to the dural surface. Lesions were produced by passing a direct anodal current of 1 mA, delivered over a 20-sec period with a lesion maker (Grass Instruments, Model DCLM5A). A clip on the animal's tail served as the cathode. Half of the rats received lesions in the right hemisphere and half in the left hemisphere. Following lesioning the electrode was removed from the rat, the hole in the skull was filled with bone wax and the wound was closed with sutures.

Test drugs

Amphetamine sulfate was dissolved in physiological saline and injected intraperitoneally. Apomorphine hydrochloride, dissolved by warming it in physiological saline, was administered subcutaneously. Each drug was injected in a volume of 1 ml/kg.

Apparatus

The animals were tested for circling in two settings. The rate and direction of circling were determined in circular 28-cm diameter plastic buckets (40 cm high) with flat bases. A cable connected each animal (by a velcro harness wrapped around the rat's rib cage) to a shaft which turned toward the left and toward the right. During the first 2 weeks of testing, a thread from a spool on a spindle was attached to the shaft. Each time the animal moved in a consistent direction, the cable and shaft turned and the thread wound around the shaft.

The number of thread winds around the shaft at 5-min intervals provided the net number and direction of circles. During the last 3 weeks of testing the shaft was connected to a device with two microswitches; this device is described in Experiment 1.

The phenomenology of circling was determined on a square elevated platform divided by a wall into an inside and an outside lane (Fig. 5). Each lane was 15 cm wide; the circumference of the 30 cm high dividing wall was 240 cm. The length of each outer side of the platform was 120 cm. The center of the platform had a square hole, 30 cm on a side.

Procedure

Pre-lesion testing. Prior to lesioning, each animal was placed into a bucket and the rate of circling was recorded over a 15-min period. Each animal was then removed from the test chamber, injected with 1.25 mg/kg of amphetamine and placed back into the test chamber for an additional 60 minutes. This test was done to determine whether individual animals had circling biases prior to the lesion.

Post-lesion testing. On each post-lesion test day, each animal was first placed in a test chamber and the rate of circling was recorded over a 15-min period. Each animal was then removed from the test chamber, injected with either amphetamine or apomorphine and placed back into the test chamber for an additional 60 minutes. The rate of circling following 1.25 mg/kg of amphetamine was determined for each rat 1, 3, 7, and 28 days following the lesion. The rate of

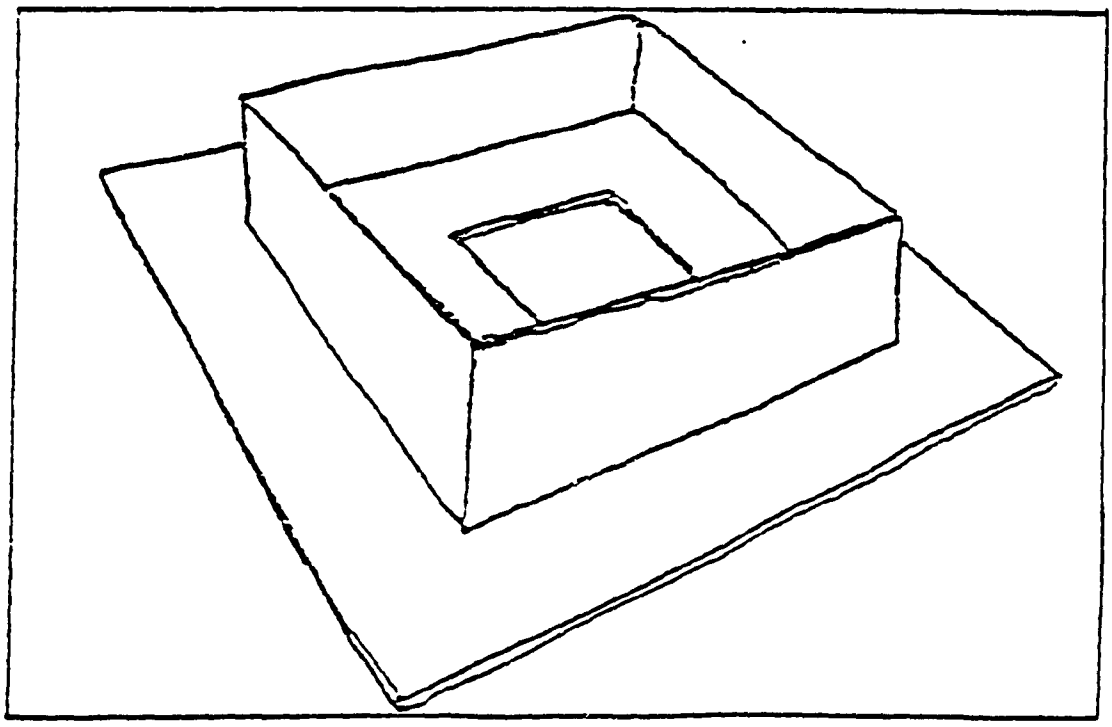

Figure 5. Drawing of the double field used in experiment 2.

circling following 1.25 mg/kg of apomorphine was determined 14 days following the lesion. In addition, eight rats (4 VTA and 4 SN) were tested following 5.0 mg/kg of amphetamine and 0.31 mg/kg of apomorphine, 30 and 32 days following the lesion, respectively.

The type of circling that occurred following apomorphine and amphetamine injections in each lane of the elevated platform was analyzed in terms of (1) the direction of circling (2) the size of the circles (3) the type of stepping movements made while circling and (4) the degree of postural asymmetry accompanying the circling. During the third week of testing each animal was tested with 1.25 mg/kg of amphetamine on one day and with 1.25 mg/kg apomorphine on another. The tests were two days apart and the order was counterbalanced. During the fifth week of testing four VTA-lesioned and four SN-lesioned rats were tested with 5.0 mg/kg amphetamine on one day and with 0.31 mg/kg apomorphine on another; the tests were again two days apart and the order of testing was counterbalanced. Fifteen minutes after injection, each animal was placed onto the platform and was observed in each testing environment for a 4-min period. Some animals were first tested on the lane outside the square dividing wall while others were first tested on the lane inside the square dividing wall.

Confirmation of lesion placement

At the completion of testing each animal was anesthetized with chloryl hydrate (400 mg/kg) and perfused with

physiological saline followed by 10% formalin solution. The brain was removed and stored in formalin for at least 4 days; it was then frozen and 40 micron sections were taken and stained with thionin for histological confirmation of lesion placement and size.

Statistical analysis

One way repeated measures analyses of variance were conducted on the net number of circles across days of testing. The net number of circles was obtained by subtracting the number of circles away from the lesioned side from the number of circles toward the lesioned side; thus a positive number reflected a greater number of circles toward the lesioned side and a negative number a greater number of circles away from the lesioned side. The net number of circles prior to the lesion was compared by post-hoc tests to the net number of circles following the lesion.

RESULTS

The rate of circling

Animals with VTA lesions were generally affected by apomorphine and amphetamine in the same way, though not to the same extent, as animals with SN lesions. VTA- and SN-lesioned animals consistently circled toward the lesioned side in response to the high dose (5.0 mg/kg) of amphetamine and toward the lesioned side following either low or high doses of apomorphine.

On the first test day, following injection with the moderate dose (1.25 mg/kg) of amphetamine, (Fig.6) VTA-lesioned

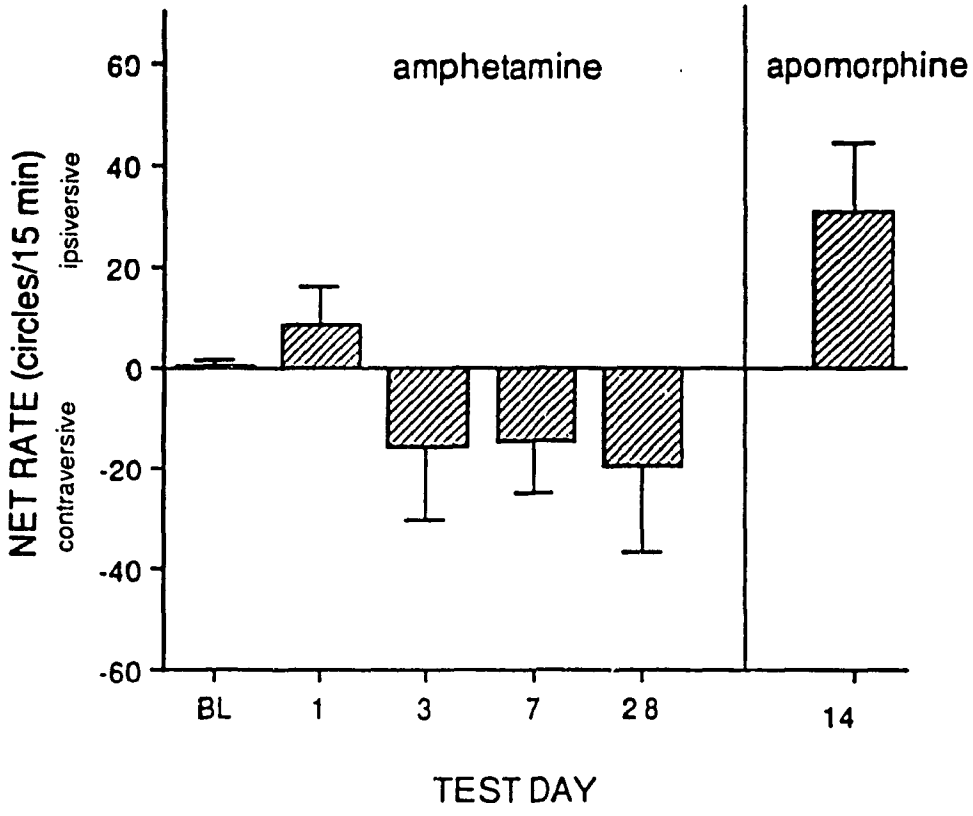

Figure 6. Rates of amphetamine-induced and apomorphine-induced circling in animals with unilateral electrolytic lesions of the VTA.

animals circled toward the lesioned side but SN-lesioned rats circled toward the unlesioned side (Fig. 7). On all subsequent test days both VTA- and SN-lesioned animals circled toward the unlesioned side following this dose; the rate of circling, on these test days, was similar for VTA- and SN-lesioned animals.

In the case of a moderate dose of amphetamine in VTA-lesioned rats, the rate of circling following the lesion was not significantly different from the rate of circling prior to the lesion (Fig. 6).($p>.05$) However, the rate of circling following the moderate dose of amphetamine (on Test Day 28) was significantly different from the rate of circling following the high dose (on Test Day 30) ($df(3)$, $t=-2.63$, $p<.05$); animals circled away from the lesioned side following the moderate dose but circled toward the lesioned side following the high dose (Fig. 8).

In the case of a moderate dose of amphetamine in SN-lesioned rats, the rate of circling following the lesion was significantly different from the rate of circling prior to the lesion ($F(4,28)=18.45$, $p<.05$), but only on Test Day 1 (Fisher PLSD, $p<.05$) (Fig. 7). The rate of circling following the moderate dose (on Test Day 28) was significantly different from the rate of circling following the high dose (on Test Day 30) ($df,3$), $t=-5.3$, $p<.05$); as was the case with VTA-lesioned animals, these SN-lesioned animals generally circled away from the lesioned side following the moderate dose but circled toward the lesioned side following the high dose (Fig. 9).

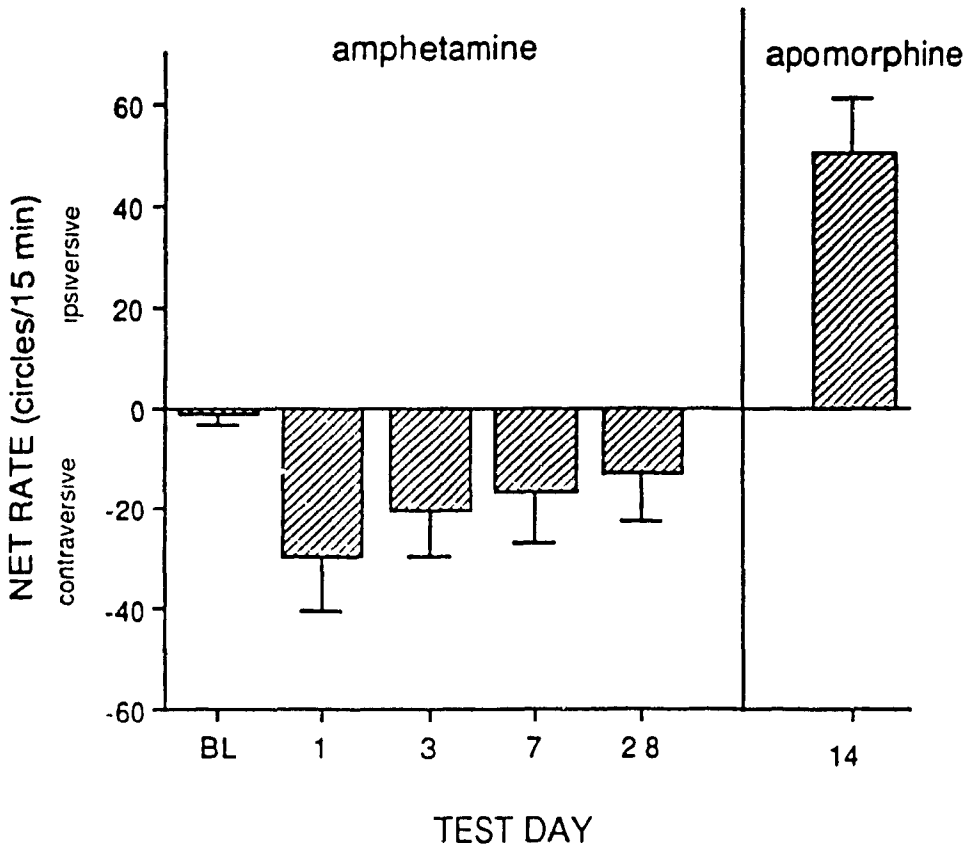

Figure 7. Rates of amphetamine-induced and apomorphine-induced circling in animals with unilateral electrolytic lesions of the SN.

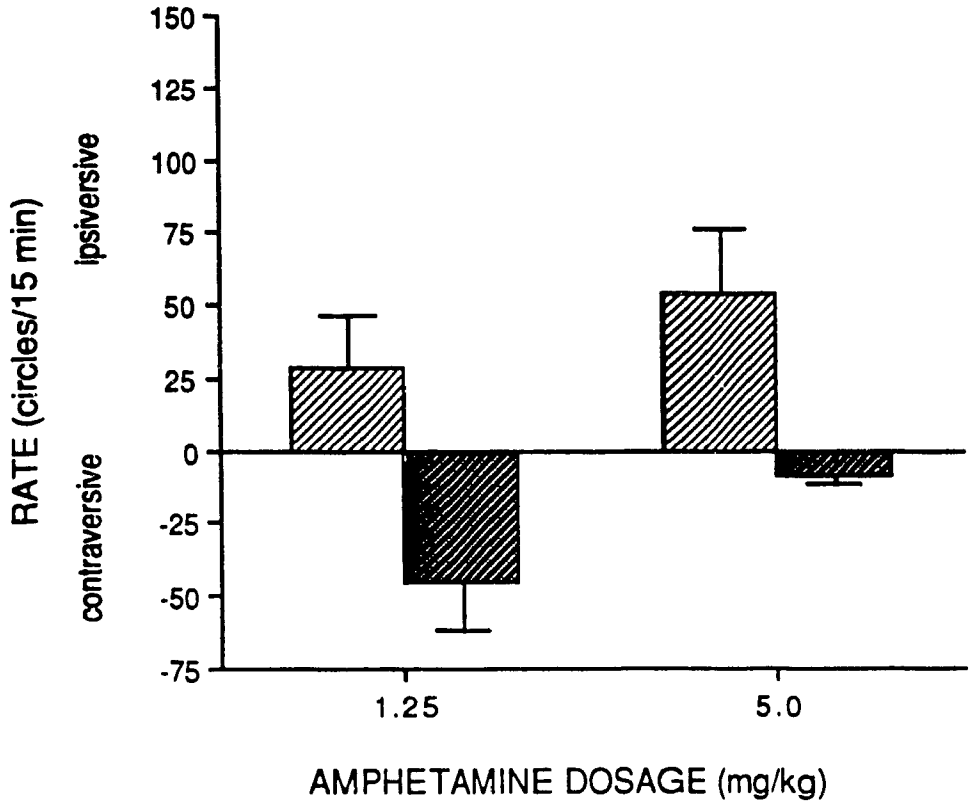

Figure 8. Rates of moderate- and high-dose amphetamine-induced circling in animals with electrolytic lesions of the VTA.

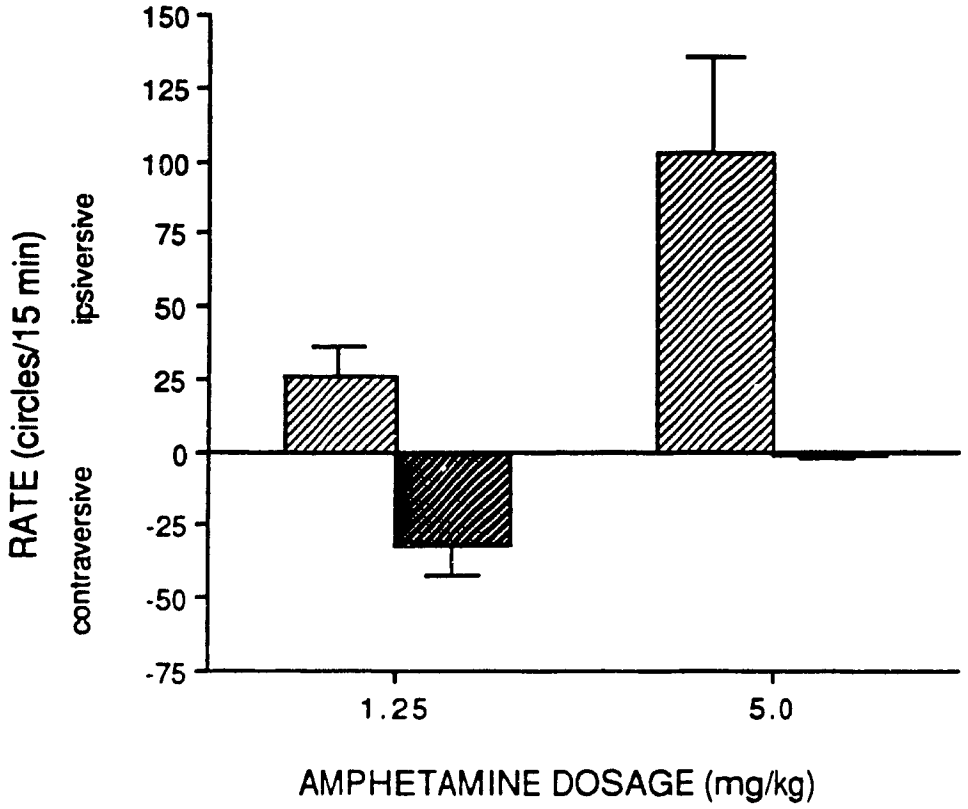

Figure 9. Rates of moderate- and high-dose amphetamine-induced circling in animals with electrolytic lesions of the SN.

Each VTA-lesioned and SN-lesioned animal circled toward the lesioned side following each dose of apomorphine. Following the low dose of apomorphine, the VTA-lesioned animals (Fig. 10) circled less than the SN-lesioned animals (Fig. 11).

The most pronounced circling under drug-free conditions occurred on the first test day following either VTA (Fig. 12) or SN lesions (Fig. 13); however, VTA-lesioned animals circled toward the lesioned side while SN-lesioned animals circled toward the unlesioned side. On the first test day, when the SN-lesioned were stationary prior to being placed into the testing chamber, the longitudinal axis of each animal's body was markedly curved toward the unlesioned side; by Test Day 3 the body of each of these animals was no longer curved when the animal was stationary. In contrast, no curving of the longitudinal axis of any VTA-lesioned animal was seen. The spontaneous circling following the VTA lesion ($F(5,35)=7.75$, $p<.05$) disappeared by the third test day while spontaneous circling following the SN lesion ($F(4,28)=12.19$, $p<.05$) disappeared more gradually.

Elevated platform observations

The type of circling observed following the moderate (1.25 mg/kg) dose of amphetamine in VTA-lesioned rats was similar to the type of circling observed following this dose in SN-lesioned animals. However, the type of circling observed following the high (5.0 mg/kg) dose of amphetamine in VTA-lesioned animals differed from the type of circling observed

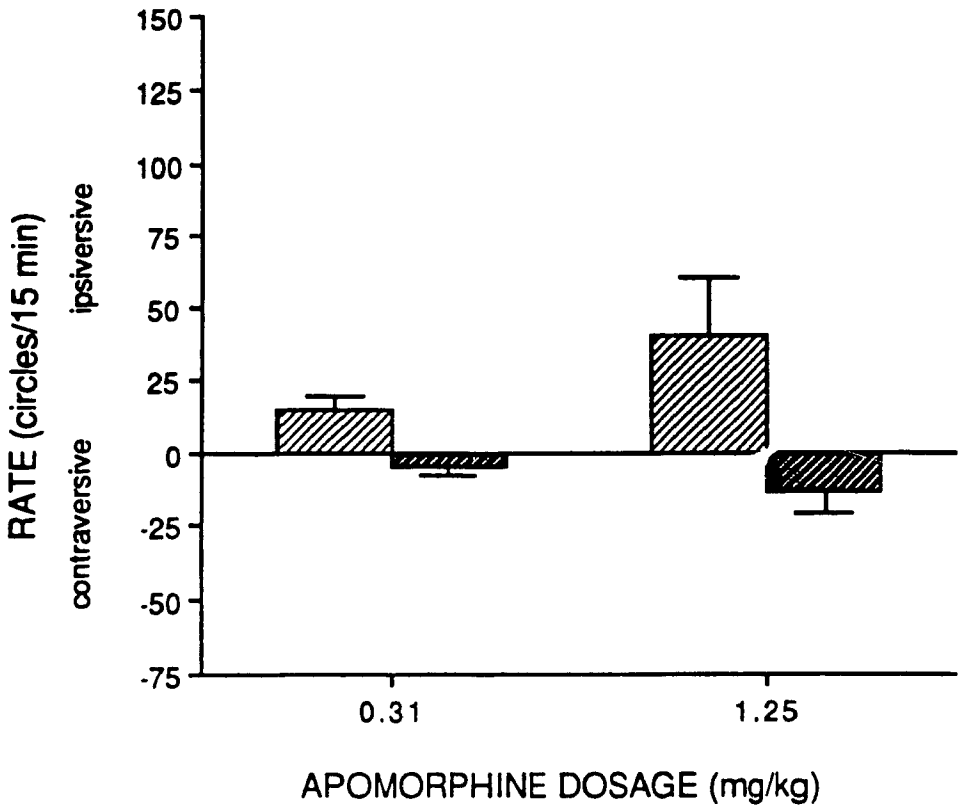

Figure 10. Rates of moderate- and high-dose apomorphine-induced circling in animals with electrolytic lesions of the VTA.

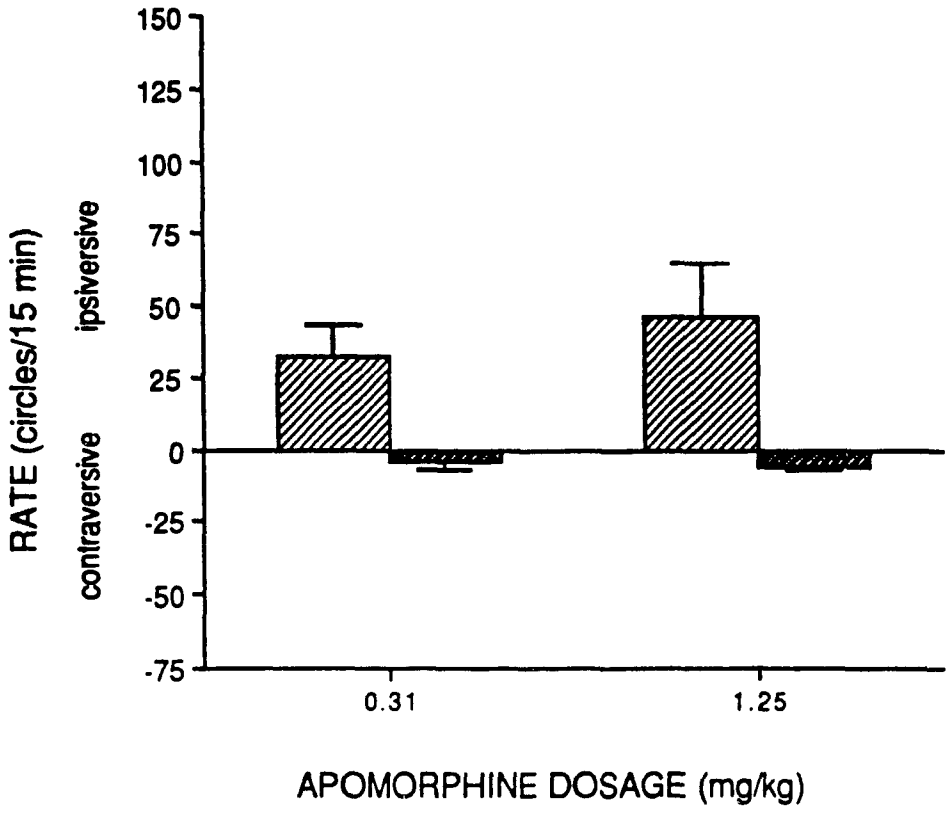

Figure 11. Rates of moderate- and high-dose apomorphine-induced circling in animals with electrolytic lesions of the SN.

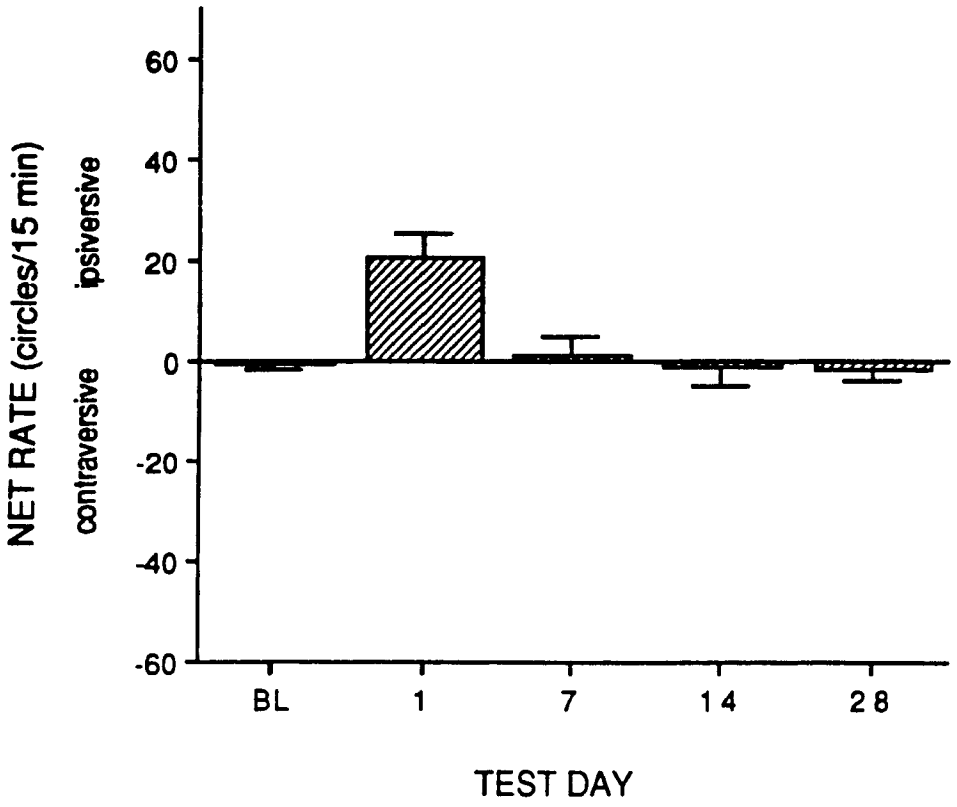

Figure 12. Rates of spontaneous circling in animals with unilateral electrolytic lesions of VTA. Baseline (BL) rates were determined on the day before lesioning.

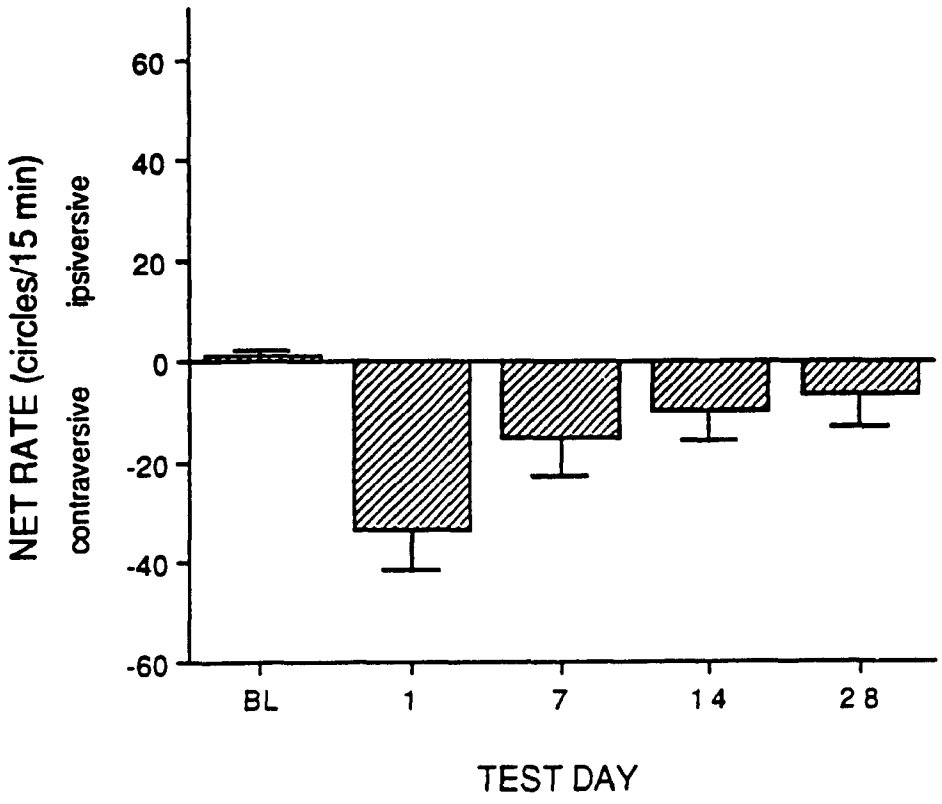

Figure 13. Rates of spontaneous circling in animals with unilateral electrolytic lesions of SN. Baseline (BL) rates were determined on the day before lesioning.

following this dose in SN-lesioned animals. Following either lesion the preferred direction of circling following the moderate (1.25 mg/kg) dose of amphetamine was generally determined by which flank the animal kept next to the open field wall. Following the moderate dose, each VTA- and each SN-lesioned rat moved along the vertical walls with the ipsilateral flank preferentially--but not exclusively--next to the wall. Approximately three out of every five circles around the perimeter of the open field were made with the ipsilateral flank next to the wall. When the ipsilateral flank was next to the dividing wall, animals turned away from the lesioned side at the corners on the inner lane and turned toward the lesioned side at the corners on the outer lane of the elevated platform. When the contralateral flank was next to the dividing wall, animals turned toward the lesioned side at the corners on the inner lane and turned away from the lesioned side at the corners on the outer lane of the elevated platform. As each animal moved next to the dividing wall, its limbs stepped with equal frequency and the longitudinal axis of its body was straight.

The type of circling observed following the high dose (5.0 mg/kg) of amphetamine differed from the type of circling observed following the moderate dose; this was true for both VTA- and SN-lesioned animals. There was a progressive change in the phenomenology across time following this high dose; the behavior during the first few minutes of open field observation was strikingly different from the behavior during

the last minutes. Initially, following this high dose, each VTA- and SN-lesioned animal moved next to the dividing wall with the contralateral flank always next to the wall; this resulted in turning toward the lesioned side at the corners on the inner lane and in turning away from the lesioned side at the corners on the outer lane of the elevated platform. While moving close to the dividing wall the limbs stepped with equal frequency and the longitudinal axis of the body was straight. After several minutes of testing the VTA-lesioned animals stopped stepping forward and began making stereotyped movements consisting of sniffing, repetitive lateral head movements and occasional shuffling of the paws from one side of the body toward the other. SN-lesioned animals also progressively stopped stepping forward, but they then began making small diameter circles toward the lesioned side, reminiscent of apomorphine-like circling (see below). When these SN-lesioned animals circled, the body was posturally asymmetric and the limbs stepped unequally; the forepaws stepped either forward or sideways while the hindpaw on the side ipsilateral to the lesion stepped predominantly backwards. The hindpaw on the side contralateral to the lesion served as a pivot and moved only when the animal had to complete a movement. Following either dose of amphetamine, VTA-lesioned and SN-lesioned animals rarely approached the inner or outer edges of the testing platform.

The circling observed following apomorphine in VTA-lesioned rats differed slightly from the circling observed in

SN-lesioned rats. Following the high dose, VTA-lesioned animals circled occasionally while SN-lesioned animals circled continuously. VTA-lesioned animals bent the longitudinal axis of the body alternately toward the lesioned and unlesioned side, while SN-lesioned animals bent the longitudinal axis of the body only toward the lesioned side.

Following either the 1.25 mg/kg or 0.31 mg/kg dose of apomorphine, the VTA-lesioned animals locomoted very little; the hindpaws were usually held stationary and the forepaws moved laterally back and forth from left to right. When the forepaws moved laterally toward the left, it resulted in the longitudinal axis of the body curving toward the right; when the forepaws moved laterally toward the right, it resulted in the longitudinal axis of the body curving toward the left. Thus asymmetrical movement appeared to precede curvature of the spine, rather than the other way around. After a number of these side to side movements, the animals circled toward the lesioned side. When circling, the forepaws moved laterally away from the lesioned side while the hindpaw on the side ipsilateral to the lesion stepped predominantly backwards. The hindpaw on the side contralateral to the lesion stepped the least, moving only to complete the shift that was initiated by movement of the other three paws. When all paws were moving the result was a small diameter circle, about the length of the animal's curved body, directed toward the lesioned side. Each circle was followed by a number of side to side bending movements before another circle occurred; there

were no occasions when an animal circled continuously. The same behavior was induced by apomorphine regardless of whether the animal was placed in the inner or outer lane of the elevated platform.

The SN-lesioned rats also remained in one region of the open field, but they circled continuously with the longitudinal axis of the body bent toward the lesioned side. The limb movements made by the SN-lesioned animals as they circled were similar to the limb movements made by the VTA-lesioned animals as they circled; the forepaws stepped either sideways or forward while the hindpaw ipsilateral to the side of the lesion stepped predominantly backwards. The hindpaw contralateral to the side of the lesion served as a pivot, moving only to complete a circle.

The degree of responsiveness to the environment following apomorphine varied between the animals. Following either dose, some VTA- and SN-lesioned animals circled off the edges of the platform while others, when reaching the edges of the platform, adjusted their position to avoid falling off.

Histology

VTA lesions. Eight of ten lesions were contained within the boundaries of the VTA (Fig. 14); these lesions were bordered laterally by the medial lemniscus and ventrally by the interpenduncular nucleus. Two of the lesions were in the red nucleus, dorsal to the VTA.; these animals were excluded from the data analysis.

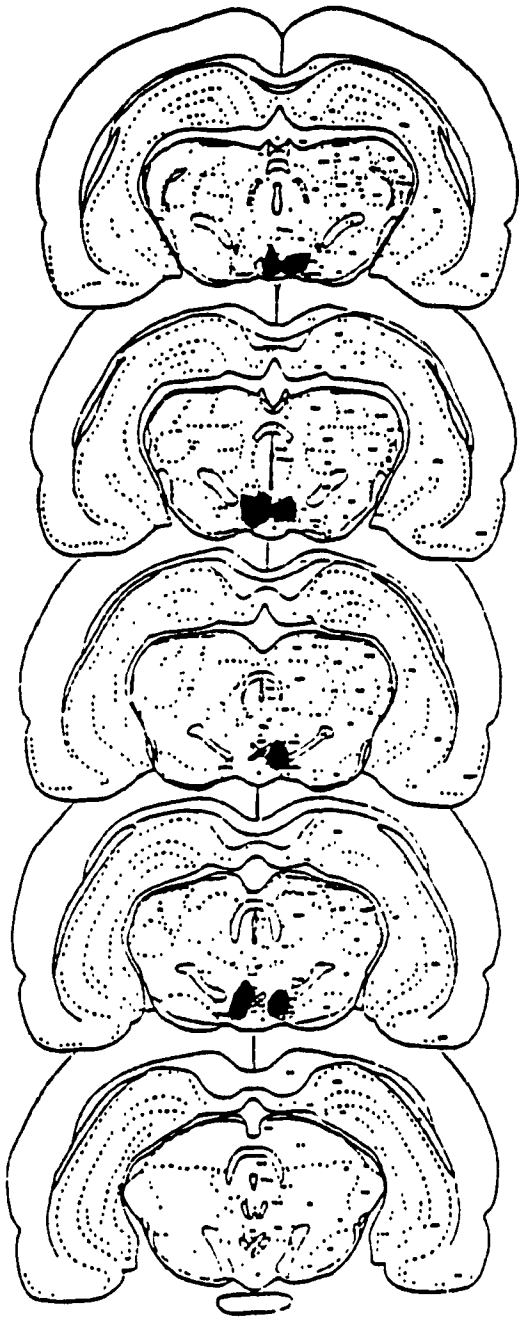

Figure 14. Histological reconstructions of the VTA electrolytic lesions. Adapted from Pellegrino, Pellegrino and Cushman (1979). Only the largest cross-section of each lesion is shown.

SN lesions. Eight of ten lesions were contained within the lateral boundaries of the SN (Fig. 15). Most of the lesions caused significant damage to both the pars compacta and the pars reticulata of the SN; the medial lemniscus was spared in these rats. Two of the lesions were located immediately dorsal to the medial lemniscus; these animals were excluded from the data analysis.

DISCUSSION

Animals with electrolytic lesions restricted to the VTA circled following amphetamine and apomorphine. In the test buckets, VTA-lesioned animals circled toward the lesioned side following the high dose of amphetamine (the side assumed to have less dopaminergic activation) but generally circled away from the lesioned side following the moderate dose; in contrast, 6-OHDA lesioned animals circled toward the lesioned side following this moderate dose. Circling in response to amphetamine injection is assumed to have resulted from asymmetric activation of the A10 system, since A10 dopamine-containing cells and their fibers likely degenerated on the lesioned side. That a high dose amphetamine injection was required before the animals showed a bias toward the lesioned side following electrolytic lesions, but not following 6-OHDA lesions, is probably related to a smaller loss of dopamine cells caused by the electrolytic lesions than the 6-OHDA lesions. The electrolytic lesions were confined to the anterior medial part of the VTA while the 6-OHDA lesions induced a total loss of VTA dopamine cells in most cases.

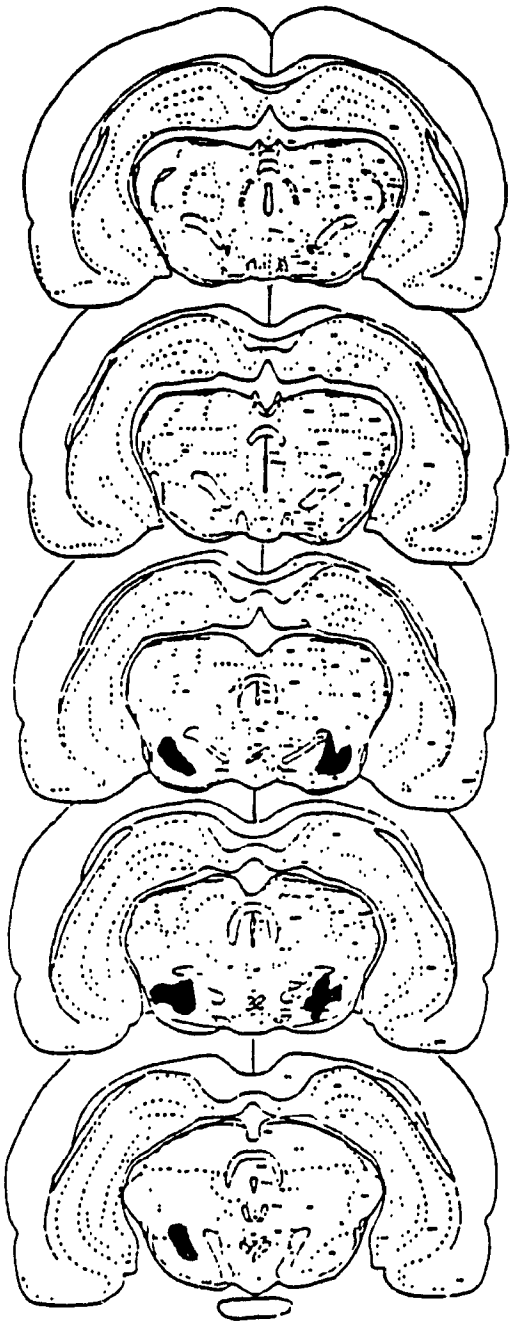

Figure 15. Histological reconstructions of the SN electrolytic lesions. Adapted from Pellegrino et al. (1979). Only the largest cross-section of each lesion is shown.

Hodge and Butcher (1979) observed that a moderate dose of amphetamine (1.5 mg) did not cause circling in animals with electrolytic lesions that caused partial damage to both the VTA and SN; however, as was the case in the present study, their animals reliably circled toward the lesioned side following a high dose of amphetamine (5.0 mg/kg).

It is presently not clear why animals with a small electrolytic lesion of the VTA do not circle toward the lesioned side following a moderate dose of amphetamine, but animals with a complete lesion of the VTA do (as was the case in experiment 1). There are data from another research area that may provide clues to this difference. Robinson and Whishaw (1988) recently reported that a moderate dose of amphetamine (1.5 mg) increased extracellular concentrations of dopamine to a similar degree on the lesioned and unlesioned sides in animals with partial dopamine lesions; thus when a lesion is partial, spared cells synthesize and release dopamine well above basal levels when challenged with a moderate dose of amphetamine (Robinson and Whishaw, 1988). When high doses are given, however, the functional pool on the partially lesioned side is exhausted, and the ability to compensate is lost (Hefti et al., 1985). Thus dopamine release is decreased on the lesioned side when high doses of amphetamine are given; this fits with the present finding that circling was seen when high but not when moderate doses were given.

Animals with electrolytic lesions that were restricted to the SN also circled following amphetamine injections. As was

the case following VTA lesions, a high dose of amphetamine was required before animals reliably circled toward the lesioned side. On the first test day, following the moderate dose, animals reliably circled away from the lesioned side; following this dose of amphetamine, animals with 6-OHDA lesions of the SN also circled away from the lesioned side. Circling away from the lesioned side on the first test day is assumed to be due to degeneration-induced release of dopamine from storage pools of lesioned neurons (Ungerstedt, 1971b). On subsequent test days, electrolytically lesioned animals did not reliably circle following the moderate dose whereas animals with 6-OHDA lesions circled toward the lesioned side. As was the case with VTA-lesioned animals, it is probable that the electrolytically lesioned animals did not circle toward the lesioned side following the moderate dose because these lesions were much less extensive than those induced by 6-OHDA. The SN electrolytic lesions in the present study damaged dopamine-containing cells in the caudal and lateral part of the SN and non-dopaminergic cells in the ventral part of the SN (pars reticulata) but spared dopamine-containing cells in the rostral and medial part of the SN. A similar finding was reported by Hodge and Butcher (1979) who found reliable circling toward the lesioned side following 5.0 mg/kg of amphetamine, but no circling following 1.5 mg/kg. Others have also reported that animals with partial SN lesions circle toward the lesioned side following high dose amphetamine injections (Costall et al., 1976; Olianas, De

Montis, Concu, Tagliamonte and Di Chiara, 1978). The circling observed following amphetamine injection in the SN electrolytically lesioned rats is assumed to have resulted from asymmetric activation of the A9 system, since A9 dopamine-containing cells and their fibers degenerate on the lesioned side.

The direction of circling following amphetamine injection was influenced by environmental stimuli. The direction of circling following these injections on the elevated platform appeared to depend on which lane the animals were tested in. For each dose of amphetamine, the direction of turning at the corners in the inner lane of the elevated platform was generally opposite to the direction of turning at the corners in the outer lane. This observation complements a report by Wise and Holmes (1986) that animals turn in opposite directions in the inner lane and outer lane of an elevated platform following unilateral activation of the mesolimbic system. This observation, however, contrasts with a report by Ziegler and Szechtman (1988) who failed to observe a change in the direction of circling following amphetamine as a function of environmental stimuli in animals with a unilaterally lesioned nigrostriatal system. It is possible that the animals in the present study responded to changes in the environment whereas those in Ziegler and Szechtman's study did not because of differences in the type of testing environment or in the size of the lesion; in Ziegler and Szechtman's study the animals were tested in a swimming pool and their lesions

were more extensive than the ones reported here. The change in the direction of circling following amphetamine injection, occurring as a function of environmental stimuli suggests that circling following amphetamine is not a simple consequence of which hemisphere contains the greatest dopaminergic activation.

If the direction of circling following amphetamine is not a consequence of which hemisphere receives the greatest dopaminergic activation, then what might determine the direction of circling following this drug? In each environment, particularly in the first few minutes following the high dose of amphetamine, animals kept the flank of the body contralateral to the lesion next to the dividing wall on the platform. This flank bias may have been caused by a sensorimotor imbalance induced by the lesions. Lesions of the ascending dopamine systems (VTA and SN) are known to induce a neglect for sensory stimuli on the side of the body contralateral to the lesion (Feeny and Wier, 1979; Ljungberg and Ungerstedt, 1976; Marshall, Berrios and Sawyer, 1980; Schallert, Upchurch, Lobaugh, Farrar, Spirduso, Gilliam, Vaughn and Wilcox, 1982). The flank that the animals in the present study kept next to the wall, the flank contralateral to the lesion, is presumed to be less receptive to sensory stimuli. In the Wise and Holmes (1986) study unilateral injections of morphine into the VTA also caused animals to locomote with the flank presumed to be less receptive to sensory stimuli next to the dividing wall (Wise and Holmes, 1986). Thus the

observations from the present experiment, along with those by Wise and Holmes (1986), suggest that the direction of some types of drug-induced circling may be determined by which side of the body is more receptive to sensory stimuli. Indeed, others have previously suggested that the direction of circling is related to sensory responsiveness (Huston, Nef, Papadopoulos and Welzl, 1980; Steiner, Bonatz, Huston and Schwarting, 1988; Szechtman 1983; Zeigler and Szechtman, 1988).

Animals with either VTA or SN electrolytic lesions circled toward the lesioned side following apomorphine injections. Each animal circled toward the lesioned side following the low and moderate dose, whether tested in the test buckets or on the elevated platform. The direction of circling following apomorphine in animals with electrolytic lesions of the VTA occurred in the the same direction as the direction of circling in animals with 6-OHDA lesions of the VTA. Since the animals in the present study did not circle away from the lesioned side following the electrolytic lesions, it is unlikely that receptors in the dopamine-containing terminal regions on the lesioned side increased in number; had these receptors increased in number, animals might have circled away from the lesioned side. Considering that the lesions in the present study were not extensive, this is not surprising. Others have reported that apomorphine fails to stimulate locomotor activity following small electrolytic lesions of the VTA, presumably because small lesions do not cause an increase in receptor number in

the nucleus accumbens (Koob, Stinus and Le Moal,1981). Since the VTA-lesioned animals circled toward the lesioned side, apomorphine presumably activated the unlesioned side more effectively than the lesioned side. Assuming that animals circle toward the side with less dopaminergic activation, it is presently not clear why apomorphine activated the unlesioned side more effectively than the lesioned side following the electrolytic lesions.

Circling toward the lesioned side following apomorphine injections in animals with electrolytic lesions of the SN contrasts with circling away from the lesioned side following apomorphine injections in animals with 6-OHDA lesions of the SN. Following extensive 6-OHDA lesions of the SN, apomorphine is believed to cause circling away from the lesioned side by stimulating up-regulated dopamine receptors in the denervated striatum (Ungerstedt, 1971c). Since the electrolytic lesions reported here only caused partial damage to dopamine-containing cells it is not surprising that the animals did not circle away from the lesioned side; it is well documented that receptor up-regulation does not occur following partial damage to dopamine-containing cells (Costall et al., 1976; Hefti, Melamed, Sahakian and Wurtman, 1980; Hefti et al., 1980; Ungerstedt and Marshall, 1975). Others have reported that animals with small electrolytic lesions of the SN circle toward the lesioned side following apomorphine injection (Costall et al., 1976; Hodge and Butcher, 1979; Iwamoto et al.,1976; Schwartz et al.,1976; Watanabe

and Watanabe, 1979; Vaccarino and Franklin, 1982). Since animals with small electrolytic SN lesions circle toward the lesioned side following apomorphine injection, apomorphine presumably activates the unlesioned side more effectively than the lesioned side. Circling toward the lesioned side following apomorphine injection is blocked by either kainic acid lesions (Di Chiara, Porceddu, Morelli, Mulas and Gessa, 1979) or electrolytic lesions (Costall et al., 1976) of the intact caudate suggesting that apomorphine induces circling in SN electrolytically lesioned animals by activating the intact caudate. It is presently not known why apomorphine activates the unlesioned caudate more effectively than the lesioned caudate following SN electrolytic lesions. Others have suggested that dopamine receptors on the lesioned side become hyposensitive following electrolytic lesions of the SN (Costall et al., 1976; Hodge and Butcher, 1979), but have not proposed how this could happen.

In the present study, the direction of circling following apomorphine injection, unlike the direction of circling following amphetamine injection, was not influenced by environmental stimuli. Both VTA- and SN-lesioned rats circled toward the lesioned side on the inner and outer lane of the elevated platform following apomorphine injection. It is not clear why the animals were less responsive to the environment following apomorphine than amphetamine. It may be that the degree of stereotypy induced by the apomorphine injections interfered with the animals ability to respond to

changes in the environmental stimuli. Szechtman (1986) suggested that apomorphine may change an animal's responsiveness to some particular range of sensory stimuli. When the animals in the present study were making stereotyped movements, they were more responsive to proximal stimuli than to distal stimuli. Thus the animals' attention was directed to the space immediately in front of them, rather than to the wall next to them. Consistent with the possibility that stereotypy interferes with an animal's ability to respond to distal stimuli is the observation that these animals responded to changes in the environment following a high dose of amphetamine, but only until they began making stereotyped movements.

One last issue that bears discussion is the finding that animals injected with the high dose of amphetamine progressively began to circle in a way that was phenomenologically similar to the circling observed following apomorphine injection. Approximately fifteen minutes following the high dose amphetamine injection, the SN-lesioned animals stopped moving and began showing apomorphine-like circling behavior and the VTA-lesioned animals stopped moving and began making stereotyped head and body movements. The time at which these animals stopped locomoting, approximately fifteen minutes following injection, coincides with the time at which this dose of amphetamine generally induces stereotypy (Randrup and Munkvad, 1974). Although the VTA-lesioned animals did not

show complete apomorphine-like circling during the observation period, they did begin moving the longitudinal axis of the body from side to side when the testing period ended, behavior associated with the onset of stereotypy (Szechtman et al., 1985). The doses of apomorphine administered in the present study also induced stereotypy. These observations suggest that stereotypy inducing doses of amphetamine and apomorphine result in circling that is phenomenologically similar. Unfortunately, since the doses of apomorphine administered in the present study were too high to cause forward locomotion, it is not known whether locomotor stimulating doses of apomorphine would result in circling that is phenomenologically similar to circling induced by locomotor stimulating doses of amphetamine.

In summary, the most significant finding of this study was that animals with electrolytic lesions restricted to the VTA circled following amphetamine and apomorphine injections. Furthermore, the direction of circling following electrolytic lesions of the VTA was the same as that following 6-OHDA lesions of the VTA. More studies are required to determine why animals with either electrolytic or 6-OHDA lesions of the VTA circle toward the lesioned side following apomorphine injection.

EXPERIMENT 3:

ELECTROLYTIC LESIONS OF DOPAMINE-CONTAINING TERMINAL REGIONS.

Experiments 1 and 2 showed that animals with unilateral lesions of the A10 dopamine-containing cells circled following amphetamine and apomorphine injection. Since some A10 cells give rise to fibers innervating the caudate (Fallon and Moore, 1978), it could still be argued that the circling following amphetamine and apomorphine injections resulted from asymmetrical activation of this caudate dopamine projection. Thus, in the present experiment animals were tested with amphetamine and apomorphine following small, unilateral, electrolytic lesions that were restricted to the nucleus accumbens. For purposes of comparison, control groups received similar lesions in the ventral or dorsal caudate and were tested with amphetamine and apomorphine.

METHOD

Subjects

Twenty male Long-Evans rats weighing 350-450 g at the time of surgery were housed individually with 24 hour access to food and water. The room lighting was maintained on a normal twelve hour light-dark cycle.

Lesions

Under sodium pentobarbital anesthesia a unilateral monopolar lesioning electrode was lowered into each rat. The monopolar electrode was a 254 μm diameter stainless-steel

wire insulated with varnish except at the cross-section of the tip. The electrode coordinates for nucleus accumbens lesions (n=8) were 3.2 mm anterior to bregma, 1.5 mm lateral to the midsagittal suture and 7.3 mm ventral to the dural surface. The electrode coordinates for the dorsal caudate (n=6) were 3.0 mm anterior to bregma, 2.8 mm lateral to the midsagittal suture and 4.0 mm ventral to the dural surface. The electrode coordinates for ventro-lateral caudate (n=6) were 3.0 mm anterior to bregma, 3.2 mm lateral to the midsagittal suture and 6.0 mm ventral to the dural surface. The incisor bar was 5.0 mm above the intra-aural line. Lesions were produced by passing a direct anodal current of 2 mA, delivered over a 10-sec period with a lesion maker. A clip attached to the animal's tail served as the cathode. Following lesioning the electrode was removed from the rat, the hole in the skull was filled with bone wax and the skin was sutured.

Test Drugs

Amphetamine sulfate, dissolved in physiological saline, was injected intraperitoneally. Apomorphine hydrochloride, dissolved by warming it in physiological saline, was administered subcutaneously. In each case, the dosage was 1.25 mg/kg injected in a volume of 1 ml/kg.

Apparatus

The animals were tested for circling in two settings. The rate of circling was determined in circular plastic buckets and the phenomenology was determined in an open field as described in Experiment 1.

Procedure

Pre-lesion testing. Pre-lesion testing followed the same procedure as that described in Experiment 1.

Post-lesion testing. On each post-lesion test day, each animal was tested for 15 minutes prior to drug injection and for 60 minutes following drug injection. The rate of circling following amphetamine injection was determined for each animal 1, 3, 7, 14 and 56 days following lesioning. The rate of circling following apomorphine injection was determined for each animal 28 days following lesioning.

Four weeks following lesioning, the open field behavior was analyzed according to (1) the direction of circling (2) the size of the circles (3) the type of stepping movements made while circling and (4) the degree of postural asymmetry accompanying the circling. Each animal was tested with amphetamine (1.25 mg/kg) on one day and with apomorphine (1.25 mg/kg) on another; the tests were two days apart and the order of testing was counterbalanced. Fifteen minutes after injection, each animal was placed into the open field and was observed for a 5 min period.

Confirmation of lesion placements

Same as described in experiment 2.

Statistical analysis:

Same as described in Experiment 1.

RESULTS

Animals with nucleus accumbens lesions reliably circled ($F(5,35)=9.01$, $p<.05$) toward the lesioned side following

amphetamine injection (Fig. 16). Animals with dorsal (Fig. 17) and ventral (Fig. 18) caudate lesions also reliably circled toward the lesioned side following amphetamine injections ($F(5,25)=6.76$, $p<.05$ and $F(5,25)=11.51$, $p<.05$, for dorsal and ventral lesions, respectively). Animals did not reliably circle toward the lesioned side following amphetamine injection prior to the lesion. Apomorphine caused more circling toward the lesioned side than the unlesioned side following each of the lesions, but these biases were not statistically reliable; overall, apomorphine injection induced less circling than amphetamine injections.

When tested under drug-free conditions, each group of lesioned animals circled more toward the lesioned side than the unlesioned side, but in no case was this bias significantly different from pre-lesion values (Fig. 19).

The circling observed following amphetamine injection in animals with nucleus accumbens lesions was similar to that observed following dorsal caudate or ventral caudate lesions. In each case, each rat generally kept the flank of the body contralateral to the lesion next to the open field wall. This resulted in turning toward the lesioned side at the corners of the open field. As each animal moved next to the wall, its limbs stepped equally and the longitudinal axis of its body was straight. Since each of these animals moved along the perimeter of the open field, the size of the circles was as large as the open field.

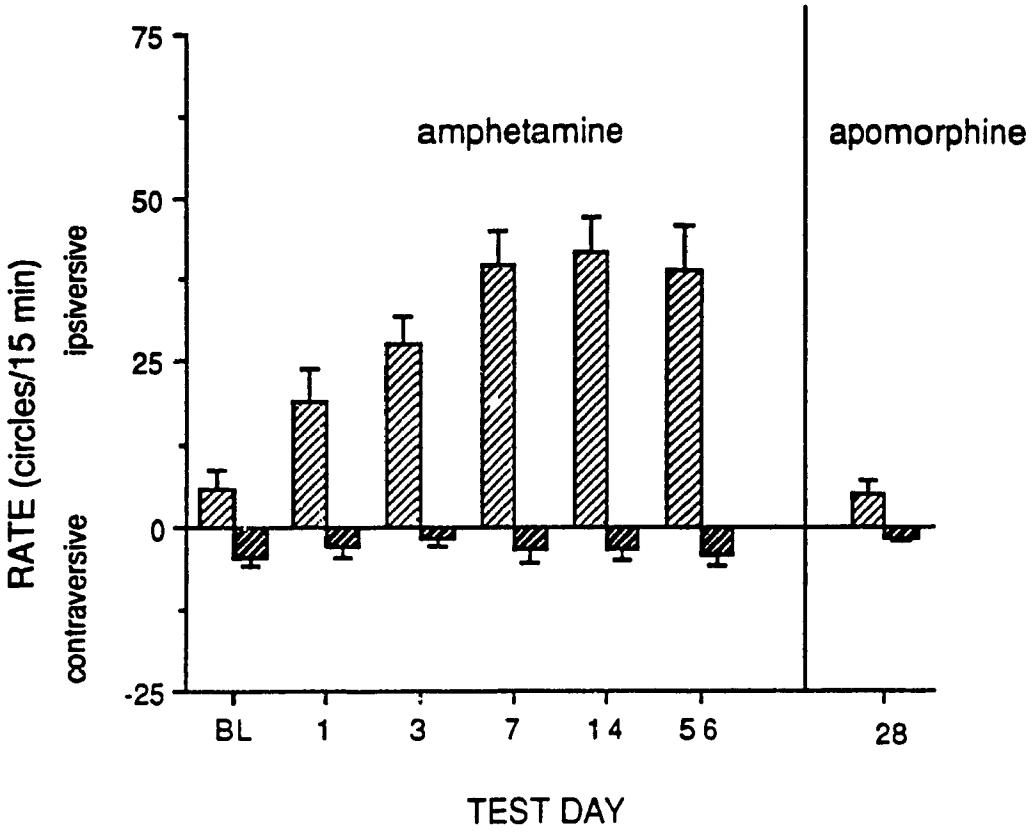

Figure 16. Rates of amphetamine-induced and apomorphine-induced circling in animals with unilateral electrolytic lesions of the nucleus accumbens. Baseline (BL) rates were determined on the day before lesioning.

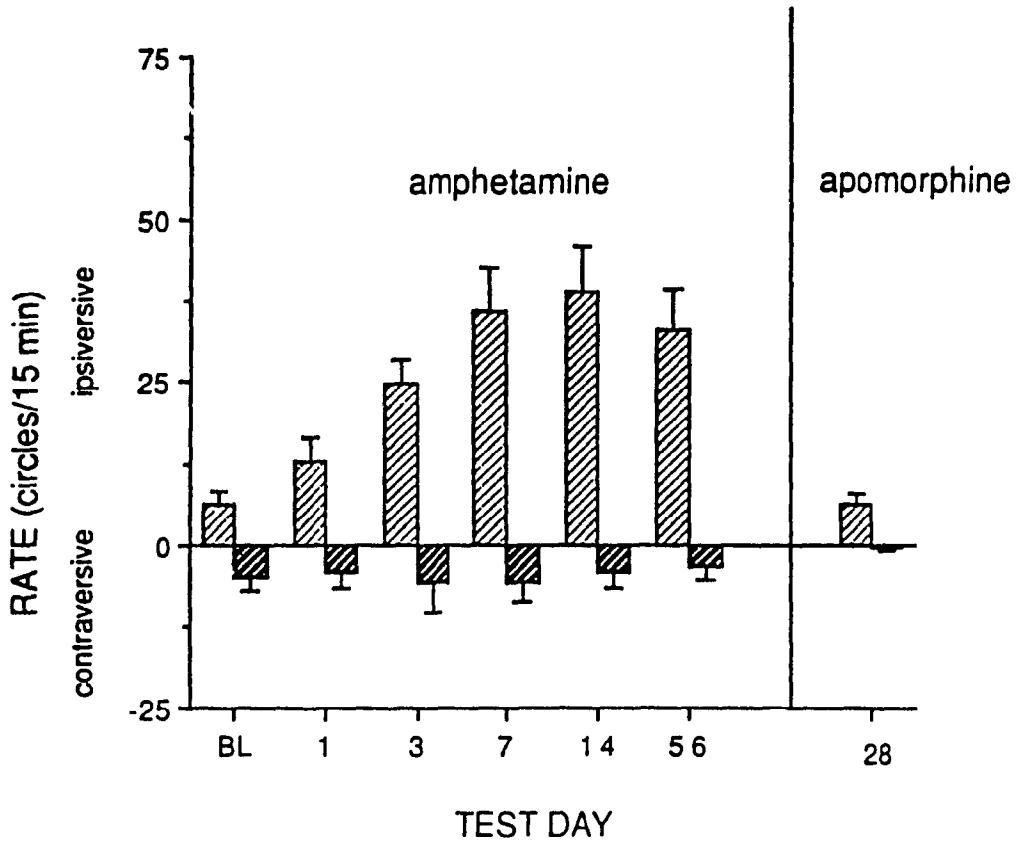

Figure 17. Rates of amphetamine-induced and apomorphine-induced circling in animals with unilateral electrolytic lesions of the ventral caudate. Baseline (BL) rates were determined on the day before lesioning.

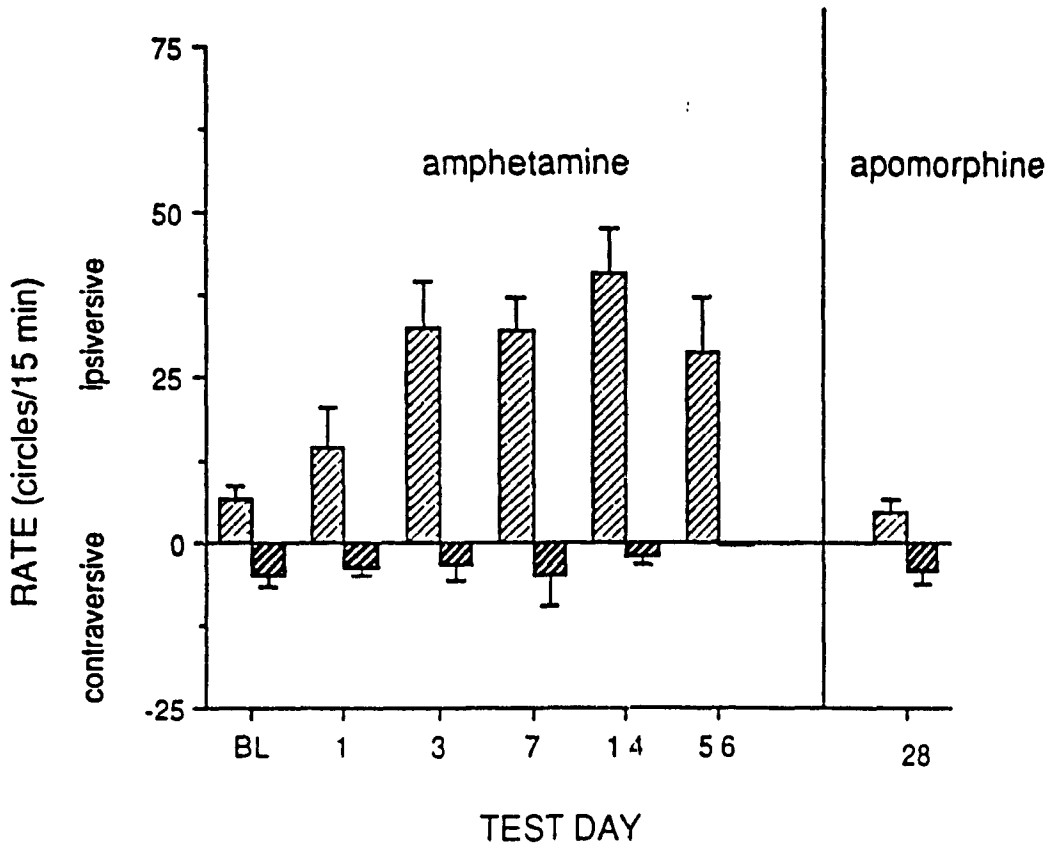

Figure 18. Rates of amphetamine-induced and apomorphine-induced circling in animals with unilateral electrolytic lesions of the dorsal caudate. Baseline (BL) rates were determined on the day before lesioning.

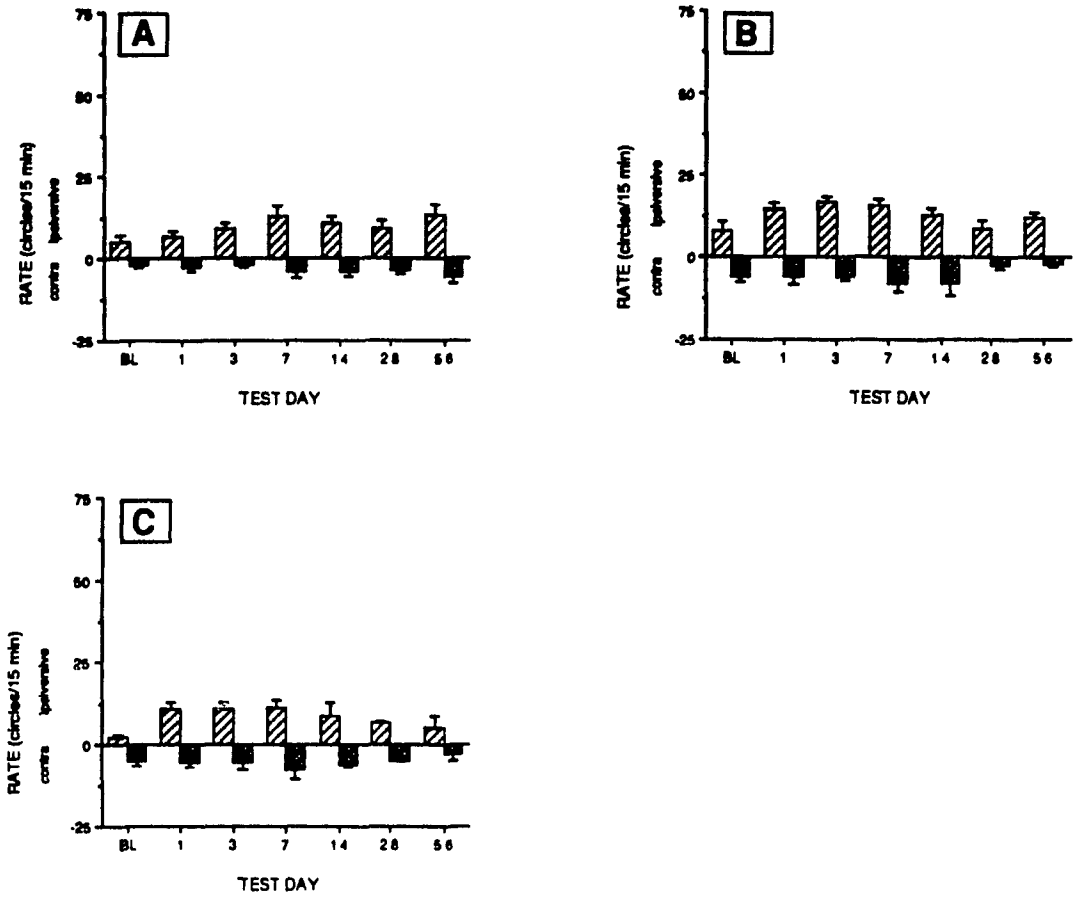

Figure 19. Rates of spontaneous circling as a function of time after electrolytic lesions. Frame A: nucleus accumbens lesions. Frame B: ventral caudate lesions. Frame C: dorsal caudate lesions.

Following apomorphine injection, each rat, regardless of lesion site, moved close to the open field walls, and stepped equally with all limbs. While moving next to the open field walls each animal repeatedly moved its head from side to side. None of the animals had a turning bias following apomorphine. If the flank of the body ipsilateral to the lesion was next to the wall, the animal turned toward its unlesioned side at the corners; if the flank of the body contralateral to the lesion next to the wall, the animal turned toward its lesioned side at the corners. Overall, there was far less movement in the open field following apomorphine injection than following amphetamine injection.

Histology

The most anterior nucleus accumbens lesions were bordered laterally by the anterior commissure, ventrally by the diagonal band of Broca and dorsally by the caudate (Fig. 20). The more posterior nucleus accumbens lesions were bordered medially by the medial septum, ventrally by the preoptic area and dorsally by the caudate. In most cases the anterior commissure was damaged and in one case tissue damage extended into the overlying caudate. The ventral caudate lesions were restricted to the ventral region of the caudate, located just dorsal to the lateral part of the nucleus accumbens while the dorsal caudate lesions were restricted to the dorsal region of the caudate, just ventral to the corpus callosum. In some cases these lesions resulted in some tissue loss within the corpus callosum.

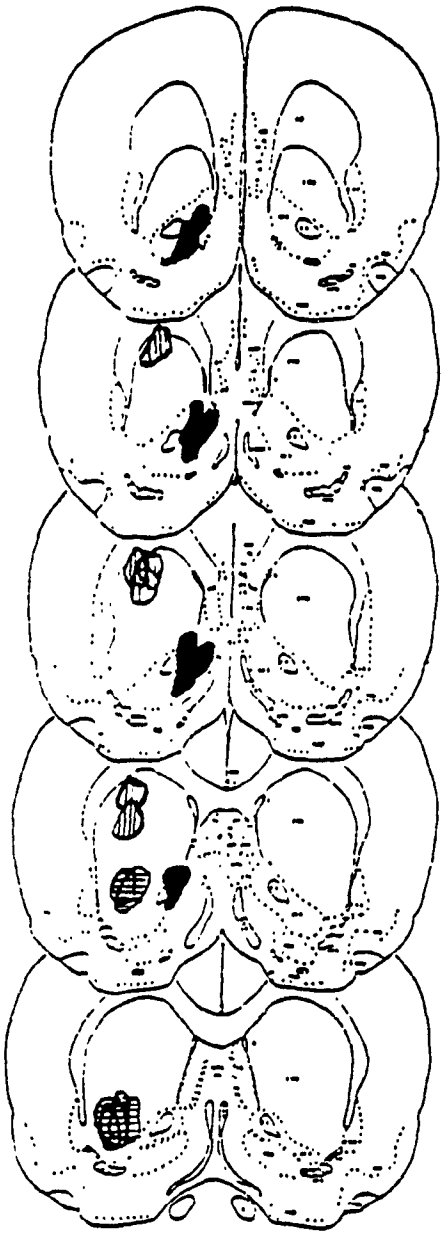

Figure 20. Histological reconstructions of the nucleus accumbens (black), ventral caudate (horizontal lines), and dorsal caudate (vertical lines) electrolytic lesions. Adapted from Pellegrino et al. (1979). Only the largest cross-section of each lesion is shown.

DISCUSSION

Animals with electrolytic lesions restricted to the nucleus accumbens circled following amphetamine injection. Since these lesions did not cause any cell loss within the nearby caudate, the asymmetry of the movement in these animals cannot be attributed to caudate damage. The rate of circling following amphetamine injections in animals with nucleus accumbens lesions was similar to the rate of circling following amphetamine in animals with unilateral 6-OHDA lesions of the A10 region. Since the lesions in this region damaged dopaminergic and non-dopaminergic inputs and their post-synaptic outputs, the circling following amphetamine injections is assumed here to have resulted from asymmetrical activation of the nucleus accumbens.

The observation that animals with unilateral nucleus accumbens circle following amphetamine complements the observations that amphetamine's locomotor stimulating effects are blocked by bilateral 6-OHDA or electrolytic lesions of the nucleus accumbens (Kelly and Iversen,1976; Kelly and Roberts, 1983; Koob, Riley, Smith and Robbins, 1978; Koob et al., 1981; Teitelbaum, Giammatteo and Mickley, 1979); in the case of unilateral lesions, the locomotor stimulating effect of amphetamine in the intact nucleus accumbens is assumed to drive the animal forward with a bias toward the lesioned side. The data from the present study, however, contrast with a report by Kelly (1975) who observed only a short lasting (15 minute) circling bias following unilateral 6-OHDA lesions of

the nucleus accumbens. Since Kelly's lesions generally spared nucleus accumbens dopamine terminals in the posterior accumbens, his lesions might have caused increased synthesis and release of dopamine in these spared terminals, and perhaps these compensated for the damage to the other accumbens terminals by activating sensitive accumbens receptors. In the present study, even though spared cells might have increased release and impulse flow of dopamine, there were fewer target cells to respond to the increased dopaminergic output because of the electrolytic lesion.

The rate of circling following amphetamine injections was similar in animals with electrolytic lesions restricted to either the ventral or dorsal caudate. The rate of circling following amphetamine in animals with electrolytic lesions of either the ventral or dorsal caudate was lower than the rate of circling following amphetamine injections in animals with extensive 6-OHDA lesions of the A9 region (experiment 1). Dunnett and Iversen (1982) also observed that animals with lesions restricted to either the ventral or dorsal caudate circled less following amphetamine than did animals with extensive lesions of the SN. This is reasonable, since the SN 6-OHDA lesions would denervate both the dorsal and ventral caudate, while the dorsal and ventral lesions would denervate only one region. In other studies, amphetamine-treated animals with large electrolytic lesions of the caudate that cause damage to both dorsal and ventral tissue circle at a

similar rate to animals with extensive lesions of the SN (Costall et al.,1983; Costall, Kelly and Naylor, 1984).

The animals with nucleus accumbens lesions did not circle following apomorphine injection. Indeed, apomorphine seemed to inhibit locomotor activity following this lesion. This finding was surprising, particularly since high rates of circling were observed following apomorphine injections in animals with either electrolytic or 6-OHDA lesions of the VTA (experiments 1 and 2). It was expected that animals would circle toward the lesioned side following apomorphine injection since the intrinsic cells of the nucleus accumbens--those on which the postsynaptic dopamine receptors reside--would have been damaged by the electrolytic lesion, resulting in more receptors and target neurons available for activation on the unlesioned side.

Animals with caudate control lesions also failed to circle following apomorphine injection. This finding was also unexpected since animals with SN lesions circled following apomorphine. Dunnett and Iversen (1982) reported that animals with small kainic acid lesions of the caudate that caused degeneration of neurons on which dopamine axons synapse did not circle following apomorphine injection. Others have reported animals with electrolytic lesions of the caudate circle at a high rate following apomorphine injection (Costall et al., 1983; Costall et al., 1984), but in these cases the lesions were substantially larger than the lesions induced here. The fact that animals did not circle following

apomorphine injections suggests that the accumbens and the caudate are more sensitive to the effects of amphetamine than apomorphine following unilateral electrolytic terminal lesions.

In conclusion, the data from the present study, along with those from experiments 1 and 2, suggest that animals with asymmetric activation of the mesolimbic dopamine system circle. This suggests that the mesolimbic system may contribute to circling behavior in a way not considered by the generally accepted 'two component' view of circling (Kelly and Moore, 1977; Moore and Kelly, 1977; Pycock and Marsden, 1978). According to the two component view, the mesolimbic system determines the rate of circling, but does not determine the direction of circling. Thus the two component view of circling must be expanded to consider the observations that unilateral activation of the mesolimbic system can direct behavior.

EXPERIMENT 4:

INTRACRANIAL AMPHETAMINE INJECTIONS.

Experiments 1 to 3 suggested that animals with unilateral lesions of the mesolimbic dopamine system circled toward the lesioned side following amphetamine injections. Amphetamine-induced circling following these lesions was assumed to reflect asymmetrical activation of the nucleus accumbens. In the present experiment, animals received unilateral injections of *d*- or *l*-amphetamine into the nucleus accumbens or ventral caudate (a dorsal control injection site). The inactive (*l*) isomer was used as a control; this drug has similar physical-chemical properties to *d*-amphetamine, and has equal potency in its effects on noradrenergic systems (Wise and Hoffer, 1977). The inactive *(l)* isomer is, however, much less effective than *d*-amphetamine in its actions as a releaser or uptake blocker in the dopamine system (Heikkila et al.,1975; Holmes and Rutledge,1976; Thornburg and Moore,1973).

METHOD

Subjects

Ten male Long-Evans rats, weighing 325-375 grams at the time of surgery, were subjects. They were housed individually with 24-hour access to food and water. Animal room lighting was maintained on a normal twelve hour light-dark cycle.

Surgical Implantation of Guide Cannula

Under sodium pentobarbital anesthesia (60 mg/kg) each animal was stereotaxically implanted with a unilateral 22-

gauge guide cannula aimed at the ventral caudate nucleus, just dorsal to the nucleus accumbens. The coordinates were 3.2 mm anterior to bregma, 2.7 mm lateral to the midline and 4.0 mm ventral to the dural surface. Following surgery, each guide cannula was fitted with a wire stylet that extended 0.5 mm beyond the guide cannula. These stylets were kept in place until testing began.

Apparatus

The animals were tested in two settings. The rate of circling was determined in circular plastic buckets and the phenomenology was determined in an open field as described in Experiment 1.

Procedure

Testing began one week following surgery. Each animal was tested once under each of 3 doses of *d*-amphetamine (5µg, 10µg, 20µg) and one dose of *l*-amphetamine (20µg) in the test buckets. Prior to injection on each test day, each rat was placed into the test chamber for 10 minutes and the rate of circling was recorded. Each animal was then removed from the test chamber and injected. Each injection was made through a 30-gauge stainless-steel injector cannula attached by polyethylene tubing to 1-µl microsyringe. Each injection was administered in a volume of 0.5 µl of physiological saline over a 1-min period and the injector cannula was left in place for an additional minute to force diffusion of the solution away from the cannula tip. Following injection, each animal was placed back into the test bucket and the rate of circling was

recorded for an additional 60 minutes. Each animal was tested (on different days) following each dose of amphetamine injected into each structure. For injections into the ventral caudate the injector cannula extended 1 mm beyond the guide cannula and for injections into the nucleus accumbens the injector cannula extended 2.9 mm beyond the guide cannula. There were at least 3 days between intracerebral injections, and the shallower caudate injections were made before the deeper accumbens injections.

Three days following the completion of the series of ventral caudate injections (in the test buckets), each animal was tested in the open field. Ten minutes following injection, each animal was observed for a 5-min period. The dose of *d*-amphetamine that had induced the highest rate of circling in the test buckets was injected for this test. The same procedure was followed three days following the completion of the series of nucleus accumbens injections in the test buckets. The type of stepping movements made while circling and the degree of postural asymmetry accompanying the circling were noted.

Confirmation of cannula placements

At the completion of testing each animal was anesthetized with chloryl hydrate (400 mg/kg) and perfused with physiological saline followed by a 10% formalin solution. Each brain was removed and stored in formalin for at least 3 days. The brains were then frozen and 40-micron sections

were taken; these sections were stained with thionin for histological confirmation of the cannula placement.

Statistical Analysis

One way analyses of variance were conducted on the circling scores following the different doses of amphetamine. The circling scores were obtained by subtracting the number of circles away from the injected side from the number of circles toward the injected side; thus a positive number indicated a greater number of circles toward the injected side and a negative number indicated a greater number of circles away from the injected side.

RESULTS

The nucleus accumbens injections were more effective than the ventral caudate injections. Animals reliably ($F(4,36)=5.4$, $p<.01$) circled away from the injected side following nucleus accumbens amphetamine injections (Fig. 21). Each dose of *d*-amphetamine into the nucleus accumbens caused more circling away from the injected side than either saline or *l*-amphetamine ($p<.05$). At each dose, each animal began circling away from the injected side within the first 10-min interval following injection (Fig. 22) and the circling rate generally peaked 20 to 30 minutes following injection. Ventral caudate *d*-amphetamine injections, 3 mm dorsal to the nucleus accumbens injection site, also caused circling away from the injected side ($F(4,36)=3.2$, $p<.05$); in this case, however, only the highest dose of *d*-amphetamine induced more circling than saline or *l*-amphetamine (Fig. 23). At the highest dose of *d*-

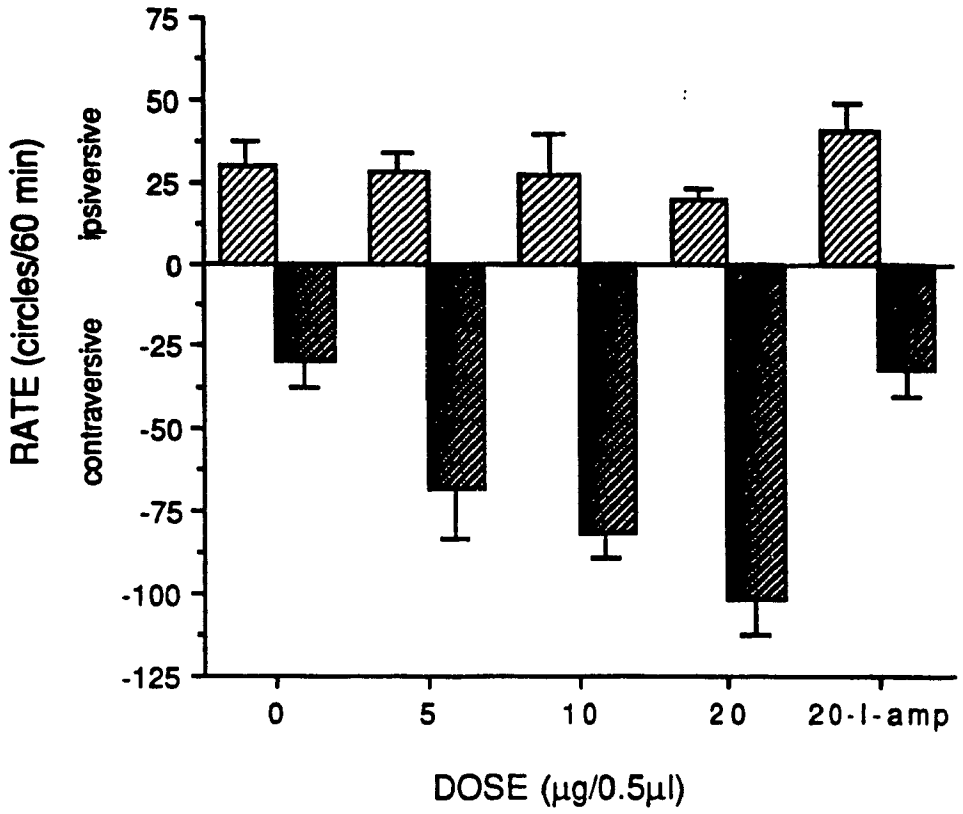

Figure 21. Rates of circling induced by intra-accumbens amphetamine as a function of injection dose.

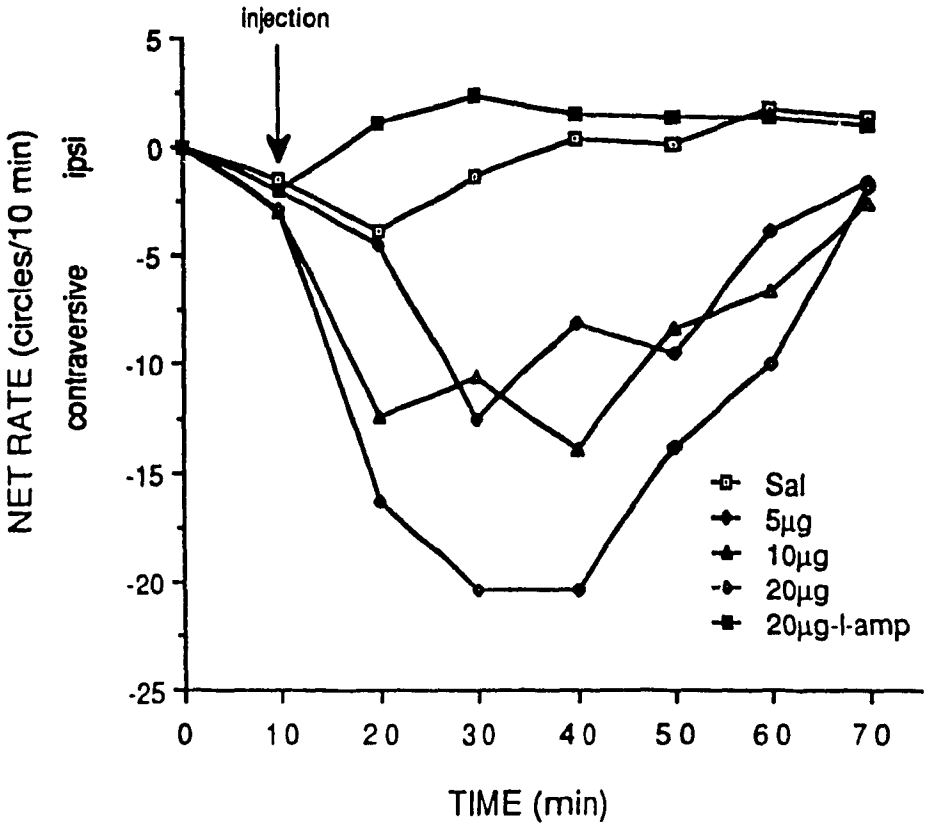

Figure 22. Rates of circling induced by intra-accumbens amphetamine as a function of time after injection.

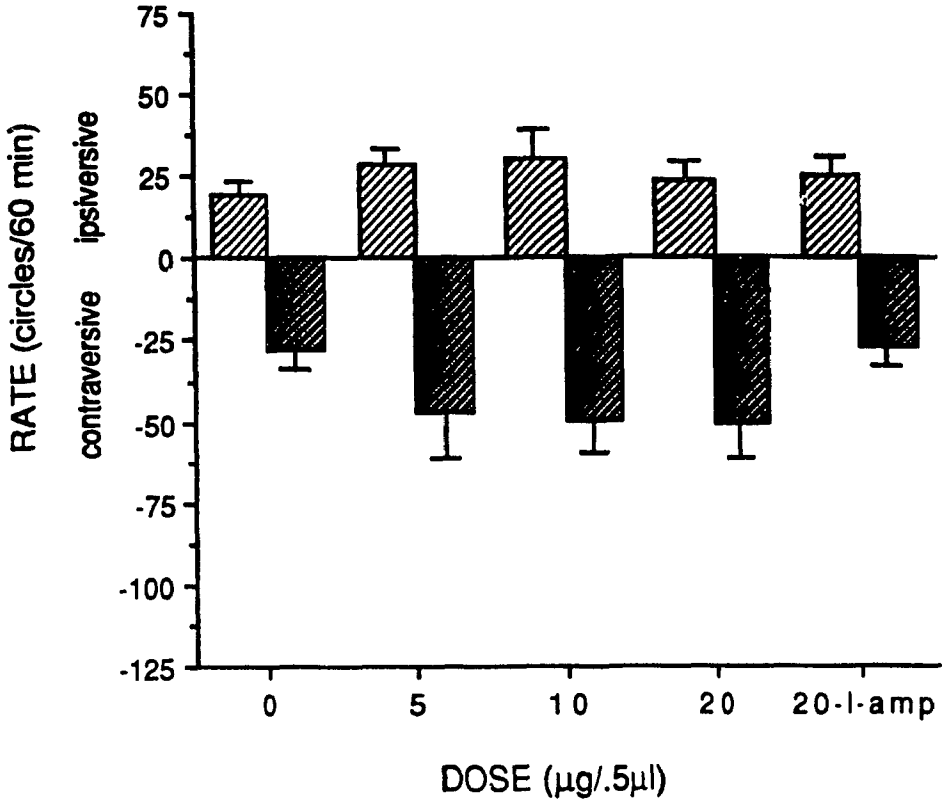

Figure 23. Rates of circling induced by intra-caudate amphetamine as a function of injection dose.

amphetamine each animal began circling away from the injected side within the first 10-min interval following injection (Fig. 24).

In the open field, following either ventral caudate or nucleus accumbens *d*-amphetamine injection, each animal moved close to the open field walls with the flank of the body ipsilateral to the injected side close to the wall. This resulted in turning away from the injected side at the corners of the open field. While moving next to the wall the limbs stepped with equal frequency and the longitudinal axis of the body was straight.

Histology

The nucleus acccumbens injection sites were bordered medially by the anterior commissure, ventrally by the preoptic area and dorsally by the caudate (Fig. 25). The dorsal control injection sites were located within the ventral part of the caudate.

DISCUSSION

Following unilateral injections of amphetamine into the nucleus accumbens animals reliably circled. There is no guarantee that centrally injected amphetamine acts at the site of injection; the most likely site of local drug efflux, however, would be up the cannula shaft to the overlying ventral caudate. Since injections in the caudate were less effective, it would appear that the effectiveness of the accumbens injections were not due to diffusion to the overlying caudate. That the animals began circling within minutes of the injection is also

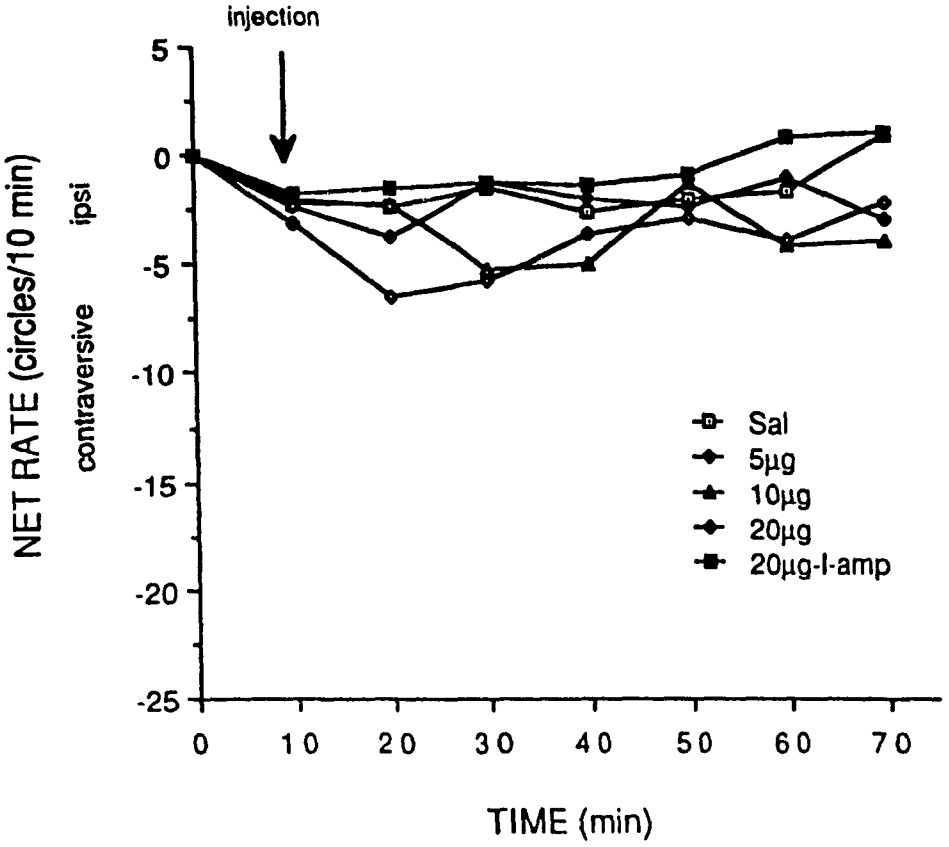

Figure 24. Rates of circling induced by intra-caudate amphetamine as a function of time after injection.

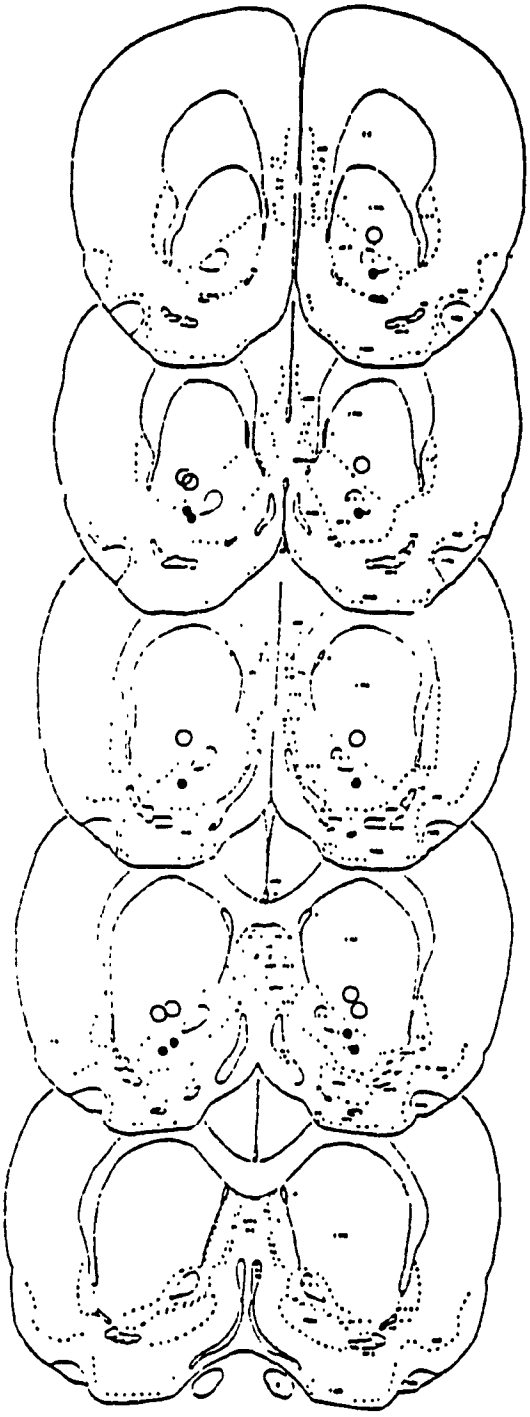

Figure 25. Histological reconstructions of the nucleus accumbens (filled circles) and caudate (open circles) injections sites. Adapted from Pellegrino et al. (1979).

consistent with the hypothesis that the nucleus accumbens was the site of primary action of these injections. The fact that *l*-amphetamine was ineffective suggests that the effect of *d*-amphetamine was due to a pharmacological action and not due to non-specific effects of local neuronal anesthetic actions, pH, osmolarity and the like. Thus, circling away from the injected side following amphetamine injections appears to have resulted from asymmetrical activation of the mesolimbic system. These observations are consistent with those seen following unilateral lesions of the mesolimbic system (Experiments 1 to 3), again suggesting that animals with asymmetric activation of the nucleus accumbens circle.

The circling observed following amphetamine injections into the nucleus accumbens is not characterized by any obvious postural asymmetry. Indeed, the most obvious effects of these injections was an increase in the general activity of the animals. This is not surprising when you consider that bilateral injections of amphetamine or dopamine into the nucleus accumbens increase locomotor activity (Carr and White, 1987; Pijnenburg et al.,1976). It appears, however, that in the case of unilateral injections, the increase in locomotion is primarily directed away from the most activated dopamine system. The directional bias in these animals, particularly when tested in the open field, was most obvious when the animals reached a corner in their testing environment; at the corners, each animal generally turned away from the injected (most activated) side. When these animals were observed in a

long hallway, it was not obvious that they had a directional bias; rather, they forward locomoted next to the wall for the length of the hallway, with the side of the body ipsilateral to the injection next to the wall. Thus it appears as though unilateral activation of the nucleus accumbens can cause directionally biased locomotion.

Microinjections of morphine, [d-pen,D-Pen5] enkephalin or neurotensin into the VTA also cause animals to circle away from the injected side (Holmes et al., 1983; Holmes and Wise, 1985a; Jenck et al., 1988; Wise and Holmes, 1986); these drugs presumably cause animals to circle by unilaterally activating the mesolimbic dopamine system. The type of circling observed following unilateral microinjections of these drugs into the VTA has been described as a directionally biased increase in locomotor activity; these injections do not result in circling that is characterized by obvious postural asymmetry (Holmes et al.,1983; Holmes and Wise, 1985a; Jenck et al., 1988; Wise and Holmes, 1986). As is the case with bilateral amphetamine injections into the nucleus accumbens, bilateral microinjections of morphine, [d-pen,D-Pen5] enkephalin or neurotensin into the VTA increase locomotor activity (Broekkamp and Phillips, 1979; Joyce and Iversen, 1979; Kalivas, Burgess, Nemeroff and Prange, 1983;), presumably by activating dopaminergic neurons that project to the nucleus accumbens. Thus it appears as though unilateral activation of the mesolimbic dopamine system, either by

activation in the cell body region or by activation in the terminal region, induces circling that is qualitatively similar.

Injections of amphetamine into the ventral caudate also resulted in circling away from the injected side, however, these injections were less effective than nucleus accumbens injections; the animals circled only following the highest dose of *d*-amphetamine. It is somewhat surprising that a high dose of amphetamine was necessary to observe reliable circling from this region since animals with electrolytic lesions in this region reliably circled following systemic amphetamine injections (Experiment 3). Others have reported circling following unilateral injections of either dopamine (Joyce et al.,1981; Wolfson and Brown, 1983) or apomorphine (Herrera-Marschitz et al., 1985; Starr and Summerhayes, 1982) into the caudate; in these other reports, as was the case in the present study, high doses of dopamine and apomorphine were necessary to induce circling following injection into this region.

The data from the present study are difficult to reconcile with the two-component view of circling (Pycock and Marsden, 1978) which predicts that unilateral injections into the caudate should induce postural asymmetry, but not circling, and that unilateral injections into the nucleus accumbens should induce forward locomotion, but not circling. It appears that unilateral activation of the nucleus accumbens can cause circling, even though animals do not show pronounced postural asymmetry.

GENERAL DISCUSSION

It is generally assumed that concommitant stimulation of both the caudate and nucleus accumbens are necessary for dopamine-dependent circling to occur (Moore and Kelly, 1977; Pycock and Marsden, 1978). According to this "two component view", activation of the caudate determines the direction, but not the rate of circling while activation of the nucleus accumbens determines the rate of circling, but not the directionof circling. The two component view of circling assumes that the functions of the nucleus accumbens and caudate are distinct and that it is only in the caudate that a left-right imbalance alters the direction of locomotion.

The results of the present experiments suggest that the functions of the nucleus accumbens and the caudate are not distinct with respect to circling behavior. The animals in the present studies circled toward the side presumed to have less dopaminergic activity following unilateral lesions of the A10-dopamine containing cell region (Experiments1 and 2), unilateral lesions of the nucleus accumbens (Experiment 3) and unilateral activation of the nucleus accumbens (Experiment 4). If the mesolimbic system could not alter the direction of locomotion, then the animals in the present studies should not have circled. Herrera-Marchitz et al. (1985) reported that unilateral microinjections of apomorphine into the caudate resulted in circling behavior. If the nigrostriatal system could not alter locomotor activity, then the apomorphine injections in the Herrera-Marchitz et al. (1985) study should have induced postural asymmetry but the animals should not have circled. Taken together, these data suggest that there is some functional

overlap in the roles of the caudate and nucleus accumbens in circling behavior.

The idea that the functions of the caudate and nucleus accumbens are not distinct and independent is not new and is not surprising. Heimer and Wilson (1975), on the basis of the anatomy of the nucleus accumbens, suggested that a functional distinction should not be drawn between the nucleus accumbens and the striatum. Heimer and Wilson (1975) considered the nucleus accumbens as a part of the ventral striatum because the nucleus accumbens and the ventral region of the striatum are morphologically similar and because both the nucleus accumbens and the ventral region of the striatum receive "limbic" afferents (Heimer and Wilson, 1975; Nauta, Smith, Faull and Domesick, 1978). Another reason for functional overlap between the nucleus accumbens and the striatum is that some of the efferents of the nucleus accumbens terminate in the SNpc while some of the efferent of the ventral region of the striatum terminate in the VTA Nauta et al., 1978).

In conclusion, the roles of the nucleus accumbens and the striatum are not as functionally distinct as suggested by the two component view of circling (Moore and Kelly, 1977; Pycock and Marsden, 1978). The present experiments suggest that asymmetrical activation of the mesolimbic division of the telencephalic dopamine system is a sufficient condition for circling behavior and that a left-right imbalance in the nucleus accumbens alters the direction of circling.

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