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Rotation Induced by Intranigral Injections of GABA Agonists and Antagonists: Zone-Specific Effects

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KOZLOWSKI, M. R. AND J. F. MARSHALL. *Rotation induced by intranigral injections of GABA agonists and antagonists: Zone-specific effects.* PHARMAC. BIOCHEM. BEHAV. **13**(4) 561–567, 1980.—Recent investigations of the function of the strionigral pathway have utilized the intranigral injection of γ-aminobutyric acid (GABA) agonist and antagonist drugs. While the unilateral application of these substances typically produces rotational behavior, the direction of this turning (ipsilateral or contralateral to the injected hemisphere) differs in several reports. The present study determines whether the direction of this drug-induced turning depends upon the locus of nigral stimulation. Picrotoxin and bicuculline methiodide were injected into either the pars compacta or the pars reticulata of the substantia nigra at several anterior-posterior levels. Injection of these drugs into the pars compacta resulted in ipsilateral turning while injection into the pars reticulata produced contralateral rotation. Both of these effects were dose-dependent and were elicited by similar threshold doses of picrotoxin. Prior 6-hydroxydopamine treatment abolished the ipsilateral but not the contralateral rotation. In contrast, muscimol injections produced contralateral turning independent of whether they were made into the pars compacta or pars reticulata. However, 6-hydroxydopamine treatment only attenuated the contralateral turning produced by pars compacta injections. These findings provide a histological basis for understanding the different types of turning behavior elicited by the intranigral injection of GABA agonists and antagonists. In addition, they suggest that GABA receptors mediate at least two independent actions in substantia nigra.

Picrotoxin Bicuculline methiodide Substantia nigra Rotational behavior 6-Hydroxydopamine

A PROJECTION from the neostriatum to the substantia nigra has been demonstrated in the mammalian brain using anatomical [9,29] and electrophysiological [6,31] techniques. Considerable biochemical and electrophysiological evidence suggests that gamma-aminobutyric acid (GABA) functions as a neurotransmitter in this pathway [7, 18, 20]. Lesions situated in the neostriatum or along strionigral axons substantially reduce the concentrations of GABA and its synthetic enzyme, glutamic acid decarboxylase, within the nigra [7,11]. In addition, both GABA and the GABA agonist, muscimol, depress the firing of the nigral neurons when applied iontophoretically [6,18]. Finally, the reduction in nigral cell firing induced by electrical stimulation of the neostriatum can be blocked by systemic injection of the GABA antagonist compound, picrotoxin [20].

In an attempt to elucidate the functions of the strionigral GABA-containing projection, several investigators have injected GABA agonist and antagonist compounds directly into the substantia nigra [16, 19, 24, 27]. The unilateral injection of these drugs typically results in rotational behavior. However, there is considerable disagreement concerning the direction of the turning produced by certain of these compounds. For example, intranigral injections of picrotoxin produce, in different studies, contralateral turning [27], either contralateral or ipsilateral rotation [24] or no rotation [16]. While such differences in the direction of turning may be due to differences in the site of injection within the nigra [10,24], a detailed study of the nigra, defining precisely the areas into which GABA antagonist injections produce each of these types of rotation, has not been undertaken. The present report represents such an analysis.

METHOD

One hundred thirty-three male Sprague-Dawley rats (Simonsen Labs, Gilroy, CA), weighing 150–200 g at the time of surgery, were used. Under Equithesin (2.5 ml/kg) anesthesia, each animal was positioned in a Kopf stereotaxic instrument (Tujunga, CA), using the plane of a standard stereotaxic atlas [12]. A 20 ga guide cannula (Plastic Products, Roanoke, VA) was implanted in the left hemisphere, so that its tip was just dorsal to the substantia nigra (coordinates: 1.6 to 2.5 mm anterior to the interaural plane, 2.0 mm lateral to the sagittal suture, and 5.0–5.8 mm ventral to the dura mater).

During the same surgical procedure, 36 of the rats were also given an injection of 6-hydroxydopamine (6-OH-DA) into the left ventral tegmental area in order to damage extensively the ascending dopamine (DA)-containing neurons of that hemisphere. Eight μg of 6-OH-DA HBr (Sigma Chemical, as the free base) dissolved in 4 μl of vehicle solution

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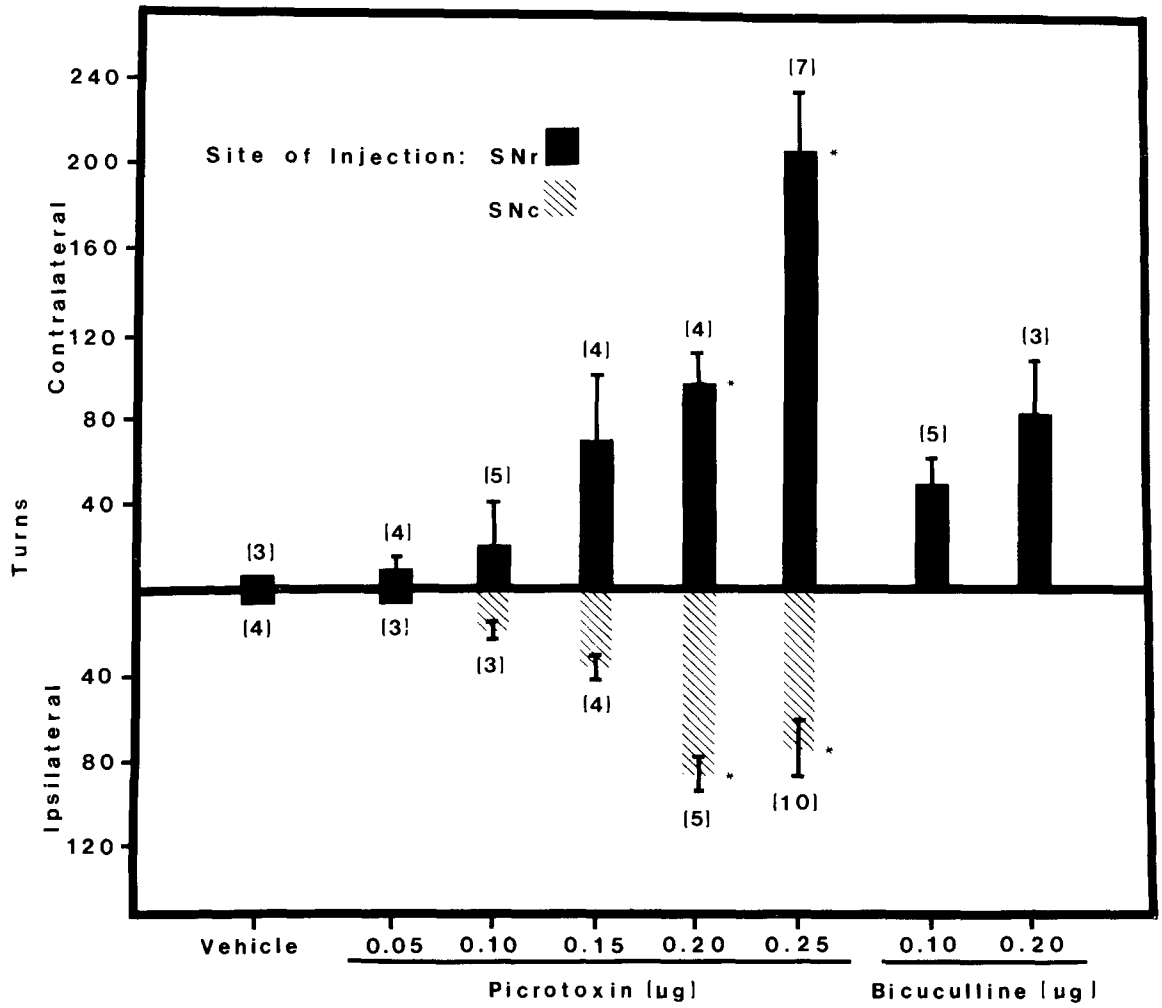

FIG. 1. Dose-response curve for intranigral injections of picrotoxin or bicuculline methiodide. Heights of the bars represent the mean number of turns for each dose following injections into either the pars reticulata (SNr) or the pars compacta (SNc). Standard errors are indicated by the error bars. Number of rats per group is given in parentheses. *Significantly different from vehicle group, Dunnett's t-test, $p<0.05$.

(0.1% ascorbic acid, 0.9% of NaCl) was injected at a rate of 1 μl/min through a 25 ga cannula (coordinates: 2.6 mm anterior to the interaural plane, 1.0 mm lateral to the sagittal suture, and 7.8 mm ventral to the dura mater). The 6-OH-DA-injected rats were given desmethylimpramine (McNeil Laboratories, 15 mg/kg, as the free base) 30 min prior to the intracerebral neurotoxin in order to protect brain norepinephrine-containing neurons [2].

Five to 9 days postoperatively, each rat received an intranigral injection of a GABA antagonist, picrotoxin (Sigma Chemical, 0.05 to 0.25 μg) or bicuculline methiodide (Pierce Laboratories, 0.10 or 0.25 μg), the GABA agonist, muscimol (0.025 or 0.05 μg), or the vehicle solution. Animals typically received a single intranigral drug injection. However, some of the bicuculline and muscimol-treated animals were given two such injections. In these cases, the animals received two intranigral injections of the same drug at different doses. The lower dose was always given first. The GABA agonists and antagonists were dissolved in isotonic saline, then adjusted to pH 7.0 with 1 N NaOH. These compounds were injected in a volume of 0.5 μl, at a rate of 1 μl/min, through a 30 ga inner cannula which extended 2.0 mm beyond the guide cannula tip. The inner cannula remained *in situ* during the subsequent one hour observation period.

For behavioral observation, the animals were placed in a rotometer bowl (54 cm diameter, 21 cm deep), where the direction of rotation and total number of 360° turns were recorded for the 60 min after the intracerebral injection. The drug-induced turning was usually completed by 60 min.

Those rats that had received intracerebral 6-OH-DA injections were also tested for their rotational behavior in response to systemic administration of apomorphine (0.25 mg/kg, as the free base, in a vehicle of 0.1% ascorbic acid, 0.9% NaCl) at 3, 5, and 7 days after the intranigral GABA agonist or antagonist injection. The occurrence of vigorous contralateral turning to IP apomorphine was used as an indicant of extensive damage to the ascending DA-containing projection [13,28]. The results from animals which failed to show at least 200 turns contralateral to the 6-OH-DA-treated hemisphere in the 60 min following apomorphine administration were not used in the subsequent analysis.

After the behavioral testing was completed, all animals were sacrificed, and their brains were removed and frozen in

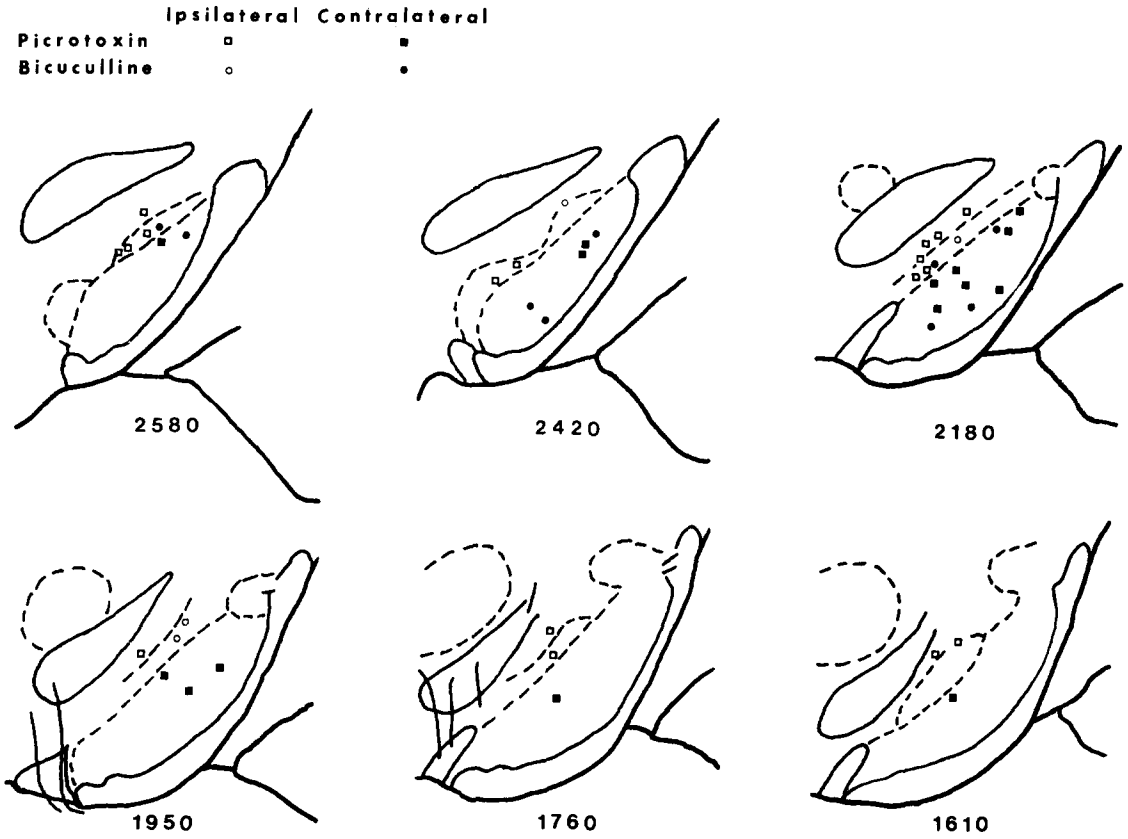

FIG. 2. Locations of the cannula tips for intact animals which received picrotoxin and bicuculline. The bottom of each symbol corresponds to the deepest penetration of the cannula tract. Numbers at the bottom of each figure represent coronal planes of a standard stereotaxic atlas [12]. Only the placements from those animals which showed more than 10 rotations in an hour are shown.

isopentane cooled to −20°C with dry ice. The brains were sectioned at 20 μm in a cryostat. Each third section through the cannula tip was saved and stained for Nissl substance with cresyl violet or thionin. The stained sections were projected at 10× magnification, and the tips of the inner cannulae were reconstructed onto the planes of a standard stereotaxic atlas [12]. In addition, the site of the 6-OH-DA injection was examined microscopically in 5 animals chosen at random from those which had received intracerebral neurotoxin injections and the extent of non-specific cell loss was estimated.

An additional group of rats was given a unilateral 6-OH-DA injection into the left ventral tegmental area, as described above, without cannula implantation. These animals were tested for their rotational behavior following apomorphine (0.25 mg/kg, IP) 5 days postoperatively. The brains of animals that showed more than 200 contralateral rotations (N=6) were assayed for catecholamines 3 days later by a liquid chromatographic procedure [22].

RESULTS

Intact Rats

The injection of GABA antagonist compounds into the substantia nigra resulted in vigorous rotational behavior. The direction of this turning (i.e., ipsilateral or contralateral to the injected nigra) depended upon the zone of the substantia nigra into which these compounds were injected. When injected into the pars reticulata, both picrotoxin and bicuculline methiodide produced tight contralateral circling (Figs. 1 and 2 and Table 1). The turning elicited by both picrotoxin and bicuculline methiodide was dose-dependent ($F=15.9$; $p<0.001$ and $F=5.8$; $p<0.05$, respectively).

In contrast to the results with injections into the pars reticulata, picrotoxin produced ipsilateral rotation when injected into the pars compacta or the tissue immediately dorsal to it. This turning was also dose-dependent ($F=6.8$; $p<0.001$). In addition, 6 of 8 animals that received an injection of 0.10 μg bicuculline methiodide into the pars compacta turned ipsilaterally (Table 1). The remaining two animals given bicuculline methiodide injections into the pars compacta turned contralaterally. On histological examination, the cannula tips for these two rats were found to be near the border of pars reticulata (Fig. 2).

Injections of the GABA agonist, muscimol, produced contralateral turning regardless of whether they were made into the pars compacta or the pars reticulata (Table 2). In addition the amount of turning produced by muscimol injections (0.05 μg) into these two regions was not significantly different.

Injections of 0.5 μl of the vehicle for these drugs failed to produce any rotational behavior, irrespective of whether the injections were made into the pars reticulata or pars compacta.

6-OH-DA-Treated Rats

The 6-OH-DA injections were found to produce a 98% loss of DA in the ipsilateral striatum, relative to the contra-

TABLE 1

CHARACTERISTICS OF ROTATIONAL BEHAVIOR IN BOTH INTACT AND 6-OH-DA-TREATED RATS FOLLOWING INTRANIGRAL INJECTIONS OF GABA ANTAGONISTIC COMPOUNDS

Drug (dose)	N	Total turns Contralateral	Total turns Ipsilateral	Duration of turning (min)	Peak rate of turning (turns/min)
		Intact rats			
		Pars Reticulata			
Picrotoxin (0.25 μg)	7	199.3 ± 25.9		41.4 ± 4.7	10.3 ± 1.2
Bicuculline (0.1 μg)	5	50.2 ± 11.0		18.0 ± 2.5	7.0 ± 1.3
		Pars compacta			
Picrotoxin (0.25 μg)	10		72.4 ± 15.2	26.5 ± 4.0	5.4 ± 1.0
Bicuculline (0.1 μg)	6		59.3 ± 31.4	13.3 ± 2.1	8.5 ± 3.2
Bicuculline (0.1 μg)	2	28, 80‡		10,22	14,7
		6-OH-DA-treated rats			
		Pars Reticulata			
Picrotoxin (0.25 μg)	11	347.9 ± 46.3*		43.8 ± 0.9	17.7 ± 0.5
Bicuculline (0.1 μg)	5	257.2 ± 70.3†		25.4 ± 1.1	15.8 ± 1.8
		Pars compacta			
Picrotoxin (0.25 μg)	3	362.7 ± 41.7		48.3 ± 0.9	16.0 ± 1.2
Bicuculline (0.1 μg)	2	163, 132‡		11, 22	21, 14

The values for the total number of turns, duration and peak rate of turning are expressed as the mean ± SEM for each group.

*Mean differs significantly (t-test, $p<0.05$) from intact rats given picrotoxin.

†Mean differs significantly (t-test, $p<0.02$) from intact rats given bicuculline (0.1 μg).

‡Datum for each animal listed separately.

lateral side (Table 3). The DA contents of the ipsilateral nucleus accumbens septi, olfactory tubercle, and frontal cortex were also substantially (53–87%) reduced after the 6-OH-DA injection. Little nonspecific damage resulted from the intracerebral neurotoxin injections. Thus, norepinephrine levels showed only a slight (27%) decrease in the frontal cortex, while the area of nonspecific cell loss was confined to a region 416 ± 105 μm in diameter at the cannula tip and did not involve the substantia nigra. Because the 6-OH-DA-induced loss of the nigral DA-containing neurons made the extent of the pars compacta difficult to observe, this zone was defined as the region 0.3 mm dorsal to the dorsal margin of the pars reticulata.

In contrast to the intact rats, none of the 6-OH-DA-treated rats that received injections of picrotoxin or bicuculline methiodide into the pars compacta turned ipsilaterally (Table 1). Of the five rats given picrotoxin (0.25 μg) injections into the region of the pars compacta, two showed no rotation, while the remaining three turned *contralaterally*. Similarly, three of the five rats given bicuculline methiodide (0.10 μg) injections into the region of the pars compacta showed no rotational behavior, while the remaining two turned contralaterally. The turning produced by muscimol injections into the region of the pars compacta was also significantly reduced (Table 2).

In addition to attenuating the turning induced by the injection of GABA agonists and antagonists in the pars compacta, the prior 6-OH-DA injection potentiated the contralateral turning seen after injection of GABA antagonists into the pars reticulata. Picrotoxin (0.25 μg) injected into this zone in 11 6-OH-DA-treated rats produced significantly greater contralateral turning than was seen in intact rats receiving pars reticulata injections of the same amount of this drug (Student's t-test, $p<0.05$). Similarly, bicuculline methiodide (0.10 μg) injected into the pars reticulata of 6-OH-DA-treated rats produced significantly more turning than was seen in intact rats given the same quantity of this compound (Student's t-test, $p<0.02$). In contrast, the contralateral turning produced by injections of muscimol (0.05 μg) into the pars reticulata of 6-OH-DA-treated rats did not differ significantly from that produced by injections of the same dose of this drug into the pars reticulata of intact rats.

DISCUSSION

The present results indicate that the direction of turning behavior elicited by the intranigral injection of GABA antagonist compounds can be predicted with a high degree of accuracy by knowing the nigral zone in which the cannula tip is located. Injection of picrotoxin or bicuculline methiodide into the pars reticulata of intact rats invariably resulted in contralateral rotation, whereas injections of these compounds into the pars compacta typically resulted in ipsilateral turning. The rotation produced by the injection of picrotoxin into either of these nigral zones was dose-dependent, with statistically significant turning occurring at doses of

0.20 μg and 0.25 μg. The contralateral turning elicited by the injection of bicuculline methiodide into the pars reticulata was also dose-dependent. The similar thresholds for the elicitation of ipsilateral and contralateral turning make it unlikely that one type of rotation occurs as a physiological response to the GABA antagonist injection while the other is a pharmacological artifact. In contrast to the results obtained using intranigral GABA antagonists, the GABA agonist muscimol produced contralateral turning after its injection into either nigral zone. These turning behaviors are probably not due to a nonspecific excitatory action of these drugs, since the unilateral intranigral injection of strychnine does not produce rotation [3].

Six-OH-DA-induced destruction of the DA-containing cells of the pars compacta abolished the ipsilateral turning otherwise seen after the injections of GABA antagonists into this structure. In addition, the contralateral rotation normally produced by the injection of muscimol into this area was significantly attenuated. These findings suggest that the turning behavior induced by the injection of these substances into the pars compacta of intact animals is mediated by the ascending DA-containing neurons. In agreement with these findings, other studies have reported that unilateral injections of muscimol into the substantia nigra produce contralateral rotation which is attenuated by systemic administration of the DA receptor blocker, haloperidol [14, 15, 19, 30]. In addition, injections of muscimol into one substantia nigra have been found to increase DA release in the ipsilateral striatum [14].

In contrast to the turning behavior produced by GABA agonist or antagonist injections into the pars compacta, the contralateral turning seen after injections of either of these substances into the pars reticulata was not attenuated by the 6-OH-DA injections. Since the injection of this neurotoxin produced a 98% depletion of neostriatal DA content, it appears unlikely that a stimulation of the few remaining DA-containing neurons could have mediated the robust and prolonged rotational behavior that occurred after reticulata GABA agonists and antagonist injections. The persistence of this contralateral turning in the virtual absence of nigrostriatal DA-containing neurons suggests that nigral GABA receptors function not only to regulate the activity of the DA-containing pars compacta neurons but also to control the activity of non-dopaminergic nigral cells.

Interestingly, the 6-OH-DA-treated rats showed greater contralateral turning after the injection of GABA antagonists into the pars reticulata than did intact animals. One possible explanation of this finding is that GABA antagonist compounds injected into pars reticulata spread to the compacta. In intact rats, an action of these drugs on the DA-containing compacta cells might tend to cancel their effect on pars reticulata neurons, thereby attenuating the contralateral turning. In 6-OH-DA-treated rats, this action on DA-containing neurons would not occur, and the tendency to turn contralaterally would be fully expressed. Similarly, a diffusion of injected compounds from pars compacta to pars reticulata might explain why some of the 6-OH-DA-treated animals

TABLE 2

CHARACTERISTICS OF ROTATIONAL BEHAVIOR IN BOTH INTACT AND 6-OH-DA-TREATED RATS FOLLOWING INTRANIGRAL INJECTIONS OF MUSCIMOL

Dose	N	Total turns contralateral	Duration of turning (min)	Peak rate of turning (turns/min)
		Intact rats		
		Pars reticulata		
0.025 μg	5	122.0 ± 42.9	45.0 ± 9.5	3.6 ± 0.9
0.050 μg	6	688.0 ± 134.8	60.0 ± 0.0	18.0 ± 3.4
		Pars compacta		
0.025 μg	6	26.7 ± 12.0	16.7 ± 6.7	1.5 ± 0.6
0.050 μg	7	457.1 ± 65.3	56.4 ± 3.6	14.1 ± 1.7
		6-OH-DA-treated rats		
		Pars reticulata		
0.050 μg	6	791.2 ± 73.2	60.0 ± 0.0	18.7 ± 2.3
		Pars compacta		
0.050 μg	4	179.8 ± 42.6*	45.0 ± 15.0	6.0 ± 3.6

The values are as in Table 1.
*Mean differs significantly (t-test, $p<0.05$) from intact rats given muscimol.

TABLE 3

REGIONAL CATECHOLAMINE CONTENT OF BOTH HEMISPHERES FOLLOWING INJECTION OF 6-OH-DA INTO THE LEFT VENTRAL TEGMENTAL AREA

	Nucleus accumbens							
	Neostriatum		Septi		Olfactory tubercle		Frontal cortex	
	DA	NE	DA	NE	DA	NE	DA	NE
Right: $\bar{X}$	7.26	0.24	5.10	1.05	4.31	0.87	0.06	0.15
SE	0.70	0.02	1.01	1.09	0.83	0.23	0.01	0.06
Left: $\bar{X}$	0.14†	0.20	0.71†	1.09	0.74†	0.71	0.03*	0.11*
SE	0.03	0.05	0.21	0.67	0.32	0.14	0.01	0.03

Values are the mean ($\bar{X}$) and the standard error (SE) expressed as μg of catecholamine per gram wet weight of tissue.
*Means significantly different, t-test, $p<0.01$.
†Means significantly different, $p<0.001$.

turned contralaterally when given GABA antagonist injections into pars compacta as well as why the contralateral turning otherwise seen after muscimol injections into this area was not completely blocked by the prior 6-OH-DA injections.

While some spread of the intranigrally administered GABA antagonists from one nigral zone to the other is possible, several factors suggest that their action was largely localized to the region of their injection. First, injections only a few tenths of a millimeter apart could produce different types of turning provided that one was made into the pars reticulata and the other into the compacta (Fig. 2). Second, ipsilateral turning resulted only when these compounds were injected into a narrow region corresponding to the pars compacta. For example, injections into the zona incerta, dorsal to the nigra produced no turning in three animals given 0.15 μg picrotoxin and slight contralateral turning in two given 0.1 μg bicuculline (data not shown). Finally, in a series of animals in which dye (1% methylene blue, 0.5 μl, 1 μl/min) was injected into the nigra, its spread was localized to the zone of injection. Thus, after injections into the pars compacta (N=6) the dye spread medially within this region but did not invade the reticulata, while after injections into pars reticulata (N=6) the dye spread through a spherical region ventral to the cannula tip but did not invade the compacta or the crus cerebri.

Although the behavioral effects of intranigral GABA agonists and antagonists are clear, the mechanisms underlying these effects appear to be complex. For instance, if GABA inhibits the DA-containing nigral neurons, intranigral GABA agonists should decrease striatal DA release and thus produce ipsilateral turning. By opposing this action of GABA, antagonists should produce contralateral turning. However, the behavioral (present results) and neurochemical [14] consequences of these injections are the opposite of what would be predicted from the preceding model. At least two explanations for the observed directions of turning suggest themselves. First, GABA agonists and antagonists may preferentially act at presynaptic GABA receptors, such that GABA agonists would cause a decrease in nigral GABA release, while GABA antagonists would increase it. Second, the affected GABA receptors may be located on nigral interneurons which are inhibitory to the pars compacta cells. Recent evidence suggests the existence of neurons within the nigra which are inhibitory to the DA containing pars compacta cells and which are themselves inhibited by muscimol [8]. These neurons have been found to be located in close proximity to the dopaminergic neurons.

An additional complexity in interpreting these data is that injections of both GABA agonists and antagonists into the pars reticulata produce contralateral turning. This finding suggests that GABA may act at two different sites within the pars reticulata. These two sites may be GABA receptors located presynaptically or postsynaptic on nigra GABAergic afferents. Alternatively, these sites may represent GABA receptors located both upon and postsynaptic to a GABAergic nigral interneuron [23]. A dual action of GABA within the pars reticulata is supported by data showing that besides producing contralateral turning [16,17], intranigral GABA agonists can cause ipsilateral turning in response to systemic injections of amphetamine or apomorphine [1, 4, 5, 26].

Our findings indicate that the direction of turning seen after GABA antagonist injections depends strictly upon the nigral zone into which these compounds are administered. No support was gathered for the claim that the direction of turning elicited by intranigral picrotoxin depends upon the anterior-posterior placement of the injection cannula [10, 21, 24] with the anterior placements producing contralateral turning, and the posterior injection sites yielding ipsilateral rotation. We intentionally varied the anterior-posterior coordinate in the present work in order to investigate this possibility. As can be seen in Fig. 2, the anterior-posterior position of the cannula tract does not appear crucial in determining the direction of turning. Both contralateral and ipsilateral turning could be elicited at the most anterior and the most posterior planes that we systematically explored. At all planes the critical variable appears to be whether the cannula tip lies in the pars compacta or pars reticulata. Since none of the experiments claiming an anterior-posterior dissociation have published histological reconstructions of their cannula tips, we can only suggest that their anterior placements were located in the pars reticulata, while their posterior placements may have been situated in the pars compacta. In one report [24], the high doses of picrotoxin used often produced odd types of behavior (e.g., a contralateral posture followed by ipsilateral turning and wild running seizures), making the results difficult to interpret. Other studies have suggested that the direction of turning elicited by the unilateral injection of GABA antagonists into the substantia nigra depends on the concentration or volume used [17, 19, 24]. In those experiments, injections of higher concentrations or larger volumes produced rotation in the direction opposite to that elicited by lesser concentrations or volumes. However, in the present study no effect of the concentration of the GABA antagonist on the direction of turning was found. Since increasing either the concentration or volume of intracerebral injections could lead to greater diffusion, injections of larger concentrations or volumes might diffuse from their area of injection to the other nigral zone and produce an effect there which over-shadows their local action. For instance, in one report [19] injections of GABA antagonists into the substantia nigra (zone not specified) using the same volume employed in the present study (0.5 μl) produced contralateral turning, while injection in a larger volume (2.0 μl) produced ipsilateral turning. We suggest that in this case the injections may have been made into the pars reticulata but that increasing the volume injected may have allowed spread to the pars compacta and the production of an action there.

In addition, our findings suggest that the contralateral turning behaviors produced by muscimol injections into the pars reticulata and pars compacta have different explanations, since damage to the ascending DA system attenuates the former but not the latter type of rotational behavior. Other studies have also shown that intranigral muscimol injections into the pars compacta produce behavioral effects which are not equivalent to those following pars reticulata injections [1].

In conclusion, the present findings demonstrate that intranigrally injected GABA agonists and antagonists can produce different behavioral effects depending on the nigral zone of their injection. We anticipate that these findings will provide a histological framework in which the different turning behaviors elicited by the intranigral injection of these substances can be understood.

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