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Circling and Bodily Asymmetry Induced by Injection of GABA Agonists and Antagonists Into the Superior Colliculus

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GEULA, C. AND D. ASDOURIAN. *Circling and bodily asymmetry induced by injection of GABA agonists and antagonists into the superior colliculus.* PHARMACOL BIOCHEM BEHAV 21(6) 853–858, 1984.—The observation that ipsiversive circling follows unilateral lesions of the deep layers of the superior colliculus (DLSC), combined with the recent demonstration of an ipsilateral inhibitory GABAergic projection from substantia nigra pars reticulata (SNr) to the DLSC suggests a role for tectal GABA in circling behavior. In the present experiment, GABA, the GABA agonist muscimol, and the GABA antagonists picrotoxin and bicuculline were injected into the DLSC through chronic cannulae. GABA and muscimol produced significantly higher ipsiversive circling and bodily asymmetry than saline injections. Picrotoxin and bicuculline resulted in significantly higher contraversive circling and asymmetry than saline injections. All drugs except bicuculline produced dose-dependent circling. GABA injections were also made into the mesencephalic reticular formation (MRF) and the periaqueductal gray (PAG). The MRF injections produced the same degree of circling and asymmetry as the DLSC injections. The PAG injections resulted in significantly lower amounts of circling than the DLSC GABA injections, but they resulted in equivalent measures of asymmetry. These results demonstrate that DLSC GABA produces circling and asymmetry, and suggest that the DLSC as well as the MRF serve as output stations for the expression of circling behavior initiated at the striatum.

Superior colliculus GABA agents Circling Bodily asymmetry

BASED upon the proposal by Ungerstedt [44] that rats will circle away from the side of greater dopamine (DA) receptor activity, a considerable body of research has emerged devoted to clarifying the anatomical and neurophysiological bases for the striatonigrostriatal (SNS) circuitry that is involved in controlling circling and motor asymmetry [37]. In addition to the work concerned with the role of the SNS loop in circling and asymmetry, recent research in this area has also focused on the contributions of some of the major striatal and nigral output pathways. One of these pathways is the nigrotectal tract (NTT) which begins in the substantia nigra reticulata (SNr) and ends in the deep layers of the superior colliculus (DLSC). The NTT has been shown to be ipsilateral [1, 5, 16, 18, 23, 39, 47], monosynaptic and inhibitory [2, 7, 11, 49], and to utilize GABA as the neurotransmitter [7, 8, 15, 26, 45].

The NTT is of interest in the present context because a number of investigators [12, 14, 29, 30, 33, 38, 42, 43] have shown that unilateral electrolytic and kainic acid lesions in the superior colliculus (SC) of rats are followed by ipsiversive circling and asymmetry, and since there is a direct output from the SNr to the DLSC, it is a reasonable speculation that the SNS control of circling and asymmetry is mediated, at least in part, via the DLSC. In support of this speculation is the finding that intraperitonial injections of the DA receptor agonist apomorphine (APo) induce ipsiversive circling in rats with unilateral DLSC kainic acid lesions long after the lesion induced circling has disappeared [12], suggesting that the APo induced activity in the SNS directed to the DLSC is being projected only through the intact SC.

The results of corollary experiments have generally shown that unilateral DLSC lesions modify APo induced circling in animals with lesions in the ipsilateral striatum or SNr [22,34], although in one study, bilateral DLSC lesions did not modify circling in animals that also had unilateral SNr lesions [10].

In keeping with the position that DLSC is a part of the output circuit of the striatum, and taking advantage of the evidence that there is a major ipsilateral GABAergic pathway from SNr to DLSC, Kilpatrick, Collingridge, and Starr [26] used measures of circling and asymmetry to assess the role of collicular GABA in this circuit. They found that injections of the GABA agonist muscimol into the DLSC of rats resulted in ipsiversive asymmetry and circling, and that DLSC muscimol injections antagonized apomorphine induced circling when 6-hydroxydopamine lesions were made in the nigrostriatal tract ipsilateral to the DLSC injections. They provided further evidence for an ipsilateral relationship between the SNS system and the DLSC by showing that the contraversive circling produced by intranigral injections of

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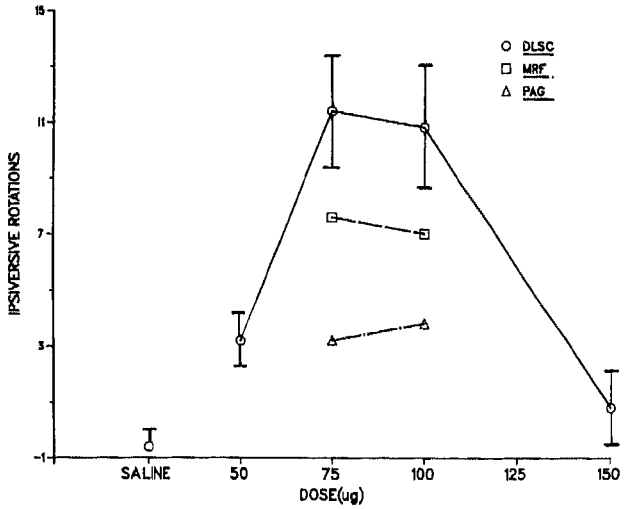

FIG. 1. Dose-response relations for circling induced by injections of GABA into the DLSC, MRF and PAG (turns/5 minutes). Each dose was injected into five animals.

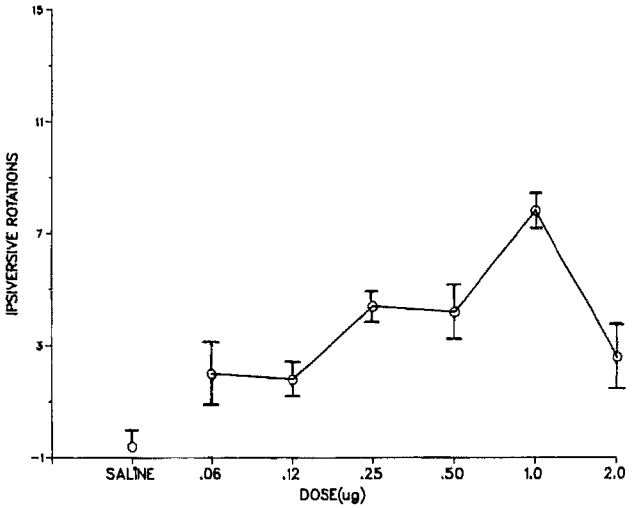

FIG. 2. Dose-response relations for circling induced by injection of muscimol into the DLSC (turns/5 minutes). Each dose was injected into five animals.

muscimol was inhibited when muscimol was also injected into the DLSC. When the GABA antagonist picrotoxin was injected into the DLSC, animals exhibited explosive motor activity and contraversive circling and asymmetry. Similar results have been reported as a result of injections of muscimol, picrotoxin and bicuculline into the DLSC-MRF complex [21] suggesting that both the DLSC and the MRF are sites important in the mediation of the effects of GABA agents on circling and asymmetry.

Since establishing dose-dependency is a necessary step in determining the currency of the pharmacological effects of receptor agonists and antagonists, one of the aims of the present study is to determine if GABA, muscimol, picrotoxin and bicuculline have dose-dependent effects on circling and asymmetry when injected into the DLSC. Our second aim is to measure the potency of GABA in producing circling and asymmetry when injected into structures adjacent to the DLSC. The adjacent structures of interest to us are the mesencephalic reticular formation (MRF) and the periaqueductal gray (PAG). Both of these structures are on the borders of the DLSC and there is evidence that they receive GABAergic fibers from the ipsilateral SNr [1, 4, 15, 19, 20, 23, 39] which raises the possibility that any GABAergic effect of injections into DLSC may be at least partially the result of the drugs gaining access to structures other than the DLSC.

METHOD

Subjects

Seventy male Sprague Dawley rats weighing between 300–400 grams were used in this experiment.

Apparatus

The guide cannulae were constructed from 23 gauge stainless steel tubing in which 30 gauge tubing was inserted as a temporary plug. The length of each guide cannula was 12 mm. Injections were made through 30 gauge tubing, 13.9 mm in length, connected to a 10 μl syringe with polyethylene tubing having an i.d. of 0.28 mm. The rotometer consisted of a stainless steel bowl with a top diameter of 55 cm, a bottom diameter of 15 cm and a height of 30 cm.

Surgery

The animals were anesthetized with IP injections of sodium pentobarbital (60 mg/kg) and were given 0.2 ml(0.1 ml IP and 0.1 ml IM) of atropine sulphate (0.5 mg/ml) to help combat congestion during surgery. Half of the cannulae were chronically implanted on the right side and half on the left. For all cannulae implants the incisor bar was fixed at 5 mm above zero. The lateral and anteroposterior coordinates were measured from ear bar zero. The dorsoventral coordinates were measured from dura. Cannulae were implanted in the DLSC (anterior 0.8 mm, ventral 4.5 mm and lateral 1.4 mm), the MRF (anterior 0, ventral 4.9 mm and lateral 1.7 mm) and the PAG (anterior 0.8 mm, ventral 4.5 mm and lateral 0.3 mm) [36]. All cannulae were implanted so that the tip of each cannula was 1.9 mm dorsal to the actual site of injection (since the injection tubing extended 1.9 mm beyond the tip of the cannula). The animals were allowed 5–7 days of recovery before any testing was carried out.

Drugs

Based upon pilot work carried out on 20 animals, various doses of GABA (50, 75, 100 and 150 μg), the GABA agonist muscimol (0.06, 0.12, 0.25, 0.50, 1.0 and 2.0 μg), and the GABA antagonists picrotoxin (0.03, 0.06, 0.08 and 0.09 μg) and bicuculline (0.06, 0.09, 0.12, 0.25, and 0.50 μg) were used (Sigma Chemical Company, St. Louis, MO). Normal saline was used as the carrier solution for all drugs, and all of the drug solutions were adjusted for pH to match the pH of normal saline.

Testing

Twenty minutes prior to each injection, each animal was placed in the bowl for 5 minutes and the number of 360 degree turns in either direction was recorded. Fifteen minutes after an animal was removed from the bowl, the plug of

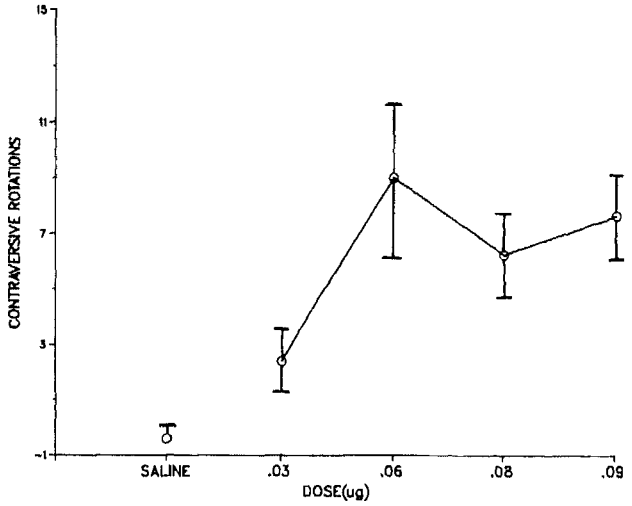

FIG. 3. Dose-response relations for circling induced by injection of picrotoxin into the DLSC (turns/5 minutes). Each dose was injected into five animals.

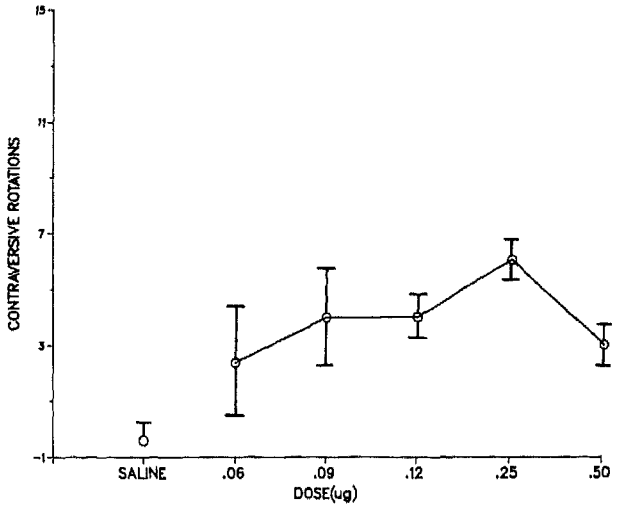

FIG. 4. Dose-response relations for circling induced by injection of bicuculline into the DLSC (turns/5 minutes). Each dose was injected into five animals.

the guide cannula was removed and the injection cannula was inserted (extending 1.9 mm beyond the tip of the cannula). Each animal received a 1 μl injection of a drug over one minute, after which the injection cannula was removed and the plug replaced. Immediately after injection each animal was placed in the bowl and the number of 360 degree turns in either direction was again recorded for 5 minutes. Each animal received a maximum of two injections, the two being 5–7 days apart and of the same drug but of different doses. When two injections were made, the lower dose of the drug was injected first. Each dose of the drug was injected into the DLSC in 5 animals. Five animals received saline injections and were tested in the same manner as drug-injected animals. In addition, two groups of five animals each received injections of the two most effective doses of GABA (75 and 100 μg) into the PAG and MRF. Three animals received injections of 1.0 μg of muscimol (which had the longest lasting effect when injected into the DLSC) into the cortex lying immediately above the SC to control for the effects of the possible spread of injected drugs to cortical layers.

During all testing, the animals were observed for degree of head tilt and bodily asymmetry. As a test of asymmetry, a modified version of the classification introduced by Costall, *et al.* [9] was used. According to this classification, a score of zero indicates no observable asymmetry. Animals which display slight asymmetry during at least 60% of the test period receive a score of one; animals displaying slight asymmetry during the entire test period receive a score of two; and finally, animals showing severe asymmetry (head overlapping tail) during the test period receive a score of three.

Animals were also observed for postinjection seizure-like activity. The criterion for seizure-like activity was jumping and running activity displayed during the test period.

Histology

When testing was completed the animals were sacrificed with an overdose of sodium pentobarbital and perfused intracardially with a 0.9% solution of saline followed with a 10% solution of formalin. The brains were removed, frozen and sectioned at 40 μ, and the sections were mounted and stained using a cresyl violet Nissl stain. Only data from animals that had the tip of the injection tubing at the correct site were used [31]. Animals that were excluded from the study because of faulty cannula placements were replaced.

RESULTS

The difference between the number of pre and post injection rotations exhibited by each animal make up the circling data in this experiment. GABA, muscimol, and picrotoxin produced dose-dependent increases in circling when injected into the DLSC (Figs. 1–3). Bicuculline injections produced increased circling but this effect was not dose-dependent (Fig. 4). These increases in rotation were in the predicted direction for each drug. Analyses of variance performed on the circling data yielded significant effects for the drugs used (GABA: $F(4,20)=11.8$, $p<0.01$; muscimol: $F(6,28)=11.3$, $p<0.01$; picrotoxin: $F(4,20)=5.5$, $p<0.01$; bicuculline: $F(5,24)=5.9$, $p<0.01$).

GABA was the most effective drug used, and 75 μg of this drug elicited the highest rate of circling observed in this study. Only 75 and 100 μg of GABA produced significantly more ipsiversive rotations than saline injections (Newman-Keuls, $p<0.05$). The most effective dose of muscimol in inducing ipsiversive circling was 1.0 μg resulting in significantly more rotations than all of the other doses used. Injections of all of the doses of muscimol except 0.06 and 0.12 μg were followed by significantly more ipsiversive rotations than after saline injections (Newman-Keuls, $p<0.05$). Picrotoxin, in all the doses used, yielded significantly more contraversive rotations than saline, and 0.03 μg of this drug resulted in significantly fewer contraversive rotations than the other doses used (Newman-Keuls, $p<0.05$). Injections of bicuculline were followed by significantly more contraversive rotations than saline injections (Newman-Keuls, $p<0.05$), however, none of the doses of this drug were significantly different from each other in inducing circling ($p>0.05$).

Of the control injections, 75 and 100 μg doses of GABA injected into the MRF produced ipsiversive circling which was not significantly different from the number of rotations following injections of the same doses into the DLSC. These doses of GABA injected into the PAG, however, resulted in significantly fewer ipsiversive rotations than DLSC injections (75 μg: $t=3.35, p<0.01$; 100 μg: $t=2.35, p<0.04$). The effects of GABA injections into the MRF and PAG on circling are shown in Fig. 1. The three animals receiving injections of 1.0 μg of muscimol in the cortex showed significantly fewer ipsiversive rotations than three animals, chosen at random, from the group that had received the same injections into the DLSC ($t=3.7, p<0.05$).

Our results showed that the DLSC injections were followed by increased locomotion as well as asymmetry. In 86% of the cases, more rotations were recorded following injections than prior to drug treatment. One indication that drug treatment produced bodily asymmetry was the finding that in 80% of the cases experimental animals circled only in the expected direction, whereas control animals circled in both directions.

The Kruskal-Wallis test applied to the asymmetry scores assigned to each subject revealed significant effects for all drugs injected into the DLSC (GABA: $H(4)=19.38, p<0.01$; muscimol: $H(6)=15.67, p<0.01$; picrotoxin: $H(4)=13.29, p<0.01$; bicuculline: $H(5)=13.8, p<0.01$). To determine the effects of the various doses of each drug in inducing asymmetry, a modified version of the Mann-Whitney test introduced by Ryan was used [28]. All doses of all drugs used produced significantly greater asymmetry than saline ($p<0.05$). However, no significant differences were found among the asymmetry scores resulting from the injections of various doses of each drug. Of all the drugs used, the asymmetry produced by muscimol injections lasted for the longest period of time, being present up to an hour after the drug injection, while the asymmetry produced by other drugs disappeared a few minutes after the injections. There were no significant differences among the asymmetries produced by GABA injections into the DLSC, MRF and PAG.

Of the two convulsant drugs used, only 0.09 μg of picrotoxin produced seizure-like activity. Two animals receiving 0.09 μg of picrotoxin were replaced because of the severity of the seizures. Doses higher than 0.09 μg consistently resulted in severe seizure-like activity and were not included in this study. The histological results (see Fig. 5) showed that a few animals developed infections as a result of injections of bicuculline. The data obtained from the infected animals were discarded and replaced with data from additional animals that showed no infections. No infections were encountered as a result of the injection of any drug other than bicuculline.

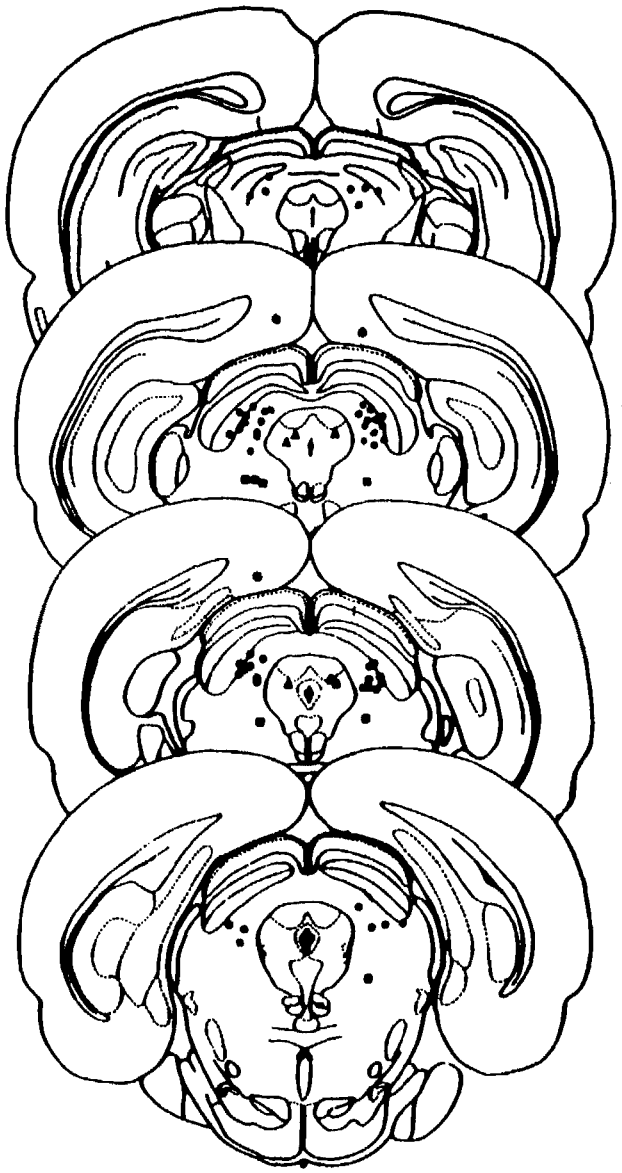

FIG. 5. Histological results showing the placement of the tip of the injection tubing in: circle—DLSC, square—MRF, triangle—PAG and hexagon—cortex. Sections are from top to bottom −5.8 *mm*, −6.3 mm, −6.8 mm and −7.3 mm posterior to bregma (from Paxinos and Watson [35]).

DISCUSSION

The results of this experiment support the hypothesis that DLSC GABA is implicated in ipsiversive circling and asymmetry [21,26] and strengthen that hypothesis by showing that these behaviors are controlled by GABAergic substances in a dose-dependent manner (excepting bicuculline).

Consistent with previous findings [21], relatively low levels of circling were observed following DLSC injections of GABAergic agents when compared with the circling levels reported following similar injections into the SN [25,32] and the ventromedial nucleus of the thalamus [13,27]. Although our injections resulted in relatively low levels of circling, our measures of bodily asymmetry were consistently high. Thus, our findings support the hypothesis that the DLSC plays a more important role in motor asymmetry than it does in circling [21].

All of the drugs used in this experiment had their effects when used in low dose ranges except for GABA which required a high dose (50–150 μg) to produce an effect. The high dose of GABA required is probably due to the rapid inactivation of this neurotransmitter [6, 24, 41, 49].

The findings of this study provide support for the position that the GABAergic nigrotectal projection is responsible for the circling observed after manipulations of the DLSC.

Other GABAergic inputs to the DLSC might exist that would contribute to this phenomenon, although none are known at this time.

The tectal efferents that might be responsible for the expression of circling and asymmetry are those projecting to areas of the nervous system known to participate in motor activity. Three major outputs from the DLSC are known. One projects to the inferior olive [17,40], but in the absence of relevant research it is not known if this projection contributes to the behaviors observed in this experiment. Another projection is from the DLSC to the neck motoneurons and has received some experimental attention. Anderson, Yoshida and Wilson [3] have shown the influence of the DLSC cells on neck motoneurons to be excitatory. To test for the involvement of this projection in asymmetry and circling, Winterkorn and Meikle [46] placed knife cuts that severed the tectospinal tract and observed that this procedure was not followed by circling or asymmetry. The involvement of DLSC-driven neck motoneurons in circling and asymmetry cannot be ruled out, however, since it has been suggested that the excitatory influence of tectal cells on neck motoneurons may be mediated through still a third DLSC projection, i.e., a tectoreticulospinal pathway rather than the tectospinal tract [2].

As the results of this experiment indicate, the DLSC is not the only midbrain structure which induces circling and asymmetry following GABA injections. Injections of GABA into the PAG, MRF and DLSC produced equivalent measures of bodily asymmetry while injections into the MRF and DLSC also resulted in equivalent measures of circling. These results are consistent with the findings of previous studies [12,21] suggesting that the DLSC and the dorsal MRF may form a functionally unitary structure involved in the expression of bodily asymmetry and circling behavior.

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