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Self-Injurious Behavior in Rats Produced by Intranigral Microinjection of GABA Agonists[1]

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BAUMEISTER, A. A. AND G. D. FRYE. *Self-injurious behavior in rats produced by intranigral microinjection of GABA agonists.* PHARMACOL BIOCHEM BEHAV 21(1) 89–95, 1984.—Bilateral injection of the GABA agonist muscimol (10–300 ng) into the caudal substantia nigra (pars reticulata) of rats produced dose-dependent stereotyped gnawing and self-biting. Limiting the opportunity to gnaw on inanimate objects shifted the dose-response curve for muscimol-induced self-injurious behavior (SIB) to the left and increased the maximum incidence of SIB. Microinjection of muscimol (30 ng) into the rostral and caudal regions of the substantia nigra were equally effective in producing SIB, though the incidence of SIB decreased sharply when muscimol was injected 1 mm rostral or caudal to the substantia nigra. Bilateral intranigral injection of THIP (100–1000 ng) and (±)baclofen (100–1000 ng) induced a low incidence of SIB. However, neither IP administration of picrotoxin (5 mg/kg) or simultaneous microinjection of (+)bicuculline methiodide (BMI; 300 or 1000 ng) along with muscimol (30 ng) blocked muscimol-induced SIB. In fact, (+)BMI increased the occurrence of self-biting and reduced the latency to onset of SIB. The involvement of GABAergic mechanisms in muscimol-induced SIB is discussed.

Self-injurious behavior Self-mutilation Muscimol Bicuculline Substantia nigra

SELF-INJURIOUS behavior (SIB) is a common problem among schizophrenic children [15,39], institutionalized mentally retarded persons [25,38], and children afflicted with the Cornelia de Lang [6,18] and Lesch-Nyhan syndromes [8,29]. Despite considerable research effort, little is known about the determinants of SIB. In recent years there has been increasing speculation that in some persons SIB may be the product of specific structural or biochemical defects in the brain [3]. Abnormalities in dopamine systems are implicated in the etiology of SIB by a report that several indices of dopamine function are dramatically reduced in the basal ganglia of Lesch-Nyhan patients [22]. Other lines of evidence suggest the involvement of serotonin, norepinephrine, purine derivatives, and the endogenous opioid peptides in human SIB [3].

Work with animals has implicated similar mechanisms in SIB. SIB can be produced in laboratory rodents by several methods including: (1) Peripheral administration of apomorphine to adult rats following neonatal destruction of catecholamine neurons by intraventricular 6-hydroxydopamine (6-OHDA) treatment [9]; (2) peripheral administration of apomorphine following destruction of nigrostriatal dopamine neurons with 6-OHDA [42,43]; (3) peripheral administration of apomorphine following unilateral intrastriatal injection of adenosine [16]; (4) chronic administration of high doses of methylxanthines [23, 32, 36]; (5) chronic opiate administration [20,24]; (6) acute peripheral administration of pemoline [14,26] or clonidine (34,35]; (7) chronic continuous administration of amphetamine [27,28]; and (8) deafferentiation of the limbs [2,11]. Recently, while studying seizure susceptibility in rats following ethanol withdrawal, we discovered that bilateral microinjection of the GABA agonist muscimol into the substantia nigra frequently produced self-biting in rats [4,13]. Other investigators [37,41] have reported anecdotally that intranigral administration of muscimol produces self-biting in rats, but this effect has not been sys-

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tematically examined. The present paper describes systematic studies designed to characterize SIB produced by microinjection of GABA agonists into the substantia nigra of rats.

METHOD

Animals

Male Sprague Dawley rats (180–220 g) were used in all experiments. The animals were purchased from Charles River Laboratories (Somerville, MA) or Harlan Industries (Indianapolis, IN) one week prior to beginning each experiment. The animals were group housed (4 to 6 per cage), and maintained on a 12 hour light-dark cycle, with food (Wayne Lab Blox rat chow) and water available ad lib.

Experimental Design

The data from six separate experiments are presented below. Each experiment was conducted over a period of several days or weeks. To control for factors that may have varied systematically across days, a representative sample of animals from all groups within a particular experiment was included on each day of testing. Separate control groups were generated for each experiment.

Surgery and Microinjection Procedure

The rats were anesthetized with diethyl ether and placed in a stereotaxic instrument (Kopf Instruments, Tujunga CA). Blunt guinea pig ear bars were used to prevent damage to the tympanic membrane. After incising the scalp and drilling burr holes in the skull, two 30 gauge stainless steel needles mounted on a single electrode carrier were lowered to the desired site. In most of the experiments described below the needles were aimed at the caudal substantia nigra (zona reticulata) (A 2.5 mm, L 2 mm, V 8 mm below skull surface, incisor bar −3 mm). In one experiment injections also were made at points rostral or caudal to this site. Stereotaxic coordinates were derived from the atlas of Paxinos and Watson [30]. All drugs were delivered bilaterally in a total volume of 0.5 μl sterile saline over a one minute period. After the injection, the needles were left in place an additional 60 seconds to allow absorption and to prevent the spread of injected fluid up the needle track. Drug doses are expressed as dose per side.

In the last experiment muscimol was injected via chronic indwelling cannulas in order to evaluate the effects of surgical stress on muscimol-induced SIB. In this experiment, the rats were anesthetized with sodium pentobarbital (45 mg/kg), and guide cannulas were placed just above the caudal substantia nigra (zona reticulata) (A 2.5 mm, L 2 mm, V 7 mm below skull surface). The cannulas were anchored to the skull with small stainless steel screws and dental acrylic cement. Stylets (32 gauge stainless steel tubing) were then placed in the guide cannulas to keep out dirt. Two weeks later each animal received bilateral intranigral microinjections of muscimol (30 ng) via 33 gauge stainless steel needles extending 1 mm below the tip of the guide tubes. The muscimol was delivered in 0.5 μl sterile saline over a one minute period. Each animal received two bilateral injections of muscimol. On the first day of testing half of the animals were kept under ether anesthesia for five minutes prior to and during the injection, while the remaining animals received no ether and were restrained by hand. Two days later the same animals were tested again, but this time the ether conditions were reversed.

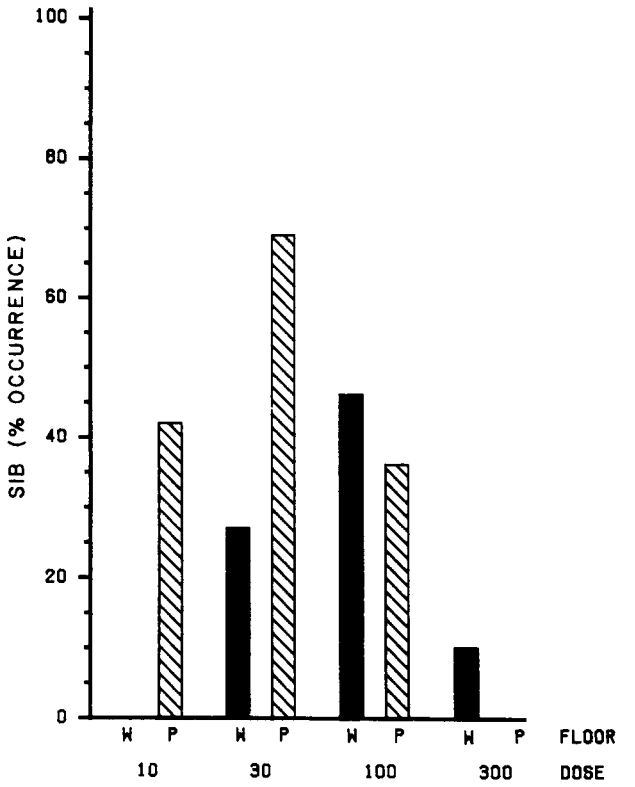

FIG. 1. Percent of animals that exhibited SIB following intranigral administration of muscimol when gnawing on the wire cage floor was allowed (solid bars) and when the opportunity to gnaw was limited (cross hatched bars).

Measurement of Behavior

Immediately following each injection, the animal was placed in a clear plastic observation cage (46×24×20 cm high). In the first experiment the observation cages were equipped with a wire mesh floor (2.5×2.5 cm, 12 ga). In all subsequent experiments Plexiglas floors were used. The animal's behavior was observed for one minute once every ten minutes for the next three hours. At the beginning of each observation period the animal was examined for the presence of lesions caused by self-biting. Self-injurious behavior was defined as self-biting that caused tissue damage. Self-biting, gnawing, and other stereotyped behaviors were measured by dividing each one minute observation period into four 15 second intervals and counting the number of intervals in which each behavior occurred (cf., [21]).

Statistical Analysis

Tests for differences between groups in the frequency of occurrence of SIB were conducted by Chi Square analysis. Analysis of self-biting and stereotypy data was conducted in the following manner: For every one minute observation period the proportion of intervals in which each behavior occurred was computed for each animal. These proportions were then transformed according to the following formula in an attempt to stabilize the variances:

$$X' = 2 \text{ ARCSIN } \sqrt{X}$$

where X is a proportion and X′ is an angle measured in

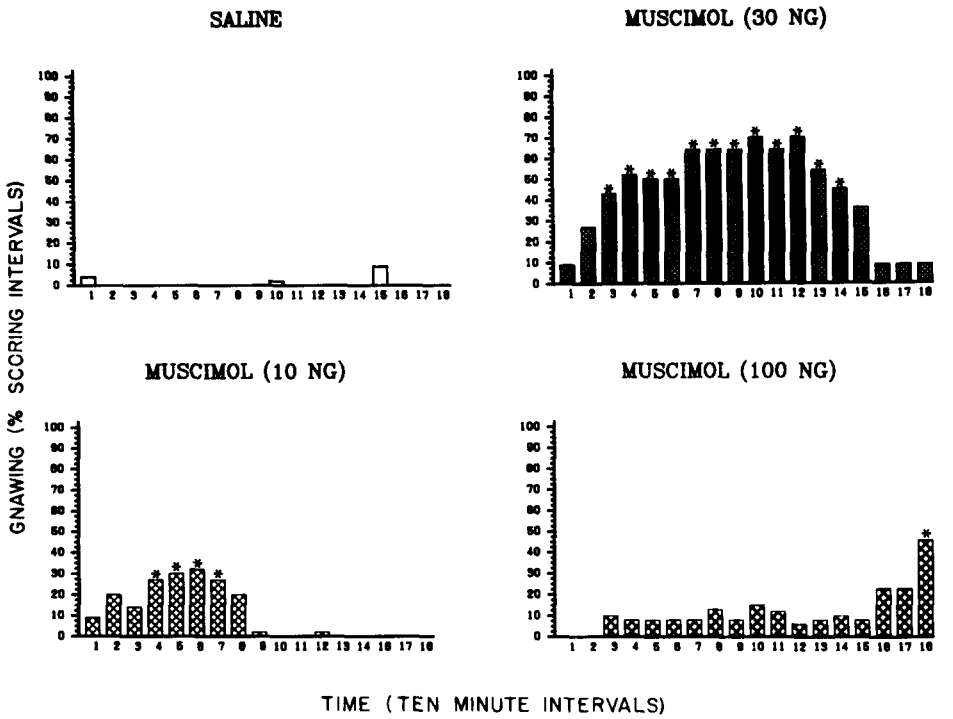

FIG. 2. Mean percent of scoring intervals in which gnawing on the wire cage floor was observed following intranigral administration of muscimol plotted as a function of muscimol dose and time from injection. *$p<0.05$ compared to microinjected saline controls.

radians [45]. The transformed scores were then analyzed with a two factor analysis of variance having repeated measures on one factor. When significant groups by trials interactions were found, a one factor ANOVA was conducted to test for differences between groups at each time point. For each one factor ANOVA that yielded a significant F ratio, pair-wise comparisons between treatment means were made using either Dunnett's *t*-test or the Tukey test.

Histology

After completing behavioral observations, the animals were sacrificed and the brains were removed and frozen. The brains were cut into 250 μm sections and the location of the needle tracks was determined by a trained examiner unaware of the intended injection site. Only the data from those animals in which the needles were correctly placed were included in the analysis.

Drugs

(+)Bicuculline methiodide (BMI) was purchased from Pierce Chemical Company (Rockford, IL), muscimol from Sigma Chemical Company (St. Louis, MO), (±)baclofen was a gift from CIBA Pharmaceutical Co. (Summit, NJ), and THIP (4,4,6,7-tetrahydroisoxazole) was a gift from Lundbeck and Co. (Copenhagen, Denmark).

RESULTS

Muscimol-Induced Self-Injurious Behavior and Gnawing

When the rats were tested in cages with wire floors, bilateral intranigral injection of muscimol at 10, 30, 100, and 300 ng produced self-biting that resulted in tissue damage in 0/11, 3/11, 6/13, and 1/10 of the animals, respectively (Fig. 1). Among the animals that exhibited SIB 67% bit their tail, 16% bit their paws, and 50% had multiple lesions. No SIB was observed following microinjection of saline (n=11) in animals tested on wire cage floors.

Microinjection of muscimol also caused dose-dependent gnawing on the wire floor (Fig. 2). Gnawing was most intense after microinjection of 30 ng of muscimol. In this group, gnawing began about 40 minutes after the muscimol injection and continued uninterrupted for an average of 109 minutes. In 3/11 animals gnawing was so intense that it persisted despite the development of lesions in the animal's mouth caused by the constant chewing. Muscimol also produced strong stereotyped sniffing and head nodding. No other motor abnormalities such as tremor, spasticity, or ataxia were observed. With the exception of the first 10–15 minutes of observation, during which time the animals were still under the influence of ether, saline microinjected controls were indistinguishable from unoperated animals. The operated saline controls spent most of their time sleeping, though normal grooming and exploratory behaviors were occasionally observed.

Effects of Limiting the Opportunity to Gnaw

To determine whether the incidence of SIB was related to the opportunity to gnaw on inanimate objects, the effects of muscimol were examined when the opportunity to gnaw was limited by removing the wire floor. Compared with tests made on the wire floor, testing animals in cages with plastic floors produced significant increases in SIB following micro-

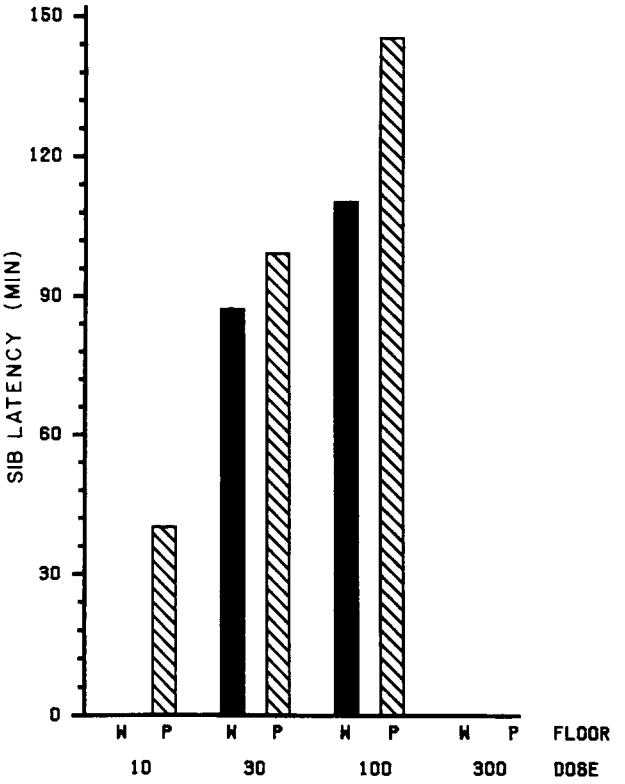

FIG. 3. Latency to onset of muscimol-induced SIB when gnawing on the wire cage floor was allowed (solid bars) and when the opportunity to gnaw was limited (cross hatched bars).

injection of 10 ng, $\chi^2(1)=5.86$, $p<0.05$, and 30 ng, $\chi^2(1)=4.19$, $p<0.05$, of muscimol. Under the plastic floor condition 5/12, 9/13, 4/11, and 0/10 animals exhibited SIB in the 10, 30, 100, and 300 ng groups, respectively (Fig. 1). Stereotyped sniffing, head nodding, and rapid repetitive movements of the forepaws toward and then away from the animal's mouth were also observed. No SIB was seen in microinjected saline controls (n=11) tested on plastic cage floors.

Figure 3 shows the latency to onset of SIB under both wire and plastic floor conditions. There was a direct relationship between the dose of muscimol injected and the latency to onset of SIB for rats tested on plastic floors. Longer latencies were observed in the 30 ng, $t(10)=3.88$, $p<0.005$, and 100 ng, $t(6)=3.28$, $p<0.01$, groups compared with the 10 ng group.

Effects of Other GABA Agonists and Antagonists

To determine whether muscimol-induced SIB was related to activation of GABA receptors, the effects of intranigral injection of other GABA agonists were also examined. The results of this experiment are presented in Table 1. Both THIP and baclofen occasionally produced SIB, though neither drug was as effective as muscimol in this regard.

An attempt was also made to block muscimol (30 ng)-induced SIB by co-administration of the GABA antagonist BMI (300 or 1000 ng). When administered concurrently with muscimol, BMI (300 ng) produced a small but significant

TABLE 1

INCIDENCE OF SIB IN RATS FOLLOWING INTRANIGRAL INJECTION OF GABAERGIC DRUGS

Drug*	Dose (ng) 100	300	1000
THIP	1/4	1/10	0/4
Baclofen	0/4	1/4	0/4
BMI†	—	0/7	0/10
Muscimol (30 ng) + BMI	—	12/16	8/8

*Muscimol (30 ng) alone produced SIB in 13/21 animals when the data for all experiments were combined. No SIB occurred in microinjected saline controls (n=29).

†(+)Bicuculline methiodide.

increase in the occurrence of self-biting (Fig. 4) and reduced the latency to onset of SIB, $t(17)=1.97$, $p<0.05$. The incidence of SIB following co-administration of 1000 ng of BMI (8/8) was significantly greater, $\chi^2(1)=4.21$, $p<0.05$, than the incidence of SIB following muscimol alone (13/21) when the data for animals in the latter group for all experiments were combined. BMI had no effect on muscimol-induced stereotyped sniffing, head nodding, or paw movements. BMI seemed to have the intended effect on GABA receptors since 1000 ng BMI administered alone or combined with muscimol produced seizures in all animals tested. However, no seizures were observed following microinjection of 300 ng of BMI. BMI alone (300 or 1000 ng), did not produce SIB or stereotyped behavior.

In another experiment, animals received 5 mg/kg (IP) of picrotoxin immediately following intranigral injection of muscimol (30 ng). The incidence of SIB among picrotoxin treated animals (6/11) did not differ from the incidence of SIB among animals receiving muscimol alone (13/21).

Rostral-Caudal Specificity of Muscimol-Induced SIB

The anatomical specificity of muscimol-induced SIB was examined next by making systematic injections of muscimol (30 ng) outside of the initial injection site (Fig. 5). In this experiment 6/7 animals exhibited SIB when muscimol was injected into the caudal substantia nigra (A 2.5, L 2, V 8 below skull surface). Injection of muscimol 1 mm rostral (A 3.5) or caudal (A 1.5) to this site produced SIB in 6/6 and 3/6 animals, respectively. The rostral placement was found to be in the rostral half of the substantia nigra, while the caudal placement was just behind the most caudal extent of the substantia nigra (Fig. 5). Muscimol from this slightly caudal placement would still have had access to the substantia nigra. No SIB occurred in animals receiving microinjections of muscimol 2 mm rostral (A 4.5) or caudal (A 0.5) to the original (A 2.5) site. Both of these placements were clearly outside the substantia nigra by 1.0–2.0 mm.

Effect of Eliminating Surgical Stress

Eliminating surgical stress produced a small but nonsignificant reduction in the incidence of SIB. Anesthetizing the animals with ether prior to microinjecting muscimol had no effect on the incidence of SIB. When muscimol (30 ng) was injected via chronic indwelling cannulas, 3/7 animals showed

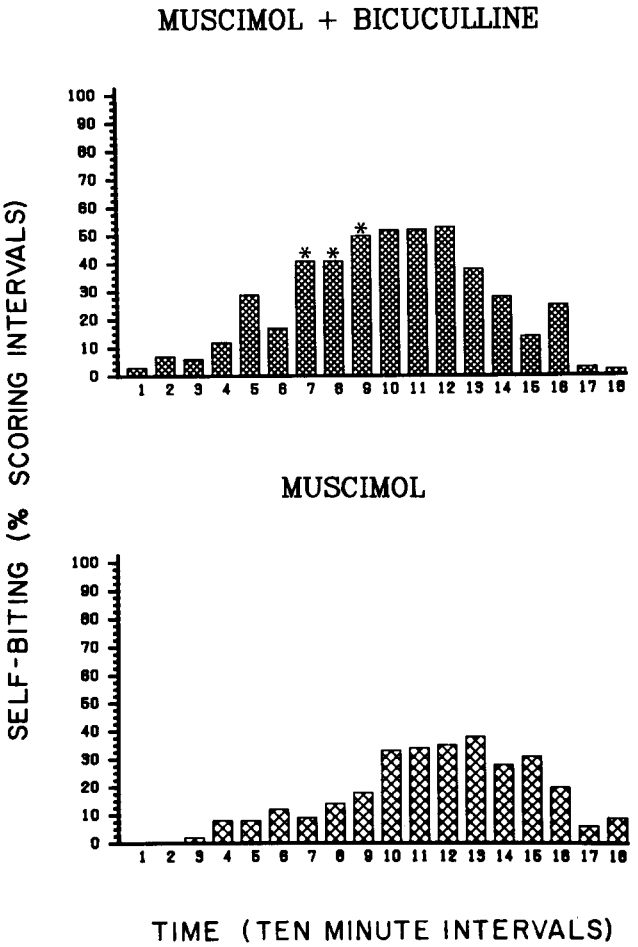

FIG. 4. Mean percent of scoring intervals in which self-biting was observed following intranigral administration of muscimol (30 ng) alone or muscimol (30 ng) plus bicuculline methiodide (300 ng). *$p<0.05$ compared to muscimol (30 ng) group.

SIB under both the ether-anesthetized and unanesthetized conditions.

DISCUSSION

This study confirms and extends anecdotal reports [37,41] that bilateral microinjection of muscimol into the substantia nigra can produce self-biting leading to tissue damage in rats. The incidence of SIB was dependent on both the dose of muscimol and the environmental context in which the animals were tested. Limiting the opportunity to gnaw on inanimate objects shifted the dose-response curve for muscimol to the left and increased the maximum incidence of SIB. There appeared to be little regional specificity within the substantia nigra for induction of SIB after bilateral microinjection of muscimol. Injection of muscimol into the rostral or caudal substantial nigra was equally effective in producing SIB. However, the incidence of SIB declined sharply when injections were made rostral or caudal to the boundaries of the substantia nigra.

The role played by activation of GABA receptors in muscimol-induced SIB is unclear. A low incidence of SIB was produced by intranigral administration of other GABA agonists, THIP and baclofen. However, neither

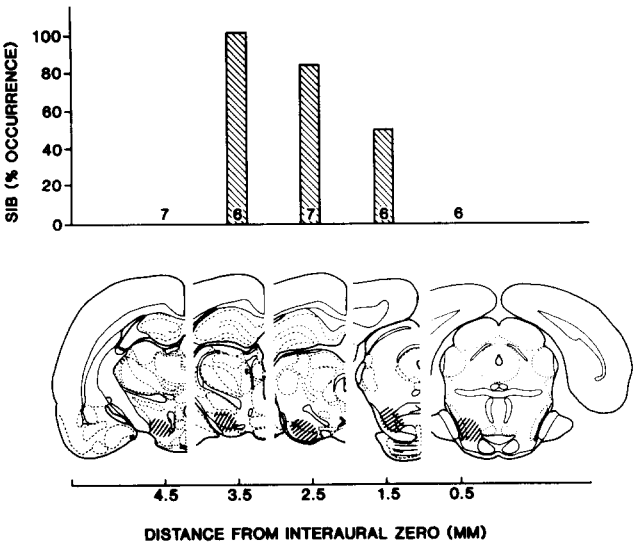

FIG. 5. Percent of animals that exhibited SIB following microinjection of muscimol at sites within or near the substantia nigra. Numbers within the bars represent sample sizes. Drawings are adapted from the stereotaxic atlas of Pellegrino, Pellegrino and Cushman [31].

(+)bicuculline methiodide (BMI) or picrotoxin blocked muscimol-induced SIB. In fact, BMI increased self-biting and decreased the latency to onset of SIB. This finding is consistent with reports that bicuculline potentiates the behavioral effects baclofen [33] and that intranigral administration of bicuculline alone, at lower doses than those used in the present study, causes self-biting in rats [1]. The seemingly paradoxical effect of BMI on muscimol-induced SIB and the relative ineffectiveness of baclofen and THIP may be related to differences in the duration of action of these drugs. In the present study, behavioral effects of intranigral administration of muscimol were apparent for up to three hours after the injection. BMI-induced seizures, on the other hand, lasted only 15 to 30 minutes; after this time the animals became inactive. It has been reported that cortical GABA concentrations following GABA transaminase inhibition are increased threefold during bicuculline-induced seizures [7]. Thus, it is possible that BMI may cause an increase in endogenously released GABA that could augment the effects of muscimol, once the GABA receptor blockade by BMI is eliminated.

It has also been suggested that certain behavioral effects of muscimol may be due to activation of bicuculline-insensitive GABA (GABA B) receptors [33]. If muscimol activates GABA B receptors to cause SIB, this could explain both the failure of GABA antagonists to block muscimol-induced SIB, as well as the apparent potentiation of this behavior by BMI. Bicuculline may preferentially enhance the activity of GABA B receptors by releasing endogenous GABA and, at the same time, blocking bicuculline-sensitive GABA (GABA A) receptors [33]. In order for this explanation to be consistent with the data presented here, it seems necessary to assume that muscimol has greater activity at the GABA B receptor than does baclofen, because the latter drug was relatively ineffective in producing SIB. Although there are data that support this hypothesis [33], most studies (e.g., [5,17]) indicate that muscimol has little activity at the GABA B receptor.

Although the data presented here preclude firm conclusions about the mechanisms underlying muscimol-induced SIB, the involvement of nigral GABA systems is consistent with evidence linking SIB in both humans [22] and animals [16, 42, 43] to perturbations in striatal dopamine function. GABAergic projections to the substantia nigra constitute a principal striatal output system [12,19]. Many behavioral consequences of striatal dopamine receptor activation appear to be mediated by the substantia nigra via the striatonigral GABA pathway [10,40]. Therefore, it is reasonable to propose that GABA systems in the substantia nigra and efferent nigral pathways mediate the expression of SIB secondary to abnormalities in the striatal dopamine function. It is also possible that defects specific to nigral GABA systems may account for some instances of SIB in humans. In either case, pharmacological therapies designed to alter GABA function may prove useful in the management of SIB in some clinical populations.

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