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Disinhibition of Muricide and Irritability By Intraseptal Muscimol

MICHAEL POTEGAL, BYRON YOBURN[1] AND MURRAY GLUSMAN

New York State Psychiatric Institute
722 West 168th Street, New York, NY 10032

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POTEGAL, M., B. YOBURN AND M. GLUSMAN. *Disinhibition of muricide and irritability by intraseptal muscimol.* PHARMACOL BIOCHEM BEHAV 19(4) 663–669, 1983.—In two experiments we have found and replicated the observation that intraseptal muscimol profoundly facilitates muricide. It also increases irritability (response to handling). These effects are specific to aggressive behaviors in that the drug affects neither activity nor chocolate chip acceptance. The effects of the GABA synthesis inhibitor thiosemicarbazide depend upon the site of injection within the septum; in more anterior loci the drug produces the expected increase in muricide latency; in more posterior sites it produces an anomalous facilitation of muricide. The serotonergic agents quipazine and metergoline have no significant effect when injected into any of these sites. These results suggest that the septal neurons mediating the muricide-inhibitory effect of electrical stimulation [29] are subject to local, GABAergic, control. Inhibition of these neurons by muscimol produces a net disinhibition of muricide.

Muricide Aggression Septum Inhibition GABA Muscimol Thiosemicarbazide
Serotonin Quipazine Metergoline

WE AND others have found recently that muricide by rats, like other forms of aggression in other species, can be inhibited by electrical stimulation of the septum [2, 28, 29]. These studies were largely focussed on the analysis of the behavioral and neuroanatomical features of the inhibition. In contrast to the progress which has been made in elucidating these aspects of septal aggression inhibition, the neurochemical bases of this effect have been more difficult to identify. Various studies have failed to find evidence for cholinergic, catecholaminergic, or glutaminergic mediation (e.g., [1]) even though these neurotransmitters have been implicated in the control of aggression in other brain regions. In searching for alternative candidate transmitters, we were inspired by recent pharmacological [8, 9, 20, 26, 30, 31, 32] and neurochemical [20, 27, 33] data implicating GABA in the neural control of aggression. We therefore elected to examine the effects of intraseptal administration of the GABA agonist muscimol and the GABA synthesis inhibitor thiosemicarbazide (TSC) on muricide and irritability in rats. In the first experiment reported here we describe the details of our finding [30] that intraseptal muscimol produces a profound and relatively specific facilitation of muricide and irritability.

We were also interested in the role of serotonin in septal muricide inhibition since evidence for a close relationship between GABA and serotonin activity has been found in histochemical [24] and pharmacological studies [12, 18, 40]. Furthermore, Gibbons *et al.* [14] had found that thresholds for inhibitory electrical stimulation of the septum could be systematically manipulated by peripheral injection of serotonergic agents. This finding is consistent with a large body of evidence implicating serotonin in the inhibitory control of muricide (see e.g., [39]). We therefore thought it of interest to compare the effects of intraseptally administered GABAergic agents to those of serotonergic agents. These results are reported in the second experiment.

EXPERIMENT 1

METHOD

Subjects and Surgery

Individually housed, male Long-Evans, hooded rats, 90 to 120 days old, were maintained on a 1 hr/day feeding schedule for 7 days. (This procedure induces muricide in 50–80% of naive rats.) On the eighth day they were screened for muricide by having a mouse placed in their home cage for 20 min; mice killed in this period were removed immediately. The rats then returned to ad lib feeding until the time of surgery, no less than 3 days later.

Animals which killed the mouse within the 20 min period were stereotoxically implanted under IP Pentothal anesthesia with a 5 mm long 22 ga guide cannula (Plastics Products 313G) aimed at the septum (coordinates: anterior=bregma+1.0 mm, lateral=midline suture+0.6 mm). A 28 ga internal injection cannula (C313I) and a stylet to maintain patency (C313DC) were cut to protrude 0.25 mm beyond the end of the guide cannula. Eight animals completed all phases of the experiment.

[1]Present address: Department of Pharmacology, Cornell University Medical College, New York, NY 10021.

Experimental Design

Each subject received all doses of both the muscimol and TSC series (one per session) over a total of 8 sessions; the minimum intersession interval was 48 hr. Half the subjects had the 4 sessions of the muscimol dose series first and the 4 sessions of the TSC dose series second; the remaining animals experienced the reverse order. Within a dose series, the order of drug doses was counterbalanced in a Latin square design.

Testing Procedures

To ensure a stable baseline of behavior, each session began with a pretest trial; if the subject killed a mouse within 5 min an intraseptal injection was given 10 min later. If it did not kill, the trial was aborted (see below). The muscimol dose series was 0.5, 0.05, 0.005 and 0.0 (saline) μg; the TSC dose series was 7.5, 2.5, 0.75 and 0.0 (saline) μg. Each drug dose was given in 0.5 μl of sterile, bacteriostatic water at an injection rate of 0.5 μl/min. To allow diffusion of the agent, the internal cannula was left in place for 30 sec following the injection.

A mouse was presented to the rat 5, 20, 40 and 60 min postinjection. (Effects of both agents have been demonstrated within this time period in previous studies [11,16].) Each mouse presentation trial lasted 5 min or until the rat killed (dead mice were removed immediately so that rats could never eat them). Latencies to attack and kill were recorded. Before each session at the lowest (saline) and highest dose for both drugs the rat's cage was placed on a Columbus Instruments activity meter. Activity was recorded for the 5 min period immediately preceding injection and for the 5 min periods preceding the last three postinjection trials.

In all sessions irritability was measured in response-to-handling tests given within 5 min of the last trial (i.e., 65 min postinjection). Each test consisted of: stroking the (1) back, (2) flank, and (3) snout of the rat with tongs, (4) "cornering" the rat with a gloved hand, (5) lifting the rat by the tail and (6) lifting it by the scruff of the neck. For each of the 6 tests we scored vocalization (0 or 1), escape (0–2, depending on intensity) and biting (0–2, depending on intensity). The cumulative irritability score for each session could range from 0 to 30.

Pretest Failures and Weight Regulation

Rats were routinely maintained at the weight they were at on the first session following surgery as long as they continued to kill on the pretest trials. If a rat failed to kill on a pretest, the remainder of the session was aborted and the rat was food deprived for a day. It was then retested under the same contingency until it killed again, whereupon it was maintained at its new weight. The few rats which fell to 80% of ad lib weight without killing again were dropped from the study.

Histological Preparation and Reconstruction of Cannula Tip Sites

Following completion of testing, rats were sacrificed with an overdose of Nembutal and perfused through the heart with 10% formalin. The brains were removed, cut in frozen sections at 25 μ, and stained with cresyl violet. In plotting cannula tip locations on plates from the Koenig and Klippel atlas [19], the AP location of each brain section containing a cannula tip was precisely determined by finding, for that section, the ratio of the distance between the medial edges of the anterior commissure (AC) to the distance between the lateral edges of the caudoputamen (CP). This ratio is a sensitive measure of AP location since, in this region of the brain, the AP distance decreases and the CP distance increases as the plane of section moves posteriorly. The range of AC/CP ratios on the 14 measured sections was 0.47 to 0.27. Since the AC/CP ratios of sections A9410, A8920, A8620, and A8380 of the Koenig and Klippel atlas are 0.51, 0.41, 0.33, and 0.30, respectively, tips were plotted in Fig. 4 as follows: $0.5 > (AC/CP) > 0.46$ were plotted on section A9410, $0.45 \geq (AC/CP) \geq 0.37$ on section A8920, $0.36 \geq (AC/CP) \geq 0.32$ on section A8620 and $0.31 \geq (AC/CP) \geq 0.27$ on section A8380.

Data Analysis

Activity and muricide latency data were evaluated using two-way analysis of variance. All latency scores were converted to common log values prior to statistical analysis. Irritability data were analyzed by a nonparametric analysis of variance based on ranks.

RESULTS

Figure 1 presents the dose-dependent decrease in muricide latency following muscimol injections into the septum. A two-way analysis of variance (dose × postinjection trial) for repeated measures revealed a significant effect of dose, $F(3,21)=12.91$, $p<0.001$, trial, $F(3,21)=3.92$, $p<0.03$, and a significant dose by trial interaction, $F(9,63)=2.41$, $p<0.03$. Analysis of orthogonal components revealed a significant linear component in the dose effect, $F(1,7)=65.02$, $p<0.001$. Although Fig. 1 shows a slight increase in muricide latency following TSC injections, a statistical analysis for TSC indicated that there was no signifncant dose, trial or interaction effects (F's<0.71, $p>0.05$). Figure 2 presents mean pretest latencies and the time course of the effects of muscimol on muricide. Despite the apparent dispersion of the mean pretest values, a one-way analysis of variance for repeated measures indicated no significant differences in pretest latencies, $F(3,21)<1.0$. At the highest dose (0.5 μg) muscimol's facilitating action on mouse-killing appears by 20 min and is still present 40 and 60 min postinjection. Attack latencies showed the same pattern of effects as kill latencies.

Irritability tests were administered immediately after the final (60 min) muricide trial at each dose. Figure 3 demonstrates a progressive increase in irritability with muscimol dose similar to the dose-related facilitation of muricide. A Friedman two-way analysis of variance indicated a significant effect of muscimol dose on the response to handling, $\chi^2_r(3)=12.7$, $p<0.001$. There were increases in all 3 response categories including biting. The increase in irritability was associated with a decline in the latency to kill for each animal. Spearman rank order correlation coefficients calculated for each rat between the mean latency to kill and the mean irritability score at each dose ranged from -0.32 to -0.80 ($\text{mean}_r=-0.63$, $SD=0.20$). The finding that all these correlations were negative is statistically significant by a two-tail binomial test ($p<0.05$). We did not find an effect of TSC on irritability, $\chi^2_r(3)=1.4$, $p>0.05$.

Activity measures on the saline and highest-dose sessions were analyzed by a two-way analysis of variance (dose × postinjection trial). There were no significant dose, trial or interaction effects (F's<1.35, $p>0.05$). These observations rule out the possibility that the muscimol-induced facilitation of muricide was secondary to changes in locomotor activity.

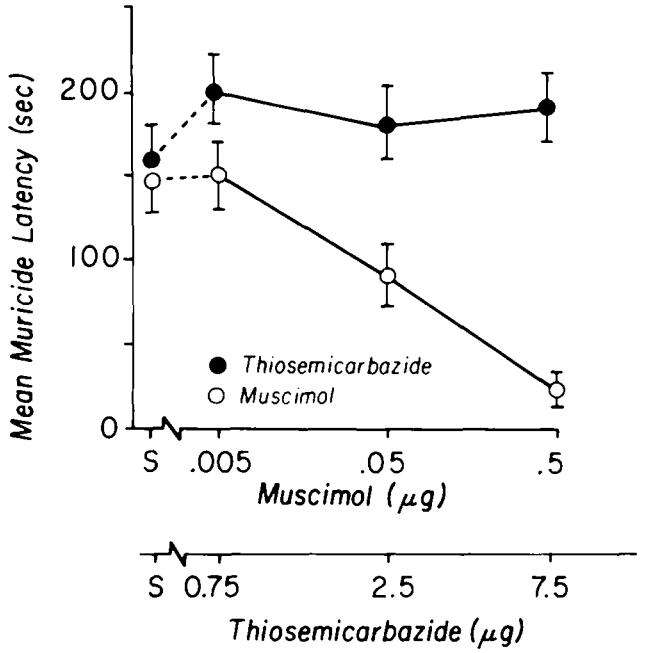

FIG. 1. Dose-response effects of intraseptal muscimol and TSC on muricide latency. Dosage scales are logarithmic. Error bars are standard errors of the mean.

In short, then, muscimol facilitated muricide and irritability but had no effect on activity, while TSC produced no significant net effect on any dependent measure.

The locations of the cannula tips, reconstructed on the left side of plates from the Koenig and Klippel atlas [19] in Fig. 4, were located in and around the medial septal nucleus and the diagonal band of Broca.

EXPERIMENT 2

In Experiment 1 we observed a muscimol-induced, dose-dependant increase in both muricide and irritability. Since there is a biting component in both of these behaviors, we became concerned about the possibility that muscimol injections in the septum might be producing a generalized facilitation of oral, biting behaviors. In the next experiment we therefore tested the effects of this manipulation on feeding (chocolate chip acceptance, [28]), another oral behavior.

In this experiment we also attempted to determine if the reported modulation of muricide-inhibitory septal stimulation by serotonergic agents [14] could be accounted for by an action of these agents within the septum. To this end we compared the effects of GABAergic agents to the effects of the serotonin agonist quipazine and the serotonin antagonist metergoline.

METHOD

Subjects

Six rats, selected, implanted and maintained as in Experiment 1, completed this experiment. The procedure was the same as in the first experiment with the modifications that the 40 min test and activity measures were dropped. The rat's latency to accept a 0.5 g chocolate chip offered 3 min before each mouse presentation was recorded.

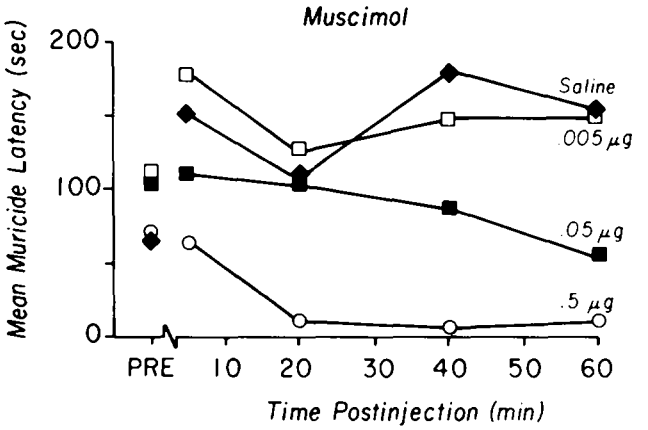

FIG. 2. Time course of intraseptal muscimol effects on muricide.

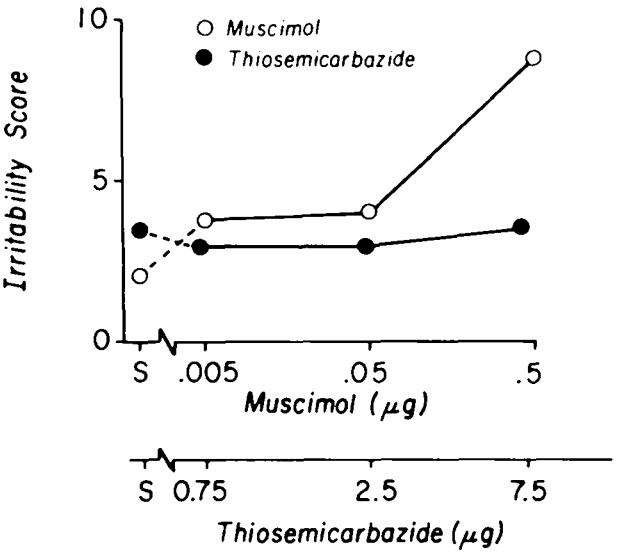

FIG. 3. Dose-response effects of intraseptal muscimol and TSC on irritability (response to handling).

The GABA series of injections consisted of saline, muscimol (0.5 μg) and thiosemicarbazide (7.5 μg). The serotonin series consisted of saline, quipazine (12.5 μg) and metergoline (1.0 μg). As before, the sequence of the series presentation and the order of drugs within a series was counterbalanced across rats.

RESULTS

The means and standard deviations of the latencies to kill mice and to accept chocolate chips following intraseptal injection of GABAergic and serotonergic agents are given in Table 1. There was a significant effect of drug on postinjection muricide latencies in the GABA series, $F(2,20)=10.39$, $p<0.001$. This effect was due to the facilitation of muricide by muscimol and was not the consequence of differential preinjection muricide latencies, $F(2,10)=1.53$, $p>0.05$. In the serotonin series there were no differences in muricide latencies before, $F(2,10)=2.14$, $p>0.05$, or after drug injec-

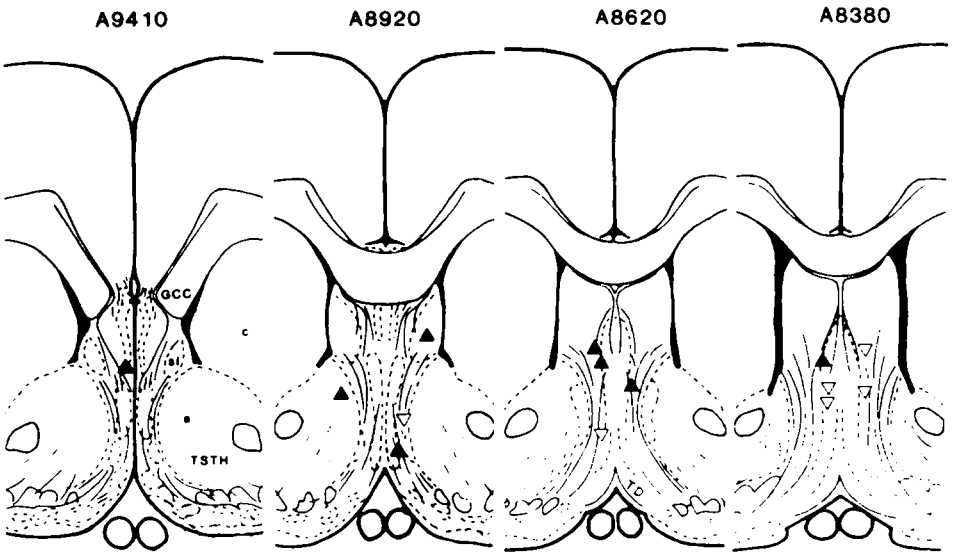

FIG. 4. Reconstruction of cannula tip locations. Tip loci of Experiment 1 are to the left of midline on each section; loci of Experiment 2 are to the right. Filled upright triangles are loci at which TSC increased muricide ($E_{tsc}>0$); empty inverted triangles are loci at which TSC reduced muricide latency ($E_{tsc}<0$). a: N. acumbens, c: caudoputamen, GCC: genu of the corpus callosum, TSTH: septohypothalamic tract. (From Koenig and Klippel [19].)

tion, $F(2,20)=2.88$, $p>0.05$. There were no significant postinjection trial or drug × trial interaction effects in any case.

Analysis of chocolate chip acceptance latencies revealed no significant differences in latencies either prior to, $F(2,10)=2.02$, $p>0.05$, or following muscimol, TSC or saline, $F(2,20)=3.14$, $p>0.05$, or prior to, $F(2,10)=3.94$, $p>0.05$, or following quipazine, metergoline or saline, $F(2,20)=0.71$, $p>0.05$. We found no significant postinjection trial or drug × trial interaction effects in either series of tests. The cannula tip locations are reconstructed on the right side of the plates in Fig. 4. As in Experiment 1, the tips were located in and around the medial septal nucleus and vertical limb of the diagonal band.

DISCUSSION

In two experiments we have found and replicated the observation that intraseptal muscimol profoundly facilitates muricide. This effect appears behaviorally specific in that the drug affects neither activity (Experiment 1) nor chocolate chip acceptance (Experiment 2). It does, however, increase irritability (response to handling). Indeed, at the highest dose, it appears to reproduce the syndrome of septal hyperirritability. The simultaneous increase of these two forms of aggression following manipulations of the septum has been noted previously (e.g., [3]). One interpretation of these results is that the facilitation of muricide is a consequence of the generalized increase in the probability of biting that is part of the septal irritability syndrome. However, in this region, as elsewhere in the CNS, irritability and muricide are dissociable within individual subjects (e.g., [3]). Therefore, another possibility is that the increases in these two forms of aggression reflect the simultaneous activation of interspecific (muricide) and defensive aggressive (irritability) mechanisms which are anatomically partially overlapping and which functionally share an increase in the probability of biting.

Our finding that intracranial administration of muscimol facilitates muricide and irritability is inconsistent with an earlier generalization that GABA is inhibitory to aggression (e.g., [20]). This generalization is based on observation of lower than control levels of GABA in the striata and/or olfactory bulbs of muricidal rats and aggressive mice [9, 20, 33]. We ourselves have recently observed higher GABA binding in combined limbic, striatal and diencephalic tissue of aggressive hamsters [27]; higher levels of GABA binding have been associated with lower levels of this transmitter [10]. Pharmacological studies have, in general, given results complementary to the neurochemical observations. In mice, systemic injection of GABAergic drugs suppresses intermale aggression and shock-elicited biting while GABA antagonists and synthesis inhibitors have the opposite effect [8, 26, 31, 32]. In rats, injections of GABAergic drugs into the olfactory bulbs reduce muricide while injections of GABA antagonists and inhibitors of GABA biosynthesis facilitate muricide [20].

Prior to our study, some exceptions to the earlier generalization had already been found. Simler *et al.* [33] reported that GABA concentrations were increased in the amygdala of isolated, aggressive DBA mice. Arnt and Scheel-Kruger [4] reported that injections of muscimol into the caudal part of the ventral tegmental area (VTA) increased aggressiveness in rats, a result resembling our own experience with septal injections.

In reformulating a generalization about GABA and aggression which can account for these exceptions, we note that GABA is an exclusively inhibitory neurotransmitter which is distributed in local circuit neurons throughout the CNS. (See [35] for histochemical evidence pertaining to the local origin of septal GABA and [13,21] for electrophysiological evidence of GABAergic inhibitory interneurons.) From this it follows that, if a given nuclear region is excitatory to

TABLE 1

EFFECTS OF INTRASEPTAL GABAERGIC AND SEROTONERGIC AGENTS ON MURICIDE AND CHOCOLATE CHIP ACCEPTANCE

	GABAergic agents			Serotonergic agents		
	Muscimol (0.5 μg)	Thiosemicarbazide (7.5 μg)	Saline	Quipazine (12.5 μg)	Metergoline (1.0 μg)	Saline
Muricide latency (sec)	17 (14)	174 (108)	148 (116)	89 (97)	127 (90)	169 (119)
Chocolate chip acceptance latency (sec)	14 (15)	8 (5)	8 (5)	5 (5)	3 (2)	7 (8)

All latency data are in seconds (standard deviations are in parentheses). Data were log-transformed before being subjected to statistical analysis.

aggression, then GABAergic activation within that region will be inhibitory. Conversely, however, if a given nuclear region is inhibitory to aggression, then GABAergic activation within that region will be disinhibitory to aggression. The latter effect seems to occur in the septum and caudal VTA, both of which inhibit aggression when electrically stimulated ([7,15] see Reference Note). This reformulation has the virtue of being readily testable since it makes unequivocal predictions about the effects of regional muscimol injections based on the effects of electrical stimulation.

A still unexplained anomaly in our results is that there was no net effect of TSC when averaged over all tip sites. However, the histological reconstruction of Fig. 4 suggests that averaging the results may produce a misleading impression. In 7 of the 9 more anterior sites, TSC did, in fact, increase muricide latency. This effect is the expected converse of the muscimol-induced reduction of muricide latency. In 4 of the 5 most posterior sites, TSC had the unexpected effect of facilitating muricide. To evaluate this phenomenon further, we defined the effect of TSC (E_{tsc}) as the mean muricide latency after 7.5 μg intraseptal TSC minus the mean latency after 0.5 μl saline. Moving anterior to posterior, the mean value of E_{tsc} at the four planes of Fig. 4 are 246, 73, 49, and −67 sec, respectively. A Pearson product-moment correlation between the E_{tsc} and the AP location of each tip site as measured by the AC/CP ratio was: $r=0.602$ ($N=14$, $p<0.05$). The main demonstrated pharmacological effect of TSC is on the GABA synthetic enzyme glutamate decarboxylase (GAD). GAD is highly localized in nerve terminals (e.g., [25]). Thus, in our study, TSC at the more anterior sites may have suppressed muricide by reducing GABA levels in the nerve terminals of the inhibitory interneurons [13,21]. We have at this time no explanation for the anomalous effect of TSC at the most posterior sites, but this may be due to other pharmacological actions of the drug.

The contrast between the effectiveness of intraseptal muscimol, a potent and specific GABA agonist, and the ineffectiveness of quipazine, a potent and specific serotonin agonist, in modulating aggression is striking. Quipazine's lack of significant effect is consistent with previous reports that destruction of the serotonergic input to the septum does not produce a major change in muricide [39] or irritability [6]. What, then, is the explanation for the serotonergic modulation of septal muricide—inhibitory stimulation found by Gibbons *et al.* [14]? One route of modulation may be through the projections from the medial septal nucleus and vertical limb of the diagonal band of Broca to the lateral habenula [17, 22, 37] and thence to the dorsal raphe (for review of these latter neuroanatomical connections see [36]). The role of these pathways in septal muricide inhibition is supported by recent evidence that habenular stimulation inhibits muricide [23] while lesions of the dorsal raphe eliminate the muricide-inhibitory effect of septal stimulation [28]. A role for these pathways in the modulation of irritability is suggested by the observation that the serotonin precursor 5-HTP reduces septal irritability [34]. The origin of the caudal projection from the septum appears to be medium-to-large neurons within the diagonal band. These neurons receive axodendritic and axosomatic contact from the terminal arborizations of axon collaterals of small, ovoid cells of that region [38]. These latter neurons have been tentatively identified as the inhibitory GABAergic interneurons that have been demonstrated in electrophysiological studies [5,21]. Medial septal neurons also receive massive input from lateral septal interneurons.

It thus appears possible that septal muricide inhibition involves medial septal neurons which project mono- or disynaptically to the dorsal raphe nucleus. Activation of these neurons by electrical stimulation excites a serotonergically mediated inhibition of muricide. Within the medial septum, the cell bodies of these projection neurons are subject to control by the terminals of inhibitory GABAergic interneurons. Activation by muscimol of the GABA receptors on the projection neurons therefore produces the net disinhibition of muricide which we observed.

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REFERENCE NOTE

Chaurand *et al.* [7] emphasize the aggression-facilitory effects of the rostral portion of the VTA. However, plates 4 and 5 of their Fig. 3 indicate that the predominant effect of caudal VTA stimulation is inhibitory.

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