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Wild Running Elicited by Microinjections of Bicuculline or Morphine into the Inferior Colliculus of Rats: Lack of Effect of Periaqueductal Gray Lesions

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BAGRI, A., G. DI SCALA AND G. SANDNER. *Wild running elicited by microinjections of bicuculline or morphine into the inferior colliculus of rats: Lack of effect of periaqueductal gray lesions.* PHARMACOL BIOCHEM BEHAV **41**(4) 727–732, 1992.—Bicuculline methiodide, a $GABA_A$ receptor antagonist, or a high dose of morphine was injected at the same site within the inferior colliculus (IC) of rats. Both drugs elicited the same behavioral activity (wild running). However, the time course and magnitude of the effects of the two drugs differed. Since the behavioral activation elicited was reminiscent of what was found with microinjections of bicuculline methiodide or morphine into the periaqueductal gray (PAG), we lesioned the PAG in another group of rats. It was found that extensive lesions of the PAG including those extending to the medial part of the superior colliculus did not significantly reduce the wild running.

Wild running Inferior colliculus Periaqueductal gray Brain lesions Morphine Bicuculline Intracerebral microinjection

MICROINJECTIONS of bicuculline or other $GABA_A$ antagonists into the periaqueductal gray (PAG) were shown to elicit a behavioral activation characterized by fast running activity interspersed by jumps (10,18,38) that was considered the overt expression of an aversive state (17). A widespread area within the tectum was described to be involved in GABA antagonists-induced running and jumping behavior. This area includes, in addition to the PAG, the superior colliculus (SC) (13,22,39) and the inferior colliculus (IC) (12,20). Microinjections of high doses of morphine into the PAG were found to elicit a very similar behavior but, in this case, it has been reported as "explosive motor behavior" (EMB) (24,25). But, such studies on morphine-induced EMB remained focused on the PAG. It has been suggested that morphine would elicit EMB through an aspecific action on $GABA_A$ receptor (26). This hypothesis leads to the assumption that a microinjection of morphine would elicit the same behavioral effects as bicuculline whatsoever the microinjection site. Indeed, we found that a microinjection of morphine into the IC elicited running and jumping similar to those observed following bicuculline microinjection (2). Therefore, in the present study we investigated whether bicuculline or morphine would elicit or not an effect quantitatively identical when injected into one and the same site of the IC. Furthermore, EMB has been considered to be an effect rather specific following microinjection of morphine into the PAG (6,40). Having in hand the finding of a behavioral effect resembling EMB following microinjection of morphine into the IC, we checked whether the elicitation of running microinjection of bicuculline or morphine into the IC was still present in rats deprived of the whole PAG.

METHOD

Animals and Surgery

Animals. Thirty-eight male Wistar rats weighing 300–400 g were purchased from the Centre de Neurochimie breeding unit (Strasbourg, France) and housed in individual cages under a 12 L:12 D cycle (light from 8:00 a.m. to 8:00 p.m.). Food and water were freely available.

Surgery. Rats were anesthetized with sodium pentobarbital (40 mg/kg, IP) and fixed with atraumatic ear bars in flat skull position into a stereotaxic apparatus. The scalp was opened and three stainless-steel anchoring screws were fixed in the skull. Two stainless steel guide canulae (0.4 mm o.d., 0.3 mm i.d.) were bilaterally lowered into the brain 1 mm above the IC microinjection site. The following coordinates were used

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(the lambda point serving as reference): AP, −0.8 mm; ML, 1.9 mm; DV, 4 mm. Dental cement was used to anchor the guide canulae to the skull and the screws. Stylets were inserted into each guide canula to prevent clogging.

In a group of 16 rats, an electrolytic lesion was made, under anesthesia, just before lowering the canulae. Fourteen elementary lesions were placed to completely destroy the PAG (7 on each side). To that end, a stainless steel electrode, 250 μm in diameter, insulated except over the lower 0.3 mm, was lowered vertically successively through each of six small holes bored in the skull. A 2-mA cathodal current was applied during 15 s at each coordinate defined with respect to the point lambda (in mm): AP, −0.8; ML, 0.6; DV, 4.4, 5.0, 5.5/ AP, 0.0; ML, 0.6; DV, 5.0, 5.5/ AP, 1.0; ML, 0.6; DV, 5.2, 5.7. In eight rats of this group, four additional lesions were placed at the following coordinates to destroy also their SC (in mm): AP, 0.0; ML, 0.6; DV, 4.1/ AP, 1.0; ML, 0.6; DV, 4.1. After surgery, rats were allowed to recover for 1 week.

Drug Microinjection

Morphine sulfate and bicuculline methiodide were dissolved in phosphate buffer 0.02 M (pH = 7). Before microinjection, the rat was placed in the experimental arena. It consisted of a cylindric transparent wall (60 cm in diameter and 30 cm high) and a flat floor made of Plexiglas divided in 12 areas of about equal surface drawn by black ink. Unilateral microinjections into the IC were made using a microinjection canula. The stylet was replaced by the microinjection canula, which extended 1 mm beyond the tip of the permanent guide canula, and a 0.2-μl volume of the drug solution was injected over 30 s via a polyethylene tubing linked to a 1-μl Hamilton syringe. After microinjection, the microinjection canula was left in place for an additional 30 s. Three microinjections—each separated from the following by a 1-wk rest period—were made with the drug sequence randomly varied.

Behavioral Responses

For quantifying locomotor activity (including wild running and calm walking), the number of the areas crossed over by the rat were detected visually and recorded over a 40-min observation period. During wild running, rats run ipsilaterally in large circles along the circular wall of the experimental arena, which made recording by the experimenter easy since he had simply to record the number of turns. In each turn, the rat crossed eight areas. The number of jumps and the occurrence of tonic seizures were also recorded. A jump was recorded if the rat left the ground vertically toward the top of the wall of the arena. A tonic seizure was considered to be present if, after a wild running episode, the rat lost its upright posture and exhibited a tonic extension of the forelimbs and a flexion of the back with the mouth open.

Statistical Analysis

The delay of action and the duration of the effects of bicuculline and morphine microinjection into the same sites were compared using the Wilcoxon test [P3D, BMDP Statistical Software, (19)]. The mean number of areas crossed and jumps per minute elicited by each drug were also compared using the Wilcoxon test.

Comparisons of the total number of areas crossed and the number of jumps after every microinjection (drug or vehicle) were assessed in the intact or lesioned rats by use of a two-way analysis of variance (ANOVA) [P2V, BMDP Statistical Software, (19)]. Drug and vehicle were the two levels of the "within factor." Intact and lesioned rats constituted two levels of the "between factor."

Histology

At the end of the experiments, rats were anesthetized with pentobarbital and perfused intracardially with NaCl 0.9% followed by 4% formalin. Brains were removed and sectioned. Twenty-μm sections were stained with cresyl violet to allow visual identification of the microinjection sites and the extent of the lesions. They were drawn on the corresponding frontal planes of the atlas of Paxinos and Watson (35).

RESULTS

Elicitation of Wild Running by Microinjection of Bicuculline or Morphine into the IC of Intact Rats

Microinjection of the vehicle elicited no noticeable behavioral effect. No jump was elicited at all after vehicle microinjection. Microinjection of bicuculline methiodide (0.06 nmol) into the IC elicited an intense running and jumping activity (referred to as "wild running"). Running was often directed ipsilaterally to the injection site. Wild running activity was continuous during 2–4 min. After this period, running was interspersed by periods of immobility and jumps directed to the edge of the experimental arena. Microinjection of morphine (50 nmol) into the same sites elicited the same kind of behavioral activity, namely, intense running and jumping. Figure 1 shows that among the 28 sites tested both bicuculline and morphine elicited wild running at 24 sites (86%), whereas at 2 sites (7%) only morphine elicited wild running and at 2 other sites (7%) the two drugs were ineffective. Moreover, tonic seizures were observed following microinjection of morphine at four sites and following microinjection of bicuculline into three other sites. The seizures occurred 2–4 min after the beginning of the wild running. Thus, no qualitative difference was found between the effects of the two drugs.

However, there was a clear difference in both the delay of action of each drug (Wilcoxon: $p < 0.001$) and the duration of the induced effects (Wilcoxon: $p < 0.001$). For bicuculline, wild running started immediately after the end of the microinjection (mean latency: 1.8 min ±0.1) and lasted for 10 min (mean duration: 9.95 min ±0.6). For morphine, this behavioral effect started after a mean latency of 8.07 min (±0.4) and lasted 30 min (mean duration: 30.4 min ±0.7). During the period lasting from the microinjection to the occurrence of wild running, rats generally showed a freezing attitude. The mean number of crossings and jumps per minute did not differ according to the drug injected (Wilcoxon, $t = 101$, NS). Thus, the important effect observed after morphine depended on the longer duration of its effect. Comparing the magnitude of the effects of bicuculline or morphine microinjection into one and the same site showed a clear difference in the total number of areas crossed (Wilcoxon: $p < 0.001$). Thus, one cannot predict the magnitude of the effects of one drug from the magnitude of the effects elicited by the other drug.

Elicitation of Wild Running by Microinjections of Bicuculline and Morphine into the IC of Lesioned Rats

After anatomical verification, 12 of 16 rats were selected as having a complete lesion of the PAG. The lesion extended caudorostrally from the IVth ventricle to the rostral limit of

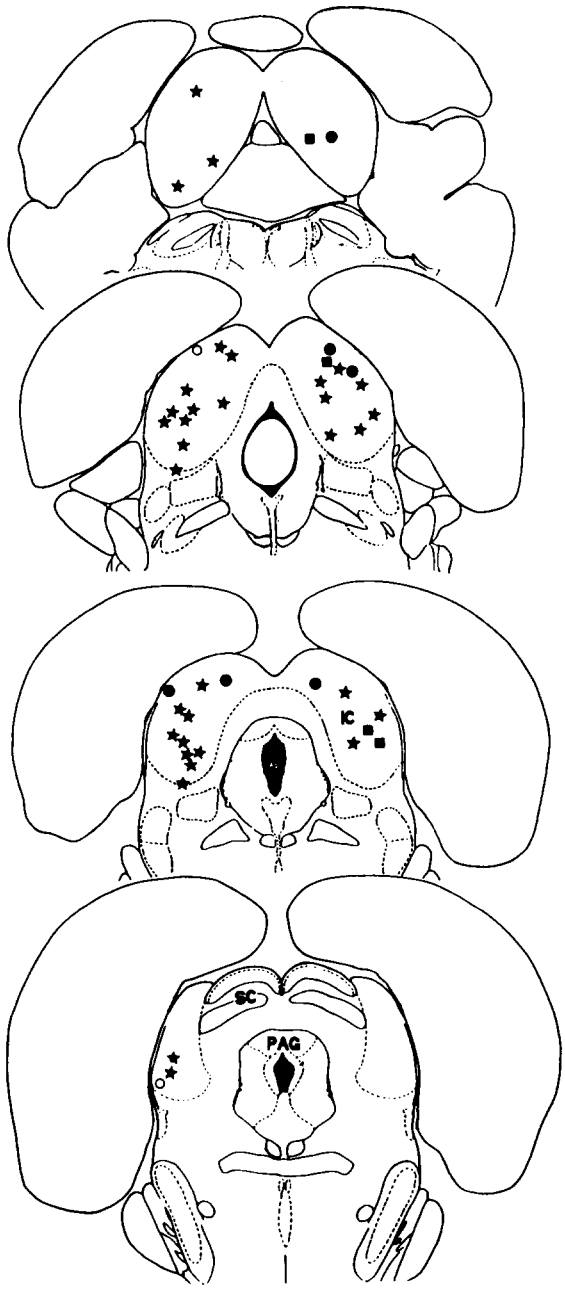

FIG. 1. Location of the microinjection sites of bicuculline methiodide and morphine sulfate plotted on planes from the atlas of Paxinos and Watson (29). Sites of microinjections into the IC of intact rats are represented on the left. Those of microinjections into the IC of lesioned rats are represented on the right. (★), sites where microinjection of 50 nmol morphine sulfate, as well as of 0.06 nmol bicuculline methiodide, elicited wild running; (●), sites where only the microinjection of morphine sulfate elicited wild running; (■), sites where only the microinjection of bicuculline methiodide elicited wild running; (○), sites where neither the microinjection of morphine nor that of bicuculline did elicit wild running. IC, inferior colliculus; PAG, periaqueductal gray; SC, superior colliculus.

the superior colliculus and mediolaterally from the aqueduct to the outer edge of the PAG. In six of these rats, the lesion comprised also the medial and dorsal part of the superior colliculus. In all instances, adjacent structures were not affected. Typical examples of lesions are represented in Fig. 2. Since no quantitative differences were observed in the effects induced in these two groups, the results were pooled.

Such large lesions did not abolish or modify the nature of the behavioral effects of bicuculline or morphine microinjection. Microinjection of each of these drugs still elicited intense running and jumping in the lesioned rats. Figure 1 (right) shows that among the 18 sites tested both bicuculline and morphine elicited wild running at 10 sites (56%), whereas at 4 sites (22%) only bicuculline elicited wild running, and at other 4 sites (22%) only morphine elicited wild running. The time course of the effects of the two drugs were similar to those of intact rats. Quantitative comparison of the mean total effects of morphine and bicuculline in intact and in lesioned rats is shown in Fig. 3.

Two-way ANOVA showed that the effects of morphine microinjection were significant for the number of crossings, $F(1,44) = 56.15$, $p < 0.001$, and for the number of jumps, $F(1,44) = 12.63$, $p < 0.001$, and that the lesion did not reduce significantly these effects [$F(1,44) = 1.82$, NS, and $F(1,44) = 2.22$, NS]. For bicuculline, similar results were found. The effects of the microinjection were significant [$F(1,48) = 60.61$, $p < 0.001$, and $F(1,48) = 31.02$, $p < 0.001$], but the lesion had no significant effect [$F(1,48) = 0.46$, NS, and $F(1,48) = 0.62$, NS].

DISCUSSION

The present results show that a microinjection of either bicuculline, a $GABA_A$ antagonist, or morphine into the IC elicited both wild running when injected into one and the same site. These results confirmed previous studies (12,20) showing wild running to be elicited by GABA blockade within the IC but also extend this finding to morphine, a drug known to interact with μ-opiate receptors (30).

Wild running elicited by bicuculline or morphine was qualitatively similar, whereas previous data describing the effects of either bicuculline or morphine separately microinjected and in several mesencephalic structures suggests that their behavioral effects may differ. For bicuculline or other GABA antagonists, depending more on the experimental situation than on the brain structure considered, the behavioral effects elicited were designated as wild running, flight behavior, defense reaction, or EMB. As a matter of fact, when animals were tested in the same experimental situation and with the same procedure as used in the present study, the qualitative aspects of the behavioral effects induced by microinjections into either of these structures (12,18) did not differ markedly from ours recently shown to be somehow related to an underlying aversive effect (4,5). It is suggested that the apparent diversity in the description of the effects of bicuculline microinjection depends upon the various significances attributed to running and jumping. For example, running and jumping reported as wild running was considered a seizure-like activity (3,21,27, 31,32), reported as "flight behavior" or "defense reaction" when GABA antagonists were injected into the PAG, considered the overt expression of an aversive effect (11,16,18,37), and reported as EMB when a GABA antagonist was injected into the PAG or the superior colliculus (29). The latter description may be the least interpretative.

Microinjecting a high dose of morphine into the PAG elic-

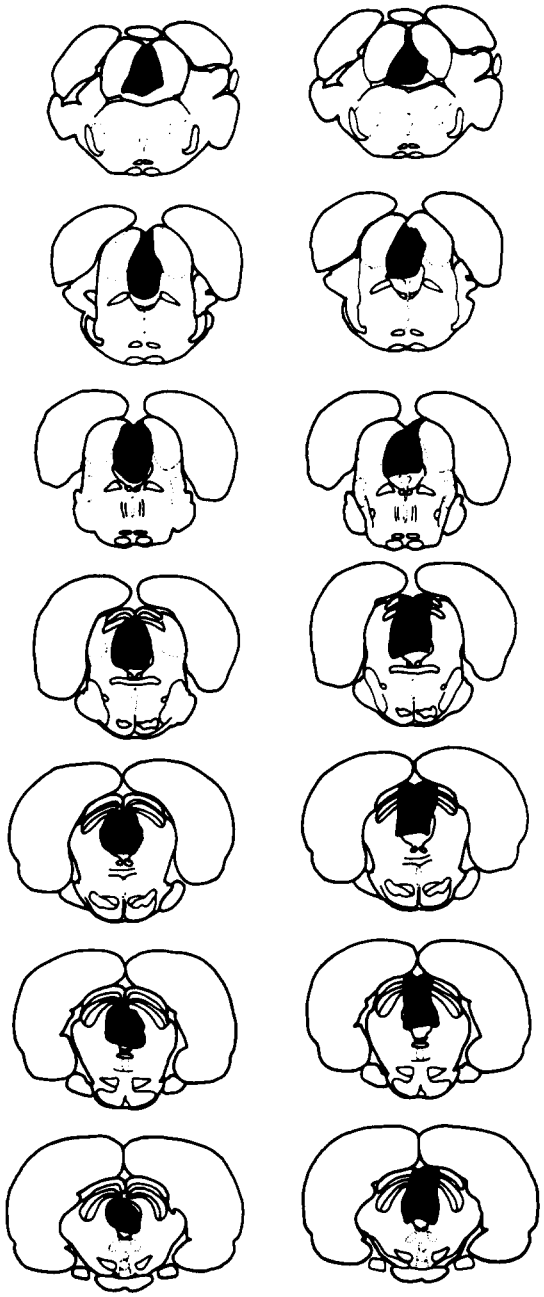

FIG. 2. Drawing of a typical lesion of the PAG (left) and a typical lesion of the PAG and the medial SC (right). The planes are from the atlas of Paxinos and Watson (29).

its EMB characterized by running, jumping, and rotations. EMB was also elicited by ICV morphine injection (7,24). The PAG was considered to be the specific target brain area of this action of morphine. Indeed, lesion of the PAG suppressed the EMB elicited by ICV morphine injection (7). Furthermore, EMB was not elicited when morphine microinjections were made 1 mm away from the PAG (40). In contradictions with this assumption, our results clearly show that the PAG is not the only structure involved in morphine-induced EMB since an EMB-like activation was elicited from the IC as well. Furthermore, this morphine-EMB like activation did not depend on the integrity of the PAG since extensive lesion of this structure did not modify the response. Noteworthy, a similar lack of effect of the lesion was observed for bicuculline that confirmed its local action within the IC.

If bicuculline- and morphine-elicited wild running were mediated by the same receptor sites in the IC, the potency of each of these drugs to elicit its behavioral effect would allow one to predict the potency of the other drug to elicit similar behavioral effects when injected into one and the same site. However, quantitative analysis of the results obtained with both bicuculline and morphine did not support this hypothesis. While the specificity of bicuculline as a $GABA_A$ antagonist is supported by numerous findings (14,15,28), the nature of the receptors involved in the effects of high doses of morphine (i.e., EMB) is still unclear. Thus, it is likely that the effects of bicuculline microinjections are due to the blockade of $GABA_A$ receptors within the IC since on one hand the IC contains a high number of GABAergic neurons and terminals (1,34,36) and on the other hand because picrotoxin, another GABA antagonist, is as well effective (21). In contrast, the effects of high doses of morphine may not result from a specific action on an opiate receptor (23). Indeed, moderate doses of morphine (10 and 15 nmol) did not elicit wild running (data not shown) even though the density of μ-opiate receptors was shown to be high in the IC (33,41) and the latency to the onset of the wild running elicited by a high dose of morphine is so long that a direct link between this behavior and opiate receptor mechanisms is less credible. Microiontophoretic studies revealed that morphine depresses and increases neuronal activity with a slow onset (9). Thus, wild running seems to be related to this excitatory effect, shown not to be antagonized by naloxone (8). It has been suggested that the effects of mi-

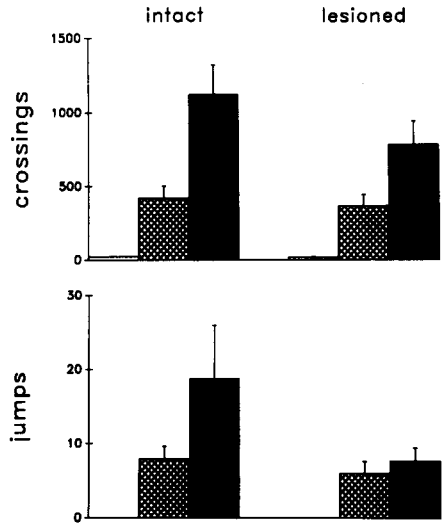

FIG. 3. Cumulative number of crossings and jumps elicited by microinjections of bicuculline methiodide (crosshatched bars) and of morphine sulfate (filled bars) into the IC of (left) intact rats and (right) rats deprived of their PAG and medial SC. Results for vehicle microinjection are represented as clear bars. No bar was drawn for the number of jumps since this behavior was not obtained at all after vehicle microinjection.

croinjection of a high dose of morphine may result from an aspecific blockade of $GABA_A$ receptors since the potencies of morphine and $GABA_A$ antagonists in producing EMB from the PAG paralleled their potencies as $GABA_A$ antagonists in a radioreceptor assay (26). However, our results do not support this idea.

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