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Is Dopamine Involved in the Hyperactivity Produced by Injections of Muscimol Into the Median Raphe Nucleus?

DAVID WIRTSHAFTER, MARK A. KLITENICK AND KAREN E. ASIN[1]

Department of Psychology, University of Illinois at Chicago
Box 4348, Chicago, IL 60680

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WIRTSHAFTER, D., M. A. KLITENICK AND K. E. ASIN. *Is dopamine involved in the hyperactivity produced by injections of muscimol into the median raphe nucleus?* PHARMACOL BIOCHEM BEHAV 30(3) 577–583, 1988.—Many studies have shown that experimental manipulations of the median raphe nucleus are able to produce profound effects on locomotor activity. Other data indicate that the raphe nuclei may exert an inhibitory influence over dopamine systems projecting to the forebrain. These results raise the possibility that the median raphe's influence over locomotion may be mediated through alterations in forebrain dopamine release. We examined this possibility in the current report by studying the role of dopamine in the hyperactivity produced by microinjections of the GABA agonist muscimol into the median raphe. Muscimol injections resulted in pronounced hyperactivity which was accompanied by a decrease in serotonin metabolism within the hippocampus and an increase in dopamine metabolism within the nucleus accumbens. Systemic injections of high doses of the dopamine antagonist haloperidol, however, were not able to attenuate muscimol's effect on activity. These results suggest that dopaminergic mechanisms do not play an essential role in mediating the effects of intraraphe muscimol on locomotor activity.

Median raphe nucleus GABA Muscimol Dopamine Serotonin Locomotor activity
Nucleus accumbens Nucleus centralis superior

NUMEROUS studies have demonstrated that electrolytic lesions of the median raphe nucleus (MR) lead to a pronounced increase in locomotor activity in novel environments [1, 2, 11, 17, 18, 25, 26, 45]. This effect does not appear to result from destruction of serotonergic elements as it cannot be reproduced by injections of neurotoxic dihydroxytryptamines or other serotonin depleting drugs [1, 4, 9, 11, 13–15, 23, 26, 27, 29, 41]. Nonserotonergic elements within the region of the MR do appear to be involved, however, since intra-MR injections of the axon sparing excitotoxin ibotenic acid result in hyperactivity [1]. Further evidence that cells within the immediate vicinity of the MR are able to influence locomotion comes from studies which have demonstrated that acute injections of the GABA-A agonist muscimol into the MR lead to a dramatic increase in locomotion [22, 37, 38]. Although early studies suggested that this effect is dependent on intact serotonergic mechanisms [37], more recent work has failed to support this view [22,47]. The increase in locomotor activity produced by injections into the MR is much larger than that observed after injections into adjacent structures such as the dorsal raphe [37] or the ventral tegmental area (unpublished observations). Hyperactivity has also been reported after injections of adrenergic agonists into the MR [35], and we have recently found that acute intraraphe injections of the rigid glutamate analogue kainic acid lead to a marked reduction in locomotor activity [28,49].

Little is known as to the mechanism through which manipulations of the MR are able to influence locomotor activity. One possibility, which has been suggested by several authors [12, 24, 37, 42, 43, 53], is that ascending projections from the MR may tonically inhibit dopamine containing cell bodies of the A-10 group located in the ventral tegmentum. Removal of this inhibitory influence, as a result of destruction or inhibition of raphe cells, would then be expected to lead to increased rates of dopamine release in the basal forebrain, an event which many studies have linked to the production of hyperactivity [16, 20, 34]. Some evidence exists which is compatible with these events. Anatomical studies have demonstrated the existence of projections from the MR

[1]Present address: Abbott Laboratories, Neuroscience Research, Abbott Park, IL.

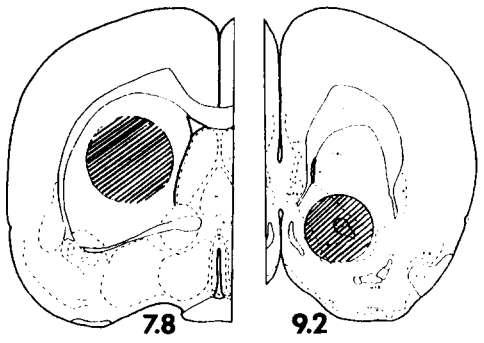

FIG. 1. Schematic illustration of the location of punches used to sample striatal (left) and accumbens (right) tissue. Numbers refer to distances rostral to the interaural line.

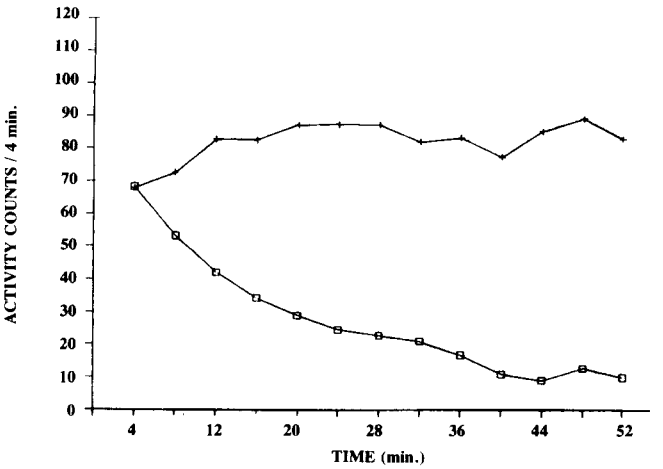

FIG. 2. Photocell cage activity over a one-hour period following intra-MR microinjections of saline (□) or muscimol (+).

to the ventral tegmentum [39] and some, but not all, biochemical studies have reported alterations in dopamine turnover after lesions of the MR [6, 8, 10, 12, 19, 30, 32, 36]. Furthermore, several authors have found that injections of neuroleptic drugs, or of dopamine depleting agents, are able to attenuate MR lesion-induced hyperactivity [24, 42–44, 53].

The current experiments were designed to investigate the possibility that intra-MR injections of muscimol induce hyperactivity as a result of disinhibition of dopamine containing cells. If this hypothesis were correct, two predictions would follow: (1) injections of muscimol into the MR should increase dopamine turnover in some forebrain sites and (2) injections of dopamine antagonists should be able to abolish the hyperactivity normally produced by muscimol infusions. The results of our studies verify the former but not the latter prediction.

Some of the results of the current experiments have been presented in abstract form [48].

EXPERIMENT 1

This experiment was designed to examine the behavioral and biochemical effects of infusions of muscimol into the MR. Locomotor activity was measured for one hour following intra-MR injections of saline or muscimol after which the animals were sacrificed and levels of dopamine, serotonin and their major metabolites were measured in the striatum, the nucleus accumbens and the hippocampus. If disinhibition of dopaminergic systems terminating in the basal forebrain plays an important role in the behavioral effects of muscimol, it should be possible to detect alterations in the levels of dopamine metabolites in these areas.

METHOD

Subjects

Subjects were 24 adult, male Sprague-Dawley derived rats obtained from a colony maintained by the University of Illinois. At the time of surgery rats weighed between 300 and 350 g. Animals were maintained on a 12:12 hr light/dark cycle in individual wire mesh cages. Food and water were available ad lib.

Apparatus

Locomotor activity was measured in an infrared photocell cage measuring 71.5×71.5 cm with 27 cm high walls. A 9×9 array of holes 3.5 cm in diameter perforated the floor. Four infrared beams were positioned 3.5 cm above the floor in order to detect horizontal movements. The walls and floor were painted black and a clear Plexiglas lid covered the cage. Lighting was provided by overhead fluorescent fixtures. Beam interruptions were collected in four-min bins on counters located in another room.

Surgery

Rats were anesthetized with sodium pentobarbital (50 mg/kg) and, using standard stereotaxic procedures, 22-gauge stainless steel guide cannulae aimed to terminate 2 mm above the MR (AP: −0.2, Lat: 0, H: −2.3 [33]) were affixed to the skull using dental cement. The cannulae were lowered along the midline following retraction of the superior sagittal sinus [44]. A 28-gauge stainless steel obdurator which extended 2 mm beyond the end of the guide cannula was then inserted. Rats received a prophylactic injection of penicillin following surgery.

Behavioral Procedure

After at least 7 days of recovery from surgery, 12 randomly selected rats were given intra-MR injections of normal saline (0.5 μl) and 12 were given injections of muscimol (100 ng/0.5 μl). This dose of muscimol was shown by Sainati and Lorens [37] to be optimal for producing hyperactivity. Injections were made through a 28-gauge cannula attached to a motor driven 5 μl Hamilton microsyringe through a length of polyethylene tubing. Injections were made over a period of one min and the cannula remained in place for an additional 30 sec to allow for diffusion. Rats were then placed in the photocell cages and activity levels were recorded in 4-min bins for a period of one hour at which time the animals were sacrificed as described below.

Biochemistry and Histology

Animals were sacrificed by cervical fracture and their brains rapidly removed. The brainstems were stored in formalin for at least two weeks at which time 64 μm frozen sections were taken through the cannula track and stained with cresyl violet to allow verification of the injection site.

TABLE 1

EFFECTS OF MUSCIMOL INFUSION ON SEROTONIN METABOLISM

	5HT (ng/g)	5HIAA (ng/g)	5HIAA/5HT
Hippocampus			
Vehicle	408	452	1.14
	±32	±22	±0.06
Muscimol	504*	377*	0.77*
	±23	±22	±0.05
Striatum			
Vehicle	521	719	1.61
	±87	±55	±0.16
Muscimol	408	591	1.60
	±67	±76	±0.11
Accumbens			
Vehicle	602	897	1.69
	±83	±92	±0.21
Muscimol	714	831	1.50
	±120	±81	±0.21

Values represent means ± S.E.M.
*Differs significantly from vehicle injections.

TABLE 2

EFFECTS OF MUSCIMOL INFUSION ON DOPAMINE METABOLISM

	DA (ng/g)	DOPAC (ng/g)	HVA (ng/g)	DOPAC/DA	HVA/DA
Striatum					
Vehicle	14032	2490	1973	0.17	0.14
	±1240	±263	±104	±0.01	±0.01
Muscimol	15989	3025	2667*	0.19	0.17
	±1618	±434	±260	±0.02	±0.01
Accumbens					
Vehicle	14183	4006	2029	0.29	0.17
	±2027	±552	±263	±0.02	±0.01
Muscimol	15664	7226*	4252*	0.50*	0.30*
	±2604	±1190	±093	±0.06	±0.03

*Differs significantly from vehicle injections.

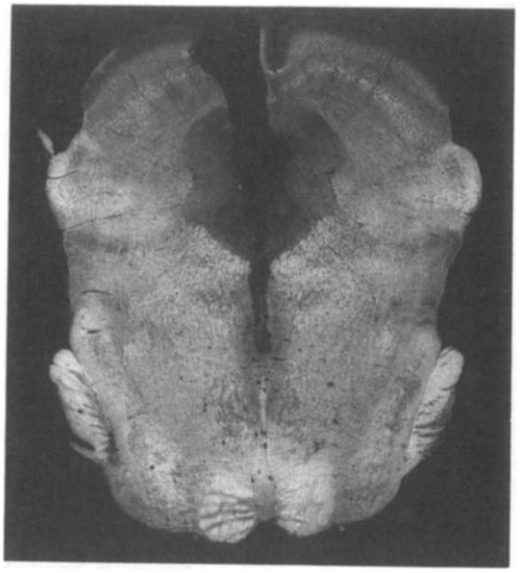

FIG. 3. A photograph of a typical cannula tract terminating within the MR.

The hippocampus was removed by gross dissection and the anterior part of the forebrain was rapidly frozen. Coronal slabs of tissue were cut on a cryostat through the striatum at the level of the anterior commissure (1 mm thick) and through the nucleus accumbens (0.75 mm thick). Bilateral samples of striatal and accumbens tissue were then removed using stainless steel punches with inner diameters of 2.7 and 2.2 mm respectively (Fig. 1). Tissue samples were weighed and then homogenized in the mobile phase described by Kilts, Breese and Mailman [21]. Following centrifugation, aliquots of the supernatant were stored at −80°C until assay. Following filtration through a 0.2 μm filter, 100 μl aliquots of the supernatants were directly injected into an HPLC system equipped with a C-18 reverse phase column and an electrochemical detection system (Bioanalytical Systems). The mobile phase was as described by Kilts *et al.* [21] with the pH adjusted to 4.2. Flow rate through the column was 1.5 ml/min and the potential of the glassy carbon electrode was set to 0.75 V versus an Ag/AgCl reference electrode. Column temperature was maintained at 30°C. The method employed allowed for measurement of serotonin (5HT), dopamine (DA), 5-hydroxyindoleacetic acid (5HIAA), dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA). Ratios of the levels of metabolites to the levels of the parent compounds were taken as indicators of transmitter turnover.

RESULTS

Behavioral results are shown in Fig. 2 where it can be seen that intra-MR injections of muscimol produced a highly significant increase in horizontal locomotor activity ($p<0.01$). (Due to technical problems, data for the last 2 time bins were lost for 2 animals, as a result data were analyzed only for the first 52 min of the session.)

The results of the serotonin assays are shown in Table 1. Muscimol injections resulted in a significant increase in hippocampal levels of serotonin, $t(22)=2.379$, $p<0.05$, a significant decrease in hippocampal levels of 5HIAA, $t(22)=2.463$, $p<0.05$, and a significant decrease in the ratio of 5HIAA to 5HT, $t(22)=4.690$, $p<0.001$. Levels of serotonin, 5HIAA and the ratio of 5HIAA to serotonin were not significantly altered in the striatum or nucleus accumbens.

The effects of intra-MR injections of muscimol on the levels of DA and its metabolites are shown in Table 2. Dopamine levels were not significantly altered in either the striatum or nucleus accumbens. In the nucleus accumbens, muscimol infusions resulted in a significant increase in levels of DOPAC, $t(22)=2.454$, $p<0.05$, HVA, $t(22)=2.999$, $p<0.01$, the DOPAC/DA ratio, $t(22)=3.496$, $p<0.005$, and the HVA/DA ratio, $t(22)=3.411$, $p<0.005$. In the striatum, levels of HVA were significantly elevated, $t(22)=2.48$, $p<0.05$, and levels of DOPAC tended to be increased but this effect was not statistically significant ($p<0.3$). The HVA/DA ratio tended to be elevated in muscimol treated rats but this difference did not attain the conventional criterion of statistical significance, $t(22)=2.018$, $p<0.07$. The DOPAC/DA ratio was not affected.

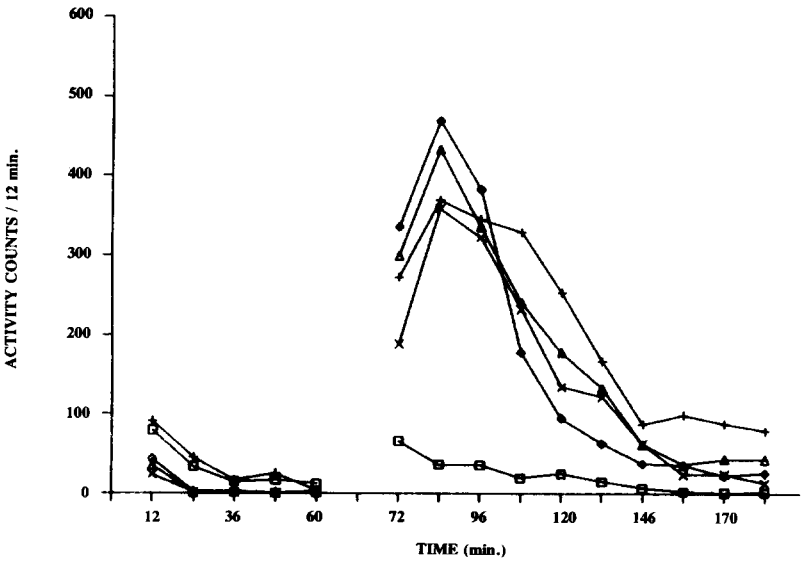

FIG. 4. Photocell cage activity across time during the one-hour habituation period and the two-hour period following intracranial injections. The baseline control run, in which animals received saline both systematically and intracranially, is represented by the open squares (□). In all the remaining runs, subjects received an intra-MR injection of muscimol one hour following placement in the activity boxes. Prior to initial placement in the boxes, rats received systemic injections of either saline (+), or 0.2 (△), 0.8 (×) or 3.2 (◇) mg/kg haloperidol.

Histological examination revealed that the injection sites were located in the dorsal portion of the median raphe nucleus. An example of a typical injection site is shown in Fig. 3.

DISCUSSION

The behavioral results of the first experiment confirm several other reports of pronounced, short latency, hyperactivity after injections of muscimol into the MR [22, 37, 38, 47]. In agreement with the finding of others [7,31], these injections also resulted in an apparent decrease in serotonin turnover within the hippocampus, suggesting that the muscimol injections inhibited serotonergic cells within the MR which projected to the hippocampus. The finding that serotonin turnover within the striatum and nucleus accumbens was not altered is in agreement with anatomical and biochemical studies indicating that the serotonergic innervation of these structures arises from the dorsal, not the median, raphe nucleus [10, 18, 31]. Our failure to detect changes in serotonin metabolism within the basal ganglia also suggests that the muscimol injected into the MR did not diffuse, in significant quantities, into the dorsal raphe [31].

The first experiment also demonstrates that injections of muscimol into the MR of behaving rats results in an increase in dopamine metabolism within the nucleus accumbens. Similar effects have been observed following electrolytic lesions of the MR [12,19]. These results are, of course, compatible with the notion that muscimol-induced hyperactivity results from a disinhibition of dopaminergic mechanisms.

EXPERIMENT 2

The second experiment was designed to determine whether the hyperactivity induced by injections of muscimol into the MR is dependent upon the normal functioning of central dopamine systems. If the increase in dopamine metabolism in the nucleus accumbens observed in the first experiment were responsible for the hyperactivity produced by the muscimol injections, one would predict that administration of a dopamine receptor antagonist would be able to attenuate the hyperactivity.

METHOD

Subjects were eight male Sprague-Dawley rats who received cannula implants aimed at the MR as described in the first experiment. Subjects received five activity tests at three day intervals using the method decribed above. On four of these runs, rats received intracranial injections of muscimol one hour following placement into the activity boxes. Immediately prior to placement in the activity boxes, the subjects were injected with either haloperidol (0.2, 0.8, or 3.2 mg/kg, SC) or its vehicle in a volume of 1 ml/kg. On the remaining run rats received an injection of saline subcutaneously prior to placement in the activity boxes, and an intracranial injection of saline one hour later. The five runs were administered in a randomized order for each subject. Following the completion of behavioral studies in the subjects, under deep pentobarbital anesthesia, were perfused transcardially with saline followed by 10% formalin. The brains were then removed and stored in formalin until histological verifications of the injection sites were performed as described above.

RESULTS

Behavioral results of this study are shown in Figs. 4 and 5

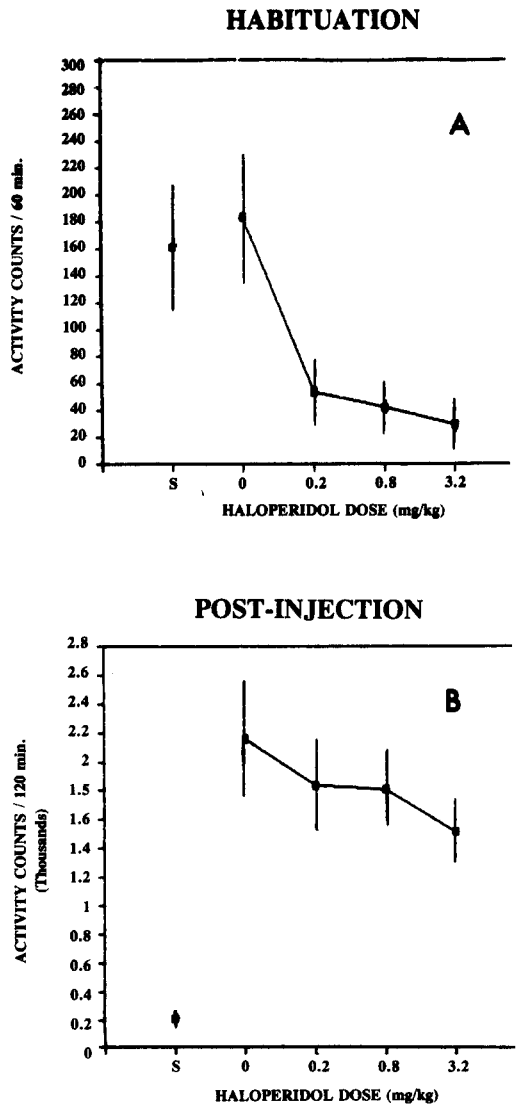

FIG. 5. Cumulated activity counts and S.E.M.'s across the one-hour habituation (A) and the two-hour postinjection periods (B) for rats receiving various doses of haloperidol. The disconnected point above the 'S' on the abscissa represents the run in which rats received saline both systemically and intracranially, while the remaining points represent runs in which rats received intracranial injections of muscimol.

where it can be seen that haloperidol injections produced a large decline in locomotor activity during the one hour baseline period. Although haloperidol tended to produce a small reduction in the magnitude of the muscimol effect on locomotor activity, repeated measures analysis of variance conducted on total activity counts during the baseline and postintracranial injection periods indicated a significant effect of haloperidol dose in the former, $F(3,31)=13.85$, $p<0.02$, but not the latter ($F=1.58$, $p>0.1$) case. All postmuscimol scores were significantly higher than those observed after saline injections ($0.001<p<0.02$) demonstrating that the muscimol injections produced a reliable increase in locomotor activity. Following the higher doses of haloperidol, rats were observed to be akinetic and cataleptic at the time of the intracranial injections, but began to move about within a few minutes after receiving muscimol. It is interesting to note that rats receiving combined treatments with muscimol and haloperidol sometimes displayed jumping behavior in addition to the rapid locomotion characteristically produced by muscimol.

Histological examination revealed that all injection sites were within the MR.

DISCUSSION

The results of the second experiment indicate that pretreatment of rats with very high doses of the dopamine antagonist haloperidol is unable to significantly attenuate the hyperactivity induced by intra-MR injections of muscimol. In contrast, spontaneous locomotor activity was significantly decreased during the hour following drug injection. In other experiments using a paradigm similar to that described here, we have found that haloperidol at a dose of 0.2 mg/kg is able to abolish the hyperactivity induced by an optimal dose of amphetamine (unpublished observations). Since haloperidol produces, at most, only a slight attenuation of the muscimol effect at doses sixteen times higher than those needed to eliminate the effects of the dopamine releasing agent amphetamine, it seems reasonable to conclude that haloperidol sensitive dopaminergic mechanisms do not play an essential role in the hyperactivity induced by muscimol.

GENERAL DISCUSSION

The current studies indicate that intra-MR injections of muscimol result in a pronounced hyperactivity which is accompanied by a reduction in serotonin metabolism within the hippocampus and by an acceleration of dopamine metabolism within the nucleus accumbens. The effects of muscimol on locomotor activity, however, were not significantly reduced by systemic injections of very high doses of a direct dopamine receptor antagonist, suggesting that increases in forebrain dopamine release do not play an essential role in the generation of the hyperactivity. These findings suggest that the hyperactivity seen after muscimol injections into the MR results, at least in part, from an action upon neural mechanisms which are either "downstream" from the dopamine receptor or which exert an influence upon locomotor activity which is independent to that of dopaminergic systems. It is possible that descending projections from the MR may play a role in the muscimol effect as we have found in other studies that knife cuts caudal to the MR result in increases in locomotor activity [50].

Given the finding that disinhibition of dopaminergic neurons does not appear to be the mechanism through which muscimol injections exert their effect on activity, the possibility must be considered that the observed changes in dopamine turnover might result from the hyperactivity itself rather than from a direct neural interaction between the raphe nuclei and dopamine containing cells. This possibility gains plausibility from several studies which have demonstrated changes in dopamine turnover or receptor density as a result of forced motor activity [3, 5, 40, 51, 52]. Since electrolytic raphe lesions also result in pronounced spontaneous hyperactivity, it is possible that, in this case as well, reported alterations in dopamine release could be secondary to the increased levels of activity shown by the lesioned rats.

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