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Behavioral Effects of the Intraventricular Administration of 5-HT and Dopamine in the Common Marmoset (*Callithrix jacchus*)

MARIA DA PAZ DE OLIVEIRA[1] AND MARIA DE FÁTIMA CAMPOS

Departamento de Fisiologia, Setor de Psicobiologia,
Universidade Federal do Rio Grande do Norte, 59072-970 Natal, RN, Brasil

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OLIVEIRA, M. P. AND M. F. CAMPOS. *Behavioral effects of the intraventricular administration of 5-HT and dopamine in the common marmoset (*Callithrix jacchus*)*. PHARMACOL BIOCHEM BEHAV **46**(1) 21–25, 1993. – The effects of IVT serotonin [5-hydroxytryptamine (5-HT)] and dopamine (DA) administration have been studied in rats and marmosets (*Callithrix jacchus*). In rats, 5-HT (114 and 170 μg/10 μl) produced the same behavioral effects observed after IP administration of its precursors and agonists. The same doses of 5-HT used for rats produced only part of the behavioral effects in marmosets after IP administration of 5-HT precursors and agonists. Ataxia, vomiting, and decreased motor activity were observed, but not drowsiness or teeth-chattering. However, IVT administration of DA (400 μg/10 μl dose) produced head movements or checking, ataxia, tongue out, and decreased motor activity. These findings differ from those observed after IP administration of *l*-DOPA and DA agonists, which increase motor activity.

Marmoset Rat Intraventricular Serotonin Dopamine

THE anatomical, physiological, and behavioral characteristics of the common marmoset (*Callithrix jacchus*) make it a laboratory animal of interest to different areas. In psychopharmacological research, these animals have been used for screening anxiolytics (6,11) and developing experimental models for Parkinson's disease (5). Many pharmacological studies have been undertaken to understand normal behavior and the effects of the activation of major neurotransmitter systems—specifically dopaminergic (2,17,19,20) and serotonergic (3).

In general, these studies show that head movements or checking tongue out, erect posture, and increased motor activity are behaviors associated with dopamine (DA) receptor activation in these animals. Teeth-chattering, ataxia, vomiting, drowsiness, and decreased motor activity are associated with serotonergic system activation. This difference was produced through IP administration of drugs of known mechanism of action.

The objective of this study was to find additional evidence that, in fact, these behaviors result from the activation of central serotonin [5-hydroxytryptamine (5-HT)] and DA receptors, respectively. This was studied through the observation of the effects of IVT administrations of 5-HT and DA. For the purpose of comparison, the same experimental procedures were used for both rats and marmosets.

METHOD

Subjects

Three- to four-month-old male Wistar rats were kept in groups of three in wire cages measuring 30 × 20 × 15 cm, at 23 ± 2°C, under a 12 L : 12 D cycle. The adult marmosets of both sexes were captured around the city of Natal and adapted to laboratory conditions for at least 6 months. These were housed in groups of two to four animals in brick cages measuring 1.0 × 2.0 × 2.0 m with wire mesh on two opposing sides. The marmosets were housed under natural conditions, roughly under a 12 L : 12 D cycle with a temperature between 28–33°C.

Drugs

Tranylcypromine (TCP, Sigma Chemical Co., St. Louis, MO) was suspended in saline and injected IP in a volume of 1.0 ml/kg body weight. Dopamine HCl and serotonin creatinine sulfate (Sigma) were dissolved in saline. Subjects received either an IVT injection of one of these compounds dissolved in 10 μl saline or 10 μl saline alone. A Hamilton syringe (Hamilton Co., Reno, NV) fitted with a stop prevented the needle from passing beyond the cannula. Doses of drugs given by the IVT route are expressed as the free base.

[1] To whom requests for reprints should be addressed.

Experiment with Rats

Eighteen animals were anesthetized with 65 mg/kg sodium pentobarbital IP and fitted with a 10-mm cannula implanted into the right lateral ventricle using the coordinates of bregma: A, −0.0; L, −1.7; V, −3.0 (14).

After 7 days, the animals received an IVT injection of either saline or 5-HT (114 and 170 μg/10 μl) and were observed for 2 h in 15-min intervals for the presence or absence of 5-HT syndrome and number of head shakes. IVT injections totaled 10 μl and were given 30 min after an IP injection of tranylcypromine (2.5 mg/kg), keeping an interval of at least 7 days between the different doses.

The behaviors considered part of the 5-HT syndrome were forepaw padding, side-to-side head weaving, head tremor, splayed hindlimbs, and Straub tail (18,21). The syndrome was considered present when at least three of these behaviors were observed simultaneously in a time interval. Head shakes were recorded quantitatively.

Experiment with Common Marmosets

Eight animals (five male, three female) were anesthetized with sodium pentobarbital (40 mg/kg, IP) and fitted with a 16-mm cannula implanted into the right lateral ventricle based on the coordinates determined by Stephan et al. (23) (A, −9.0; L, −1.25; V, −12.5) adapted on the vertical line 1.2 mm lower than the proposed value. A stereotaxic apparatus used was specially adapted for *C. jacchus* (22). After 7 days, the animals were IVT injected with either saline or 5-HT (114 or 170 μg/10 μl) and observed for 2 h at 15-min intervals. The IVT injections were given 30 min after an IP injection of tranylcypromine (2,5 mg/kg). Animals were kept in wire cages measuring 60 × 75 × 90 cm and observed through a one-way mirror. The behaviors recorded during this phase were: number of head shakes (similar to that observed in rats), motor activity (number of squares, totaling 24, on all parts of the cage the animal crossed), teeth-chattering (rhythmic and repetitive movements of mandible), ataxia (difficulty walking, jumping, or staying on the roost), drowsiness (eyes closed for at least 5 s), and vomiting. The total number of head shakes and the motor activity were measured; the other behaviors were recorded in a one/zero fashion. The behavioral effects of IVT DA administration (400 μg/10 μl) following pretreatment with TCP (2.5 mg/kg) were also observed in animals in good physical condition after the above treatments. The behaviors observed were the same as in the previous phase with the addition of tongue out (number of times the marmoset extended the tongue, not including when it licked the body for cleaning) and head movements (number of movements of the head laterally, about 90° with the body still).

TABLE 1

SEROTONERGIC SYNDROME AND HEAD SHAKE PRODUCED IN RATS AFTER IVT ADMINISTRATION OF SALINE OR 5-HT (114 AND 170 μg/10 μl, 13 ANIMALS/DOSE) DURING A 2-h OBSERVATION PERIOD

Treatment (μg/10 μl)	Number of Animals With Syndrome	Head Shake (Mean ± SD)
Saline	0/13	6.4 ± 10.6
5-HT (114)	4/13	236.2 ± 184.9*
5-HT (170)	9/13†	161.7 ± 251.1‡

Different from control: *$p < 0.01$, ‡$p < 0.05$ (Student's t-test), and †$p < 0.005$ (binomial test).

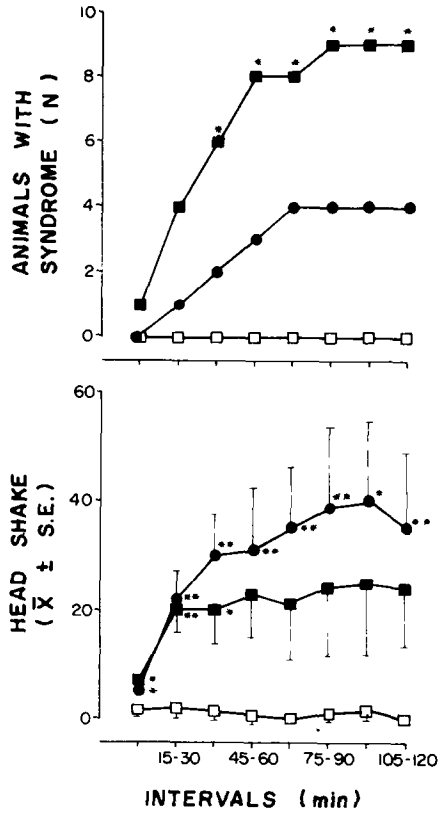

FIG. 1. Serotonergic syndrome and head shake induced in rats after IVT administration of saline (□) or serotonin [114 (●) and 170 (■) μl/10 μl] at 15-min intervals during 2 h of observation. *$p < 0.05$ and **$p < 0.01$ (binomial and Student's t-test).

Statistical Analysis

Significant differences in head shaking, motor activity, head movement, and tongue out were identified using one-way analysis of variance (F-test). Pairwise comparisons were done using Student's t-test for dependent samples. Significant differences in drowsiness, ataxia, vomiting, teeth-chattering (in marmosets), and serotonergic syndrome (in rats) were identified using the Cochran Q-test and binomial test.

RESULTS

Histological observations showed that in five rats the cannulae were not placed in the ventricle. Therefore, according to Table 1, IVT administration of 5-HT, in doses of 114 and 170 μg/10 μl, induced the serotonergic syndrome in four and nine animals, respectively; only the animals in the latter group (170 μl) differed significantly from the control group.

This table also shows, that contrary to the above tendency with respect to the serotonergic syndrome, 114 μg 5-HT induced higher rates of head shaking than 170 μg 5-HT. How-

TABLE 2

BEHAVIORAL EFFECTS INDUCED IN MARMOSETS (*C. JACCHUS*) AFTER IVT TRICULAR ADMINISTRATION OF SALINE OR SEROTONIN (114 AND 170μg/10 μl, 5 ANIMALS/DOSE) DURING A 2-h OBSERVATION PERIOD

Treatment (μg/10 μl)	Number of Animals Presenting				Head Shake (Mean ± SD)	Motor Activity (Mean ± SD)
	Teeth-Chattering	Ataxia	Drowsiness	Vomiting		
Saline	0	0	0	1	7.4 ± 7.7	197.0 ± 183.0
5-HT (114)	0	5*	0	5	13.4 ± 14.8	28.4 ± 3.6
5-HT (170)	0	5*	1	5	10.0 ± 10.3	27.3 ± 22.3*

Different from control: $*p < 0.05$ (binomial and Student's *t*-test).

ever, both doses of 5-HT caused statistically significant increases in head shaking when compared to control. This behavior occurred in all animals injected with the lower dose and in 10 of 13 animals injected with the higher dose.

A time course analysis of the serotonergic syndrome (Fig. 1) shows that, despite an evident action of the drug in a few animals in the first 30 min, the maximal effect occurred 60 and 75 min after 170 and 114 μg/10 μl injection, respectively. This persisted during the rest of the observation period. Occasionally, the syndrome persisted for 4 h after drug injection in some animals. This figure also shows that head shakes presented a similar time course of occurrence, except that the maximal effect appeared earlier.

Results in Table 2, concerning IVT 5-HT administration in *C. jacchus,* refer only to five animals; in the other three, the cannulae did not reach the ventricle.

Table 2 shows that 5-HT, injected directly into the brain, only induced ataxia, vomiting, and decreased motor activity. Teeth-chattering and drowsiness were totally absent following IVT 5-HT. These effects are different from those obtained after IP administration of 5-HT precursors and agonists (3). As observed after IP administration of 5-HT precursors and 5-HT agonists, head shaking was not elicited after IVT 5-HT. Though the 114 and 170 μg/10 μl 5-HT did not differ statistically, each experimental group was significantly different from control.

IVT administration of dopamine in these animals (Table 3) induced slow and lateral head movements, ataxia, and tongue out, similar to that observed after IP administration of precursors and agonists of this neurotransmitter (2). In contrast to previous data, however, IVT dopamine decreased motor activity. The time course analysis of motor activity, and slow and lateral head movements produced by dopamine (Fig. 2), demonstrated that motor activity decreased, especially in the first 30 min, while rates of head movement were sustained from 30 min to the end of each observation period.

DISCUSSION

The results obtained after IVT administration of serotonin in rats were similar to those described in the literature about IVT and IP injections (9,21). Serotonin at doses of 114 and 170 μg/10 μl induced forepaw padding, tremor, side-to-side head weaving, splayed hindlimbs, Straub tail, and head shakes, the latter behavior being most evident after the lowest dose and the others after the highest. This shows that behaviors presented by these animals after IP administration of 5-HT precursors and agonists are a consequence of the activation of central serotonin receptors.

C. jacchus, different from the rat, showed vomiting, ataxia, and decreased motor activity. These behaviors have already been described as being characteristic of the action of precursors and agonists of serotonin in these animals when administered IP (3). It is surprising, however, that IVT serotonin administration in this species did not produce drowsiness or teeth-chattering, behaviors observed after IP administration of precursors and agonists of this neurotransmitter system. In the rat, differences between IP and IVT injections of 5-HT were not found. According to Campos and Rodrigues (3), it is possible to justify the absence of drowsiness because this behavior was not elicited by some of the 5-HT agonists or by some doses of precursors or agonists. Though teeth-chattering is dose dependent, it was observed in almost all animals injected with a 5-HT precursor or an agonist.

In an attempt to explain the absence of teeth-chattering, several hypotheses can be formulated. The first is that the serotonin dose used was not sufficient to activate the CNS

TABLE 3

BEHAVIORAL EFFECTS INDUCED IN MARMOSETS (*C. JACCHUS*) AFTER IVT ADMINISTRATION OF SALINE OR DOPAMINE (400μg/10μl, 3 ANIMALS/DOSE) DURING A 2-h OBSERVATION PERIOD

Treatment (μg/10 μl)	Ataxia (No. of Animals)	Head Shake (Mean ± SD)	Motor Activity (Mean ± SD)	Head Movements (Mean ± SD)	Tongue Out (Mean ± SD)
Saline	0	5.3 ± 6.8	200.3 ± 181.0	440.6 ± 88.3	53.7 ± 54.4
Dopamine	3	11.0 ± 3.6	114.7 ± 159.0	614.3 ± 123.6	120.3 ± 202.4

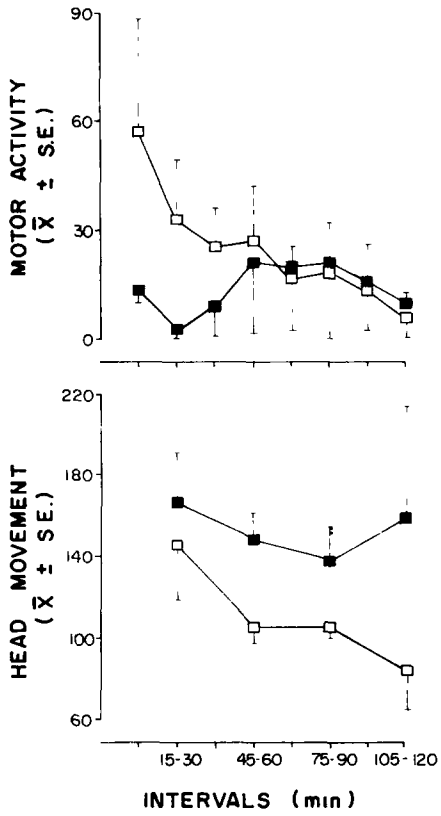

FIG. 2. Motor activity and head movement (mean ± SE) induced in the common marmoset (*C. jacchus*) after IVT administration of saline (□) or dopamine (■), 400 μg/10 μl dose, at 15-min intervals during 2 h of observation.

receptors responsible for this behavior. Data from our laboratory (Oliveira and Campos, unpublished observations) suggest that teeth-chattering seems to be a consequence of 5-HT_2 receptor activation, which is blocked by pirempirone, a specific antagonist of these receptors. Since serotonin has greater affinity for 5-HT_1 receptors (1), it is possible that only these receptors would have been activated after the doses of 5-HT used. This is unlikely, however, because marmosets, but not rats, had a greater sensitivity to the serotonergic compounds when administered IP (3).

A second hypothesis is that teeth-chattering is caused by activation of peripheral serotonin receptors. This, however, can be rejected because neural mechanisms related to jaw movements are located at the brainstem. At any rate, it is possible that IVT 5-HT did not reach this area because the distribution of IVT-injected drugs does not reach all cerebral tissue uniformly (8).

A third hypothesis is that teeth-chattering induced by IP 5-HT precursors or agonists results from an indirect action of their metabolites. It is known that buspirone, an agonist of 5-HT_{1A} receptors (15), induces different effects in the forced swimming test according to the administration route used; it has been demonstrated that this differential action results from the formation of a peripheral metabolite that antagonizes part of the central action of buspirone (4).

The last and most probable hypothesis is that IVT 5-HT and IP agonists and precursors of 5-HT must be acting on different 5-HT projections. Gerson and Baldessarine (10) and Davis et al. (7) showed that, depending upon the route of administration, the action of 5-HT on motor activity and the acoustic startle response have a differential effect, being either excitatory or inhibitory.

In relation to dopamine, the present study did not evaluate its effects in the rat. Previous work has shown, however, that DA agonists and its precursor *l*-DOPA, when administered systemically (IP or SC), produce increased locomotor activity and stereotyped behavior characterized by continuous sniffing, licking, biting, and gnawing (12,13,16).

Similar effects have also been observed when these drugs and DA are administered in the striatum or nucleus accumbens (13).

The behavioral effects observed after IVT administration of DA to marmosets were similar to those following IP administration of apomorphine, methamphetamine, and *l*-DOPA (2). So, the behaviors that most represented the actions of these drugs in both experimental situations were head movements and tongue out. Concerning motor activity, while IVT DA induced a decrease in this activity, the above drugs induced an increase. This difference can be related, as in the case of 5-HT, to the route of administration of these drugs, but subsequent observations in our laboratory suggest that increases in locomotor activity might be related to the size of the cage where the observations were carried out. The cages used by Campos and Arruda (2) were much smaller (20 × 30 × 20 cm) than those used in this study (60 × 75 × 90 cm).

Once neurotransmitters reproduced the behaviors induced by its precursors and agonists, we suggest that these behaviors are a consequence of the activation of central receptors.

Anyway, it is necessary to confirm these data through other measures.

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