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Action of Ipsapirone and 8-OH-DPAT on Exploratory Behavior in Hamsters (*Mesocricetus auratus*): Effects of Antagonists and *p*-CPA

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FERNÁNDEZ-GUASTI, A. AND C. LÓPEZ-RUBALCAVA. *Action of ipsapirone and 8-OH-DPAT on exploratory behavior in hamsters* (Mesocricetus auratus)*: Effects of antagonists and* p-*CPA*. PHARMACOL BIOCHEM BEHAV **50**(3) 375-382, 1995. – The effect of the serotonergic drugs 8-OH-DPAT (0.0625, 0.125, and 0.25 mg/kg) and ipsapirone (5.0 and 10.0 mg/kg) on the exploratory behavior shown by hamsters under light : dark conditions was studied. These drugs produced an increase in the number of transitions similar to that induced by diazepam (0.25, 0.5, and 1.0 mg/kg), suggesting an anxiolytic action. The antagonists, methiotepin (0.31 mg/kg), pindolol (2.0 mg/kg), and alprenolol (5.0 mg/kg), did not modify the number of transitions per se and were partially effective in reverting ipsapirone's action. Similarly, methiotepin and pindolol partially blocked 8-OH-DPAT actions, whereas alprenolol lacked an effect. Drug-induced increases in this behavior occurred despite the administration of *p*-CPA (400 mg/kg × 3 days). The neurochemical analysis revealed that this treatment decreased 5-HT levels (from 40% to 60%). Motor activity was assessed to control unspecific drug actions; 8-OH-DPAT produced an increase that was effectively blocked by methiotepin, but was unaffected by pindolol, alprenolol, or *p*-CPA. These results suggest that the increase in the number of transitions produced by 8-OH-DPAT cannot be interpreted on the basis of a reduced anxiety state. Data are discussed in terms of the similarities and differences between the actions of 5-HT_{1A} drugs in hamsters when compared with rats and mice.

Anxiety Hamsters Exploratory behavior 5-HT_{1A} agonists Ipsapirone 8-OH-DPAT Postsynaptic action

THE ROLE of the serotonergic system in the mediation of anxiety remains unclear [for reviews see (4,11,24)]. However, an increasing amount of evidence indicates that the 5-HT_{1A} agonists, ipsapirone (9,17,18,38) and 8-OH-DPAT [8-hydroxy-2-(di-*n*-propylamino) tetralin] (12), possess anxiolytic activity. Most of the basic research data in this field have been obtained in rats (*Rattus norvegicus*) and exceptionally in mice (*Mus musculus*) [for review see (11)]; only few studies have considered other animal species such as Syrian golden hamsters (*Mesocricetus auratus*) (5) or Mongolian gerbils (*Meriones unguiculatus*) (8).

Recently, we reported on the species differences in the anxiolytic action of the serotonergic agonists ipsapirone and indorenate between rats and mice (14). It was found that, in both species, these serotonergic agonists induced a clear reduction in burying behavior [denoting a lowered anxiety state (39)] that in rats was antagonized by the selective β-blocker practolol, whereas in mice the serotonergic antagonist methiotepin (0.31 mg/kg) and the mixed β/5-HT_{1A} antagonists pindolol (3.1 mg/kg) and alprenolol (5.0 mg/kg) were all able to block the anxiolytic effect of the 5-HT_{1A} agonists. These results suggest that a different mechanism underlies the anxiolytic action of these drugs in both species.

While analyzing whether the anxiolytic action of serotoner-

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gic compounds is mediated via the stimulation of pre- or postsynaptic receptors, we recently found that the anxiolytic effect of ipsapirone and 8-OH-DPAT was effectively prevented by the lesion of 5-HT neurons with 5,7-dihidroxytryptamine (5,7-DHT) in rats (31). These data suggest that the anxiolytic effect of these compounds is mediated, in rats, via the stimulation of presynaptic receptors. Moreover, direct administration of ipsapirone and 8-OH-DPAT into the dorsal raphe (where 5-HT_{1A} presynaptic receptors are located), but not into the hippocampus (where 5-HT_{1A} postsynaptic receptors are found), produces antianxiety actions (31). These results further support the notion that the anxiolysis induced by these drugs is mediated by the stimulation of somatodendritic receptors.

The purpose of the present study was to analyze whether the serotonergic anxiolytics 8-OH-DPAT and ipsapirone also have an antianxiety effect in hamsters. The action of these drugs was compared with the well-established anxiolytic effect of the benzodiazepine diazepam. Additionally, the putative blockade of the anxiolytic action induced by these drugs using 5-HT antagonists, such as methiotepin, pindolol, and alprenolol, was explored. These antagonists were selected on the bases of previous studies demonstrating that the β-blockers pindolol and alprenolol, as well as the serotonergic antagonist methiotepin, effectively counteracted the actions of 5-HT_{1A} agonists in rats and mice (13,16,20,21,40).

The stimulation of somatodendritic 5-HT_{1A} receptors results in an inhibition of 5-HT release (22,32,36). It is also well documented that *p*-chlorophenylalanine (*p*-CPA) administration produces an inhibition of tryptophan hydroxylase, the rate-limiting enzyme for the synthesis of 5-HT (23,27). Thus, drugs acting on 5-HT_{1A} somatodendritic receptors lose their effect in 5-HT-depleted neurones (by *p*-CPA treatment) (10,19,21). Therefore, several studies have used *p*-CPA to discern if 5-HT_{1A} agonists act on pre- or postsynaptic receptors (10,19,21). In the present work, the effect of 8-OH-DPAT and ipsapirone was evaluated in *p*-CPA- or vehicle-treated hamsters, to analyze the participation of pre- or postsynaptic receptors in the anxiolytic action of 5-HT_{1A} agonists. The proper neurochemical control groups were included. Because the anxiety test used in the present experiment involves ambulatory behavior, a final experiment studying putative drug-induced changes in ambulation was conducted.

METHOD

Animals

Male hamsters (*Mesocricetus auratus*) weighing 100–150 g were used in these experiments. All animals were individually housed in a room under reversed and controlled light : dark conditions (12L : 12D, lights on at 2200 h). Animals had free access to tap water and commercial Purina chow throughout the experiments.

Anxiety Test

The anxiety test used was the black–white transitions test based on the avoidance exploratory behavior shown by hamsters. This paradigm was previously described for mice by Crawley and Goodwin in 1980 (7). Briefly, this model consists of a propylene test chamber measuring 44 × 21 × 21 cm darkened with black spray paint over one-third of its surface. An opening of 13 × 5 cm separates the dark third from the bright two-thirds of the cage. Fluorescent light above the cage illuminates the bright area of the chamber. At the beginning of the test, the animal was placed in the bright side of the cage. The number of transitions from one side to the other was recorded over a 10-min period. Because it has been reported that in this paradigm the animals can be tested several times (3), a balanced Latin square design was used. With this design, two main series were done: dose-response and agonists-antagonists studies. Within each series the animals were randomly divided into various groups (each group consisting of at least eight hamsters) in such a way that each animal received the following treatments:

Series I: a) diazepam (0.25, 0.5, and 1.0 mg/kg, −30 min); b) 8-OH-DPAT (0.0625, 0.125, and 0.25 mg/kg, −20 min), and c) ipsapirone (5.0 and 10.0 mg/kg, −30 min).

Series II: Animals were injected with either saline, the 5-HT_{1A} agonists (ipsapirone 5.0 mg/kg or 8-OH-DPAT 0.25 mg/kg), the antagonists (pindolol 2.0 mg/kg, alprenolol 5.0 mg/kg, or methiotepin 0.31 mg/kg), or the combination of the 5-HT_{1A} agonists plus the antagonists. Antagonists were administered simultaneously with the 5-HT_{1A} agonists.

A three-day interval was left between each test. The dose-response and the agonist-antagonists data were statistically compared using the Friedman two-way analysis of variance (ANOVA) followed by the Wilcoxon matched-pairs signed-ranks test (33).

In another group of experiments, *p*-CPA (400 mg/kg) was injected during 3 consecutive days. On the fourth day, the animals received either saline, ipsapirone (10.0 mg/kg, −30 min), or 8-OH-DPAT (0.25 mg/kg, −20 min). The control groups were injected with methyl-cellulose during 3 consecutive days and on the fourth day treated like the experimental groups. For these experiments an independent group design was used (each group consisted of eight animals) and the results were statistically compared by means of the Mann–Whitney *U*-test (33).

TABLE 1

EFFECT OF VARIOUS DOSES OF THE SEROTONERGIC ANXIOLYTICS AND DIAZEPAM ON THE NUMBER OF TRANSITIONS OF MALE HAMSTERS

Treatment (mg/kg)	*N*	Number of Transitions
Control	16	8.9 ± 1.3
Diazepam (0.25)		8.4 ± 0.6 NS
Diazepam (0.5)		10.1 ± 0.9 NS
Diazepam (1.0)		19.3 ± 2.5*
$X^2(3) = 25.48, p < 0.001$		
Control	12	12.6 ± 1.1
8-OH-DPAT (0.0625)		10.2 ± 0.9 NS
8-OH-DPAT (0.125)		14.0 ± 1.8 NS
8-OH-DPAT (0.25)		19.3 ± 1.8*
$X^2(3) = 17.66, p < 0.001$		
Control	10	12.8 ± 1.8
Ipsapirone (5.0)		16.3 ± 1.1 NS
Ipsapirone (10.0)		18.5 ± 2.2†
$X^2(2) = 6.02, p < 0.05$		

Table shows mean ± SE of the number of transitions. Wilcoxon matched-pairs signed-ranks test, NS, nonsignificant ($p > 0.05$), *$p < 0.01$, †$p < 0.02$.

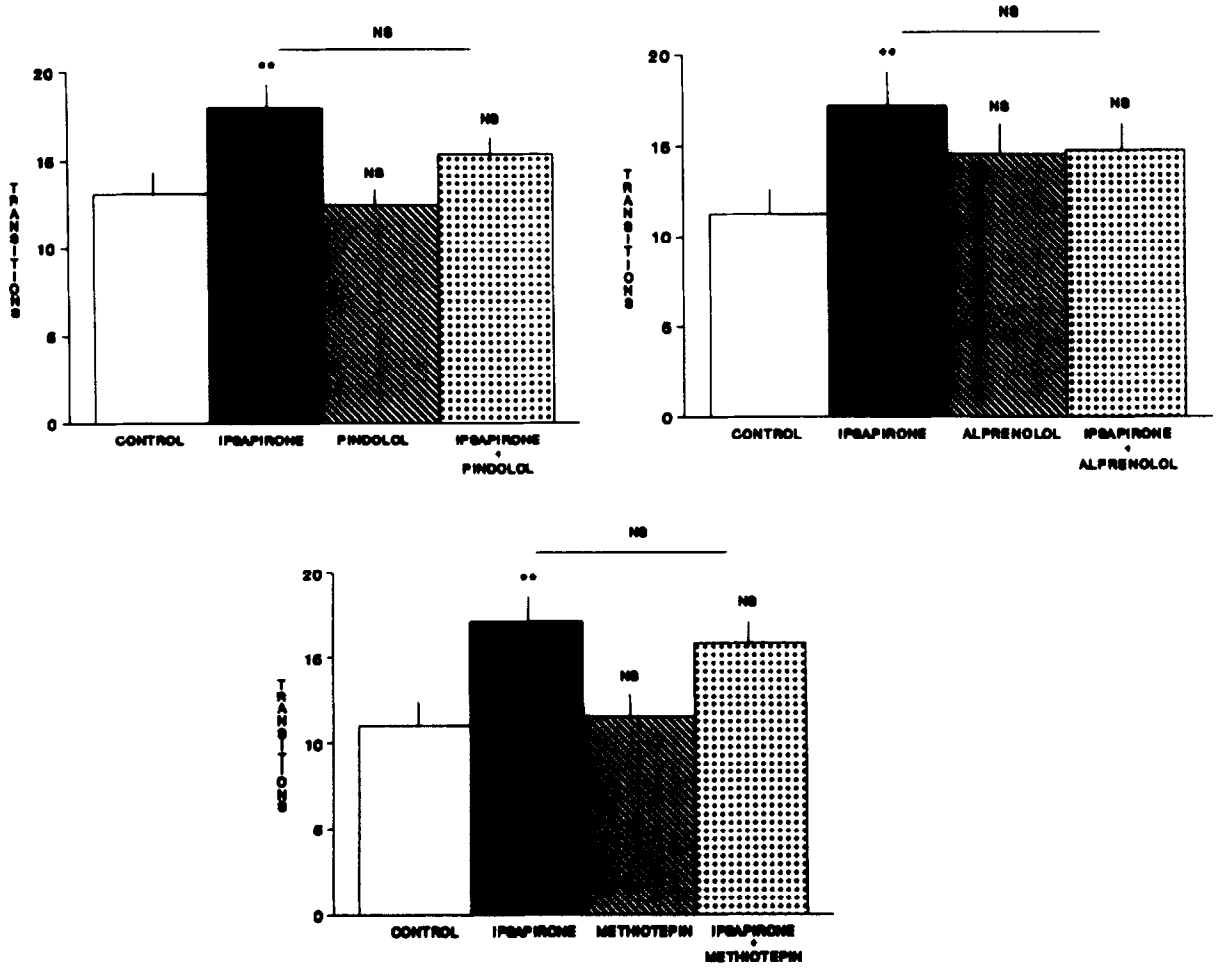

FIG. 1. Effect of methiotepin (0.31 mg/kg, n = 8), pindolol (2.0 mg/kg, n = 8), and alprenolol (5.0 mg/kg, n = 8) on the number of transitions after ipsapirone (10.0 mg/kg) administration to male hamsters. The three panels of the figure show the mean ± SE number of transitions after vehicle, ipsapirone, the antagonist alone, and the combined treatment of ipsapirone plus the antagonist. Asterisks over columns represent the statistical comparisons vs. the vehicle control group. Wilcoxon matched-pairs signed-ranks test, $^{**}p < 0.02$.

Activity Test

The ambulatory behavior was recorded in a box measuring 43 × 36 × 19 cm that was placed over a sensitive plaque (48 × 40 cm) of an activity meter (Stoelting Co., IL) connected to a counter (Stoelting, Co.). After the pharmacological treatment the animal was placed in the cage and the number of counts was recorded over a 10-min period. The data are expressed as counts per minute and were statistically analyzed using the Mann-Whitney U-test (33).

Drugs

The drugs used in this study were: 8-hydroxy-2-(di-*n*-propylamino) tetralin (8-OH-DPAT, Research Biochemicals Inc., Natick, MA), ipsapirone (Miles Pharmaceutical Division, West Haven, CO), diazepam (Hoffmann-La Roche, México City, México), pindolol (Sandoz, Basel, Switzerland), alprenolol (Hässle AB, Mölndal, Sweden), methiotepin (Hoffmann-La Roche, Basel, Switzerland), and *p*-chlorophenylalanine (p-CPA, Sigma, St. Louis MO). All drugs, except diazepam and *p*-CPA, were dissolved in physiological saline and injected in a volume of 4.0 ml/kg. Diazepam was dissolved in propylene glycol 40% and *p*-CPA was suspended in methylcellulose.

Neurochemical Analysis

The animals belonging to the groups included in the neurochemical analysis were sacrificed by decapitation. Their brains were removed, placed on a cold plate, and the hippocampus, brain stem, and frontal cortex were dissected according to the method described by Payne et al. (30). The tissue was weighed and placed in a vial containing 1 ml of 0.1 M perchloric acid and 0.05 mM ascorbic acid, frozen in liquid nitrogen, and stored at −70°C until analyzed, at the most 36 h after dissection. Biogenic amines were determined by HPLC with electrochemical detection (2,26). After thawing, vials were spiked with 100 ng of 3,4-dihydroxybenzylamine (DHBA) as internal standard. Then tissue was homogenized and the suspension was centrifuged at 37,013 × g for 20 min at 4°C. Aliquots of 0.1 ml of the supernatant were injected into a liquid chromatography system (Waters Associates, Milford, MA) and cou-

pled to an amperometric detector (Bioanalytical Systems, West LaFayette, IN). The system was equipped with a reverse-phase column biophase ODS of 5 μm particle size (BAS) eluted with a mixture of 925 ml of 0.15 M monochloroacetic acid buffer, pH 3.0, containing 0.86 mM of sodium octyl sulphate, 75 ml of acetonitrile, and 18 ml of tetrahydrofuran. The column was kept at room temperature. Detection was carried out using a glassy carbon working electrode maintained at +800 mV against Ag/AgCl, and the resulting current was recorded. Retention times were 3.13, 4.01, and 11.93 min for NA, DHBA, and 5-HT, respectively. The comparisons were performed between the *p*-CPA-treated groups and their proper controls. The data were statistically compared using Student's *t*-test.

RESULTS

Table 1 shows the effect of diazepam (0.25, 0.5, and 1.0 mg/kg), 8-OH-DPAT (0.0625, 0.125, and 0.25 mg/kg), and ipsapirone (5.0 and 10.0 mg/kg) on the number of transitions. A clear dose–response increase in the number of transitions was observed after diazepam, 8-OH-DPAT, and ipsapirone.

Figure 1 shows the effect of the 5-HT_1 antagonists, methiotepin, pindolol, and alprenolol, on the anxiolytic action of ipsapirone. All three antagonists at the doses tested (methiotepin, 0.31 mg/kg; pindolol, 2.0 mg/kg; alprenolol, 5.0 mg/kg) produced no effect per se and were only partially able to revert the increase in the number of transitions induced by ipsapirone. The results obtained with the administration of these same antagonists plus 8-OH-DPAT (0.25 mg/kg) are shown in Fig. 2. As in the previous series of experiments, none of the antagonists, at the doses used, produced by themselves changes in the number of transitions. It is clear from this figure that methiotepin and pindolol partially antagonized the response, whereas alprenolol lacked an effect.

Figure 3 compares the effects of ipsapirone and 8-OH-DPAT on the number of transitions in control and *p*-CPA-treated hamsters. Treatment with *p*-CPA did not modify the

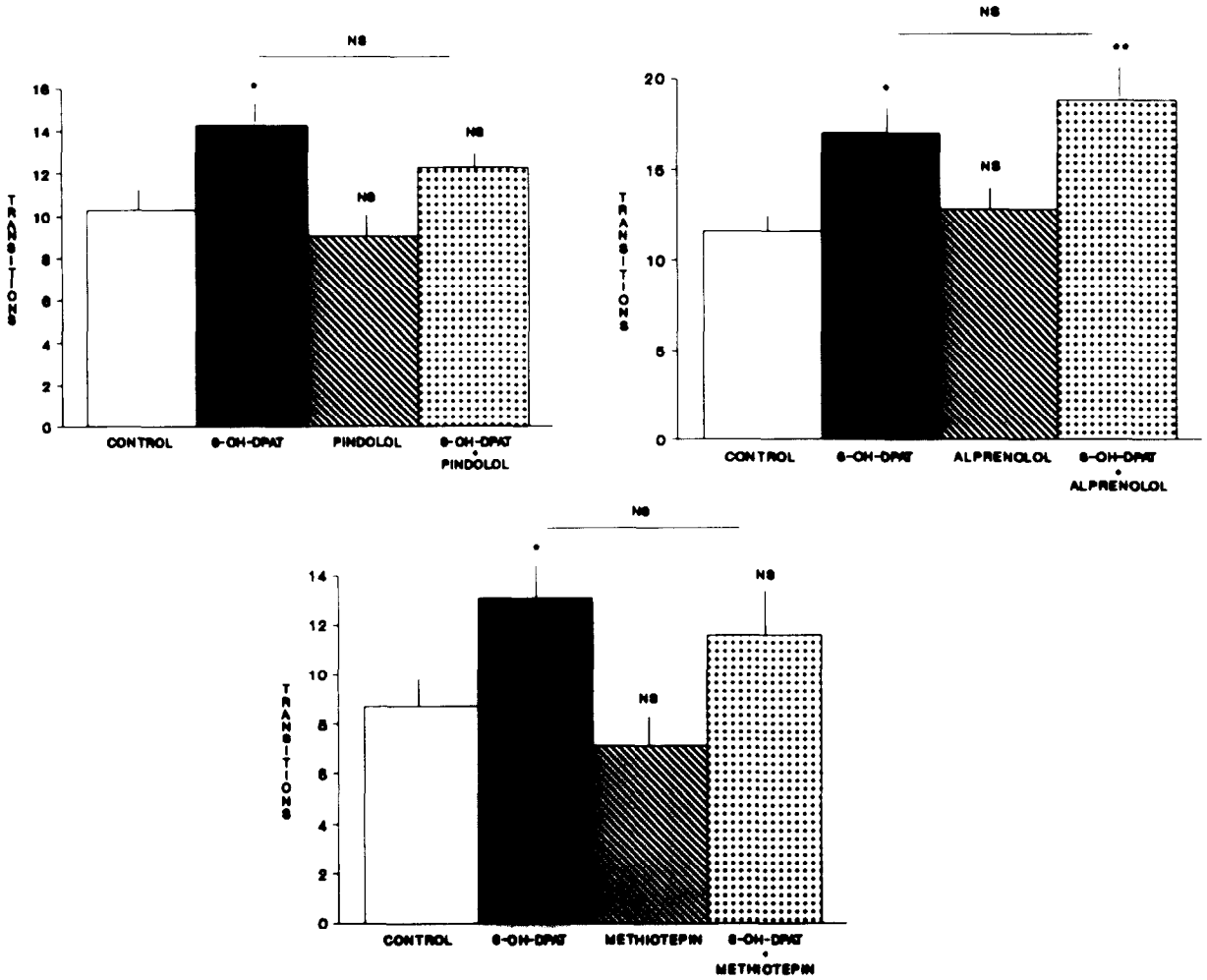

FIG. 2. Effect of methiotepin (0.31 mg/kg, $n = 8$), pindolol (2.0 mg/kg, $n = 8$), and alprenolol (5.0 mg/kg, $n = 8$) on the number of transitions after 8-OH-DPAT (0.25 mg/kg) administration to male hamsters. All panels of the figure show the mean ± SE number of transitions after vehicle, 8-OH-DPAT, the antagonist alone, and the combined treatment of 8-OH-DPAT plus the antagonist. Asterisks over columns represent the statistical comparisons vs. the vehicle control group. Wilcoxon matched-pairs signed-ranks test, $*p < 0.05$, $**p < 0.02$.

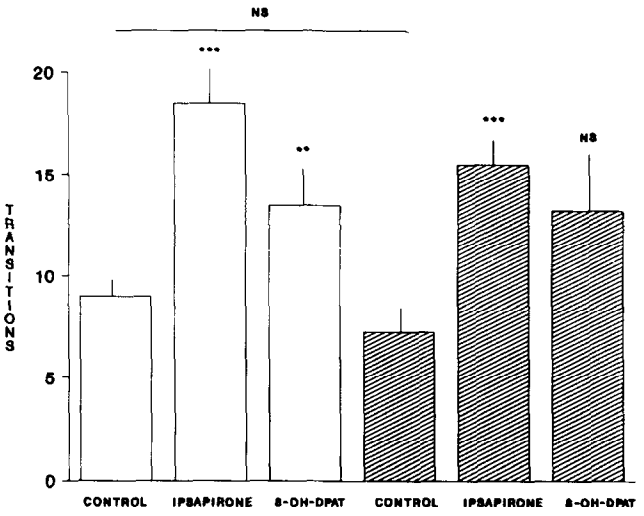

FIG. 3. Effect of ipsapirone (10.0 mg/kg) and 8-OH-DPAT (0.25 mg/kg) on vehicle (open bars, n = 8 for control, n = 8 for ipsapirone, and n = 8 for 8-OH-DPAT) or p-CPA (400 mg/kg × 3 days) treated (dashed bars, n = 8 for control, n = 8 for ipsapirone, and n = 8 for 8-OH-DPAT) male hamsters. Figure shows mean ± SE of the number of transitions. Asterisks over columns represent the statistical comparisons vs. the nontreated group. Mann-Whitney U-test, $^{**}p < 0.02$; $^{***}p < 0.01$.

number of transitions compared with vehicle-treated animals. Similarly, the increase in the number of transitions produced by ipsapirone and 8-OH-DPAT was also observed in animals pretreated with p-CPA. Table 2 summarizes the neurochemical data obtained after treatment with p-CPA. A clear reduction in the levels of 5-HT in the brain stem, hippocampus, and hypothalamus was found, whereas no change in the levels of NA in these brain areas was detected.

The results of the drug effects on the ambulatory behavior are shown in Table 3. The 5-HT$_{1A}$ agonist, 8-OH-DPAT (0.25 mg/kg), produced a statistical significant augmentation in ambulatory activity. Such enhancement was effectively blocked by pindolol (3.1 mg/kg) or methiotepin (0.31 mg/kg) administration. Neither alprenolol (5.0 mg/kg) nor treatment with p-CPA (400 mg/kg × 3 days) was able to counteract this effect. Ipsapirone (10.0 mg/kg) and p-CPA treatment (400 mg/kg × 3 days) per se induced no change on the general ambulatory behavior.

DISCUSSION

The findings from the present experiments reveal that in hamsters: a) the serotonergic agonists 8-OH-DPAT and ipsapirone produce an increase in the number of transitions similar to that induced by diazepam; b) the serotonergic antagonists methiotepin and pindolol partially blocked the 8-OH-DPAT- and ipsapirone-induced increase in number of transitions, and alprenolol partially antagonized the ipsapirone action but had no effect on 8-OH-DPAT; c) p-CPA treatment was unable to prevent the increase in the number of transitions induced by these compounds; and d) 8-OH-DPAT, but not ipsapirone, produced an increase in ambulatory behavior that was blocked with methiotepin but not by p-CPA treatment.

In 1989, Buhot and colleagues (5) reported on the changes in exploratory behavior in hamsters after injection of 8-OH-DPAT. In this study it was found that 8-OH-DPAT enhances the cognitive components of the exploratory behavior, such as object-oriented exploration and, under certain temporal conditions, the response-to-change. However, based on the fact that drug-injected animals did not differ from controls when no exploratory object was present, it was concluded that 8-OH-DPAT had no role in nonoriented exploratory activity. In contrast with these observations, present data showed a clear and drastic increase in ambulatory behavior after 8-OH-DPAT. Indeed, the increase in the number of transitions observed in the light : dark anxiety test could be the result of an unspecific action of this compound on general activity in this species. This result demonstrates the importance of analyzing the drug-induced general ambulatory behavior before drawing a conclusion.

Recently, Tominaga et al. (37) reported a significant phase advance of wheel-running activity under constant light conditions in hamsters injected with 8-OH-DPAT. Additionally, these authors demonstrated that pindolol was able to prevent the effects of 8-OH-DPAT in this test. Present data show that both the increase in the number of transitions in the dark : light test and the increase in ambulation induced by 8-OH-DPAT were partially blocked by pindolol and methiotepin, and were not antagonized by alprenolol. Pindolol and alprenolol share both β and 5-HT$_{1A}$ antagonistic actions (6,28,29); however, it has been reported that alprenolol has higher affinity for β than for 5-HT$_{1A}$ receptors compared with pindolol

TABLE 2

EFFECT OF p-CHLOROPHENYLALANINE (p-CPA) TREATMENT ON SEROTONIN (5-HT) AND NORADRENALINE (NA) LEVELS IN VARIOUS BRAIN AREAS OF MALE HAMSTERS

	Treatment	5-HT	NA
Brain stem	Control	748 ± 47	521 ± 26
	p-CPA	293 ± 56* (61%)	674 ± 25 NS (129%)
Hippocampus	Control	363 ± 18	363 ± 16
	p-CPA	213 ± 43† (41%)	389 ± 14 NS (107%)
Hypothalamus	Control	1001 ± 108	2306 ± 173
	p-CPA	546 ± 105* (49%)	2586 ± 364 NS (112%)

Table shows mean ± SE of 5-HT and NA content expressed as ng/g of tissue (n = 10 hamsters × group). Statistical comparisons were performed using the Student's t-test, NS, nonsignificant ($p > 0.05$), $^{*}p < 0.01$; $^{\dagger}p < 0.02$. Numbers in parentheses represent the percentage of change.

TABLE 3

EFFECT OF 8-OH-DPAT AND IPSAPIRONE ON GENERAL AMBULATORY BEHAVIOR IN MALE HAMSTERS

Treatment (mg/kg)	N	Counts/Min	
Control	8	53.4 ± 4.6	
Diazepam (1.0)	8	45.8 ± 4.7	
8-OH-DPAT (0.25)	8	73.7 ± 4.5*	
+ Alprenolol (5.0)	8	92.1 ± 9.1	*
+ Pindolol (3.1)	8	62.2 ± 4.1	
+ Methiotepin (0.31)	8	45.3 ± 6.5	
Ipsapirone (10.0)	8	57.4 ± 5.8	
+ Alprenolol (5.0)	8	51.5 ± 4.7	
+ Pindolol (3.1)	8	50.6 ± 9.9	
+ Methiotepin (0.31)	8	53.1 ± 4.4	
p-CPA (400 mg/kg × 3 days)	8	44.5 ± 1.6†	‡
+ 8-OH-DPAT (0.25)	8	71.1 ± 4.3	
+ Ipsapirone (10.0)	8	45.5 ± 6.5	

Table shows mean ± SE of the number of counts per minute. Statistical comparisons were performed between the 5-HT_{1A} agonists or *p*-CPA and the control group. Other comparisons are indicated by brackets. Mann-Whitney *U*-test: *$p < 0.02$, †$p < 0.05$, and ‡$p < 0.01$.

(29). These binding differences could underlie the dissimilar antagonistic effects found in the present study. The antagonism found with the administration of pindolol and methiotepin is in agreement with previous findings (37) and suggests that the actions of 8-OH-DPAT on ambulatory behavior, in this species, could be mediated via the stimulation of the 5-HT_{1A} receptor subtype. In the rat, by contrast, it has been reported that alprenolol, pindolol, and the selective β-blocker, betaxolol, potentiate the increase in the ambulatory behavior produced by this 5-HT_{1A} agonist (25). This result suggests that the increase in ambulatory behavior induced by 8-OH-DPAT is mediated, in the rat, via the β-adrenoceptor. Further studies should be undertaken to understand these species differences.

As mentioned, the administration of *p*-CPA results in a depletion of 5-HT; thus, drugs acting at 5-HT_{1A} somatodendritic receptors lack an effect (10,19,21). It is worth noting that the treatment with *p*-CPA in hamsters was unable to prevent the increase in ambulatory behavior observed after 8-OH-DPAT injection. This result suggests that in this species the enhanced ambulation produced by 8-OH-DPAT occurs after the stimulation of postsynaptic receptors.

In the present experiments, the ipsapirone-induced increase in the number of transitions was not accompanied by an unspecific increase in general ambulatory behavior, therefore suggesting that this drug has anxiolytic properties in this species. The analysis of the anxiolytic action of ipsapirone in hamsters shows some similarities and differences when compared with other species that are worth mentioning. We recently reported that ipsapirone produced an anxiolytic action in mice tested in the dark : light paradigm (13). Furthermore, this reduction in anxiety was effectively blocked by the antagonists pindolol, alprenolol, and methiotepin. These observations have been replicated in other animal models of anxiety, such as the burying behavior paradigm (14). Present data show that these same antagonists were partially able to prevent the anxiolytic actions of ipsapirone in hamsters. Taken together, these results suggest a similar mechanism for the mediation of the anxiolytic effect of ipsapirone in mice and hamsters: the stimulation of 5-HT_{1A} receptors. Conversely, it has been reported that in the rat the anxiolytic action of ipsapirone is prevented by the β-blocker, practolol, but not by other antagonists such as pindolol or methiotepin (14). Thus, it can be proposed that in the rat, the β-adrenoceptor participates in the antianxiety effect of these drugs. Further studies are required to explore this possibility.

Regarding the site of action of these drugs, there are data showing that, in the rat, the lesion with 5,7-DHT did not prevent the anxiolytic action of ipsapirone, indorenate, or buspirone, but effectively interfered with the reduction in burying behavior produced by 8-OH-DPAT (15). Furthermore, in mice, treatment with *p*-CPA does not affect the increase in the number of transitions produced by serotonergic anxiolytics (López-Rubalcava and Fernández-Guasti, unpublished data). Present data, obtained in hamsters, show similar results to those found in rats and mice. From these three series of experiments it can be proposed that in rats, mice, and hamsters the anxiolytic action of ipsapirone is mediated via the stimulation of postsynaptic receptors. However, we found that using another anxiety test, the rat social interaction paradigm, ipsapirone did not produce anxiolysis in 5,7-DHT-lesioned rats (31). Moreover, this compound reduces anxiety when administered directly into the dorsal raphe nucleus, but not into the hippocampus (31). These data indicate that for this particular anxiety test, ipsapirone mediates its anxiolytic effect by acting at presynaptic receptors. Thus, it appears that both pre- and postsynaptic 5-HT_{1A} receptors are involved in the anxiolytic effects of 5-HT_{1A} ligands. This apparent participation of pre- and postsynaptic receptors seems to be paradoxical. A possible explanation could be based on the assumption that the intrinsic activity of these drugs is different at pre- and postsynaptic receptors; that is, it has been reported that these compounds have agonistic properties at presynaptic receptors (1,34,35) and antagonistic (or partial agonistic) actions on

postsynaptic receptors (1,36). Moreover, it seems that 5-HT_{1A} ligands act either on pre- or postsynaptic receptors depending on the animal model of anxiety used. Each animal model of anxiety studies different behaviors and may represent different types of anxiety (4). Therefore, it seems logical to consider that these behaviors are modulated in dissimilar ways. It could be speculated that these compounds act on either pre- or postsynaptic receptors depending on the behavioral component affected. Additional studies should be undertaken to further investigate at which 5-HT_{1A} receptor do 5-HT_{1A} compounds act to mediate their anxiolytic activity.

In summary, it can be stated that from the drugs tested in this species only ipsapirone produced a clear anxiolytic action that seems to be mediated by postsynaptic 5-HT_{1A} receptors.

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