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Histaminergic Drugs in the Rat Caudate Nucleus: Effects on Learned Helplessness

J. A. LÓPEZ-GARCÍA,[1] C. RAMIS, M. C. NICOLAU, G. ALEMANY, B. PLANAS AND R. RIAL[2]

Laboratory of Animal Physiology, Department of Biology and H.S., University of the Balearic Islands, 07071 Palma de Mallorca, Spain

LÓPEZ-GARCÍA, J. A., C. RAMIS, M. C. NICOLAU, G. ALEMANY, B. PLANAS AND R. RIAL. *Histaminergic drugs in the rat caudate nucleus: Effects on learned helplessness.* PHARMACOL BIOCHEM BEHAV 45(2) 275–282, 1993. – The effect of pharmacological manipulation of histaminergic receptors in the caudate nucleus (CN) has been examined in rats previously submitted to inescapable electric shock to produce learned helplessness (LH). Histamine H_1 agonist 2-tiazolylethyl amine (TEA) microinjection produced protective effects, preventing the activity and cognitive loss typical in LH. Injection of the H_1 antagonist astemizole (AZ) produced effects symmetrical to those produced by TEA, further reducing activity and impairing cognitive functions. The histamine H_2 agonist 4-methyl-histamine (4MH) produced a shift on the side preference for rotation that interfered in the learning tests and obscured the effects of this drug on LH. Injection of the H_2 antagonist cymetidine (CYM) caused LH-like effects in control animals. Thus, brain histamine seems to play a relevant role in the control of motor and cognitive functions of the CN.

Histamine agonists Histamine antagonists Caudate nucleus Learned helplessness Experimental depression

THE underlying neurophysiological mechanisms of depression have not been clearly identified yet despite the enormous attention focused on this issue during the last decades. In fact, most antidepressant agents available for clinical use interact simultaneously with several neurotransmitter systems at one or more points of their physiology although no single action seems to be essential by itself. In this context, depression can be regarded as a complex phenomenon whose symptoms could be supported by several patterns of dysfunction involving different neurotransmitter systems and brain structures.

Notorious progress has been achieved in the understanding of the roles of several neurotransmitters such as noradrenaline (2), acetylcholine (7), and serotonin (10,36) in depression. The roles of these substances have been discussed in the relevant literature on the basis of experiments carried out both in humans and animals.

However, histamine has received little attention specially with respect to animal behavioral experiments. This is somehow surprising because there are reports on antihistaminic properties of several antidepressant agents (1,14,20,26,31, 32,38) and on the differential distribution of histamine in brain areas (22,25,33). This leads to suspect an important role of histamine in central processes of the mammalian brain [see (27) for a survey].

Three histamine receptors (H_1, H_2, and H3) have been described in the CNS (15). In this article, we will focus only on H_1 and H_2 histamine receptors on depression because the effects of antidepressant drugs on H_3 receptors have not been fully documented yet.

The H_1 receptors have been found mainly in neuronal membranes and in a smaller proportion in glial cells (5) but neither in mast cells nor in blood vessels (9). Some antidepressant drugs, such as doxepin and amitriptyline, show a high affinity for H_1 receptors and their powerful antagonism at this site seems to be their strongest action in the brain (32,39). They act as competitive inhibitors (31) although no interaction with the metabolism of histamine has been detected (26).

The H_2 receptors have been reported in neuronal membranes (20), mast cells, and blood vessels (9). Amitriptyline and imipramine among other antidepressants of different families antagonize H_2 receptors with the same affinity as they antagonize the muscarinic receptors (1,14).

At pharmacological doses, all these antidepressants may act on histaminergic systems mainly by interacting with H_1 receptors (31,32). The affinity of these drugs to H_1 receptors correlates well with their sedative action (14,16).

The caudate nucleus (CN) shows a considerable amount of histamine when compared to other brain structures. Its percentage in neuronal localization ranges from medium to high and its half-life is the shortest of all brain areas (25,33). This suggests a high activity of histaminergic neurons in the CN. Further, the CN has important motor and cognitive func-

[1] Current address: Department of Physiology, University of Leeds, The Worsley Medical and Dental Building, Leeds LS2 9NQ, UK.
[2] To whom requests for reprints should be addressed.

tions (8), both of them involved in depression and largely treated in the theoretical grounds of animal models of depression.

The aim of this research is to evaluate the role of H_1 and H_2 receptors of the CN on the deficits produced by inescapable shock as described in the learned helplessness (LH) (34,35) model of depression. Results are reported in a series of four experiments. Experiment 1 was designed to check the validity of the basic hypothesis of the LH model under the present experimental conditions. Experiment 2 aimed at evaluating the impact of cranial surgery and intracerebral vehicle microinjection into the caudate nucleus on the baseline performance of the tested groups. Experiments 3 and 4 were designed to study the effects of H_1 and H_2 receptor agonists and antagonists microinjected into the CN.

GENERAL METHOD

SUBJECTS

A total of 110 male Wistar rats, 100 days old, weighing 300–350 g at the beginning of the experiments, were used. Rats were kept in groups of five at a constant temperature (23 ± 1°C) and under a 12 L : 12 D cycle. Food and water were continuously available except during experimental sessions. Experimental groups had either 8 or 12 animals each.

SURGERY

Sodium pentobarbitone-anesthetized rats (50 mg/kg, IP) were placed in an LPC stereotaxic frame. Each animal's head was shaved and a hole 1.5 mm anterior and 2.7 mm lateral to bregma was drilled in its skull. A stainless steel 10-mm cannula was then lowered 4 mm through the hole. Using these coordinates, the tip of the cannula should lay 2 mm above the center of the head of the caudate nucleus according to the atlas and stereotaxic plane of Skinner (37). Two stainless steel screws were attached to the skull and cemented together with the cannula.

PROCEDURE

All experiments shared the same general schedule, which was as follows.

Days 1–10

On the first day, animals were submitted to surgery and allowed to recover in individual cages. The three groups of Experiment 1 did not undergo surgery but were also placed in individual cages for a 10-day period.

Day 11

All rats received one of the three following treatments in soundproof boxes where fans provided background noise.

Control treatment. Animals were restrained in a 24 × 8-cm PVC tube during 80 min. Electrodes were attached to their tails but they received no shock.

Inescapable shock treatment. Inescapable shock treatment consisted of a series of 80 unscrambled electric shocks (0.9 mA, 5 s) delivered by a standard source (Letica, LI2700) via electrodes attached to the tail of animals while they were restrained in PVC tubes as described above. The electrical contacts were augmented with conductive gel. Shocks were presented in a variable time schedule (range 15–110 s, average 60 s). Animals had no control on the shock termination.

Escapable shock treatment. Only one group in Experiment 1 was submitted to this treatment. Animals of this group were restrained in a PVC tube in which the frontal end had been substituted by a lever mechanism that animals could operate with their nose tips. After restraining, 10 learning trials were run. In each of these, the shock (0.9 mA, maximal duration 15 s) administered through the tail could be terminated by a single lever pressing. Two lever pressings were required to escape the shock in the 80 subsequent trials. The parameters in this treatment were carefully selected to deliver a similar amount of electric shock to escapable and inescapable groups because they were non-yoked. Pilot studies showed that the escape time was stable (6.3 ± 0.9 s) in the second half of the treatment under the present conditions. The escape times were under 5 s only in 1% of the trials. Two animals produced fast escape responses (under 5 s) in three consecutive trials. An extra lever pressing was required to terminate the shock in these two cases.

Day 12

All rats underwent the following procedures.

Tail-flick test 1 (baseline pain response). Animals were restrained in a PVC tube with their tails lying on a small rail in which a thermal lamp raised the temperature at a constant rate. As soon as animals flicked their tails, the heat was switched off and the reaction time automatically recorded (4).

Activity test 1 (baseline activity). Rats were placed in their home cages and their spontaneous activity in a dark environment was recorded every 5 min over a period of 30 min by means of a standard activimeter (Panlab 0603).

Hand restraining and intracerebral injection with either vehicle (Experiment 2), H_1 receptor drugs (Experiment 3), or H_2 receptor drugs (Experiment 4). Each animal was restrained in the hands of the experimenter for 3 min. During this time, all cannula-implanted animals received a 1-μl injection inside the caudate nucleus containing either polyethylene glycol 400 (PEG) (selected as vehicle because astemizole is not water soluble) or PEG added with drug. The used drugs and doses were 2-tiazolilethyl amine (TEA) 9.7 nM (Smith Kline & French, Philadelphia, PA), astemizole (AZ) 1.25 nM (Janssen Pharmaceutica, Beerse, Belgium), 4-methyl histamine (4MH) 12.4 nM (SK&F), and cymetidine (CYM) 1.0 nM. Injections were administered with a 1-μl Hamilton syringe (Hamilton Co., Reno, NV) connected to a fine needle by a piece of polytylene tubing. The tip of the needle protruded 2 mm from the tip of the guide cannula. All injections were made in the conscious animal at a slow rate to avoid tissue damage. Although nonoperated rats (Experiment 1) were not injected, they were also hand restrained.

In a previous pilot study (and in the histological controls; see below), animals were injected with 1 μl PEG containing methylene blue and sacrificed 40 min later. Postmortem analysis of the spread of the dye revealed that it was almost spherical in shape and about 2 mm in diameter (Fig. 1), giving an approximate volume of less than 4 μl, small compared to the volume of the whole CN. From this study, we concluded that any effects of drugs administered using this procedure should be attributed to an action within the limits of the CN provided the injection site was correct. After these data, the dosage of TEA, 4MH, and CYM was calculated to achieve, in a theoretical volume of 4 μl brain tissue, an 80–85% occupancy for the desired receptors (H_1 for TEA, H_2 for 4MH and CYM) and less than 10% for the nondesired ones. The receptor saturation percentages were calculated according to the ED_{50} given

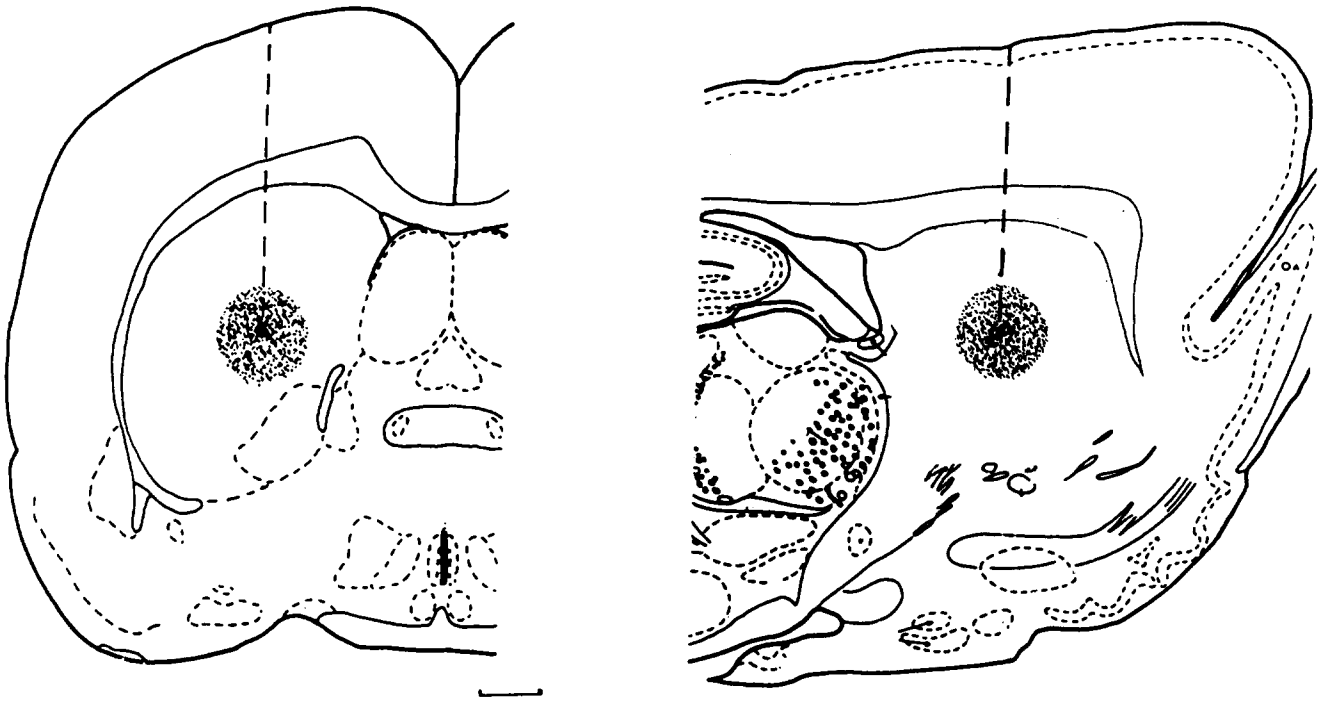

FIG. 1. Frontal and longitudinal plates of the stereotaxic atlas showing the injection site and the spread of 1 μl of PEG plus methylene blue (dotted area) with respect to the CN size. Callibration bar: 1 mm.

by Green (13). The ED_{50} of AZ in the brain is not known but with the used dose a 80% occupancy (approx.) was found for guinea pig lung H_1 receptors (21).

Activity test 2 (postinjection activity). Identical to activity test 1.

Tail-flick test 2 (postinjection pain responsiveness). Identical to tail-flick test 1.

Choice escape learning test (assessment of deficits produced by inescapable shock). All animals were submitted to an escape learning test in a symmetrical Y-maze. The arms of the maze were 23 cm long, 11 cm wide, and 14 cm high. The floor was a metallic grid (3-mm bars separated by 1.25 cm center to center) and the roof was covered with transparent methacrylate. At the beginning of the test, rats were allowed 5-min habituation inside the maze. During this period, the exploratory locomotor activity was counted as the number of complete displacements from one arm of the maze to any other arm. Right–left choices were also recorded. After habituation, 40 signaled escape trials were presented on a fixed time base (45 s). Each trial started with the simultaneous onset of a signaling tone and a 0.9-mA scrambled electric shock delivered through the floor grid. Both sound and shock terminated when the animal produced a left turn (correct response) in the Y-maze. Right turns were recorded as errors and the shock continued until a left turn was produced by the rat or 40 s had elapsed from the onset of the shock without a correct response. The time to complete the first correct turn was also recorded as reaction time.

Histological control. At the end of the experiments, animals were anesthetized with ether and the injection site marked with 1μl methylene blue. Then, they were perfused with saline-formaline and their brains were removed and frozen. Three-hundred-micrometer thick slices were obtained and analyzed with a binocular microscope. Only results from animals in which the injection had correct spread and location were considered for further analysis.

STATISTICS

Parametric statistics (Student's *t*-test) were used to compare differences between means after assessing normality of data using the Kolmogoroff test.

EXPERIMENT 1

RESULTS

No significant differences were found in tail-flick latency between inescapable shocked, escapable shocked, or controls. Values of this variable were stable (range 8–9 s). No differences between the first and second test were detected either.

The average spontaneous activity of each group is shown in Table 1. Control animals were more active than shocked animals ($p < 0.01$) but no significant differences in activity were found between escapable and inescapable shocked groups. All groups were more active in the first activity test than in the second one ($p < 0.01$). Parallel results were obtained in the exploration of the Y-maze during the 5-min habituation period: Nonshocked animals explored more arms than animals coming from both shocked groups (Table 2). No significant differences were found between the number of right and left choices during this period (Fig. 2).

Figure 3 (Experiment 1) shows the evolution of the mean latency to complete the first correct escape response all along the Y-maze escape learning test. By the end of the test, inescapable shocked animals were slower than nonshocked control animals ($p < 0.05$) whereas escapable shocked animals were faster than controls ($p < 0.01$). All groups showed a decrease

TABLE 1

MEAN NUMBER OF SPONTANEOUS ACTIVITY COUNTS ± SEM IN THE FOUR EXPERIMENTS

	Groups		
	Controls	Inescapable Shock	Escape
Experiment 1			
Baseline	422 ± 53	268 ± 31	231 ± 27
Test	209 ± 23	110 ± 17	115 ± 11
Experiment 2			
Baseline	400 ± 47	262 ± 23	
Test	218 ± 20	97 ± 14	
Experiment 3			
TEA			
Baseline	445 ± 63	240 ± 25	
Test	192 ± 14	82 ± 17	
AZ			
Baseline	460 ± 68	281 ± 34	
Test	92 ± 13	86 ± 15	
Experiment 4			
4MH			
Baseline	420 ± 63	330 ± 38	
Test	170 ± 22	60 ± 19	
CYM			
Baseline	500 ± 48	200 ± 36	
Test	180 ± 16	80 ± 13	

in percentage of trials with one or more errors as the learning test progressed (Fig. 4, Experiment 1). However, by the end of the test inescapable shocked animals had a higher percentage of trials with error than controls ($p < 0.01$) while escapable shocked animals had a lower percentage than controls ($p < 0.01$).

DISCUSSION

These results demonstrate that pain reactivity was equivalent in all groups at the beginning of the choice escape learning test and also show that exposure to electric shock produced a decrease of activity irrespective of the degree of control animals had on the termination of the shock. This punishment-bound reduction of activity has been known for a long time (3).

TABLE 2

MEAN NUMBER OF ARMS EXPLORED DURING THE FIRST 5-MIN PERIOD IN THE Y-MAZE PREVIOUS TO THE CHOICE LEARNING PROCEDURE

	Controls	Inescapable Shock	Escape
Experiment 1	14.6	10.6	11.1
Experiment 2	13.0	9.7	
Experiment 3 (TEA)	12.8	11.4	
Experiment 3 (AZ)	9.6	6.6	
Experiment 4 (4MH)	12.5	7.3	
Experiment 4 (CIM)	14.7	7.1	

Although stress-induced analgesia was not tested (23), the tail-flick latency was used to assure the lack of effects of histaminergic drugs in pain reactivity in the following experiments.

Results obtained in the choice escape learning test are remarkably similar to those obtained by Jackson et al. (17,18) using a similar experimental design. They are also consistent with the LH model's predictions despite the fact that escapable and inescapable shocked groups were nonyoked. Note that shocks were presented with the same variable time schedule in both cases and that the escapable group received a slightly higher amount of shock than the inescapable group (90 shocks instead of 80). It is well known that under inescapable conditions the amount of shock keeps a certain direct relationship with the deepness of the deficits (24). Therefore, the differences in the amount of shock received by the escapable and inescapable groups during the treatment in this experiment would never favor the performance of the escape group. Despite this, inescapable shocked animals produced a higher number of errors in the choice escape test than controls and escapable shocked animals. Because this particular test has been proven to discriminate between activity and associative deficits (17), we conclude that associative differences between inescapable and escapable shocked groups should be attributed to the controllability of the shock: Exposure to electric shock produced activity deficits but only exposure to inescapable shock produced associative or cognitive deficits.

EXPERIMENT 2

RESULTS AND DISCUSSION

The results obtained in this experiment were similar to those obtained by control nonoperated animals in the first experiment. Pain reactivity as estimated by the tail-flick test was within the range of 8–9 s and was not altered following PEG 400 injection.

Both baseline and postinjection activity measures (Table 1) were close to those obtained in the first experiment (no statistical differences found). The level of activity fell in the postinjection measurement as was the case following hand restraining in the first experiment. This indicates that hand restraining or habituation to the activity test situation could account for the decrease in activity while PEG 400 injection had little or no effect.

During the 5-min period of habituation to the Y-maze, right–left choice kept close to the 50/50 ratio (Fig. 2). During the choice escape learning test, the evolution of reaction times (Fig. 3, Experiment 2) and the proportion of trials with one or more errors (Fig. 4, Experiment 2) was similar to that of nonoperated controls with no significant differences.

Therefore, we conclude that intracranial surgery plus PEG 400 microinjection did not produced significant changes in any of the measured variables.

EXPERIMENT 3

RESULTS

Neither inescapable shocked animals nor control animals showed changes in pain reactivity and activity counts (Table 1) following TEA microinjection. During habituation to the Y-maze, right–left percentage of choices remained unchanged and close to the 50/50 ratio in both groups (Fig. 2). Inescapable shocked animals injected with TEA were slightly more

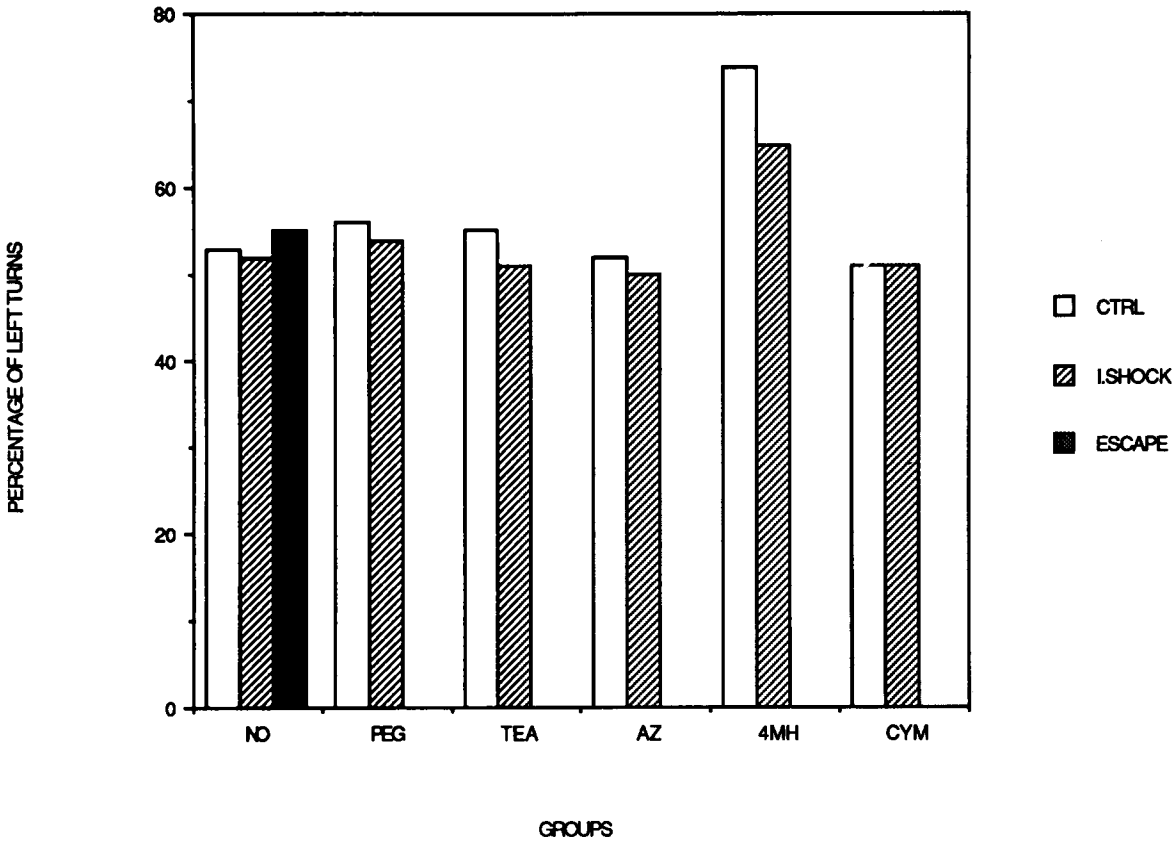

FIG. 2. Percentage of left choices in the "Y" maze. Abbreviations are referred to the drug injected: NO = no drug injected; PEG = vehicle; TEA = 2-Tiazolyletyl amine; AZ = Astemizole; 4MH = 4-metyl-histamine; CYM = Cymetidine.

active than both inescapable shocked animals injected with vehicle alone and uninjected in the exploration of the Y-Maze (Table 2) but differences were not significant. These animals also performed much better in the choice escape learning test: By the end of the test, the reaction time (Fig. 3, Experiment 3) and the percentage of trials with one or more errors (Fig. 4, Experiment 3) were smaller than those obtained by inescapable groups not injected with TEA ($p < 0.01$). Control animals injected with TEA performed in a similar way to uninjected controls of Experiments 1 and 2, but those TEA injected produced faster reaction times by the end of the learning test (Fig. 3, Experiment 3).

No changes were detected in pain reactivity after AZ injection. The activity of the control AZ-injected group was lower than the activity recorded from controls of Experiments 1 and 2 not injected with AZ (Table 1). Right-left choice remained close to the 50/50 ratio after AZ administration (Fig. 2). Both inescapable shocked and control groups showed a decreased exploration of the Y-maze ($p < 0.01$) (Table 2). Control AZ-injected animals performed much worse than controls not injected with AZ in the learning test: Reaction times were longer ($p < 0.01$) and the percentage of trials with errors was higher ($p < 0.01$) by the end of the test (Figs. 3, Experiment 3 and 4, Experiment 3).

DISCUSSION

These results show that the activation of H_1 receptors inside the caudate nucleus by TEA considerably improved some deficits induced by exposure to inescapable shock while inactivation of these receptors by AZ caused deficits in control nonshocked animals comparable to those induced by inescapable shock. Both motor and cognitive factors were altered by manipulating H_1 receptors. These observations suggest that H_1 receptors of the caudate nucleus play an important role in the control of deficits produced by exposure to inescapable shock. It is reasonable to attribute a tonic control of cognitive and motor functions to H_1 receptors of the caudate nucleus because both the agonist and antagonist showed effects on their own and these effects were rather symmetrical.

EXPERIMENT 4

RESULTS

Neither 4MH nor CYM injections changed pain responsiveness. The results concerning the activity of animals injected with these substances are difficult to analyze because the baseline measures of activity were different from those of other groups.

All animals injected with 4MH showed an increased preference (74–65%, $p < 0.01$) for left choices during the exploration of the Y-maze (Fig. 1).

Both 4MH-injected groups performed much better than their controls (Figs. 3, Experiment 4 and 4, Experiment 4, respectively). By the end of the test, reaction times and percentage of trials with errors of both groups were smaller than

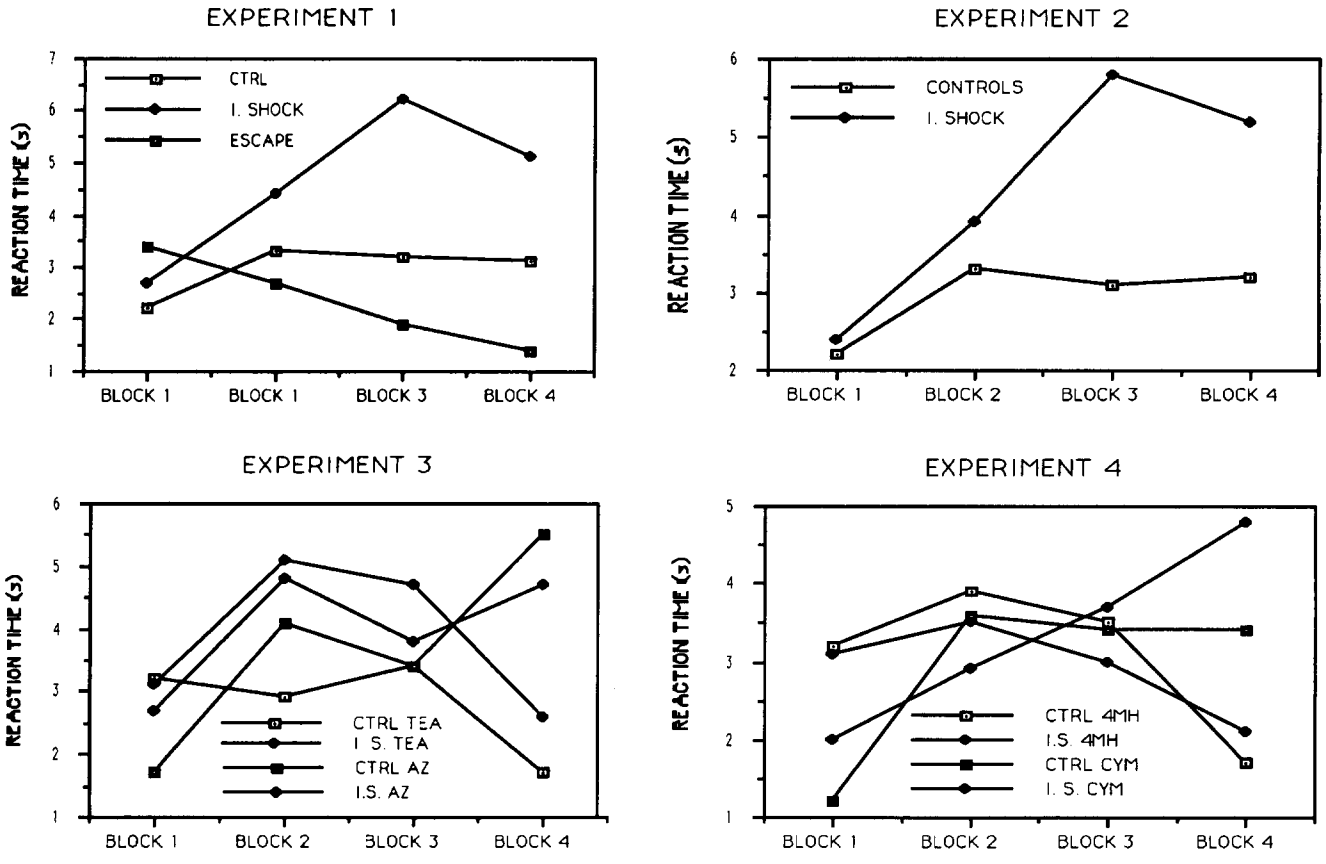

FIG. 3. Time course of mean reaction time for successful response in seconds (ordinate) vs. blocks of ten trials of the escape learning test in the "Y" maze. Abbreviations: Ctrl: nonshocked group; I.S. and I. Shock = inescapable shocked group. TEA, AZ, 4MH and CYM refers to the injected drug. In experiment 2 both controls and inescapable shocked groups were injected with vehicle (PEG).

those obtained by equivalent groups of animals injected with PEG or not injected ($p < 0.01$).

Control CYM-injected animals showed a bad performance in the escape learning test when compared to noninjected controls. This group produced longer reaction times and more trials with errors than the inescapable shocked group (Figs. 3, Experiment 4 and 4, Experiment 4).

DISCUSSION

The most striking result in this experiment was the 4MH-induced change in side preference prior to the starting of the choice escape learning test. This effect has been already reported (30) and several issues related to the mechanism underlying this effect are currently being addressed at our laboratory, particularly those concerning possible interactions with dopaminergic, cholinergic, or serotoninergic systems that are involved in brain assymetry (12,19,28). Whatever the mechanism of action, it is known (12) that the right-left preference depends upon functional asymmetries between the two striatal systems, that is, an overactive right striatum or an inhibited left striatum would cause a left side turning preference. Therefore, 4MH may have exerted an important inhibitory action on the left caudate nucleus, where it was injected.

Because CYM injections did not produce the opposite effect, H_2 receptors of the caudate nucleus could exert their control of side preference through a phasic mechanism.

The unexpected change in side preference obscured the interpretation of reaction times and errors produced by 4MH-injected animals. The low values of these variables all along the test could be secondary to the change in choice preference because left choices were considered correct responses. This change in choice preferences may have facilitated the performance of this group without any cognitive effort and from this experiment no clear effects on inescapable shocked animals can be claimed after activation of H_2 receptors.

On the other hand, CYM produced an increased response time and a high number of trials with errors in nonshocked control animals. This should be a true pharmacological action because the small dose used has been considered without effect on receptors other than H_2 (14). Therefore, despite the lack of clear effects of 4MH in cognition the negative effects of CYM injection suggest the existence of a tonic role for H_2 receptors of the CN in the control of cognitive functions.

GENERAL DISCUSSION

The experimental design used has shown to be reliable in the following two aspects:

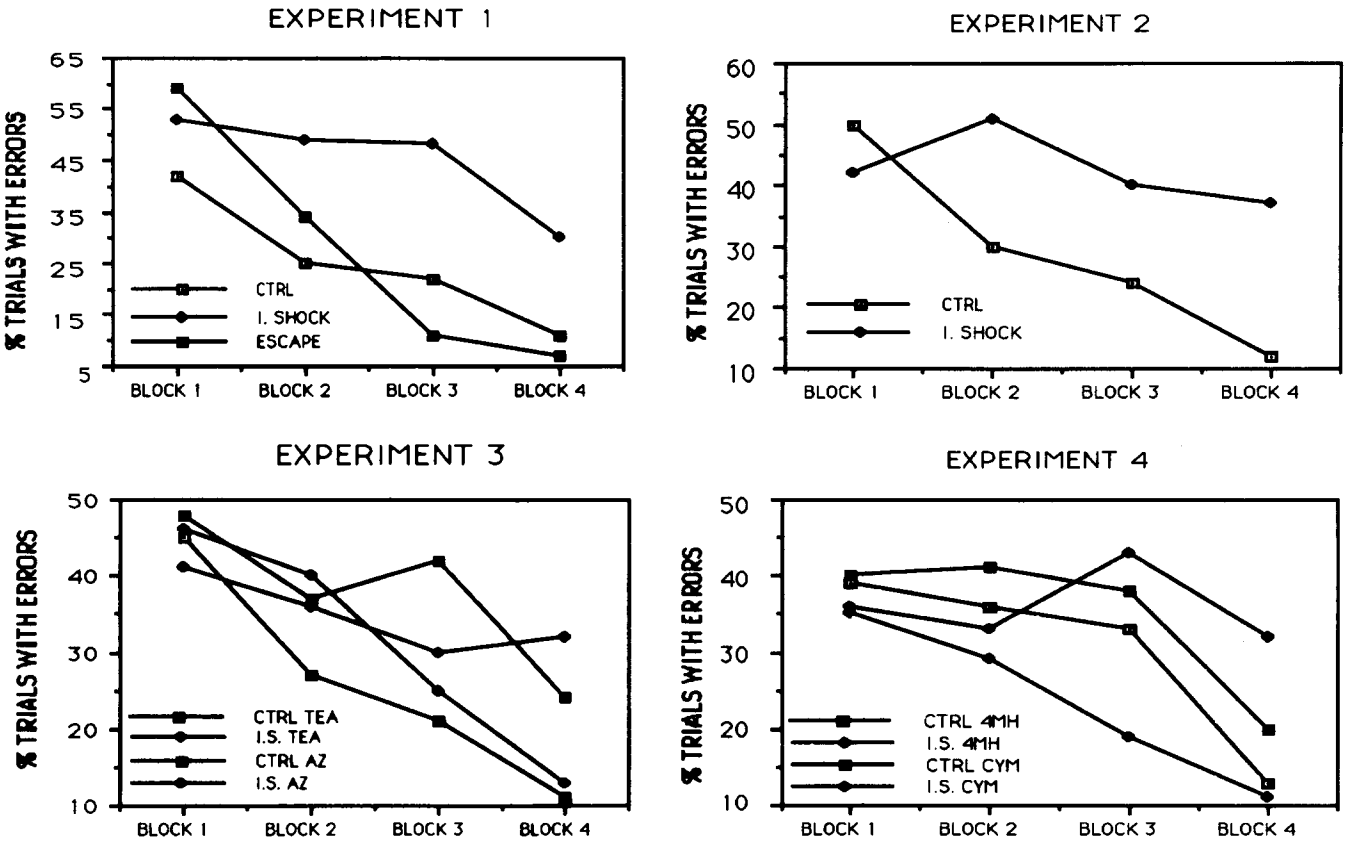

FIG. 4. Percentage of trials with one or more errors in the escape learning test. Same abbreviations as in Fig. 2.

1. The results of Experiment 1 are consistent with those expected in an LH paradigm despite the use of a nonyoked design. Exposure to electric shock produced motor deficits but no changes in pain reactivity measured before reinstating the punishment were detected. Only inescapable shock produced an additional associative deficit whereas escapable shocked animals were more efficient in learning. These results are also consistent with results obtained by other authors (17) using similar experimental designs.
2. The results of Experiment 2 clearly show that neither the surgery nor the PEG injection produced significant changes in the studied parameters.
3. The results of both pilot studies and histological controls show that the exogenous volume injected into the CN is far too small to spread out of the boundaries of the CN. In addition, all drugs used in these experiments were administered in concentrations small enough to minimize cross effects with undesired receptors.

These points settled, the results found in Experiments 3 and 4 should be considered true pharmacological effects of TEA, AZ, 4MH, and CYM acting on histamine receptors in the CN.

With respect to the effects on the H_1 receptors, injection of the H_1 agonist TEA slightly enhanced the motor activity and clearly improved the cognitive capabilities of inescapable preshocked animals (helplessness group). Nearly opposite effects were found after injection of the H_1 antagonist AZ. None of the H_1 drugs modified the baseline pain reactivity by its own.

The results obtained with these H_1 drugs were almost symmetrical for the agonist and antagonist, and this symmetry of effects adds value to the hypothesis of an important and active role for histamine contained in the CN. These symmetry of effects also suggest the existence within the CN of a tonic histaminergic system controlling or modulating motor and cognitive functions involved in LH.

Our results, however, show some striking features in the effects of the H_1 agonists and antagonists when compared to those previously reported by other authors. Depressogenic-like effect of histamine intraventricularly injected has been reported (6,11,29) and the antagonism of histamine receptors by antidepressant drugs has already been discussed in this article. These two known effects point out conclusions that are contradictory with the results obtained in the present experiments. This contradiction may be solved by considering that intraventricular and systemic ways of administration should affect simultaneously several central structures. The observable behavior is the sum of multiple local actions that may be of a different sign. An H_1 antagonist could exert an antidepressant influence when acting on the whole CNS and a depressogenic influence when locally administered into the CN. The diversity of actions of a drug in different places of the CNS has been often neglected; however, it may have important theoretical consequences in explaining the failure in correlating drug receptor affinities to behavioral effects.

The effects of 4MH upon the right-left preference were unsuspected up to now and precluded the ascertaining of other effects on LH that may or may not be the opposite of those found after CYM injection.

Summarizing, the results produced by TEA and AZ should be considered as demonstrative of the importance of the histaminergic H_1 receptors in the LH. Those produced by 4MH may be indicative of a role of H_2 receptors in CN motor functions although an effect of these receptors on the associative ones cannot be excluded after considering the effects of CYM. On the whole, the results strongly suggest a role for histamine in motor activity and cognition but not in pain reactivity.

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