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Histaminergic systems of the limbic complex on learning and motivation☆

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Abstract

The possible role of histamine sensitive sites in hippocampus and the nucleus accumbens on memory and exploratory motivation was studied. As a model of memory, the learning of an active avoidance response to an ultrasonic tone anticipating an electric shock was used. As a model of motivation, an elevated asymmetric plus-maze with arms differing in the presence or absence of walls (APM) was used. All rats were implanted with microinjection cannulae into the ventral, dorsal hippocampus or the nucleus accumbens. Animals were stimulated with histamine, with or without histamine receptor antagonists 5 min before training trials in memory or exploration tests in the APM. Results show that histamine in ventral hippocampus inhibits evocation, impairing the efficiency of learning (37.5 ± 6.5 vs. $75 \pm 5.2\%$ of accumulated conditioning responses; histamine vs. saline, $P < 0.01$). This inhibitory action was blocked by pyrilamine (H_1-histamine receptor antagonist) but not by ranitidine (H_2-histamine receptor antagonist). In dorsal hippocampus no significant inhibitory effect due to histamine stimulation was observed. In the APM, histamine in the nucleus accumbens increased exploration of the fear-inducing arms (45 ± 12 vs. 16 ± 8 counts per 5 min; histamine vs. saline, $P < 0.01$) and also increased the emotionality index. These effects were blocked by both histamine receptor antagonists. In conclusion, data suggest a modulating role for histamine in learning and motivation/emotionality processes in the rat brain.

Keywords: Ventral hippocampus; Nucleus accumbens; Histamine; Motivation; Learning

1. Introduction

There is agreement that histamine and histaminergic systems have an important role in several physiological processes in the brain [2–4,11,20,23,26,31,35,36]. Our laboratory has been interested in characterising the possible functional role of histamine and its receptors in some specific brain processes such as cognition and novel environment-motivated exploration. Evidence has been found suggesting that some structures of the limbic system and related neural components, such as the hippocampal formation or the nucleus accumbens, appear to be involved in these mechanisms [2–4,10,12,21,26,27,33,36]. Since histamine receptors have been located in the hippocampus and also in the nucleus accumbens [16,29], it was of interest to examine these structures in connection to cognitive and motivation-related processes in the rat.

2. Materials and methods

2.1. Animals

Male rats of the Holtzman-derived colony, weighing 250–320 g, 90-day-old and maintained in thermoregulated (22–24°C) and controlled light conditions (06:00–20:00 h) were used. Standard rat chow and water were available ad libitum.

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2.2. Implantation procedures

The localised chemical stimulation produced by microinjections of drugs into the ventral hippocampus or into the nucleus accumbens was used as a general method to activate post-synaptic receptors in the brain tissue. Animals were anaesthetised with ether and unilaterally implanted with guide steel cannulae (23-gauge, 15 mm length) into the ventral hippocampus or into the nucleus accumbens as described earlier in detail elsewhere [2–4,21]. In some experiments, rats were implanted in the dorsal hippocampus.

2.3. Drugs

Histamine dihydrochloride (HA, Sigma, USA), Pyrilamine Maleate (PYR, Sigma) and Ranitidine (RAN, R.B.I., USA) freshly prepared in saline solution were used.

2.4. Behavioural techniques

Two general experimental approaches were used, (i) learning of an active avoidance response, as a model of memory processes; and (ii) exploration of a conflictive environment, as a model of motivation-emotionality processes.

2.4.1. Learning of an active avoidance response

The one-way active avoidance response to an ultrasonic tone of 40 kHz as outlined in Fig. 1(A) was used. Prior to the acquisition trials, an adaptation training was given to the animals, which consisted in letting the rats to freely pass from compartment 2 to compartment 1 through the swinging door. Rats were conditioned to escape through after the ultrasonic tone was on. When animals avoided the electric shock passing from compartment 2 to compartment 1 before the ultrasonic tone was off, a 'positive' response was considered. If the animal failed to escape after 60 s the ultrasonic tone is off, a 'negative' response was considered. Electric shocks were given at a rate of one each 15 s and the total time during which the ultrasonic tone is on was 30 s. Accordingly, rats have up to 30 s to avoid punishment. Variables registered under this experimental set-up were, (i) latency (the time the animals take to escape after the onset of the conditioning tone) and (ii) percentage of conditioned avoidance responses (% CAR, the sum of the positive responses during one session, divided by the number of trials of the session). A total of eight trials compose one session and two sessions were necessary for control animals to learn the avoidance task. In the experiments of the dorsal hippocampus, rats needed three sessions in order to learn the task. Additional details have been described elsewhere [2–4].

2.4.2. Exploration in a conflictive environment

The elevated asymmetric plus-maze (APM) was used as a model of conflictive novel environment for studying exploratory motivation in rats [21,25,26]. General outline of the APM is shown in Fig. 1(B). The degree of asymmetry of each arm was as follows, (i) no wall (NW); (ii) single wall (SW, 15 cm high); (iii) two walls (HL, one of them 15 cm high and the other 6 cm high); and (iv) two high walls (HH, both of them 15 cm high). The APM was elevated 60 cm from the floor and placed in the centre of the experimental room. Illumination was supplied by one 30 W fluorescent lamp above the APM. Rats were tested in the APM only once. At the onset of the test, rats were individually placed in the centre platform (see Fig. 1B) and during 5 min all the displayed behavioural activity was videotaped. At a later time, behaviours were measured by an observer operating a digital counting device, which displayed counts at a rate of about 2 counts per s. The following variables were measured, (i) exploration score (exploratory activity displayed by the animal in any arm). The following behaviours were included in this score, (i.1) locomotion into any arm, sniffing to any side while the rat walks in or out the arm; (i.2) rearing on any wall or into the air during at least 2 s; (i.3) sniffing a localised spot in any arm for at least 2 s; and (i.4) head-dipping at the end of any arm for at least 2 s. The exploration score was considered an index of exploratory motivation [1,25,26]. (ii) Permanency score (stationary behaviour), all the non-exploratory activity displayed in any arm while the rat is stationary in some point of the arm. The following behaviours were included in this score, (ii.1) grooming for at least 2 s; (ii.2) resting immobilisation for at least 2 s; and (ii.3) sleeping. As already described elsewhere, the permanency score was considered an inverse index of emotionality [1,25,26].

2.5. General procedures

Animals were implanted with guide cannulas for microinjection into the ventral hippocampus, dorsal hippocampus or the medial nucleus accumbens. Rats rested 72 h before any experimental treatment was applied. After this recovery period, rats implanted into the hippocampus were subjected to the learning schedule, and rats implanted into the nucleus accumbens were subjected to the 5-min sessions of the APM. Once the experiments were finished, all rats were sacrificed with ether excess and their brains dissected for histological verification of sites of implant. Sites of microinjections for the hippocampus were restricted to CA_2–CA_4 region in the ventral or dorsal zone and were located at about the coronary plane of 3.2 mm caudal to bregma, referring to the Pellegrino's rat brain co-ordinates atlas [22]. Sites of microinjections for the nucleus accumbens

were restricted to the most ventral zone of the nucleus at about a coronary plane 3.2-mm rostral to bregma, referring to the Pellegrino's rat brain co-ordinates atlas [22].

2.6. Experimental schedule

The day of the experiment, implanted rats were gently microinjected into either the ventral, dorsal hippocampus or the nucleus accumbens with 1 μl of either saline solution (SAL), histamine antagonists or histamine antagonist and histamine, according to the injection schedule shown in Fig. 1(C). In the case of the avoidance response task experiments, animals were microinjected twice, one before trial 1 begins and secondly before trial 5 begins.

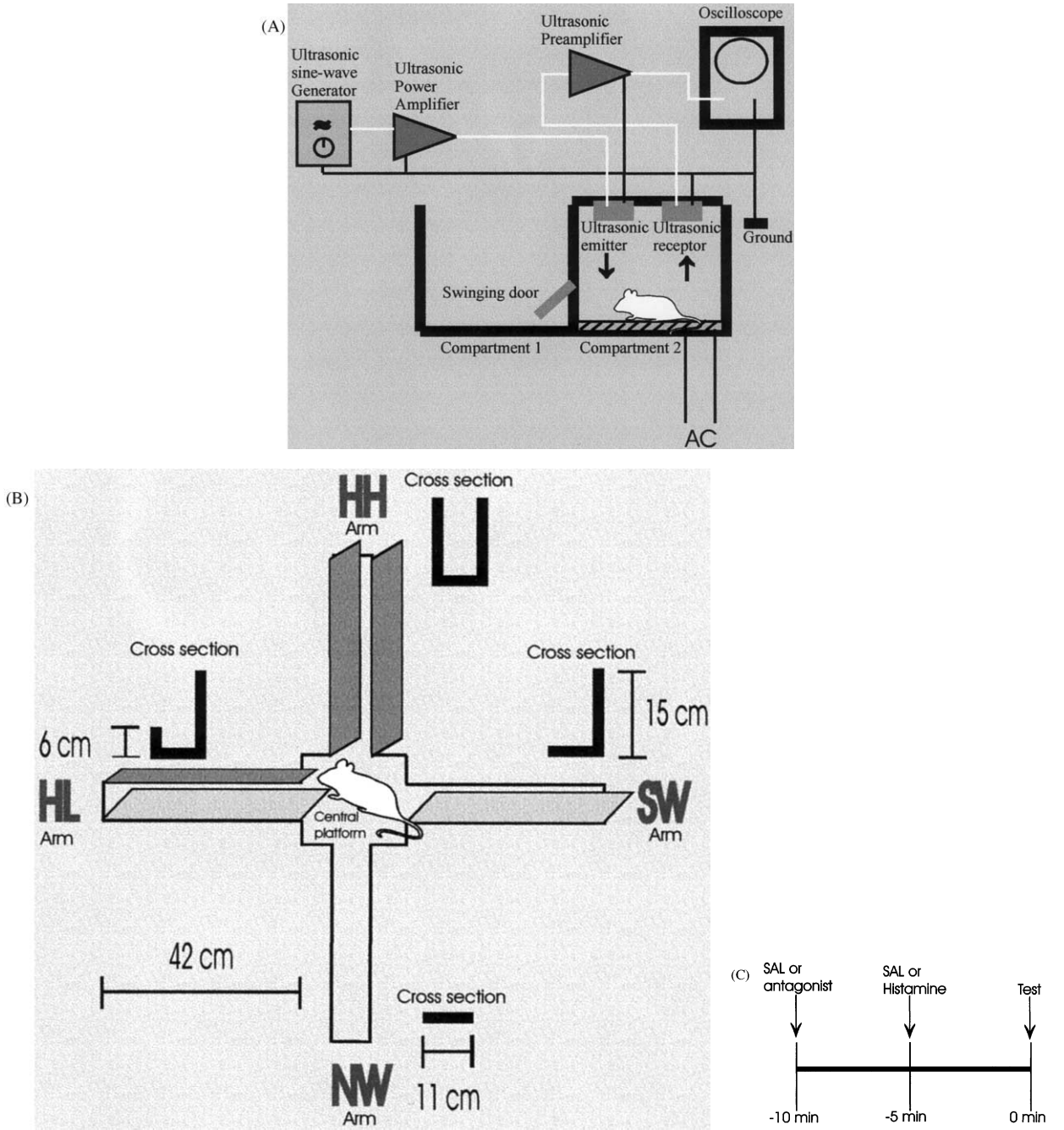

Fig. 1. Schematic drawing of the experimental approaches used for the study of the role of histamine on learning and motivation-emotionality processes in the rat. (A) Set-up for the acquisition of an active avoidance response. See text for details, and also references [2,4]. (B) Set-up for exploration in a conflictive environment in the elevated asymmetric plus-maze (APM). NW, no walls; SW, single wall; HL, a high and a low wall; HH, two high walls. Additional details in [26,25]. (C) Schedule for the administration of drugs into the hippocampus or the nucleus accumbens.

2.7. Experiments

Three experiments were performed.

2.7.1. Experiment 1: the effect of histamine and its receptor antagonists into ventral hippocampus on memory acquisition processes

The purpose of this experiment was to investigate the effect of localised histamine stimulation of the ventral hippocampus on the acquisition of the avoidance response to an ultrasonic tone. Dose of histamine was 45 nmol/μl. Dose for the histamine receptor antagonists was 67.7 nmol/μl. Saline microinjection (1 μl) was considered control.

2.7.2. Experiment 2: the effect of histamine into the dorsal hippocampus on memory acquisition processes

The purpose of this experiment was to investigate the possible action of histamine into the dorsal part of the hippocampus in relation to the acquisition of the avoidance response to the ultrasonic tone. Doses of histamine used were 9, 45 and 90 nmol/μl. Saline microinjection was considered control.

2.7.3. Experiment 3: the effect of histamine and histamine receptor antagonists into the nucleus accumbens on the behavioural activity displayed in a conflictive environment

The purpose of this experiment was to investigate the possible action of histamine into the nucleus accumbens on the behavioural expression displayed by rats subjected to a conflictive environment such as the APM. Doses of histamine were 9, 45 and 90 nmol/μl. Dose of the histamine receptor antagonists was 45 nmol/μl.

2.8. Statistical analysis

The non-parametric test of Dunn [9] was used for all multiple comparisons, since data were not normally distributed. $P < 0.05$ was considered statistically significant. All data are presented as the median $\pm$ standard error of the median (S.E.M.).

3. Results

3.1. Experiment 1

As shown in Fig. 2(A), the localised application of histamine into the ventral hippocampus increased significantly the latency time to show the avoidance response. Control rats typically showed a median of about 8 s, while histamine-treated rats showed a median value well over the 30 s limit for six consecutive trials (Fig. 2A). Eventually, histamine-treated rats had a latency time not different from control animals (trials 7 and 8). This inhibitory effect of histamine is blocked when Pyrilamine is administered 5 min before histamine (Fig. 2A). Interestingly, the application of Ranitidine in the same conditions did not modify the histamine effect. Examining carefully the 'Ranitidine + histamine' curve in trials 6–8, it was possible to observe that the inhibitory effect of histamine on the acquisition of the avoidance response was extended up to the end of the session (Fig. 2A). Considering the efficiency of learning (% CAR), histamine treatment significantly diminish the percentage of accumulated positive responses during training (Fig. 2 B). The histamine curve was displaced to the right reaching a median efficiency of about 40% at the end of the session. Pyrilamine treatment has a blocking effect on the histamine actions, since learning efficiency reached normal scores in trial 4 (Fig. 2B). The Ranitidine treatment not only was completely ineffective to counteract the histamine effects but it appeared to increase the inhibitory action of the imidazolamine since a median of 0% CAR at the end of the session was observed.

3.2. Experiment 2

The dorsal hippocampus appeared to be more sensitive to chemical stimulation than the ventral hippocampus, since it was necessary to increase up to three training sessions so that implanted rats reached a similar learning efficiency than rats bearing implants into the ventral hippocampus. Histamine treatment was not effective in modifying significantly the learning curve of rats (Fig. 2C).

3.3. Experiment 3

The exploration and emotional behavioural pattern of rats implanted into the nucleus accumbens and chemically stimulated with histamine is shown in Fig. 3. Control rats showed a higher exploration score in the HL and HH walls (about 80 counts per 5 min, Fig. 3A). Less exploratory activity was associated with the SW arm (about 50 counts per 5 min) and even less in the NW arm. Histamine treatment significantly increased the exploratory activity in the NW and also in the SW arm (Fig. 3A). No effect or an inconsistent effect was found in the other APM arms. Regarding the emotionality-related index (permanency score), control rats showed the greatest value in the HH arm (Fig. 3B). The histamine treatment did not affect this score in the NW and SW arms but significantly decreased the permanency in the HL and HH arms (Fig. 3B). When the histamine-receptor antagonists (PYR and RAN) were microinjected 5 min before the histamine treatment, both were effective to block the 45 nmol histamine effects on exploration of the NW and HH arms (Fig. 4A). Also both histamine-receptor antagonists blocked

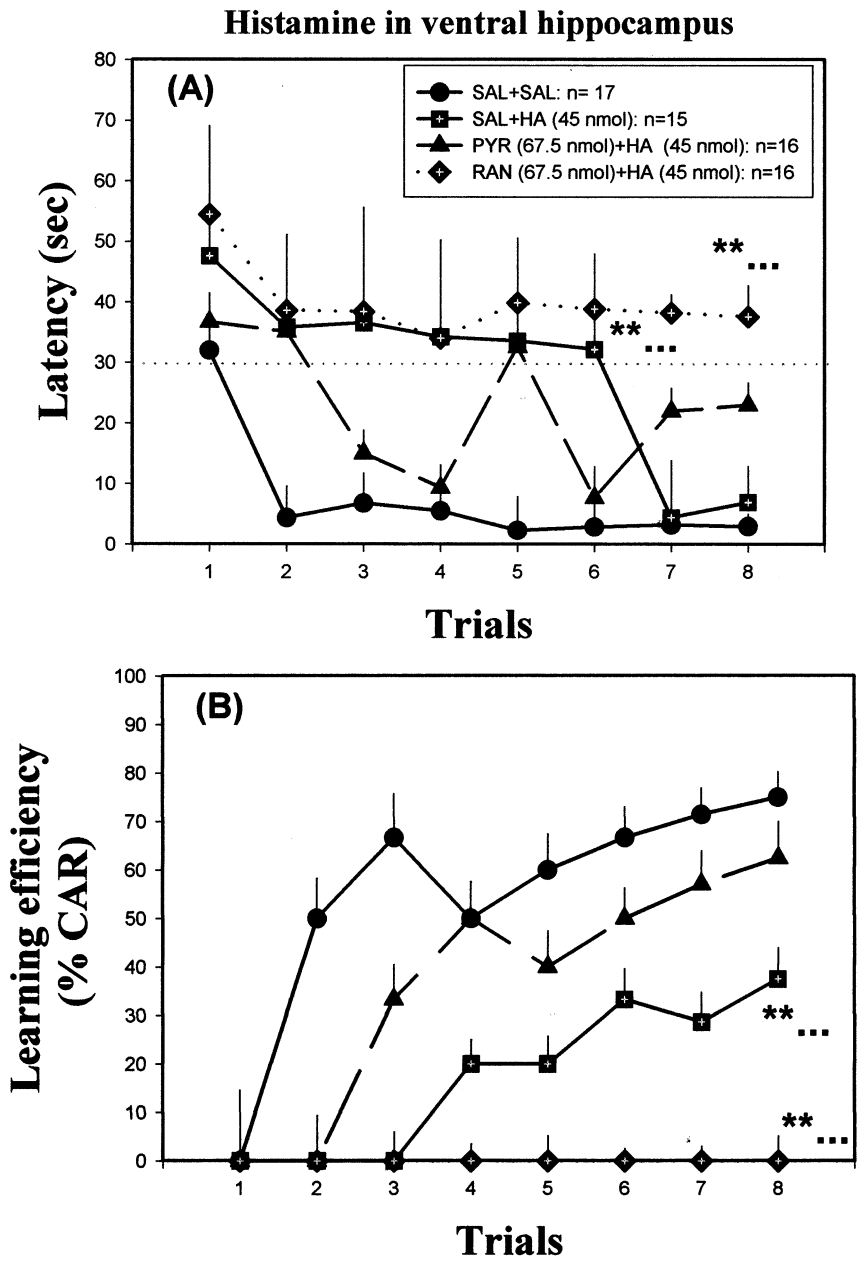

Fig. 2. Acquisition of an active avoidance response to an ultrasonic tone of 40 kHz in hippocampal implanted rats microinjected with histamine and histamine receptor antagonists. (A) and (B) are from the same group of rats. **, $P < 0.01$ compared with SAL + SAL curve, except trial 1 where there was no difference.

the decrease in permanency observed in the HL arm. Nevertheless, nor PYR or RAN were able to counteract the histamine effect on the HH arm (Fig. 4B).

4. Discussion

It is known that histamine synthesising neurons appear to be concentrated in the posterior hypothalamus of the rat brain, projecting its fibers to different brain structures such as the hippocampus and the nucleus accumbens [16,32]. It should be expected that histamine fibers reaching these neuronal zones should exert some type of physiological control. Present data give some support to this idea. As shown in Fig. 2(A) and (B), the localised application of histamine into the ventral hippocampus (Experiment 1) was able to interfere the acquisition phase of the avoidance response. Consequently, learning efficiency was impaired (Fig. 2B). This is not a surprising result, it is known that histamine locally applied into the ventral hippocampus inhibits the evocation of the avoidance response [2,4]. This interfering action of histamine in the hippocampal neurons appears to be mediated by H_1-histamine receptors

[4]. Data from Fig. 2(A) and (B) are in agreement with earlier findings [2,3]. A less clear picture is obtained regarding the possible participation of the hippocampal H_2-histamine receptors. The H_2-histamine receptors appear to exert some type of modulating effect on the inhibitory action of the H_1-histamine receptor activity, since the selective blocking by Ranitidine appears to enhance the histamine actions on the hippocampal H_1-histamine receptors (Fig. 2A, B). Data from Fig. 2(A) and (B) strongly suggest that histamine might be an endogenous hippocampal regulator in the learning processes in the brain. However, the histamine role in the hippocampus is far from being definitively established. As shown in Fig. 2(C), the localised application of histamine into the same neuronal area (CA_1–CA_4) but in the dorsal part of the hippocampus showed a different result (Experiment 2). In general, histamine was not effective in modifying the learning efficiency. It is known that the hippocampal structure is not functionally regular along its axis [13] and for the case of cholinergic-, noradrenaline- and serotonin-neurons a gradient increasing from dorsal to ventral hippocampus have been described [14,17,18]. Perhaps a decreased histamine receptor neurons in this hippocampal zone can be an explanation for these results. New experiments are being performed in our laboratory to further study this problem.

The second point of interest in our laboratory is centred on the possible role of histamine on the motivational mechanisms of the brain. Although the term 'motivation' has been restricted usually to those brain processes that recognise sex, food or thirst as primary stimuli, there is evidence also that the brain is able to incorporate some other sensorial stimuli [6,7,15,19,24–26]. In a wider context, motivation can be viewed as a brain mechanism processing incentive stimuli originated from the environment in such a way that behavioural patterns of approach, rejection or indifference to the stimuli are produced if the 'environmental clues' are 'motivating' or not. However, it should be quite simplistic to consider that only this factor regulates exploration induced by a novel environment. When something from the environment represents some risk to the animal, the so called 'conflictive environment', fear plays an important role in the final behavioural pattern showed by the animal [1,26]. Then, it is possible to speculate that exploration of a conflictive novel environment is governed by motivation and fear (emotionality). We have considered that the APM is an appropriated experimental approach to simulate a conflictive environment. Since maze arms are asymmetric, the apparatus gives to rat a graduated motivating (or fearful) stimuli spectrum (Fig. 1B). Restricting observations to only those behavioural patterns related to exploration and emotionality (fear), a better characterisation of these brain mechanisms has been assumed. The nucleus accumbens has been implicated in motivational processes [5,8,21,24,27,28,30,34] and Experiment 3 of the present study intends to evaluate the role of histamine in this nucleus. Results show that control animals view NW and SW arms as highly fear-inducing stimuli (Fig. 3B). However, since rats did perform

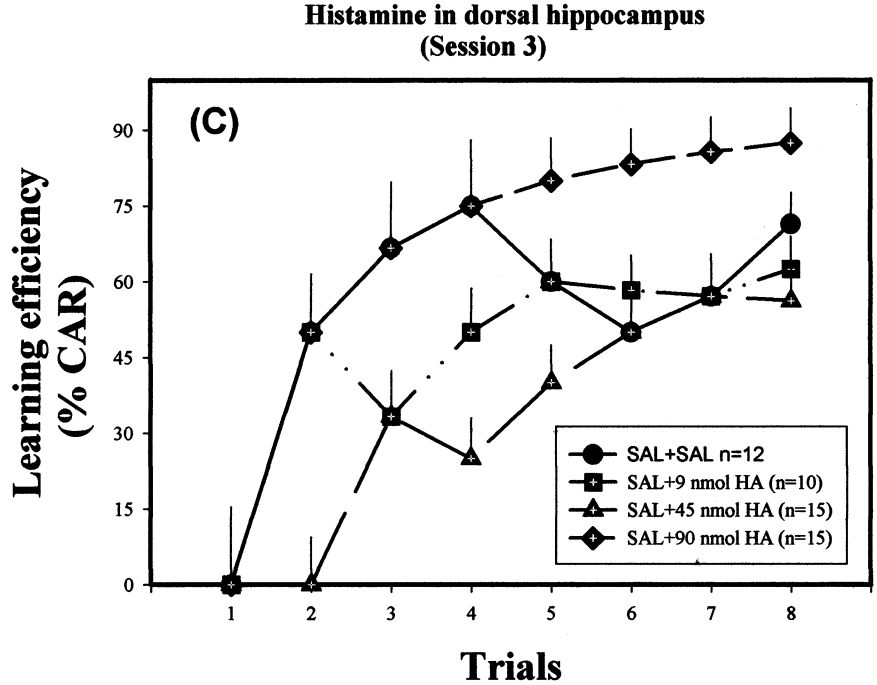

Fig. 2. (*Continued*)

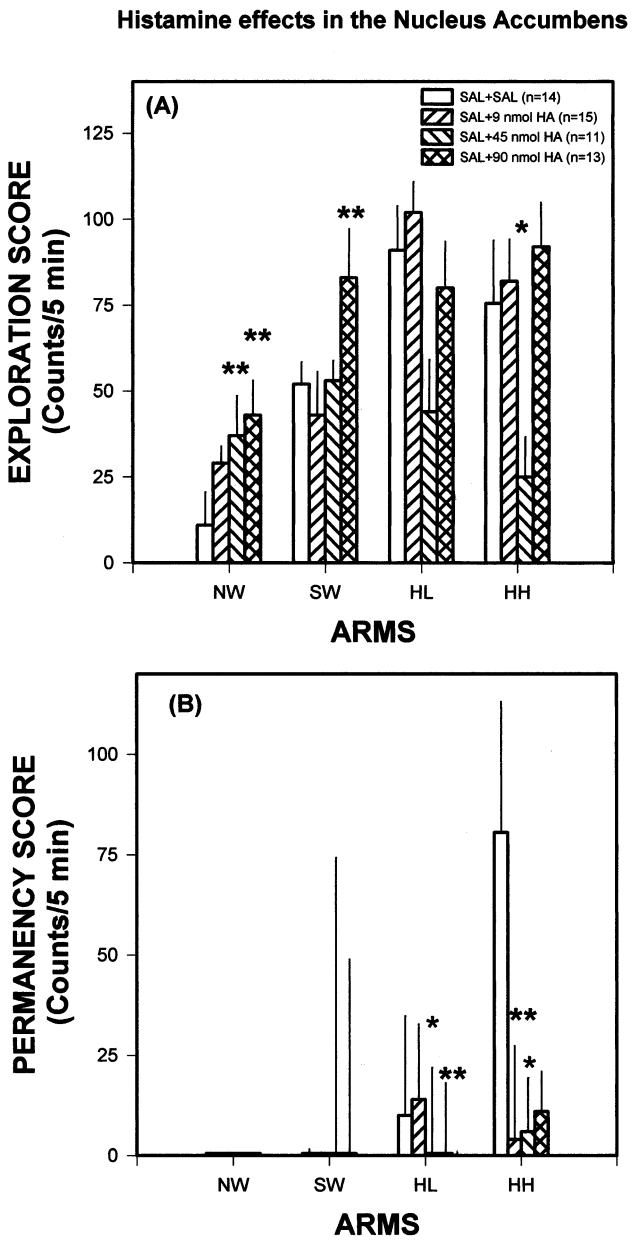

Fig. 3. Exploration and emotionality in the nucleus accumbens-implanted rats microinjected with histamine. *, $P < 0.05$ compared with the SAL + SAL group. **, $P < 0.01$ compared with the SAL + SAL group. Additional details, see [21].

exploration (Fig. 3A), this evidence suggest that at the same time these arms are considered 'attractive'. The histamine treatment increased exploration in these arms with no apparent change in the permanency score. These data can be interpreted as the imidazolamine in the nucleus accumbens increasing motivation. It is unlikely that histamine has some 'anxiolytic' effect and because of this, exploration is increased in the NW and SW arms. The imidazolamine clearly increased the emotionality since permanency was decreased in the less fear-inducing arms (HL and HH arms). Inspection of results shown in Fig. 4, reveals that the facilitating effect of histamine on exploration is mediated by H_1- and H_2-histamine receptors. However, the decreased permanency score observed for the HH arm in the histamine-treated rats, can not be explained by this mechanism, since the histamine antagonists were not able to block the histamine action.

As concluding remarks, the evidence presented in this study support the view about histamine as neuromodulating substance in the brain. Also, in the complex processes such as cognition and motivation-emotionality, which involve at least the hippocampus or the nucleus accumbens, histamine appears to fulfill a physi-

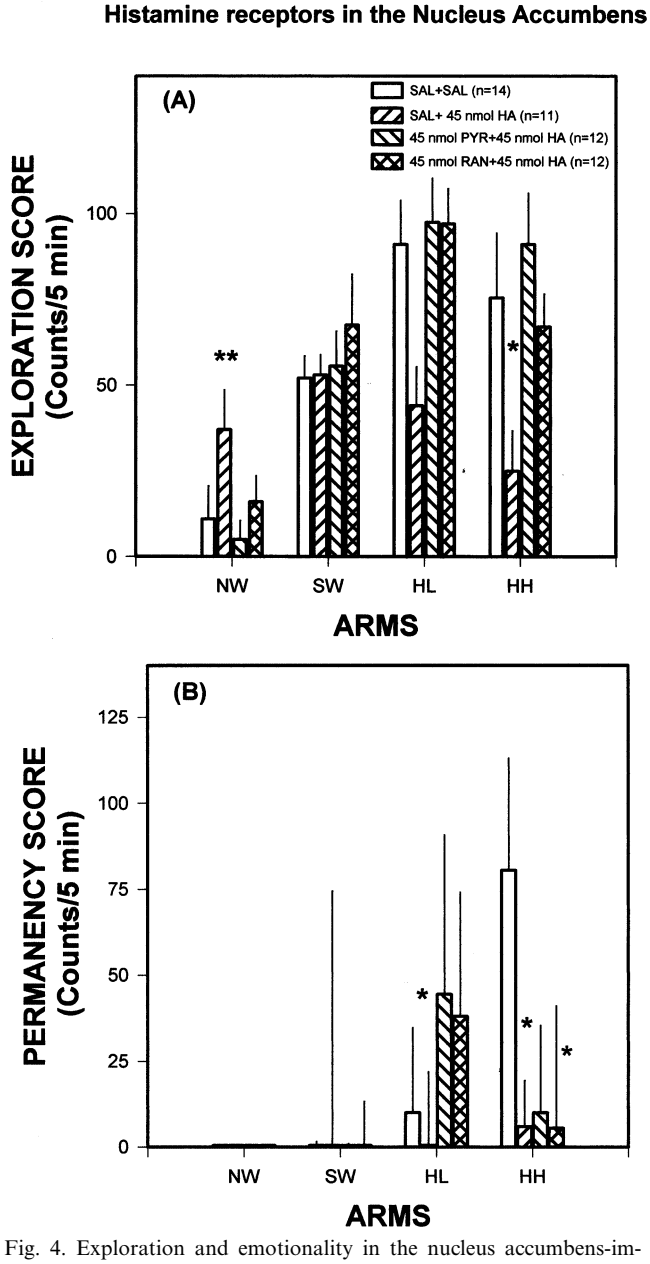

Fig. 4. Exploration and emotionality in the nucleus accumbens-implanted rats microinjected with histamine and histamine receptor antagonists. *, $P < 0.05$ compared with control (SAL + SAL group). **, $P < 0.01$ compared with control. Additional details in [21].

ological role. It is expected that future research will help to consolidate or modify these concepts.

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