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Sex Differences in Memory Performance in the Object Recognition Test. Possible Role of Histamine Receptors

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GHI P., M. ORSETTI, S. RICCI GAMALERO AND C. FERRETTI. *Sex differences in memory performance in the object recognition test. Possible role of histamine receptors.* PHARMACOL BIOCHEM BEHAV **64**(4) 761–766, 1999.—The mnemonic performances of male and female rats were compared in an object recognition test. Females were still able to recognize a previously identified object after a 90-min between-trial interval, compared with only 60 min in the males. Because histamine (HA) involvement in memory processes has been strongly suggested, the effect of H3-HA autoreceptor antagonist thioperamide was investigated. This drug was found to produce a dose-dependent promnestic effect in both sexes, but it did not influence the time course of memory retrieval. These behavioral data were compared to the density of H1-HA, H2-HA, and H3-HA receptors in cortical membranes. The densities of H1-HA and H2-HA receptors were greater in the females, whereas that of H3-HA was substantially the same in both sexes. The behavioral effect of thioperamide was very similar in both sexes, and this agrees with a similar H3-HA receptor density; however a better memory performance might have been expected in the female after thioperamide treatment (in view of different H1-HA and H2-HA receptor density), but this was not found. Because thioperamide has also been demonstrated to influence the acetylcholine release, its possible role in regulating the cholinergic memory effect was investigated. The scopolamine-reduced visual retrieval was antagonized by thioperamide in a similar way in both sexes. In conclusion, these data have shown a better performance of the female in a visual memory test, but this behavioral difference could not be affected by an H3-HA receptor-dependent manipulation of histaminergic and cholinergic systems. © 1999 Elsevier Science Inc.

Memory Sex differences Object recognition test Histamine receptors

HISTAMINE (HA) is a neurotransmitter or neuromodulator (1). Histaminergic neurons in the mammalian brain are located in the tuberomamillary nucleus of the posterior hypothalamus, and send projections to different forebrain areas, i.e, cortex and hippocampus (34,35). HA exerts its neurotransmission effects by interacting with both the postsynaptic H1-HA and H2-HA receptors and the presynaptic H3-HA autoreceptor (29).

Consistent with its wide-ranging output, the histaminergic neuron system regulates various activities of the brain, such as the arousal state, thermoregulation, circadian rhythm, neuroendocrine and locomotor activity, feeding, drinking, sexual behavior, and analgesia (36). Recent evidence has also revealed that endogenous HA plays an important role in learning and memory (6,33).

The central cholinergic system is the one mainly involved in modulating cognition, but complex interactions between cholinergic and histaminergic systems in brain areas involved in learning and memory processes are suggested by pharmacological and biochemical evidences. This interaction seems mainly due to the hypothalamic and cortical H3-HA receptors. Systemic or intracerebroventricular injections of HA or HA agonists or antagonists have been shown to modulate extracellular cortical and hippocampal acetylcholine levels (2,26), and different behavioral performances (19,24,25) through the H3-HA receptors. The cognitive performance of rats in object recognition and passive avoidance tasks is strongly impaired by the H3-HA agonists IMETIT and R-(−)-α-methyl-histamine (2). Accordingly, procognitive effects of the H3-HA antagonist theoperamide have been de-

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scribed both in olfactory–social memory and passive avoidance paradigms (24).

Substantial differences in cognitive function between men and women have been recognized for well over 50 years, and there is increasing evidence that fluctuations in sex hormones in both men and women are associated with changes in cognitive pattern (17). Women excel in an object location memory test. This observation is of interest in studying the role of HA in cognitive processes, because it is also well known that H1-HA and H2-HA receptors number is greater in female than in male rats (11,30), while a sex difference in H3-HA receptor number has not yet been investigated.

In the present study, sexual differences in memory performances has been evaluated, using the object recognition test, to verify the hypothesis that HA release (induced through an H3-HA autoreceptor antagonism) plays a role in these processes. The data have been correlated to the H3-HA receptor number present in cortical areas of rats of both sexes. Last, the possibility that thioperamide could influence memory processes, by acting on H3-HA heteroreceptors located on cholinergic neurons, has been examined by administration of thioperamide alone or in association with the antimuscarinic compound scopolamine.

METHODS

Animals

Male and female Wistar rats (Charles River Italy, Calco, Lecco), 40 days old, housed under controlled temperature (23 ± 1°C), relative humidity (55–65%), and lighting conditions (12 D:12 L cycle), were divided into two groups for biochemical and behavioral tests, respectively.

Before behavioral testing, each rat was handled and placed in a unfamiliar cage for 2 min and this procedure was repeated daily for at least 1 week. To minimize circadian rhythm influences, all behavioral tests were conducted between 0900 and 1300 h. In the time course experiments male and female rats were divided into five groups (n = 8–18), and after the first object recognition trial, they were submitted to a second such trial 30, 60, 90, or 120 min later. In a second experiment, three groups of male and female rats were submitted to a first object recognition trial. Forty minutes before the second trail, rats were injected intraperitoneally with 0.7 mg/kg, 2 mg/kg, and 5 mg/kg thioperamide. The interval between the first and second trial in this experiment was kept at 90 min for males and 120 min for females, a time at which no significant memory retention was found, respectively, in the two sexes.

To test the effect of thioperamide on scopolamine-induced amnesia, groups of male (n = 8–18) and female (n = 8–18) rats were submitted to a first-object recognition trial, and 40 min before the second trail, they were injected intraperitoneally with either 0.5 mg/kg scopolamine, 2 mg/kg thioperamide, or scoploamine together with thioperamide. The second trial was conducted at an intertrial time at which retention of memory was still significant and scopolamine could, therefore, induce amnesia. These intertrial times were of 60 min for males and 120 for females, respectively.

Behavioral Task

Object recognition. A two-arm maze was placed in a sound-isolated room equipped with constant illumination (a 60-W lamp located 150 cm above the center of the maze). The experiment consisted of two trials separated by different retention time intervals. The objects to be discriminated were glass bottles and metal boxes that were too heavy to be displaced by a rat. In the first trial, two identical objects were placed at the ends of the two arms and the rats were placed in the middle of the maze, their heads oriented in the opposite direction to the objects. They were allowed to explore the maze for 12 min. During the second trial, one object was replaced by a different one, and the animals were allowed to explore the maze for 8 min under the same conditions as in the first trial. The number of visits and the duration of exploration of each object were recorded. From rat to rat, the nature of the two objects used during the test, whether familiar or novel, was randomized and counterbalanced. The position of the novel stimulus was at the left of the starting place for half the rats and at the right for the other half. The objects and the maze were cleaned, after testing each animal to eliminate olfactory stimuli.

H3-HA Receptor Binding Assay

[3H]*N*-α-Methyl-histamine binding was determined according to Korte et al. (18) with minor modifications. Tissues were homogenized in 40 vol (w/v) of cold 50 mM Tris HCl buffer, pH 7.4, using a Teflon glass potter homogenizer. Homogenates were centrifuged at 1000 × g × 15 min, and the supernatants spun at 40,000 × g × 15 min. The pellet of the second centrifugation was resuspended in cold Tris-HCl, pH 7.4. A 300-μl aliquot of the particulate fraction (about 500 μg protein) was incubated for 30 min at 37°C in the presence or absence of 5 μM thioperamide (Cookson Chemicals Ltd., UK). The incubation was started by addition of 50 μl of the same buffer containing 0.15–3.00 nM [^{3}H]-N-α methyl-histamine (specific. activity 2960 GBq/mmol, NEN DuPont) and ended by the addition of 5 ml cold Tris-HCl buffer and rapid filtration under vacuum on AAWP Millipore filters (0.8-μm pore size). The tubes were rinsed with 5 ml cold buffer and filters were washed twice with 5 ml of the same buffer. The radioactivity retained on the filters was measured with a liquid scintillation counter at 45% efficiency.

Saturable binding was calculated as the difference between total and nonspecific binding obtained in the presence of 5 μM thioperamide. Receptor density (B_{max}, pmol/g proteins) and affinity (K_d nM) values were obtained by Scatchard analysis of the saturation curves provided by the cortices of two or more animals.

H2-HA Receptor Binding Assay

[3H]-HA binding was determined according to the procedure of Barbin et al. (1), with minor modifications. Tissues were homogenized with a Teflon glass Potter-type homogenizer in 30 vol (w/v) of cold 50 mM Tris-HCl buffer, pH 7.4. Homogenates were centrifuged at 1000 × g for 10 min and the supernatants spun at 15,000 × g for 25 min. The pellet of the second centrifugation was resuspended in cold Tris-HCl containing 50 mM NaCl. A 300-μl aliquot of the particulate fraction (containing 500 μg protein) was preincubated for 15 min at 30°C. Incubation was started by addition of 150 μl of the same buffer containing 1–10 nM [^{3}H]-HA (specific activity, 1185 GBq/mmol, Amersham, Buckinghamshire, UK) and 5 μM unlabeled HA. Incubation was ended after 15 min at 30°C by the addition of 3 ml cold Tris-HCl buffer and rapid filtration under vacuum on AAWP Millipore filters (0.8-μm pore size, Millipore, Bedford, MA). Tubes were rinsed with 5 ml

cold buffer, and filters were washed twice with 10 ml of the same buffer. Saturable binding of the [^{3}H]-HA was calculated as the difference between total and nonspecific binding obtained in presence of 5 μM unlabeled HA.

H1-HA Receptor Binding Assay

[^{3}H]-mepyramine (specific activity 1110 GBq/mmol, Amersham, Buckinghamshire, UK) was determined according to Chang et al. (4). Incubation was carried out at 25°C for 40 min, and ended by rapid filtration under vacuum on Whatman GF/B glass fiber filters. Specific binding was determined in the presence of 2 μM triprolidine.

The linearity of all Scatchard plots was confirmed by Hill analysis, and pointed to the presence of a single binding site. Protein values were calculated according to Lowry et al. (20) with bovine albumin serum as standard.

Statistics

Behavioral data were analyzed by a three-factor, mixed-designed analysis of variance (ANOVA). To test significance of memory performance at different experimental times, the between factors were intertrial delay (four levels) and sex (two levels), while, in experiments employing drugs, the between factors were sex (two levels) and treatment (four to two levels).

In all experiments the within factor was the nature of the object (two levels, novel and familiar). The significance of specific effects was tested by contrast analysis (Fisher test) and post hoc 2 × 2 comparisons were performed by Newman–Keuls test (NK), when appropriate. Significance of binding data was tested by Student's *t*-test. In all cases a value of $p < 0.05$ was considered to be significant.

Animal Care

Procedures involving animals and their care were conducted in accordance with out institution's guidelines, which conform to national and international laws and policies (EEC Council directive 86/609, OJL 358, 1 December 12, 1987: NIH Guide for Care and Use of Laboratory Animals, NIH Publication No. 85-23, 1985).

Drugs

Thioperamide maleate (Tocris Cookson Ltd.) was dissolved in HCl 1 N, diluted and adjusted to pH 7.00 with sodium bicarbonate. Scopolamine hydrochloride (Sigma Chemical Co.) were dissolved in 0.9% w/v saline.

RESULTS

Our work has shown a sex difference in memory performance, as measured by the object discrimination test, which was found to depend on the intertrial interval, as indicated below. Male rats spent more time in exploring the novel object than the familiar when the interval between the first and the second trial was either 30 or 60 min ($p < 0.05$ by NK test), but this difference could not be observed at intervals of 90 to 120 min. In female rats there was a different exploration time for a new object compared to familiar one, at intervals of 30, 60, and 90 min (all showing values of $p < 0.05$ by NK test), but not at intervals of 120 min. This sex difference was also confirmed by contrast analysis of the interaction of delay × sex, from which a significant difference in the exploration time at 90 min was evident, $F(1, 72) = 12.12$, $p < 0.001$, while no differences were observed at 30, 60, and 120 min, respectively (Fig. 1).

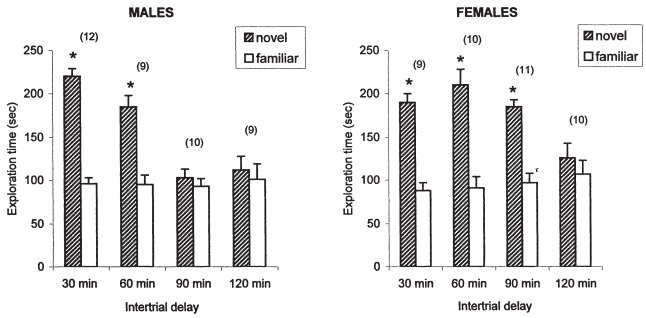

FIG. 1. Effect of different intertrial delays on object discrimination in male and female rats. The time spent by rats in exploring the novel and familiar objects during the second trial is reported. Number of rats are enclosed in brackets. Data are the means ± SEM. $p < 0.05$ by ANOVA and Newman–Keuls tests; familiar vs. novel object.

To examine the effect of thioperamide on memory performance, 0.7, 2, and 5 mg/kg thioperamide were injected intraperitoneally 40 min prior to the second trial. The interval between the first and second trial was kept constant at 90 min in the male and at 120 min in the female, respectively. Thioperamide (0.7 mg/kg) had no effect in both sexes; conversely, 2 and 5 mg/kg thioperamide increased exploration time in both males, $F(1, 85) = 15{,}24$ $p < 0.01$, and $F(1, 85) = 22{,}9$ $p < 0.001$; (ANOVA test) and females, $F(1, 85) = 15{,}24$ $p < 0.001$, and $F(1, 85) = 10.1$ $p < 0.002$ (ANOVA test). Testing for significant differences by contrast analysis [2 (sex) × 4 (treatments) × 2 (objects)] also showed no sex interaction in the thioperamide-enhanced visual recognition memory, in the same range of doses (Fig. 2).

To verify a possible antagonism of thioperamide on the scopolamine-induced amnestic effect, 0.5 mg/kg scopolamine was injected intraperitoneally, either alone or together with 2 mg/kg thioperamide, 40 min prior to the second trial. In this case, the exploration time was measured at a time when the retention of visual memory was still present: i.e., at 60 min of intertrial delay for males and at 90 min for females.

Scopolamine-induced amnesia in rats of both sexes, as expected [male, $F(1, 74) = 10.16$ $p < 0.002$; female, $F(1, 74) =$

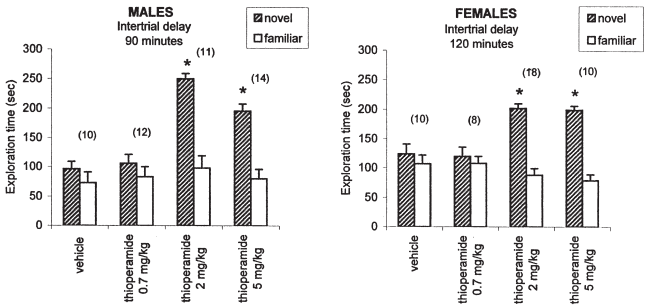

FIG. 2. Effect of three doses of the histamine H3 receptor antagonist thioperamide on visual recognition memory when it was injected IP 40 min prior to the beginning of the second trial in male and female rats. Number of rats are enclosed in brackets. Data were the means ± SEM. $p < 0.05$ by ANOVA and Newman–Keuls tests; familiar vs. novel object.

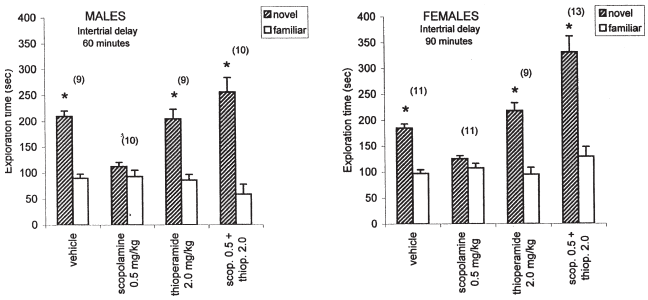

FIG. 3. Effect of visual recognition memory of scopolamine, thioperamide, and scopolamine plus thioperamide in male and female rats. Both drugs were injected IP 40 min prior to the beginning of the second trial. Number of rats are enclosed in brackets. Data were the means ± SEM. $p < 0.05$ by ANOVA and Newman–Keuls tests; familiar vs. novel object.

4.37, $p < 0.04$; ANOVA test; scopolamine vs. vehicle]. At this intertrial interval thioperamide alone had no effect on memory retention in rats of either sex. However, this drug could completely antagonize the scopolamine-induced amnesia in male, $F(1, 74) = 8.32$, $p < 0.005$, and female rats, $F(1, 74) = 13.1$ $p < 0.001$, as shown by contrast analysis. However, here again, no sex difference was found in drugs interaction (Fig. 3).

[^{3}H]*N*-α-methyl HA, [^{3}H]-HA, and [^{3}H]-mepyramine binding constants from cortical membrane preparations of 60-day-old males and females, representing the H3-HA, H2-HA, and H1-HA receptor binding sites, respectively, are summarized in Table 1. No significant differences in H3-HA binding site density and affinity were observed, whereas H1-HA and H2-HA binding density showed significant increases in the females (both $p < 0.05$, Student's *t*-test).

DISCUSSION

Many studies have illustrated typical cognitive differences between men and women. Men, in fact, appear to excel in mathematical reasoning (3,21) and perception of the horizontal (13,15), whereas women have a better verbal memory (32) and larger color vocabularies (14), and have also been shown to shine in object location memory tests (31). These findings have stimulated further investigation with animal models that reproduce human behavioral performances and enable a more precise study to be made of the neurochemical phenomena responsible for the higher cognitive processes. In this work, the object recognition test has been employed, and a longer lasting memory retrieval in female than in male rats has been confirmed. The neurochemical basis for such sex differences has also been investigated, paying particular attention to the role of the central HA system in these processes. Previous works have demonstrated the marked effect exerted by the sex steroid hormones on mood, including protection against depression and onset of schizophrenia and Alzheimer's disease in women (9). Fink et al. (9), in particular, have illustrated the ability of estrogens to boost the expression of the 5-HT_{2A} receptor genes and increase their density on the cortex, which is well known to be associated with emotional and mnemonic/cognitive functions in both humans and rats. The histaminergic system, whose involvement in learning and memory processes is demonstrated by a growing body of evidence, displays also significant sex-linked differences in receptor density for the postsynaptic sites H1-HA and H2-HA (10). The ontogenetic development of the H1-HA and H2-HA sites has also been shown to be under estrogenic control (11,30), and it is certain that estrogens exert a deep modulatory effect in the mammalian brain by piloting formation of the neuronal pathways during fetal life, as well as by controlling the activity of the existing neuronal circuits in the adult (22,23). As shown by other workers, alteration of central HA levels influences a rat's cognitive performance. HA reduction induced by α-fluoromethylhistidine, a histidine decarboxylase inhibitor, damages the acquisition and recall of active avoidance responses (16), whereas treatment with the histaminergic precursor histidine offsets the scopolamine-induced acquisition deficit in the elevated plus-maze test in mice (25). Because the concentration of HA within the CNS seems to be crucial in various behavior expressions, one would anticipate that a blockade of the H3-HA autoreceptors may, by increasing the release and the availability of synaptic HA, potentiates the postsynaptic effects of HA interacting with H1-HA and H2-HA receptors. Experiments designed to verify this hypothesis have, in fact, demonstrated the promnestic efficacy of the H3-HA antagonist thioperamide in four behavioral tasks: namely passive avoidance response (24), social memory in rats (28), habituation of exploratory activity (12), and the staircase maze (27). In agreement with these findings, the postacquisition administration of thioperamide has now been showed to prolonge the retention interval in both sexes, suggesting that this drug improves retrieval. The fact that it acts at the same doses and that it maintains the same temporal profile in the memory retention in both sexes, agrees with our binding results showing equal H3-HA receptor density and affinity in both sexes. However, the finding that the effect

TABLE 1

HISTAMINE RECEPTOR DENSITY AND AFFINITY IN CORTEX OF MALE AND FEMALE RATS

Receptor Subtypes (ligand)	Male		Female	
	B_{max} (pmol/g•prot)	K_d (nM)	B_{max} (pmol/g•prot)	K_d (nM)
H1 ([^{3}H]-mepyramine)	43.76 ± 2.12	5.78 ± 1.84	103.27 ± 0.72*	5.64 ± 0.33
H2 ([^{3}H]-histamine)	38.26 ± 5.66	4.58 ± 1.46	74.12 ± 6.23*	9.57 ± 5.20
H3 ([^{3}H]-*N*-α-methtyl-HA)	87.07 ± 9.07	0.50 ± 0.07	90.29 ± 9.97	0.67 ± 0.07

Data are the means ± SD, $n = 3$; $p > 0.01$ vs. male rats (Student's *t*-test).

of thioperamide in object recognition was qualitatively and quantitively equal in the two sexes disagrees with the H1-HA and H2-HA receptor kinetics. Because these receptors are more numerous in females, thioperamide should have augmented the difference in behavior between the sexes by strengthening the HA's postsynaptic effect. It is, thus, most unlikely that H3-HA–mediated variations in HA release can by themselves explain the results obtained with thioperamide in these present experiments.

There is the evidence that thioperamide increases the release of acetylcholine in a dose-dependent manner (5), and that the agonists H3 IMETIT and R-(−)-α-methyl-HA reduce its release in rat cortex slices. The action of this drug on cognitive performance could, therefore, be due to interference with the cholinergic system. Further support for this view comes from the observation that thioperamide offsets scopolamine-induced amnesia (25) and improves the performance of the senescence-accelerated rats only in repeated passive-avoidance tests, because their learning capacity and memory are impaired by comparison with normal animals of the same chronological age. The passive-avoidance response and object recognition are known to be damaged by the administration of cholinergic antagonists (7). Our data also confirm the amnestic action of scopolamine in visual recognition memory in both sexes. The amnesia thus caused is effectively countered by the simultaneous administration of thioperamide. Thus, it may be supposed that this drug inhibits the presynaptic H3-HA heteroreceptors on the terminals of the cholinergic neurons, resulting in an augmented acetylcholine release sufficient to overcome the effect of the antagonist and restore cognitive efficiency (5).

In conclusion, or data provide a further illustration of a significant sex difference in visual recognition memory in the rat. This difference does not appear to be due to sex-specific differences in the H1-HA and H2-HA receptors. Even so, HA can certainly be included among the neurotransmitters that can modulate the main neurotransmission systems involved in mnemonic processes.

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