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Hypothalamic Histamine Release in Normal and Stressed Rats Is Affected by Sex and Aging

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FERRETTI, C., M. BLENGIO, P. GHI, T. ADAGE, P. PORTALEONE AND S. RICCI GAMALERO. *Hypothalamic histamine release in normal and stressed rats is affected by sex and aging.* PHARMACOL BIOCHEM BEHAV **59**(1) 255–260, 1998.—Changes in the baseline and in the 40 mM K^+-evoked release of histamine from hypothalamus slices were compared in male and female rats aged 2, 6, 12, 18, and 24 months. The baseline release declined in the 12-, 18-, and 24-month males. In contrast, the K^+-evoked release remained constant in the males, but in the females it decreased in animals more than 2 months old. The efficiency of the H_3 receptors was also determined by measuring the reduction of the K^+-evoked release induced by the H_3 receptor agonist (R)-alpha-methylhistamine. This substance significantly decreased the amount of HA released in all age groups, except the 24-month-old males. Histamine release was also measured after exposure to a weak electrical stress. In 2- and 6-month-old males, there was a marked reduction of both the baseline and the K^+-evoked release, and also of the inhibitory effect of the H_3 agonist. There were no changes in the 12- and 18-month age groups, but both releases were enhanced in the 24-month group. In females, electrical stress had no significant effect, except in the youngest age group. Stress-dependent release of plasma corticosterone was decreased in males older than 12 months and in females older than 6 months. These changes gave a good correlation with variation in the H_3 receptors. This study, therefore, demonstrates that aging modifies, in a sex-dependent way, the basal and stress-stimulated functions of the hypothalamic presynaptic histaminergic neurons. © 1998 Elsevier Science Inc.

Histamine release H_3 receptors Corticosterone Aging Foot shock stress Hypothalamus Sex (R)-alfa-methylhistamine

IT is now unequivocally established that histamine (HA) acts as a neurotransmitter in the brain. It regulates some neuroendocrine functions, in particular, corticosterone secretion following environmental stress, by modulating the secretion of ACTH at the hypothalamo–hypophyseal axis (4,10,14,20,31,35). Furthermore the sex steroid, estradiol, also affects the H_1 and H_2 receptors by modulating their ontogenetic development (9,34).

HA exerts its neurotransmission effects by interacting with the two postsynaptic (H_1 and H_2) and the presynaptic autoreceptor (H_3) (33). H_3 receptors have been characterized as a presynaptic autoreceptor that inhibits neuronal HA release and synthesis in the CNS (2,3). Recently it has also attracted much attention as a possible regulatory mediator of the release of other neurotransmitters (15,16,23,24,28,30).

The impairment of the main neurotransmission systems are well characterized during aging (1,12,22,27,32,36,37), while there is little information about this histaminergic system (21). It is therefore possible that it may either undergo functional variations, following the changes in steroid hormone secretion that occur during the menopause (38), or could be progressively unable to respond to stress. To assess the validity of this hypothesis, a study was undertaken to investigate the age-related changes in HA release by slices of hypothalamus from male and female rats. HA release was also investigated after application of a weak stress. This stress was induced by an electric foot shock, which significantly increases plasma corticosterone and the turnover of HA and modifies the affinity and the density of H_1 and H_2 receptors in the hypothalamus (4,10,19). Brain slices have been proven to be useful tools for the investigation of the electrophysiology of presynaptic neurons. Superfusion of brain slices with medium containing K^+ elicits changes in neuron spike amplitude and eletrochemical monoamine overflow responses that are re-

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coverable, dose dependent, reproducible, and $Ca^{2}+$ dependent (36). Furthermore, with regard to HA, this system allows accurate evaluation of neuronal HA release, because it eliminates the HA mast cell contamination present in other experimental systems (2) and provides information concerning the activity of the presynaptic neuron both at rest and when stimulated. Lastly, it also enables the functional efficiency of the H_3 autoreceptors to be assessed by measuring inhibition of the K^+-evoked release in the presence of a high-affinity agonist such as (R)-alpha-methylhistamine (Ra-HA) (2,3).

METHOD

Animals

Male and female rats of the Wistar–Kyoto strain (WKY), bred at Charles River Italy (Calco, Lecco), of various ages (2, 6, 12, 18, and 24 months) were housed under controlled temperature (23 ± 1°C), relative humidity (55–65%) and lighting (12 D: 12 L cycle) conditions.

Stress was induced by consecutive administration of an inescapable electric foot shock. Rats were individually placed in a shock-box and received a 1-s electrical foot shock (1 mA) five times consecutively, at 1-min intervals. Rats placed in the shock-box but not stressed were used as a control. Each experimental group was composed of eight animals. Rats were killed by decapitation 30 min after the last foot shock. Trunk blood was collected into tubes for determination of plasma corticosterone, and the brain was rapidly removed and dissected on a glass surface on ice.

HA Release

HA release was evaluated according to the method of Hill and Straw (13), with some minor modifications. Hypothalamic slices (250 × 250 μm), obtained from a pool of four rats, were prepared with a McIlwain tissue slicer and washed three times with 50 ml of a modified Krebs medium: 120 mM NaCl, 2 mM KCl, 2.6 mM $CaCl_2$, 0.7 mM $MgSO_4$, 1.2 mM KH_2PO_4, 27.5 mM $NaHCO_3$, 10 mM glucose, pH 7.5, oxygenated with 95% O_2 and 5% CO_2. Slices were transferred to 25 ml of a depolarizing Krebs medium containing 40 mM KCl and incubated at 37°C under an atmosphere of 95% O_2 and 5% CO_2 for three periods of 5 min (medium changed after each incubation), to stimulate the release of endogenous HA. Slices were then washed immediately with 50 ml of Krebs medium containing 2 mM KCl and resuspended in 2 ml of Krebs medium containing 100 μCi [^{3}H]-histidine (53 Ci/mmol Amersham Int, UK). After 40 min, the slices were washed three times with 25 ml Krebs medium and allowed to settle under gravity. Aliquots (100 μl) of the gravity packed suspension, corresponding to about 2 mg of protein, were incubated in the presence or absence of 1 μM Ra-HA (R.B.I., Natick, MA) in a final volume of 1 ml of Krebs medium.

The tubes were oxygenated with 95% O_2 and 5% CO_2, capped, and incubated at 37°C for 7 min before the addition of KCl at a final concentration of 2 mM for baseline release or 40 mM for K^+evoked and Ra-Ha inhibited release. Incubations were ended 7 min later by rapid centrifugation at 12000 × g × 30 s. Samples (800 μl) were added to ECONO columns, containing 0.5 ml Amberlite CG 50 resin (BIO-RAD, Segrate, MI), which had been equilibrated with 10 ml of 10 mM Tris/HCl pH 8.0, to separate [^{3}H]-HA from [^{3}H]-histidine, as described previously (3). The columns were washed sequentially with 40 ml of 10 mM Tris/HCl pH 8.0 and 20 ml 0.02 M HCl, to remove [^{3}H]-histidine. [^{3}H]-HA was finally eluted with 3 ml of 1 M HCl and tritium determined by liquid scintillation counting at 45% efficency. The contamination with [^{3}H]-histidine after ion-exchange separation was negligible. The data were adjusted using the recovery value for [^{3}H]-HA (about 70%) and by the pellet protein concentration, assayed by the method of Lowry et al. (17) with bovine serum albumine as standard.

Corticosterone Assay

The corticosterone was extracted from the plasma (0.1 ml) with diethyl-ether (1 ml). After vigorous shaking, the diethyl-ether was dried under a stream of nitrogen. The dried residue was taken up with 100 μl of 50 mM phosphate buffer containing 0.5% (w/v) NaN_3, 4 mM EDTA, 1% (w/v) BSA, pH 7.4. Corticosterone was determined by RIA using: 100 μl corticosterone standard (0.025–2.5 ng/tube, 50 μl [^{3}H]-corticosterone, corresponding to 8,000 dpm (84 Ci/mmol, Amersham, UK), and 50 μl corticosterone antiserum 3-CMO-BSA, diluted 1:1000 (UCB bioproduct, S.A Brain, Alleud Belgium). After overnight incubation at 4°C, 200 μl dextran (0.05% w/v) and activated charcoal (0.5% w/v) mixture were added to each tube. The contents were mixed for 15 s, allowed to stand for 15 min, and centrifuged at 1,000 × g for 15 min at 4°C. Finally, the supernatant was decanted and dissolved in 5 ml Picofluor (Packard, USA). The sensitivity of the assay was 10 pg/ml. The inter- and intraassay coefficients of variation were 11.2 and 2.2%, respectively.

Animal Care

Procedures involving animals and their care were conducted in accordance with our 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 the Care and Use of Laboratory Animals, NIH Publication No 85-23, 1985).

Statistics

The effect of aging on the baseline and K^+-evoked release of HA and on the action of Ra-HA was evaluated by one-way analysis of variance (ANOVA), followed, where necessary, by the Newman–Keuls test for multiple comparison of the means. Two-way ANOVA was used to assess the interaction between basal/K^+-evoked release, or between K^+-evoked/Ra-HA-inhibited release in relation to aging, sex, and stress. It was also employed to evaluate the interactions between baseline levels of corticosterone and those induced by stress, both between rats of different age and the same sex, and between those of the same age, but of different sex.

RESULTS

Changes in the baseline and 40 mM K^+-evoked HA release in the absence or presence of 1 μM Ra-HA in hypothalamus slices from rats of different age and sex are illustrated in Fig. 1. In males, the baseline release was significantly reduced in animals aged more than 6 months [one-way ANOVA, $F(4, 25) = 10.17, p < 0.01$]. In contrast, it was constant, in females, throughout aging. The difference between males and females of the same age was only significant ($p < 0.01$) for animals aged 2 months and 6 months [one-way ANOVA, $F(1, 10) = 39.8$, and $F(1, 10) = 35.5$, respectively] (Fig. 1).

When hypothalamic slices from male rats were incubated with a depolarizing concentration of 40 mM K^+, HA release was increased by a similar percentage in all groups with a

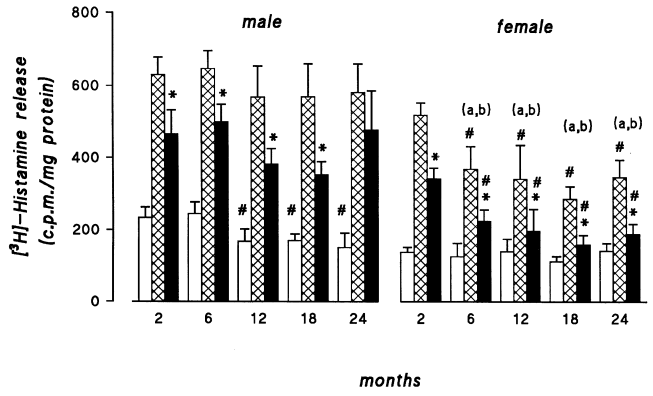

FIG. 1. HA release from hypothalamus slices from WKY rats of different ages and sex: baseline (open bar) and 40 mM K^+-evoked release in the presence (solid bar) or absence (crosshatched bar) 1 μM Ra-HA. *Significant differences in Ra-HA inhibition of the K^+-evoked release (one-way ANOVA and Newman–Keuls tests, $p < 0.05$). #Significant differences in the same type of release compared with the 2-month-old animals of the same sex (one-way ANOVA and Newman–Keuls tests; $p < 0.05$). [a]Significant interactions between variations in baseline release, K^+-evoked release, in function of age assessed against the 2-month-old animals of the same sex (two-way ANOVA, $p < 0.01$). [b]Significant interactions between variations of the baseline and the K^+-evoked release in function of sex, evaluated in the same-age groups (two-way ANOVA, $p < 0.01$). The data are expressed as the means ± SD of six replicates obtained from two independent experiments.

mean increase of 225% over baseline. In the 2-month-old females, this increase was 275%, whereas in older animals it declined to about 140% (Fig. 1). It can also be seen that this K^+-evoked release was significantly higher in males than in females. Last, stimulation of the H_3 autoreceptors by Ra-HA significantly reduced this increase in all groups, except the 24-month-old males.

To determine whether the inhibition of the K^+-evoked release by Ra-HA was due to its interaction with the H_3 autoreceptors, slices were incubated with 10 μM thioperamide, a selective H_3 antagonist. In all groups, there was complete antagonism by thioperamide on the action of Ra-HA, showing the full efficiency of the pharmacological response of the H_3 receptor (data not shown).

The findings were also subjected to two-way ANOVA to look for significant differences in relation to sex and aging. This showed an absence of any significant difference between 2-month and older males in the K^+-evoked release. In the same way, there were no appreciable differences between the Ra-HA-dependent decreases (Fig. 1). Alternatively, in the females there were significant reductions in the percentage increase of the K^+-evoked release between the 2-month and the older animals, whereas the percentage of Ra-HA inhibition showed no significant differences.

Lastly the existence of sex-dependent responses in the baseline, K^+evoked, and Ra-HA inhibited release in rats of the same age were assessed. Here the two-way ANOVA showed that, with the exception of the 2-month-old animals, the percentage increase in the K^+-evoked release was significantly less ($p < 0.01$) in the females, $F(1, 20) = 64.7$ for 6 months, $F(1, 20) = 12.5$ for 12 months, $F(1, 20) = 38.7$ for 18 months, and $F(1, 20) = 21.8$ for 24. There were no such sex-dependent percentage differences in Ra-HA inhibition.

In the second part of the experiment, comparisons were made of changes in HA release induced by a weak stress (electric foot shock, 1 mA/1 s, five times). In the 2-month-old animals (Fig. 2), the electric foot shock greatly lowered (by about 30%) the baseline and the K^+-evoked release in both sexes [one-way ANOVA, males: baseline, $F(1, 10) = 34.4$; K^+-evoked, $F(1, 10) = 14.9$; females: baseline, $F(1, 10) = 10.4$; K^+-evoked, $F(1, 10) = 26.2$; all $p < 0.01$]. However, foot shock also significantly reduced the percentage of K^+-evoked increases above the baselines [two-way ANOVA, males $F(1, 20) = 22.9$; females $F(1, 20) = 16.2$; all $p < 0.01$] and the percentages of Ra-HA inhibition of both male and female [males, $F(1, 20) = 4.40$; females, $F(1, 20) = 4.89$; all $p < 0.05$].

The same effects were particularly apparent in the 6-month-old males (Fig. 3). In contrast, in the females stress reduced the K^+-evoked release [one-way ANOVA, $F(1, 10) = 9.51$, $p < 0.05$], but had no effect on the baseline. Two-way ANOVA also showed that stress did not cause any significant differences in either the K^+-evoked increase or in the percentage of inhibition by Ra-HA.

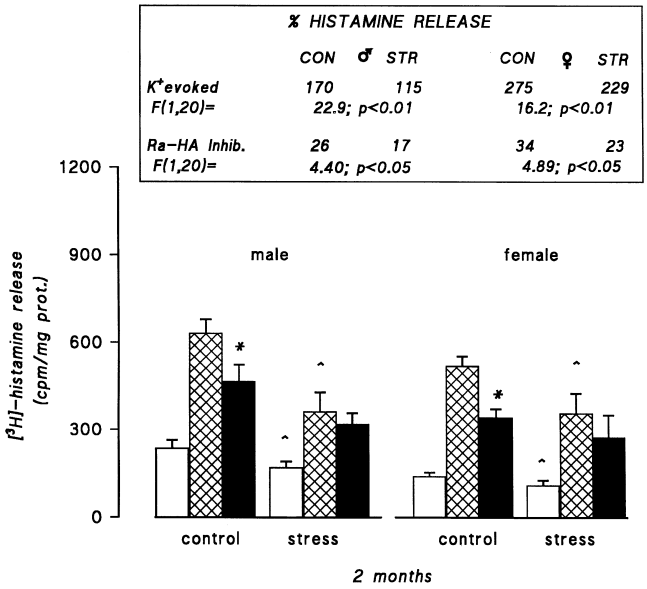

FIG. 2. Changes in HA release from hypothalamus slices from 2-month-old male and female rats 30 min after application of a foot shock (1 mA × 10 s × 5 times): baseline (open bar) and 40 mM K^+-evoked release in the presence (solid bar) or absence (crosshatched bar) of 1 μM Ra-HA. *Significant differences in Ra-HA inhibition of the K^+-evoked release (one-way ANOVA, $p < 0.05$). ^Significant differences in the same type of release compared with controls of the same sex (one-way ANOVA; $p < 0.05$). Insert (top part): percent changes in K^+-evoked compared to baseline release (calculated as a ratio of the means) in controls (CON) and stressed rats (STR) of both sexes, together with the two-way ANOVA F-values for the interaction between baseline and K^+-evoked release for the same sex in respect to stress. ns = not significant. Insert (bottom part): percent inhibition of the K^+-evoked response by Ra-HA, calculated as $(Mean_{K^+_{evok}} - Mean_{Ra\text{-}HA})/Mean_{K^+_{evok}} * 100)$, together with the F-values for the interaction between K^+-evoked release and the Ra-HA inhibited release for the same sex in respect to stress. The data are expressed as the means ± SD of six replicates obtained from two independent experiments.

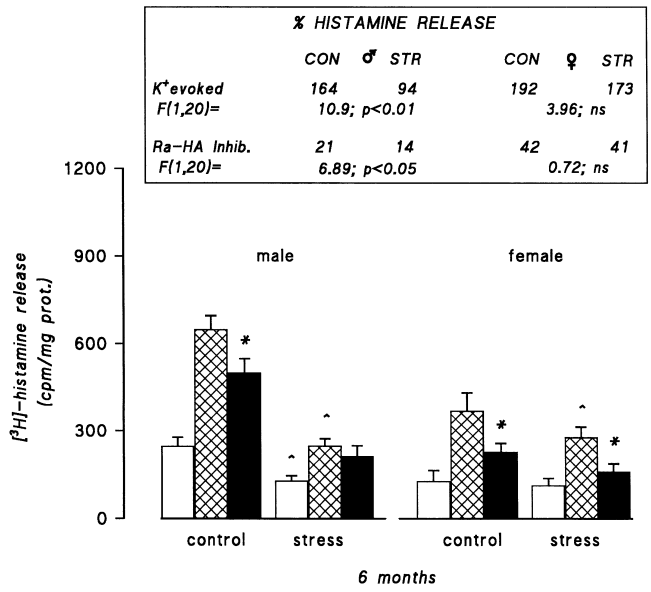

FIG. 3. Same as Fig. 2: 6-month-old males and female rats.

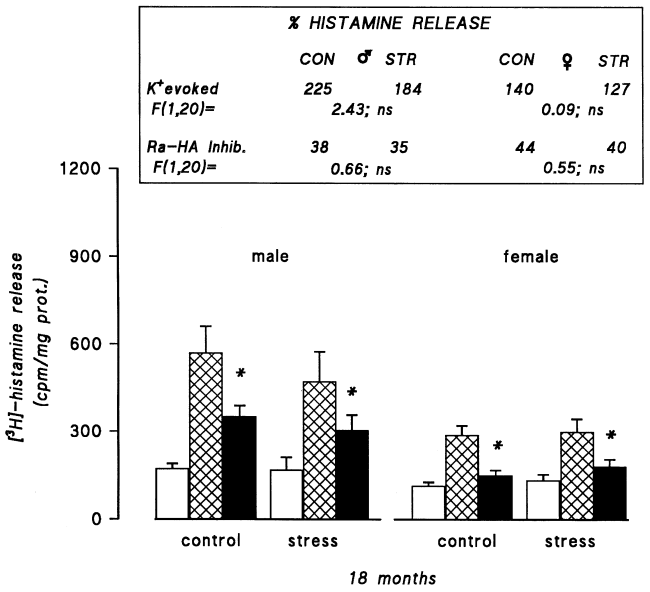

FIG. 5. Same as Fig. 2: 18-month-old male and female rats.

Stress provoked no changes in male and female rats aged 12 and 18 months (Figs. 4 and 5). The absence of any effect persisted in the 24-month-old females (Fig. 6), but the males displayed a marked increase in the baseline [one-way ANOVA, $F(1, 10) = 5.74$, $p < 0.05$, and in the K^+-evoked release, $F(1, 10) = 38.1$, $p < 0.01$, coupled with an inability of Ra-HA to significantly inhibit the K^+-evoked release.

Figure 7 illustrates the changes in plasma corticosterone observed 30 min after the foot shock.

Stress significantly raised the basal levels in all groups. In the males, this response was less pronounced in the 12- and 18-month age groups, whereas in the females it was already depleted in the 6-month-old group. Comparison, using two-way ANOVA, of the effect of aging on the increase in corticosterone between the 2-month and the other age groups showed that in the males this increase was only significantly reduced at the 12 months and 18 months, $F(1, 36) = 5.83$, $p < 0.05$, and $F(1, 36) = 21.1$, $p < 0.01$, respectively. In contrast, in the females, the reduction was significant in all groups [6 months, $F(1, 36) = 18.2$; 12 months, $F(1, 36) = 29.1$; 18 months, $F(1, 36) = 24.9$; 24 months, $F(1, 36) = 62.3$; all $p < 0.01$]. Comparison of the differences between the sexes at the same age showed that the increase in corticosterone was significantly higher in the 2-month-old females [two-way ANOVA,

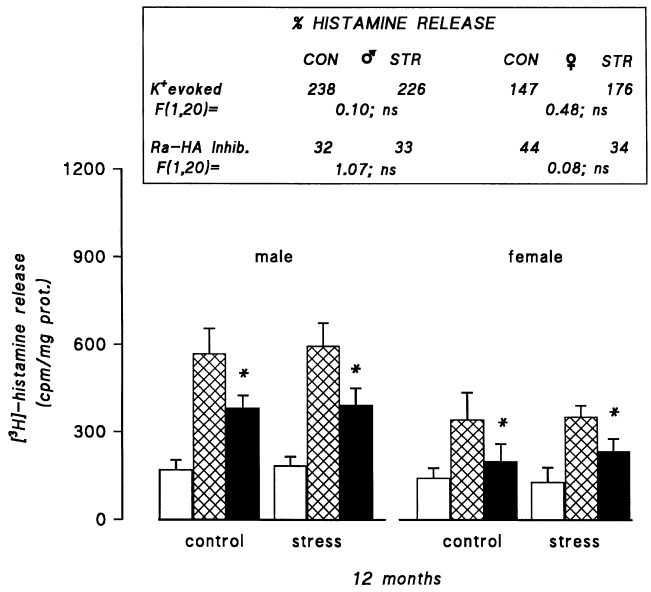

FIG. 4. Same as Fig. 2: 12-month-old males and female rats.

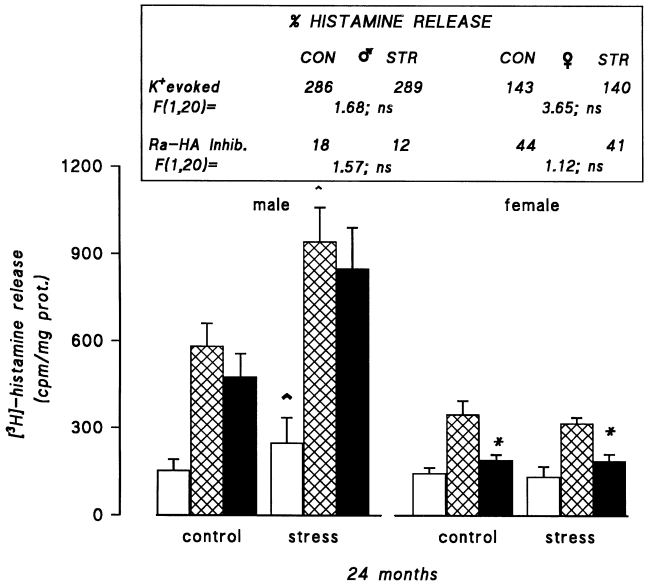

FIG. 6. Same as Fig. 2: 24-month-old male and female rats.

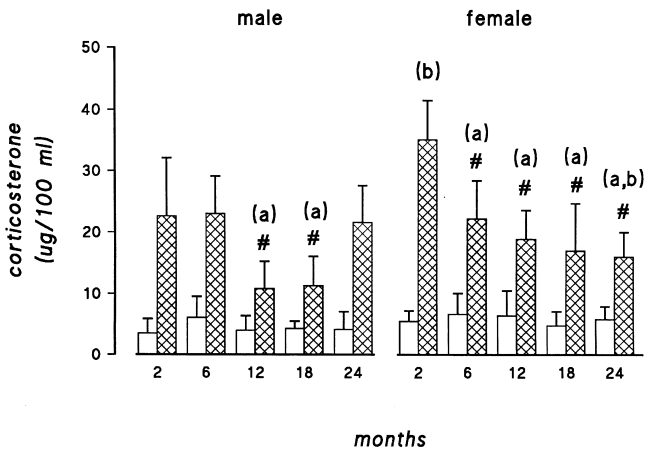

FIG. 7. Changes in plasma corticosterone 30 min after application of the foot shock in male and female rats of different ages: controls (open bar), stressed (crosshatched bar). #Significant differences in variations compared with the 2-month-old animals of the same sex (one-way ANOVA and Newman–Keuls tests; $p < 0.05$). [a]Significant interactions between baseline and stress-induced corticosterone in respect to age compared with the 2-month-old animals of the same sex (two-way ANOVA; $p < 0.01$). [b]Significant interactions between baseline and stress-induced corticosterone in respect to sex, evaluated in same-age groups (two-way ANOVA; $p < 0.01$).

$F(1, 36) = 5.83$, $p < 0.05$], lower in the 24-month group, $F(1, 36) = 18.1$, $p < 0.01$, and similar in the 6-, 12-, and 18-month groups.

DISCUSSION

In the first part of this investigation, a sex-dependent difference in the rat hypothalamic histaminergic system is evident. On comparing the baseline HA release in the two sexes it was found that in females it was constant and lower than males in all age groups. However, differences in baseline release are of only minor interest to the investigation of the changes in neuronal activity. As described in the introduction, it is K^+evoked release that is most suitable for this purpose (36). Using this parameter, a further age-dependent difference between the two sexes in HA release has been demonstrated: the K^+-evoked release was unchanged in the males, but in the females it was significantly reduced after 2 months, and then remained constant until 24 months.

It is probable that, in females, there are alterations of the functional efficiency of the presynaptic neuron either in respect to its sensitivity to excitation or its release mechanisms, rather than alterations in the endogenous formation of HA, because in this case there should also be changes in the baseline release. It has been demonstrated that the ontogenetic development of the H_1 and H_2 system is under estrogen control (9,34). It is possible to assume that age-related changes in female steroid hormone secretion can modulate the excitability of the presynaptic histaminergic neurons either directly, through H_3receptors, or indirectly through modulation of the response of the H_1 and H_2 receptors and those of other neurotransmitters, such as the dopaminergic receptors, which are also sensitive to these hormones (7,18).

These findings illustrate the age-dependent variation of this system in a no-stress situation. They do not provide any information about the possible functional impairment of one of the main actions of the hypothalamic histaminergic system, namely the response to stress. It has been amply demonstrated that stress provokes rapid changes in the release of numerous neurotransmitters (5,6,25,26), and in the kinetics of various receptor subtypes in different areas of the brain (8). Changes have also been described in the concentration and turnover of HA and in its receptors after various kinds of stress (4,10,11,19,31).

This article shows that aging results in an alteration of the efficiency of the response of the presynaptic histaminergic neurons to stress, especially in females. Also in 2-month-old rats of both sexes stress reduces the baseline and the K^+-evoked release, as well as the inhibiting effect of Ra-HA.

Because it has already been shown that stress increases the release of hypothalamic HA (19), one can logically postulate a diminution of histidine decarboxylase activity due to stimulation of the H_3 receptors (2,3). In addition, stimulation by the released neuromediator could result in their rapid downregulation, as occurs in other receptor systems (8). The downregulation hypothesis is suggested both by the depressed Ra-HA–induced inhibition observed in this study, and by data from other literature showing that the diminution in H_3 density is dependent on the type of stress, its intensity, and duration (11).

Male 6-month-old rats are more sensitive to stress than females: a greater decline in baseline, and in K^+-evoked releases, probably due to H_3 desensitization, is evident. A significant decrease in the percentage increase of K^+-evoked release, over baseline, is also observed in stressed male rats. However, in females the reduction in baseline and K^+-evoked release is less intense and there are no significant differences between the respective percentage increases. This could be due to a gradual inability of females to organize the biochemical responses that result in an increased hypothalamic HA turnover. This diminished HA release is also in agreement with the disappearance of H_3 downregulation. This lack of response to stress persists until 24 months in females, whereas in males it only appears at 12 months and 18 months.

At 24 months there is a new and different response characterized by a distinct elevation of the releases. At this advanced age, and only in males, it may be suggested that the presynaptic histaminergic neuron becomes insensitive to stimuli owing to the H_3 alteration revealed by the reduced ability of Ra-HA to inhibit the K^+-evoked release. This effect, however, could be further enhanced by an age-related degeneration in the heteroreceptors, such as the α_2-adrenergic, serotoninergic, glutamatergic, cholinergic, dopaminergic receptors whose modulation of HA release in the central nervous system has been demonstrated (15,16,23,24,28,29,30).

This study, therefore, shows that a foot shock provokes age- and sex-dependent plasma corticosterone differences. Because the literature data indicates that corticosterone secretion is modulated by the hypothalamic histaminergic system (4,10,14,20,31,35), it is interesting to note that variations in release and in H_3 function are inversely correlated with the changes in corticosterone secretion. In 2- and 6-month-old males a marked increase in corticosterone is accompanied by a reduction of both K^+-evoked increase and H_3 receptor response, whereas in 12- and 18-month old animals corticosterone increases much less and there is no reduction in HA release or receptor responsiveness. The same correlations are found in females: a decreased corticosterone secretion is coupled with a weaker response to stress of the K^+-evoked release and the H_3 receptors response.

The conclusion to be drawn, therefore, is that there are differences between males and females with regard to stress-dependent hormone secretion during aging. The response of 2-month-old female rats to stress is more intense, whereas that of older animals does not vary, and their H_3 system remains responsive. In males, on the other hand, there is a greater persistence of the response, but at the same time a greater vulnerability to aging, as shown by deterioration of the autoreceptor system controlling the release of hypothalamic histamine.

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