Histamine Involvement in Visual Development and Adaptation

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Purpose. This study evaluated the level of histamine in the interaction between the environment and the visual system during lifespan development, exploring potential sex differences.

Methods. Male and female Wistar rats, reared in standard laboratory or enriched-environment cages from birth to prepuberty or adulthood, were sacrificed during the critical period for visual development at postnatal day (P) 25 (P25) or in adulthood at P90. Additionally, animals born in standard conditions were exposed to an enriched environment at P90 and sacrificed at P150. The optic chiasm and the visual cortex were dissected out and tissue histamine was quantified fluorophotometrically. Statistical analyses were performed by ANOVA.

Results. Histamine levels in the optic chiasm were higher in male than in female rats at all ages. Comparable sex differences in the visual cortex were observed only during prepuberty. Basal histamine content in the optic chiasm was higher in prepuberty and decreased in adulthood in a sex-independent manner. Exposure to an enriched environment decreased optic chiasm histamine levels in both sexes and resulted in no sex difference in the cortical histamine levels at any age. Increased amine levels were detected in the optic chiasm of female rats exposed to an enriched environment during adulthood.

Conclusions. This study presents first evidence associating central histamine levels with the visual system development and environmental adaptation, thus providing the lead for the investigation of the hitherto elusive role of histamine in the regulation of visual processes. Furthermore, the findings challenge the impact of laboratory animal raising environments in developmental and behavioral studies. (*Invest Ophthalmol Vis Sci.* 2012;53:7498–7503) DOI:10.1167/iovs.12-10809

Histamine, an endogenous short-acting biogenic amine, is synthesized in several cell types of peripheral and central tissues and possesses a wide spectrum of activities, including its function in neurotransmission.[1] Although histamine has been one of the most studied and therapeutically exploited substances in medicine for a century, its strong association with the pluripotent mast cell and the atopic diseases seems to have deterred the investigation of its (patho)physiological role in other systems. Its presence in the brain was first shown more than 60 years ago, but research into its significance in the central nervous system has been delayed for many decades and still awaits elucidation.[2,3] Brain histamine is synthesized in neurons of the tuberomammillary nucleus of the posterior hypothalamus, which provides broad projections to most regions of the mammalian brain, including the visual cortex.[4] Acting on the four known types of histamine receptors—designated as H_1R, H_2R, H_3R, and H_4R—histamine is commonly implicated in basic homeostatic and brain functions, including sleep-wake regulation, circadian and feeding rhythms, body temperature, locomotor activity, learning and memory, and recently, neuroinflammation.[1,4,5]

In the visual system, histamine is localized in the retina, optic nerve, and choroid layer.[6] Projections from the posterior hypothalamus descending to the optic chiasm and forming the retinopetal axons communicate through the optic nerve with dopaminergic amacrine cells in the rat and primate retina.[3,7] Retinopetal axons have been suggested to play a role in light adaptation through histamine receptors in the retina.[2,7,8] Following the visual information, histamine was reported to influence the neocortical synaptic plasticity in vivo, while cortical histaminergic activation increases the degree of plasticity in the mature thalamocortical communication suggesting that the central histaminergic system plays an important role in regulating synaptic plasticity.[9]

Until now, no studies have exposed the effect of environmental stimuli on the histaminergic circuit of the brain pertaining to the visual system.[10,11] The effects of environmental enrichment vary from cellular and molecular to behavioral changes. In particular, studies have shown that enrichment increases the dendritic branches and length,[12,13] as well as the number of dendritic spines and the size of spines in some neuronal populations.[14–17] Differential housing also showed that the enriched environment increased cortical weight and thickness.[18] In addition, an enriched environment increases hippocampal neurogenesis leading the integration of newly born cells to functional neuronal circuits.[19,20] As far as the visual system is concerned, enrichment plays a beneficial role in the development of the retina through brain-derived neurotrophic factor, an effect which is more evident when combined with maternal enrichment.[21,22] Moreover, enrichment has been reported to increase plasticity in the adult visual cortex.[23]

Despite the sporadic reports of the histaminergic influence on the visual system, the role of histamine in its development as well as any related sex differences have not been explored to date. This study provides first demonstration of histamine involvement in the postnatal development and adaptive response of the visual system in mammals.

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Figure 1. The enriched-environment IMAC Criceti 16 cage. The second floor, feeding bowls, water bottle, bridge, tunnel, and plastic house are shown.

Methods

Animals

Male ($n = 30$ in total) and female ($n = 30$ in total) Wistar rats were housed under controlled 12:12 light-dark cycle, 24°C and 60% ± 5% humidity and they received a standard diet and water ad libitum.

Pregnant animals ($n = 4$) were placed in individual cages, under standard or enriched environmental conditions. The pups were born in the respective cages. Culling took place at postnatal day (P) 3 (P3) and each litter contained 10 animals (five male and five female). Animals sacrificed before puberty ($n = 20$; five for each group) were not weaned and they remained with their mothers until sacrifice. Animals sacrificed in adulthood were separated from their mothers at P26 and housed in groups of five according to sex and environmental conditions ($n = 20$; five for each group). Twenty additional adult animals were used for the third part of the study ($n = 5$ for each group); 60 animals being studied in total.

All procedures were performed by fully trained and experienced personnel and complied with ethical codes and regulations according to license number EL 25 BIO 010 of the General Veterinary Directorate of the Greek Ministry of Rural Development and Food and the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research. Efforts were made to minimize the number of animals used and to reduce their suffering.

Enriched Environment Animal Model

Cages (IMAC Criceti 16; IMAC, Vicenza, Italy) with two running wheels, two platforms as the second floor, two tunnels, two feeding bowls, one plastic house, one bridge, and three water bottles (Fig. 1) were used for the enriched-environment experiments (dimensions: W 0.80 m × D 0.49 m × H 0.38 m; Pet City, Athens, Greece). Every second day, the place of each object in the cage was changed and the room was reorganized.[24,25] For control experiments, standard laboratory cages (dimensions: W 0.60 m × D 0.40 m × H 0.20 m) were used. Five animals were placed in each standard or enriched-environment cage in order to exclude social interaction as a confounding factor.

The animals were divided into the following groups ($n = 5$ each): male rats in standard cages; female rats in standard cages, male rats in enriched-environment cages, and female rats in enriched-environment cages. Pregnant animals were placed alone in a standard or enriched-environment cage and the pups were born in the respective cages. The pups were observed twice daily from P7 onwards. The day that the eyelids were separated and the cornea was exposed as well as the onset of fur development were recorded. In experiment 1, the animals ($n = 5$ for each group) were sacrificed by decapitation at P25, so as to ensure that females had no estrous cycle and the rats were still within the critical period for the development of the visual system.[26] In experiment 2, the animals ($n = 5$ for each group) were treated as described for experiment 1, but they were sacrificed at P90.

In experiment 3, male and female animals were raised in standard cages until P90 and they either remained in the standard cage or were placed in enriched-environment cages at P90. Animals were divided into four groups ($n = 5$ each), similar to experiments 1 and 2 above, and they were sacrificed at P150. In experiments 2 and 3, the phase of the estrous cycle of female rats was determined during the last week before sacrifice, with the use of vaginal smears.[27]

In all experiments, the brain was rapidly removed after decapitation. The optic chiasm and the primary visual cortex were rapidly dissected out on ice using standard microsurgical techniques. The wet weight was recorded and the samples were immediately frozen at –80°C until assayed.

Quantification of Histamine

Histamine was extracted from the optic chiasm and the primary visual cortex and quantified as described previously.[28] Briefly, the tissue was homogenized in 0.4 N perchloric acid on ice and histamine was extracted sequentially in *n*-butanol, 0.1 N sulphuric acid and *n*-

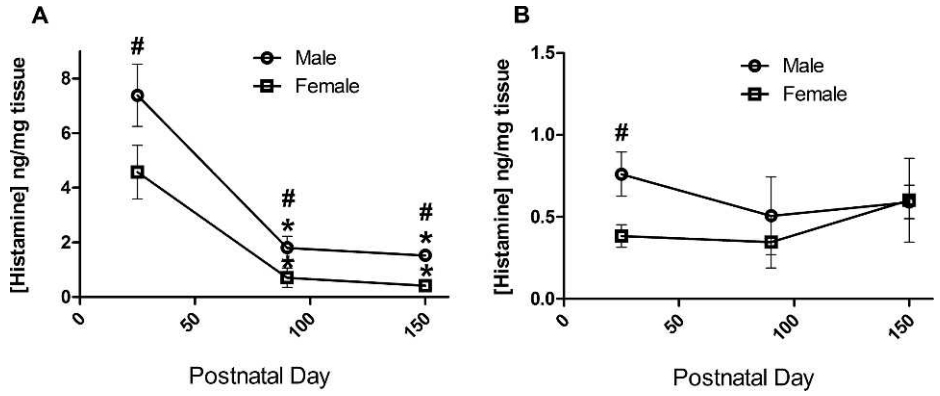

Figure 2. Basal histamine levels in male and female animals. (**A**) Optic chiasm. (**B**) Visual cortex. Decreased histamine levels were observed in the optic chiasm (**A**), but not in the visual cortex (**B**) at postnatal days P90 and P150 compared with P25 in both sexes. Significantly increased histamine levels in the optic chiasm of male compared with female animals were observed at all ages studied (**A**), whereas comparable increases in the visual cortex were observed only at P25 (**B**). $^*P < 0.05$ versus respective P25, $\#P < 0.05$ versus respective female.

Table. Phases of the Estrous Cycle of Female Rats Sacrificed at P90 and P150

Estrous Phase	Number of CT Animals		Number of Animals in EE	
	P90	P150	P90	P150
Proestrus	2	2	–	1
Estrus	–	–	2	–
Metestrus	2	1	1	1
Diestrus	1	2	2	3

heptane, any residual amounts of histidine being removed by washing in NaCl-saturated 0.1 N sodium hydroxide. Tissue histamine levels were then determined fluorometrically at 360 nm excitation and 450 nm emission, following condensation with *o*-phthalaldehyde (Sigma Chemical Company, St. Louis, MO). Histamine standards of 20 and 50 ng/mL as well as sample and standard blanks were always included in the measurements, while the quantification was based on a histamine standard curve ranging from 0 to 250 ng/mL. All reagents were of analytical grade.

Statistical Analysis

The results are expressed as ng of histamine per mg of wet tissue and are presented as mean ± SEM. Statistical analyses were performed using statistical software (SPSS for Windows, version 20; SPSS, Inc., Chicago, IL). Significant differences were determined by two-way ANOVA for each experiment followed by Bonferroni post hoc comparisons, with $P < 0.05$ being regarded as a critical level of significance.

Results

Basal Histamine Levels at Various Postnatal Ages

Basal histamine levels in the optic chiasm were higher than those determined in the visual cortex (Fig. 2), while male rats had significantly ($P < 0.05$) higher histamine levels in the optic chiasm compared with female rats at all ages studied (Fig. 2A). Higher levels of histamine were observed in the optic chiasm at prepuberty compared with adulthood, significant decreases ($P < 0.05$) being observed in both male and female animals at P90 and P150 compared with P25 (Fig. 2A). In contrast, similar decreases in histamine levels with age were not observed in the visual cortex (Fig. 2B), where significantly higher levels ($P < 0.05$) were detected in male than female animals only during prepuberty at P25 (Fig. 2B).

Although, the number of female rats in each phase of the cycle was relatively small, statistical analysis revealed no significant effect ($P > 0.9$) of the phase of the cycle (Table) on basal histamine levels in either tissue of female rats sacrificed at P90 or at P150.

Histamine Levels in Environmental Enrichment Rearing to Prepuberty

Animals of both sexes reared in an enriched environment opened their eyes (Fig. 3A) and grew fur (Fig. 3B) earlier than control animals reared under standard laboratory conditions. Significant differences ($P < 0.01$) of these developmental observations were observed between the two groups of animals.

Histamine levels in both tissues examined were significantly different ($P < 0.05$) between male and female control rats reared in standard laboratory cages and sacrificed at P25 (experiment 1; Fig. 4). In prepuberty, basal histamine levels were found to be nearly half in female compared with male animals in both the optic chiasm (61.9% ± 13.3%) and the visual cortex (50.4% ± 8.9%). External stimuli facilitated by the enriched environment had significant effects in the optic chiasm (Fig. 4A), decreasing the histamine levels in both sexes ($P < 0.05$) and maintaining the sex difference observed in the basal histamine levels; amine content in the female tissue being 55.2% ± 13.9% of the male tissue. On the other hand, the enriched environment induced no significant alterations ($P > 0.2$) in the histamine content of the visual cortex (Fig. 4B).

Histamine Levels in Environmental Enrichment Rearing to Adulthood

The basal histamine content of the optic chiasm, although lower in animals sacrificed at P90 (experiment 2), exhibited sex difference (Fig. 5A) comparable with that observed in the rats in prepuberty (Fig. 4A), tissue amine levels in female animals being 39.4% ± 9.9% of the male counterparts.

Rearing in the enriched environment resulted in significant ($P < 0.05$) increases in the histamine content of the optic chiasm (Fig. 5A), but not of the visual cortex (Fig. 5B) in both sexes. Moreover, the sex difference observed in the control animals was maintained, the histamine content in the female tissue being 53.2% ± 10.0% of the male tissue (Fig. 5A). Comparing the levels of histamine in the optic chiasm of prepubescent (Fig. 4A) and adult (Fig. 5A) animals reared in enriched environment, no significant difference was found ($P > 0.1$). Finally, there was no statistically significant effect ($P >$

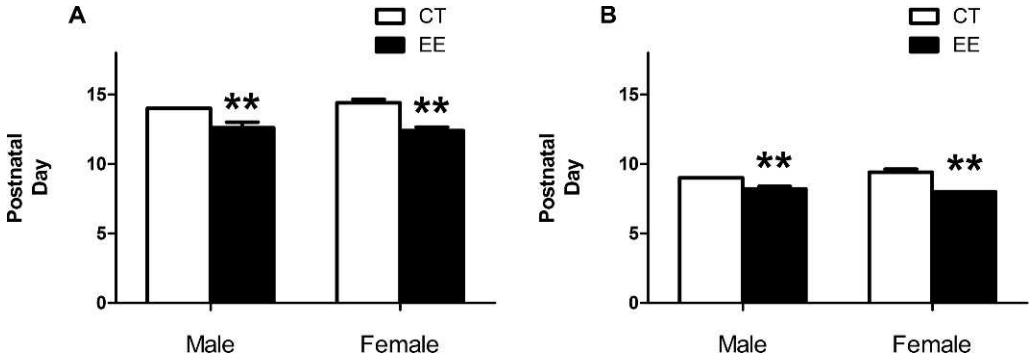

Figure 3. Animals housed in standard conditions (CT; control) or an enriched environment (EE). (**A**) Eye opening. (**B**) Onset of fur development. Both male and female animals housed in EE opened their eyes earlier than their control counterparts (**A**). Similarly, fur growth was observed earlier in animals housed in EE than the respective controls (**B**). $^{**}P < 0.01$.

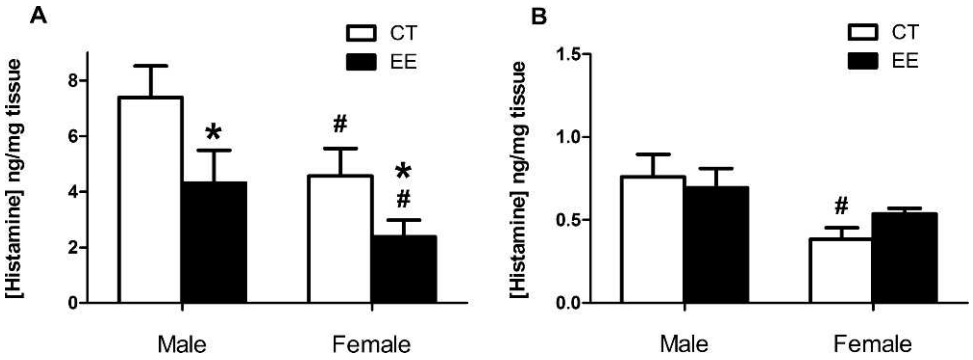

Figure 4. Histamine levels of animals in prepuberty, reared under standard (CT; control) or enriched environment (EE) conditions until P25. (**A**) Optic chiasm (**B**) Visual cortex. Lower basal histamine levels were observed in both tissues of female compared with male animals. Environmental enrichment decreased the levels of histamine in the optic chiasm (**A**) of both sexes, thus maintaining the sex difference observed in the basal tissue levels, but failed to induce any significant sex-related alteration in the histamine content of the visual cortex (**B**). $^{*}P < 0.05$ versus respective CT, $\#P < 0.05$ versus respective male.

0.3) of the phase of the estrous cycle (Table) on histamine levels in either tissue in animals reared in enriched cages.

Histamine Levels in Environmental Enrichment Housing during Adulthood

Similarly to P90 (Fig. 5A), a sex difference in the basal histamine levels of the optic chiasm (Fig. 6A) but not of the visual cortex (Fig. 6B) was detected at P150, amine content in the female optic chiasm being 27.1% ± 3.7% of that detected in the male tissue.

Housing of adult animals in the enriched environment (experiment 3) had no significant effect ($P > 0.1$) on the histamine content of the visual cortex (Fig. 6B). Interestingly, the presence of external stimuli in the enriched environment induced a sex-dependent effect on the histamine levels of the optic chiasm as evidenced by the significant increase in the tissue histamine content in female ($P < 0.05$) but not in male adult animals (Fig. 6A). Similar to the findings of experiment 2, there was no statistically significant effect ($P > 0.2$) of the phase of the estrous cycle (Table) on histamine levels of either tissue in animals housed in enriched cages.

Discussion

In the present study, histamine levels in the postnatal visual system from birth to adulthood were studied in the rat. Basal histamine levels in the optic chiasm were higher in prepuberty than in adult life in both male and female animals, thus providing first indication for a sex-independent role of histamine in the development of the visual system. Yet, during the critical developing period, the histamine content in both the optic chiasm and the visual cortex was approximately double in male than in female animals. This sex-related difference is suggestive of the histamine involvement in the increased synaptic plasticity in males, in accordance to the existing literature[9] and may potentially explain certain sex-related performances in human vision.[29–31]

At birth, the rat retina resembles that of a 6-month-old human fetus that needs further development before being exposed to environmental visual stimuli.[21] When the retina of the rat is fully developed and ready to transform photon to electric energy via phototransduction, the eyelids are separated and the cornea is exposed to the environment.[21,22] Despite the lack of consensus in the enriched environment–related research,[32] our results are consistent with previous studies demonstrating that housing in richer environments promotes the development of this photosensitive layer of the eye.[21,22] Moreover, the earlier onset of fur growth in the enriched environment implies that rearing in the presence of enhanced external stimuli may have a positive effect on the overall animal development.

Interestingly, rearing in richer environments resulted in a partial circumvention of the lower cortical histamine levels observed in females at prepuberty. Since histamine has been

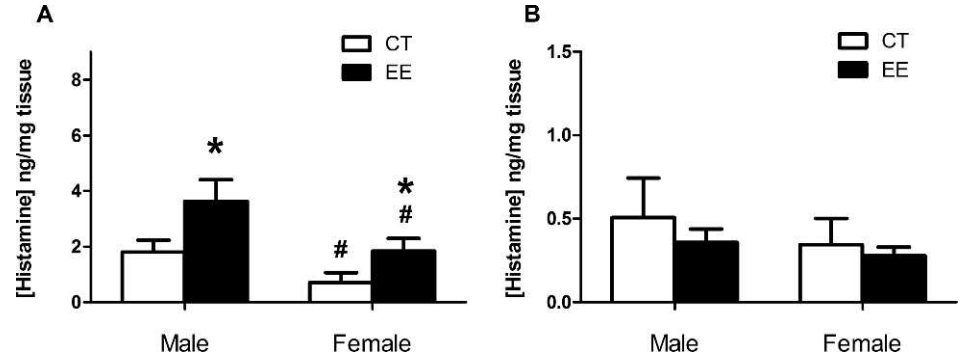

Figure 5. Histamine levels of adult animals, reared under standard (CT; control) or enriched environment (EE) conditions until P90. (**A**) Optic chiasm. (**B**) Visual cortex. Significantly lower basal histamine levels were observed in the optic chiasm (**A**) but not in the visual cortex (**B**) of female compared with male animals. Environmental enrichment increased the levels of histamine in the optic chiasm (**A**) of both sexes, thus maintaining the sex difference observed in the basal tissue levels, and induced no significant alteration in the histamine content of the visual cortex (**B**). $^{*}P < 0.05$ versus respective CT, $\#P < 0.05$ versus respective male.

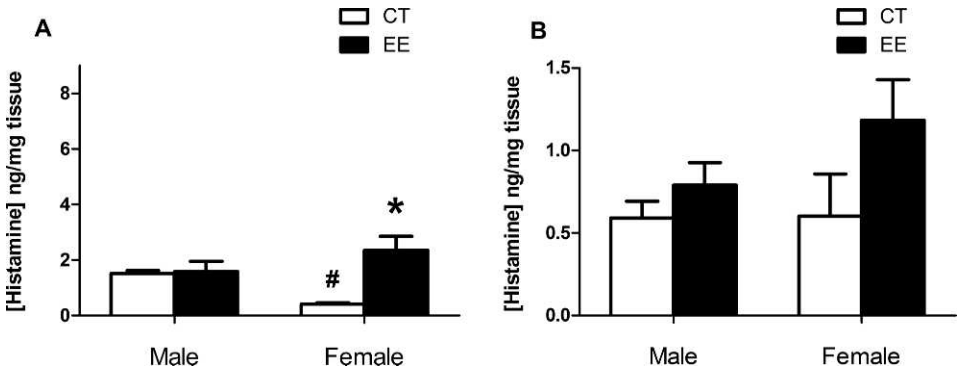

FIGURE 6. Histamine levels of adult animals housed under standard (CT; control) or enriched environment (EE) conditions during P90 to P150. (**A**) Optic chiasm. (**B**) Visual cortex. Significantly lower basal histamine levels were observed in the optic chiasm (**A**), but not in the visual cortex (**B**) of female compared with male animals. Environmental enrichment increased the levels of histamine in the optic chiasm (**A**) of female animals only. The EE had no effect on the visual cortex (**B**). $^*P < 0.05$ versus respective CT, $\#P < 0.05$ versus respective male.

shown to enhance the neocortical synaptic plasticity,[9] these data are indicative of an advantage in synaptic plasticity in males over females during the early stages of development that may be compensated in females upon rearing in the presence of enhanced external stimuli. Furthermore, environmental enrichment failed to induce any significant alterations in the cortical histamine content of adult animals. Therefore, it can be postulated that, beyond its contribution to the sex-related early cortical plasticity, histamine may have a fundamental role in the synaptic formation of the visual cortex, which is unrelated to the characteristics of the external stimuli triggering the transmission of visual information.[2,3,9]

On the other hand, the putative adaptive response of the female cortical histaminergic system during prepuberty was not detected in the optic chiasm. Histamine levels in the optic chiasm of either sex remained relatively constant during rearing in the enriched environment from birth to adulthood, in contrast to the corresponding decreases throughout adulthood in control animals. Interestingly, however, transfer to the enriched environment during adulthood increased the histamine content of only the female optic chiasm to levels comparable with those obtained upon rearing in an enriched environment from birth, suggesting a differential adaptive capacity of the visual system in adult males and females. These observations, along with the altered histamine levels in the optic chiasm of animals reared in richer environments, support a likely specific role of histamine, without excluding the participation of anatomical and/or biochemical pathways in the observed elevated postnatal histamine levels—such as for instance, increased numbers of histamine-containing neurons during the first days of life or altered histamine synthesis.[1,5] Moreover, the identification of the subtype(s) of histamine receptors mediating the observed alterations in histamine levels will provide compelling evidence toward the dissection of any opposite or complementary specific pathways underlying the role of histamine in the developmental and adaptive responses in the visual system. Although related existing literature is essentially lacking, the findings of this study point to the involvement of histamine in the functional environmental adaptation of eye tissues in addition to the putative modulatory action of the amine during the critical period for the development of the visual system. Future efforts to map the anatomy of histaminergic neurons and the time course over which histamine levels change by measuring time points earlier in prepuberty and in between P90 and P150 during adulthood could help to elucidate the role played by histamine in various aspects of development. Thus, the hypothesis that optimal histamine levels are vital for the development and function of the optic nerve and/or of the retina following exposure of the cornea to the environment as well as the uncovering of any sex-related differences and the identification of the histamine receptor subtype(s) underlying these processes are currently under investigation.

In conclusion, this study presents first evidence associating the central histamine levels with the development and the environmental adaptation of the visual system and provides the lead for the investigation of the yet elusive role of histamine in the regulation of both sex-related and -unrelated pathways underlying these vital physiological processes in mammals. In addition, the findings raise questions on the dramatic impact that the rearing environment may have on the development of rats and/or other laboratory animals[32] and call for a more cautious interpretation of data acquired from developmental and behavioral studies performed under controlled and contrived laboratory conditions.

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