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# Age-related changes in brain histamine

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*Abstract*

**The effect of age on brain histamine levels and histamine methyltransferase activity (HMT) was investigated. Male Sprague-Dawley rats (12 months old) displayed significantly higher hypothalamic, midbrain and cortical histamine concentrations than three-month-old animals. In contrast, HMT activity was significantly decreased in all three brain regions. The increase in brain histamine concentration of old rats could have been partially attributed to decreased activity of HMT since elevated levels of brain histamine are known to occur following HMT inhibition. Present results indicate that similarly to the reported changes in the concentration, synthesis and/or metabolism of other central neurotransmitters in old rats, brain histamine regulation may also be affected in the process of aging.**

## *Introduction*

Several reports indicated deficiencies in central catecholaminergic, serotoninergic and cholinergic systems occurring with aging [1]. In contrast, the role of brain histaminergic system has been almost unexplored. Histamine has gained recognition as a putative central neurotransmitter [2–4]. Although brain histamine involvement in thermoregulation [5], hormonal regulation [6] and stress [7–10] was indicated, the significance of brain histamine still remains enigmatic.

The purpose of this investigation was to explore whether central histaminergic system may also participate in the complicated biochemical changes which ensue with aging.

## *Materials and methods*

### Histamine determinations

The tissues were assayed for their histamine content according to a modification of the double isotope technique of TAYLOR and SNYDER [11]. This procedure depends on the methylation of endogenous histamine in the tissues by added histamine *N*-methyl-transferase using *S*-adenosyl-L-methionine (methyl $^{14}C$), (59 mCi/mmole, New England Nuclear) as the methyl donor. A tracer amount of ($^{3}H$)-histamine (5–10 Ci/mmole, New England Nuclear) was added to correct for the varying degree of histamine methylation in different samples. Endogenous *S*-adenosyl-L-methionine was destroyed by boiling the tissue, a procedure which also served to precipitate protein.

The ($^{14}C$) ($^{3}H$)-methylhistamine and ($^{14}C$)-methylhistamine were separated from ($^{14}C$)-*S*-adenosyl-L-methionine and ($^{3}H$)-histamine by extracting into chloroform from a salt saturated sodium hydroxide solution. The chloroform was evaporated and ethanol and scintillation fluid (Econofluor, New England Nuclear) were added to the residue and counted in a Beckman LS 8100 liquid scintillation spectrometer.

### Histamine *N*-methyltransferase (HMT) assay

Samples of homogenates were centrifuged at 50,000 × *g* for 10 min on a Beckman L5-50 preparative ultracentrifuge. HMT activity in supernatant (50 µl) was determined by a modification of the isotopic microassay method of TAYLOR and SNYDER [11] as described earlier [12]. Protein estimation of 50 µl supernatant samples was determined by a modification of the method of LOWRY et al. [13]. HMT activity is expressed as µmoles of methylhistamine formed per gram of supernatant protein per hour of incubation.

## *Results*

Old rats displayed a significantly higher hypothalamic midbrain and cortical histamine concentration (Fig. 1) than that seen in the young animals. The greatest increase was noted in the cortex (36% above the concentration found in young rats) followed by the hypothalamus (29%) and midbrain (20%). HMT activity was significantly reduced (Fig. 2) in all three brain regions. The greatest reduction (39% of that seen in young animals) was observed in the hypothalamus. Midbrain and cortical HMT activity was reduced to 55% and 67% (of that seen in young rats), respectively.

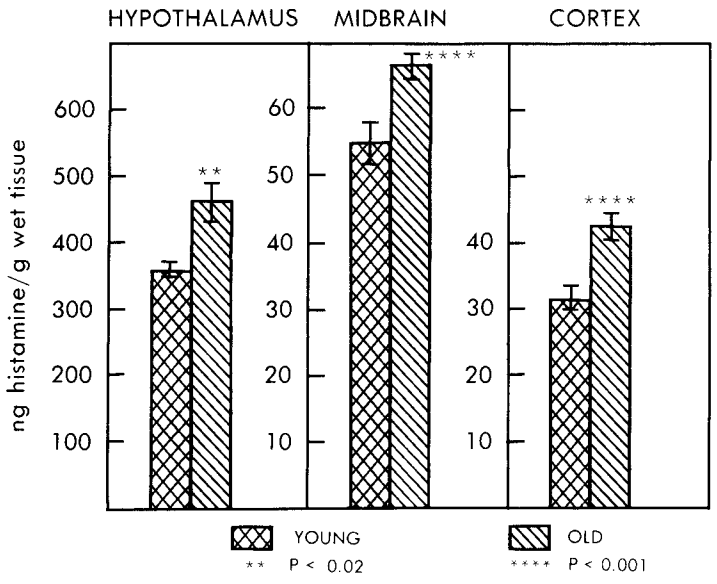


*Figure 1*
Histamine concentration (ng/g) in the hypothalamus, midbrain and cortex of the young and old rats. The results represent the mean ± SEM of 8 experiments for each group. Student's *t*-test was used for statistical significance.

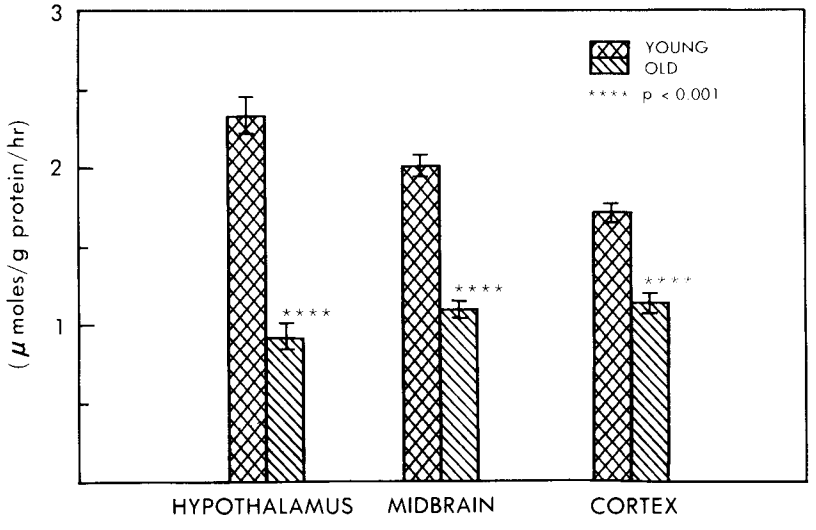


*Figure 2*
Histamine methyltransferase activity in the hypothalamus, midbrain and cortex of young and old rats. The results represent the mean ± SEM of 8 experiments in each group. Student's *t*-test was used for statistical analysis.

*Discussion*

Present studies demonstrated definite differences between young and old rats in the regional brain histamine concentration. The elevation in hypothalamic midbrain and cortical histamine levels of old rats was associated with a significant decrease in HMT activity in all three brain regions which may suggest a decreased histamine metabolism. It is possible that changes in histamine methylation could influence histamine release and/or binding characteristics. Age-induced alterations in L-histidine uptake and/or histamine synthesis could have also occurred.

The increase in brain regional histamine concentration associated with decrease in the HMT activity may not be surprising as methylation is considered to be the major route of histamine metabolism and inactivation in the mammalian brain [14–16]. HMT appears to be widely distributed in the central nervous system [17,18].

The distribution of tele-methylhistamine, the inactive histamine metabolite, correlates well with the distribution of histamine [19].

*In vivo* studies had indicated that HMT inhibition by metoprine increased histamine levels in the whole rat brain [20] and in the rat hypothalamus, thalamus and cortex [21]. Similarly to our findings, the greatest increase occurred in the cortex while hypothalamic histamine levels were less elevated.

Presently observed changes in brain histamine levels and HMT activity of old rats are in line with the repeatedly reported alterations in the brain concentration of other neurotransmitters ensuing with aging [1]. However, in our studies the regional brain histamine concentration was significantly increased while norepinephrine and 5-hydroxytryptamine levels in several brain regions of the old rats were often decreased, although strain, age and regional differences seem to occur [1]. For example, in Wistars rats (15 months old) norepinephrine levels were significantly lower in the hypothalamus, pons and medulla but higher in the thalamus, hippocampus and cerebral cortex [22].

It is of interest that central histamine displays also a different developmental pattern than catecholamines and 5-hydroxytryptamine. The latter neurotransmitters increase from late gestation to maturity [23]. In contrast, histamine concentration in the fetal brain decreases after birth and declines steadily to low adult values [24–26].

The decrease in HMT activity observed in all three brain regions of old rats in this investigation is in line with the age-related decrease in the activities of the synthesizing and/or metabolizing enzymes of catecholamines, 5-hydroxytryptamine and acetylcholine [1]. Interestingly both histamine and dopamine stimulated adenylate cyclase activity in the hypothalamus, frontal cortex and anterior limbic cortex (and dopamine stimulated adenylate cyclase activity in striatum) were reported to decline (by about 50%) as rabbits aged from 5.5 months to 5.5 years of age [27].

The importance of changes in the regulation of other central neurotransmitters was documented. While alterations in striatal tyrosine hydroxylase activity may account for some difficulties in movement [28], central cholinergic deficit has often been suggested to be involved in age-related memory disfunction [29–31].

Further studies are needed to elucidate the significance of age-induced changes in brain histamine regulation. However, the present investigation indicates that similarly to other central neurotransmitters, the central histaminergic system is affected by the aging process.

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