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Diurnal and Age-Related Changes in Cerebrospinal Fluid Tele-Methylhistamine Levels During Infancy and Childhood

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KIVIRANTA, T., L. TUOMISTO AND E. M. AIRAKSINEN. *Diurnal and age-related changes in cerebrospinal tele-methylhistamine levels during infancy and childhood.* PHARMACOL BIOCHEM BEHAV **49**(4) 997–1000, 1994.—Histamine is a neurotransmitter participating in many physiological functions and behavior, including control of arousal and modulation of the circadian rhythms. Diurnal variation in cerebrospinal fluid (CSF) levels of tele-methylhistamine (t-MH), the main histamine metabolite, has been detected in several animal studies. In humans, such changes have not been described. Little is known on the development of histaminergic neurons in human brain. In children, the levels of CSF t-MH are not known. Therefore, we have measured the concentrations of CSF t-MH in 81 children, age ranging from 3 months to 14.6 years. t-MH levels were higher in infants, and near adult values were measured in adolescents, the relation between CSF t-MH and age being; CSF t-MH = -0.217 year + 7.31 ($n = 81$, $r = 0.26$, $p = 0.021$). The mean t-MH concentration was higher during the daytime (7.07 ± 0.46 pmol/ml, mean ± SEM) than in the night (5.35 ± 0.60 pmol/ml, $p = 0.0019$, ANOVA). The results show a developmental change in the concentration of t-MH during childhood and a difference in t-MH levels between the daytime and night indicating a more active metabolism of brain HA in the waking period.

Tele-methylhistamine Cerebrospinal fluid Circadian rhythm Development

CENTRAL nervous system histamine (HA) is known to be a neurotransmitter or neuromodulator in the mammalian brain. Histaminergic neurons are involved in the regulation of a variety of basic physiological functions, such as thermoregulation, energy metabolism, control of arousal, and modulation of the circadian rhythms (2,3,5,11,13,17,20,22). Classic antihistamines, which cross the blood–brain barrier, mediate their sedative effects via central H_1-receptors (23).

In mammalian brain, histamine is metabolized primarily by histamine-*N*-methyltransferase (HMT) to form tele-methylhistamine (t-MH) which is converted to tele-methylimidazole acetic acid (t-MIAA) by monoamine oxidase and aldehyde dehydrogenases. There are no other significant sources of t-MH or t-MIAA in brain and measurements of these metabolites in brain reflect histaminergic activity (15). Because the histaminergic neurons are in contact with CSF, changes in their activity might be reflected in the level of these metabolites in CSF (22), as concentrations of t-MH and t-MIAA in CSF represent histamine that has been released and subsequently metabolized (15).

There is little information as yet available on the development and maturation of the histaminergic neurons in the human brain (9,21). The data of the human CSF t-MH concentrations are based solely on adult values. Diurnal fluctuations in levels of histamine metabolites has been detected in rhesus monkey (13) but not in human samples.

The aim of the present study was to obtain information on the development and circadian variation of the histaminergic neural functions by measuring the CSF t-MH concentrations in infants and children.

PATIENTS AND METHODS

The cerebrospinal fluid samples were collected according to clinical indications from 81 children after informed consent from the parents. The study protocol was accepted by the

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TABLE 1
DESCRIPTION OF THE STUDY GROUP

Number of Cases	Female/Male	Age		Drugs	
		Mean (Years)	Range (Years)	Antipyretic Agents *n* (%)	Benzodiazepines *n* (%)
81*	36/45	4.1	0.25–14.6	49 (60)	31 (38)

*Diagnoses: Febrile convulsions (34), febrile infections (15), acute leukemia (13) or malignant mediastinal lymphoma (1) before cytotoxic chemotherapy, epileptic symptoms (7), diverse neurological symptoms including vertigo (3), neck pain (2), headache (1), limping (1), Brown's syndrome (1), suspected delay in the neurological development (3).

ethical committee of the hospital and was in accordance with the declaration of Helsinki. Most (53) of the children were febrile, and 34 of them had had a febrile convulsion. The rest of the children were afebrile with different clinical symptoms. Patients with meningitis or encephalitis were excluded. A detailed description of the children is given in Table 1. The body temperature was recorded immediately before the lumbar puncture. Most of the febrile children had received antipyretic analgetics (usually paracetamol) during the last 24 h. Diazepam or other benzodiazepines were used as anticonvulsant or sedative drugs before the lumbar puncture when needed (Table 1). Only one child had received a peroral antihistaminergic drug (brompheniramine) during the last 24 h.

Sample Collection and Analysis

CSF samples were taken by lumbar puncture. Only samples with normal counts of leukocytes (0–5 × 10^6/l) were accepted. The first 1.5 ml was sent for other purposes and next 2.0 ml sample was frozen quickly and stored at −70° until analyzed for tele-methylhistamine. Tele-methylhistamine was measured with gas chromatography-mass spectrometry by the method of Hough et al. (1), as adapted to brain samples (19).

Statistical Methods

The effects of age on CSF t-MH concentrations were analyzed by using Pearson's correlation analysis. Analysis of variance (ANOVA) was used to test the differences of CSF t-MH levels during the day and night periods using age and sex as covariants.

RESULTS

There was a negative correlation (p = 0.021) between age and CSF t-MH concentration (Fig. 1). The mean CSF t-MH concentration was higher during the daytime from 0600–2000 h (7.07 ± 0.46 pmol/ml, mean ± SEM, n = 50) than in the night from 2000–0600 h (5.35 ± 0.60 pmol/ml, n = 31, p = 0.0019, ANOVA, Fig. 2). The statistical difference still exists, if we replace the time limits from 0600–1800 h (p = 0.002).

DISCUSSION

Our results show a negative correlation between age and CSF t-MH concentration in childhood. In young children, t-MH-levels tended to be higher than values described in the literature for adults (14,15), but by the age of puberty, the levels became closer to the adult values.

There are few reports on the development of histamine in

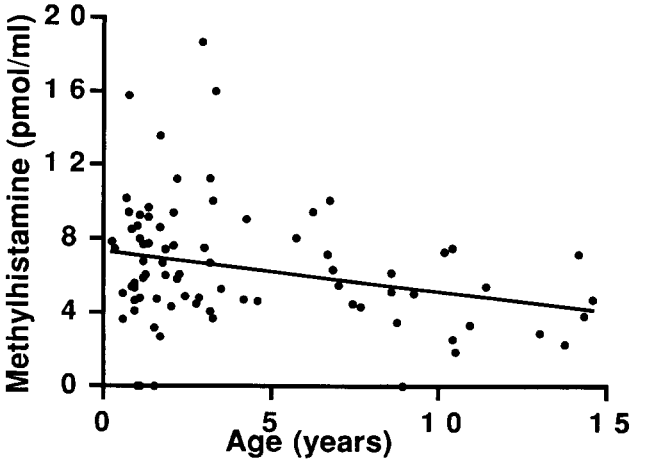

FIG. 1. The correlation between cerebrospinal fluid tele-methylhistamine levels and age. The equation of the regression line is y = −0.217x + 7.31. n = 81, r = 0.26, p = 0.021 (Pearson's correlation analysis).

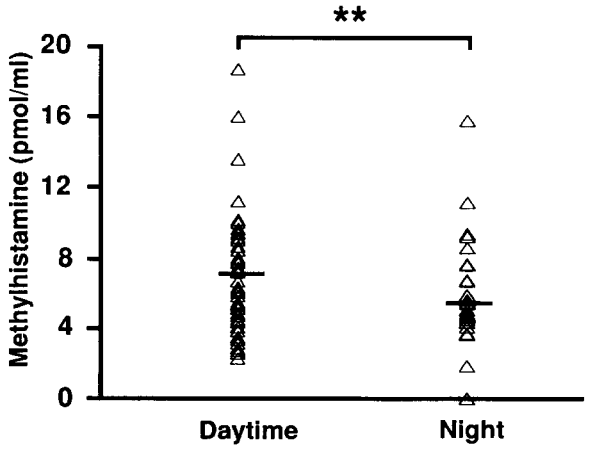

FIG. 2. The concentrations of cerebrospinal fluid tele-methylhistamine during the day (from 0600–2000 h, n = 50) and night period (from 2000–0600 h, n = 31). The mean concentration of each group is marked with a cross line. **p = 0.0019 (ANOVA).

the human brain (21). In animal studies, the maturation of histaminergic neuron system varies between different species (18). In the human newborn, histamine is more evenly distributed than in the adult brain and activity of the histamine metabolizing enzyme (HMT) is already well developed, although still lower than in the adult (9,21). The higher concentration of CSF t-MH in young children detected in the present work could be related to a higher HA turnover in the younger age groups. On the other hand, in adults the CSF t-MH levels tend to rise during aging, which is in favor of increased histamine turnover in brain as one gets older (15). CSF production has been demonstrated to vary with age being 50% lower in elderly subjects than in young persons (6). The higher concentrations of CSF t-MH could partly be explained by dissimilar dilution of HA metabolites into a smaller amount of CSF in elderly subjects.

A rostral-caudal concentration gradient of t-MH both in rhesus monkeys (12) and humans (14) has previously been detected: the level of t-MH was higher in ventricular than in lumbar space. Theoretically, the shorter spinal space in smaller children could lead to a higher concentration of t-MH in lumbar CSF samples. To prevent the possible effect of this concentration gradient, the CSF samples were always collected in a standard order after the first aliquot of 1.5 ml.

Circadian rhythms of the concentrations of brain HA and t-MH have been measured in a number of studies [see (20)]. The results suggest that histamine turnover is elevated in rats during the night when body temperature and motor activity are maximal. A circadian variation in the spontaneous release of histamine in the anterior hypothalamic area, where histaminergic terminals are densely confined, has been detected by Mochizuki and co-workers (7). Diurnal fluctuation of histamine metabolites has also been found in the ventricular CSF of rhesus monkeys (13): the levels of t-MH were significantly higher during the light phase than during dark. Our results on CSF t-MH in children agree well with those results. To our knowledge, such day and night variation in the levels of CSF t-MH has not been described earlier in humans. In our study, the mean concentration of CSF t-MH was significantly higher in samples taken between 0600 and 2000 h, when small children are awake, than in the samples taken during the night. The difference was observed, although the day and night rhythm must have been temporarily disturbed in these sick children that had to be taken to the hospital during the night time.

Fluctuations in CSF production may influence the concentrations of different substances released from the brain into the CSF. According to magnetic resonance imaging studies, there is a circadian variation in the production of adult human CSF: minimum production at 1800 h and a nightly peak production at 0200 h (8). This could dilute the night samples. However, a statistically significant difference between the day and night values of CSF t-MH remains even if the lowest and highest production rates of CSF belong to the same time period, e.g., to the night period from 1800–0600 h. The observed difference in t-MH concentrations is unlikely to be explained by different rates of CSF production.

The pathologic conditions of the children were quite diverse, because in childhood it is not ethically possible to get CSF samples from healthy donors and, therefore, they always have some medical symptoms. However, there is no difference in CSF t-MH concentration of children in different diagnosis groups: febrile–afebrile, convulsive–nonconvulsive (4), or in children having diverse neurological symptoms compared with the rest of the study population ($p > 0.05$, Kruskal–Wallis test). Benzodiazepine derivates and other psychotropic drugs at moderate doses may change histamine turnover in the brain (10,16). Our earlier results showed no differences in CSF t-MH levels between those children receiving or not receiving these drugs (4).

The information concerning the concentrations of CSF t-MH in childhood is of pioneering nature. In our child population, a negative correlation between age and CSF t-MH concentrations was found. For the first time in humans, higher concentrations of CSF t-MH were detected during daytime than in the night, indicating a circadian variation in brain histamine metabolism.

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