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In vivo release of neuronal histamine in the hypothalamus of rats measured by microdialysis

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Summary. Using an in vivo intracerebral microdialysis method coupled with an HPLC-fluorometric method, we investigated the extracellular level of endogenous histamine in the anterior hypothalamic area of urethane-anaesthetized rats. The basal rate of release of endogenous histamine in the anterior hypothalamic area measured by this method was 0.09 ± 0.01 pmol/20 min. When the anterior hypothalamic area was depolarized by infusion of 100 mM K^+ through the dialysis membrane or electrical stimulation at 200 μ A was applied through an electrode implanted into the ipsilateral tuberomammillary nucleus, histamine release increased to 175% and 188%, respectively, of the basal level. These increases were completely suppressed by removal of extracellular Ca^{2+}. The basal release of histamine was also suppressed after infusion of 10^{-6} M tetrodotoxin or i.p. administration of 100 mg/kg of α-fluoromethylhistidine. On the other hand, 3-fold increase in the basal release was observed after i.p. administration of 5 mg/kg thioperamide. These results clearly indicate that both the basal and evoked release of histamine measured by our method are of neuronal origin.

Key words: Histamine – Neurotransmitter release – Microdialysis – α-Fluoromethylhistidine – Thioperamide

Introduction

Histamine is widely distributed in the mammalian central nervous system and is regarded as a neurotransmitter or a neuromodulator (Prell and Green 1986; Schwartz et al. 1986; Hough 1988; Yamatodani et al. 1991). Histaminergic neurons have been identified in mammalian brains by immunocytochemical methods using antibodies raised against L-histidine decarboxylase (HDC; Watanabe et al. 1984), the sole enzyme responsible for histamine synthesis, or against histamine itself (Panula et al. 1984). The cell bodies of the histaminergic neurons are localized in the tuberomammillary nucleus in the posterior hypothalamic region (Inagaki et al. 1990), while their fibers are found in almost all regions of the brain (Inagaki et al. 1988; Panula et al. 1989). The involvements of the histaminergic system in multifarious brain functions and various behaviors have been reviewed (Prell and Green 1986; Schwartz et al. 1986; Hough 1988; Yamatodani et al. 1991). However, details of the neurochemical mechanism of histaminergic neurotransmission and its physiological roles are still not clear.

Recently, an in vivo microdialysis technique has been widely used for measuring the extracellular concentrations of many substances in the brain (Ungerstedt 1984; Sharp et al. 1986). This technique is suitable for determining the dynamics of neurotransmitters in vivo even in conscious and freely moving animals (Damsma et al. 1987; Westerink et al. 1987). However, there have been few studies on histamine release in the brain due to difficulty in quantification of histamine in the dialysate.

In this study, we used this microdialysis technique in combination with a highly sensitive high-performance liquid chromatographic method (HPLC; Yamatodani et al. 1985) to determine the extracellular level of endogenous histamine in the anterior hypothalamic area of rats, which is the region of the brain with the highest concentration of histaminergic fibers (Inagaki et al. 1988; Panula et al. 1989).

Materials and methods

Microdialysis method. Male Wistar strain rats weighing 180–240 g were anaesthetized with urethane (1.2 g/kg, i.p.) and placed in a stereotaxic frame (Kopf Instrument, Tujunga, CA, USA). The skull was exposed and holes were drilled for a dialysis probe and a stimulating electrode. The microdialysis probe (CMA/10, membrane length 2 mm, Carnegie Medicin, Stockholm, Sweden) was implanted unilaterally into the anterior hypothalamic area with the coordinates AP: 1.5, L: 0.5, V: 9.2 mm relative to the bregma and

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the skull surface (Paxinos and Watson 1986), and fixed with dental cement. A bipolar stainless electrode (diameter 0.2 mm) was inserted into the tuberomammillary nucleus (AP: 4.3, L: 1.3, V: 9.6 mm).

The anterior hypothalamic area was perfused with artificial cerebrospinal fluid (CSF), consisting of 140 mM NaCl, 3 mM KCl, 2.5 mM $CaCl_2$ and 1 mM $MgCl_2$, pH 7.4. High K^+ CSF containing 100 mM KCl was prepared by replacing NaCl isoosmotically. Ca^{2+}-free CSF containing 4 mM EDTA was also prepared. Just after the implantation, the probe was perfused with CSF at 8 µl/min for 160 min to achieve rapid stabilization of histamine release. Then the flow rate was reduced to 1 µl/min and fractions were collected for every 20 min. At this perfusion rate, the recovery of histamine from the surrounding fluid in the dialysate (relative recovery) was estimated to be about 39.2 ± 1.8% (mean ± S.E.M., $n = 4$) by an in vitro perfusion test, in which the probe was placed in a test tube containing 1 µM histamine dissolved in phosphate buffered saline, pH 7.4 and was perfused at 37° C at a flow rate of 1 µl/min.

After the first 3 fractions had been collected, drugs were administered as follows: Tetrodotoxin (TTX, 10^{-6} M; Sigma Chemicals, St. Louis, MO, USA) was added to CSF and infused into the anterior hypothalamic area. α-Fluoromethylhistidine (FMH, 100 mg/kg; donated by Dr. J. Kollonitsch, Merck, Sharp & Dohme, Rahway, N.J., USA), an irreversible inhibitor of HDC (Garbarg et al. 1980; Maeyama et al. 1982), and thioperamide (5 mg/kg; donated by Dr. J. C. Schwartz; Centre Paul Broca de l'INSERM, Paris, France), an antagonist of presynaptic H_3-autoreceptor (Arrang et al. 1987) were administered intraperitoneally (i.p.).

The histaminergic cell bodies in the tuberomammillary nucleus were stimulated electrically with biphasic square wave pulses (50 Hz, 0.1 msec, 100 or 200 µA) during a collection period of 20 min.

After experiments, the brains were removed, fixed in 4% paraformaldehyde in 0.1 M sodium phosphate buffer pH 7.4, immersed in 30% sucrose, and cut into 50 µm coronal sections in a cryostat to confirm the location of the probe and the electrode.

Histamine analysis. The histamine content of the dialysate was determined by a sensitive HPLC-fluorometric method (Yamatodani et al. 1985) with slight modifications. The dialysate was mixed with 1/30 volume of 60% perchloric acid, and 20 µl of the mixture was injected into the HPLC column. Histamine was separated on a cation exchanger, TSKgel SP2SW (Tosoh, Tokyo, Japan; particle size 5 µm) eluted with 0.25 M KH_2PO_4 at a flow rate of 0.6 ml/min using a constant flow pump (Model CCPM, Tosoh, Tokyo, Japan). The levels of interfering substances in the dialysate were negligible, so a shorter column (4 mm i.d. × 50 mm) than in the original method was used to attain higher sensitivity and reduce the analysis time. Histamine in the eluate was derivatized using an on-line automated Shore's *o*-phthalaldehyde method (Yamatodani et al. 1985), and the fluorescence intensity was measured at 450 nm with excitation at 360 nm in a spectrofluorometer equipped with a flow cell (Model F-1050, Hitachi, Tokyo, Japan) and a chromatographic data processor (Model C-R3A, Shimadzu, Kyoto, Japan). Figure 1 shows typical chromatograms of the standard solution of 1 pmol histamine (a), a dialysate of normal CSF (b) and a dialysate of high K^+ CSF (c). The detection limit with this system was approximately 10 fmol per injection.

In each experiment, mean of the first 3 fractions was defined as the mean basal release, and following fractions were expressed as percent of the mean basal release except in Fig. 2. The differences between the mean basal release and the evoked release, and between the release of drug-treated and control animals were tested using Wilcoxon's non-parametric test.

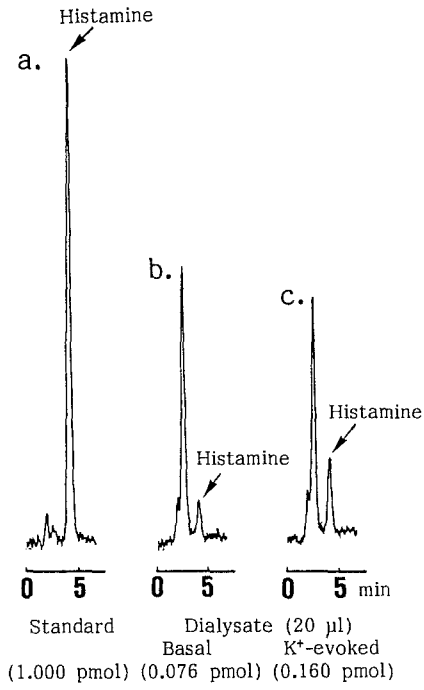

Fig. 1 a–c. Chromatograms of a standard solution of histamine (**a**), a dialysate with normal CSF (**b**) and a dialysate with high K^+ CSF (**c**). The absolute values of the histamine peaks are indicated in *parentheses*

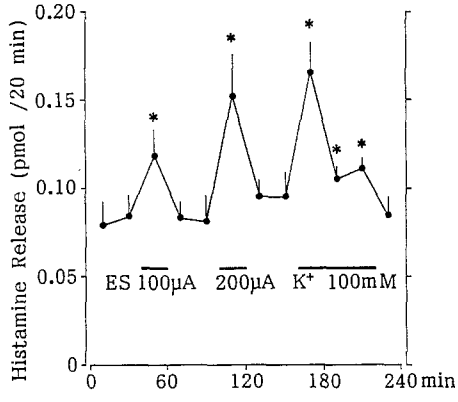

Fig. 2. Effects of an electrical stimulation of the tuberomammillary nucleus and high K^+ CSF perfusion of the anterior hypothalamic area on histamine release in the anterior hypothalamic area. Results are mean values and their standard errors as *vertical bars* ($n = 6$). *, $P < 0.05$ *vs.* the mean basal release

Results

Release of histamine in the anterior hypothalamic area

Figure 2 shows the release of endogenous histamine in the anterior hypothalamic area in vivo. The mean basal release was 0.09 ± 0.01 pmol/20 min. Histamine release was significantly increased to 133 and 166% of the mean basal release ($P < 0.05$) by electrical stimulation of the tuberomammillary nucleus at 100 or 200 µA, respectively. Histamine release was also increased to 188% of the basal level ($P < 0.05$) when the anterior hypothalamic area was depolarized by perfusion of high K^+ CSF.

Effects of Ca^{2+} removal on histamine release

Removal of Ca^{2+} from the CSF did not affect the basal release, but completely inhibited the release evoked by

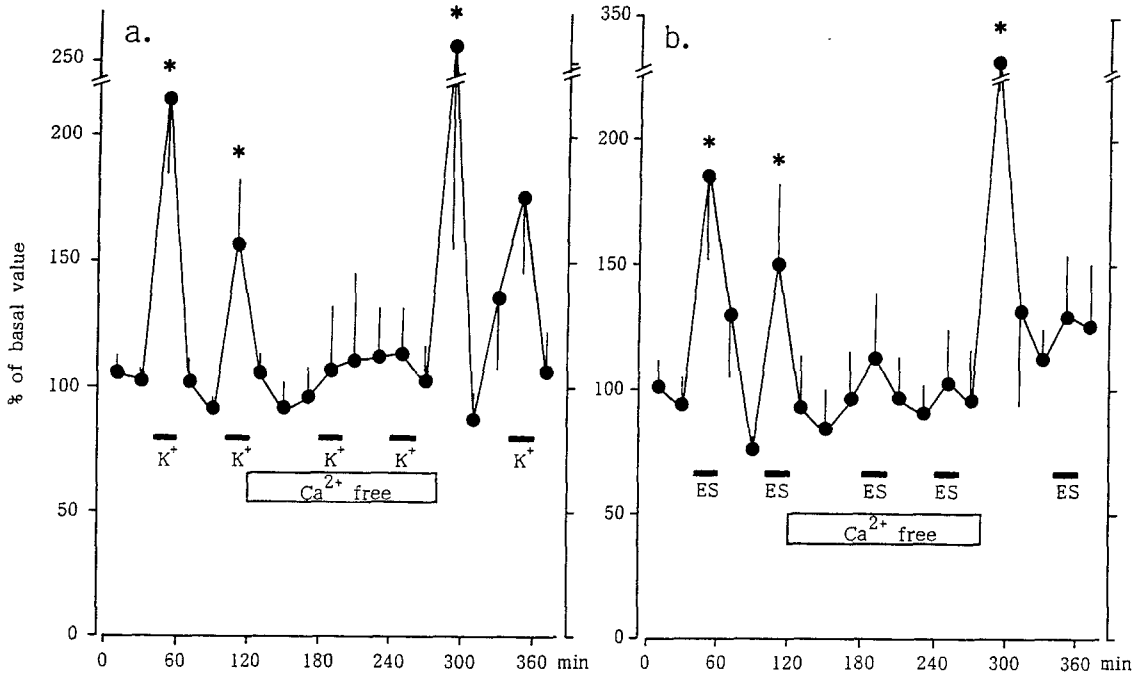

Fig. 3a, b. Effect of removal of extracellular Ca^{2+} on histamine release in the anterior hypothalamic area evoked by high K^+ CSF perfusion in the anterior hypothalamic area (**a**) and electrical stimulation of the tuberomammillary nucleus (**b**). Results are mean values and their standard errors as *vertical bars* ($n = 3$). *, $P < 0.05$ *vs.* the mean basal release

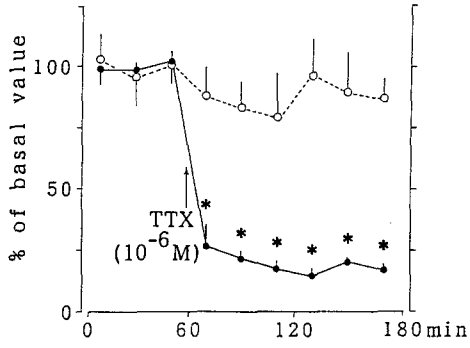

Fig. 4. Effect of TTX infusion on histamine release in the anterior hypothalamic area. The average values of the first three fractions (*closed circle*, TTX experiment; *open circle*, control experiment) are taken as 100%. The beginning of TTX infusion is indicated by an *arrow*. Results are mean values and their standard errors as *vertical bars* ($n = 3$). *, $P < 0.05$ *vs.* the value of control animals

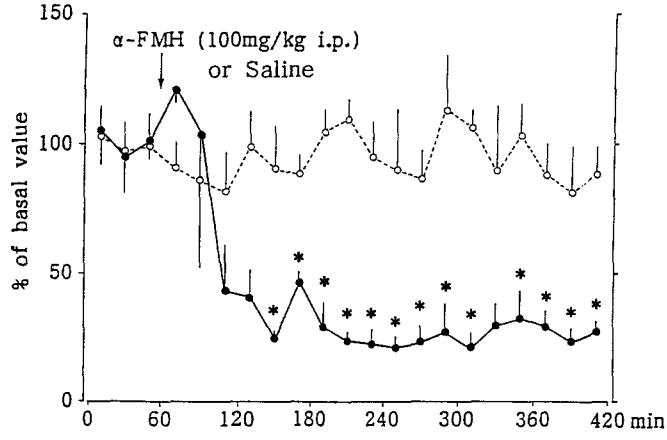

Fig. 5. Effect of α-FMH injection (i.p.) on histamine release in the anterior hypothalamic area. The average values of the first three fractions (*closed circle*, FMH experiment; *open circle*, control experiment) are taken as 100%. The time of FMH or saline injections is indicated by an *arrow*. Results are mean values and their standard errors as *vertical bars* ($n = 3$). *, $P < 0.05$ *vs.* the value of control animals

high K^+ CSF perfusion (Fig. 3a) and electrical stimulation (Fig. 3b). On reintroduction of normal CSF, histamine release showed a transient large increase and then rapidly returned to the basal level within 20 min.

Effect of TTX on histamine release

As shown in Fig. 4, on addition of TTX to the CSF, the basal histamine release promptly decreased to less than 20% of the control value ($P < 0.05$).

Effect of FMH on histamine release

The basal histamine release in the anterior hypothalamic area decreased to about 40% of the control value 1 h after i.p. injection of FMH ($P < 0.05$), and decreased further to less than 20% of the control value in the next 2 h (Fig. 5).

Effect of thioperamide on histamine release

The basal histamine release in the anterior hypothalamic area increased to about 300% of the control values within

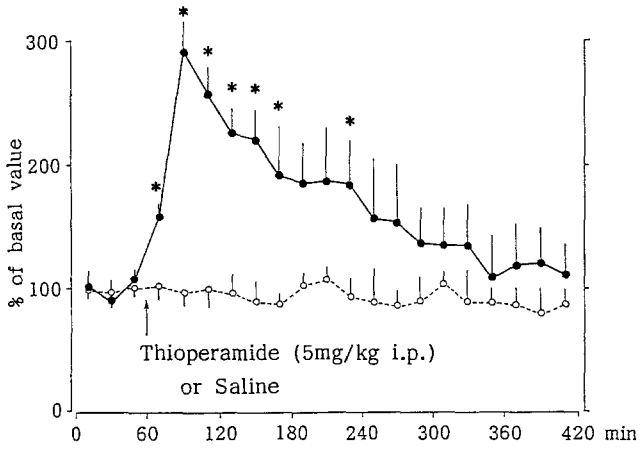

Fig. 6. Effect of thioperamide injection (i.p.) on histamine release in the anterior hypothalamic area. The average values of the first three fractions (*closed circle*, thioperamide experiment; *open circle*, control experiment) are taken as 100%. The time of thioperamide or saline injections is indicated by an *arrow*. Results are mean values and their standard errors as *vertical bars* ($n = 3$). *, $P < 0.05$ *vs.* the value of control animals

1 h after injection of thioperamide ($P < 0.05$), and then gradually returned to the control level (Fig. 6).

Discussion

In vivo microdialysis is a method for determining the interstitial concentrations of various substances in living tissues, and has been used to study the dynamics of neurotransmitters in discrete areas of the brain (Benveniste 1989). In this study, using the microdialysis method, we examined in vivo release of endogenous histamine in the anterior hypothalamic area, which is the region of the brain with the highest density of histaminergic fibers (Inagaki et al. 1988; Panula et al. 1989). The existence of the histaminergic neuron system in rat brain has been established (Schwartz et al. 1986; Yamatodani et al. 1991), but there are non-neuronal storage pools of histamine in the brain, i.e. mast cells and vascular endothelial cells (Hough 1988). The presence of a large quantity of non-neuronal histamine makes it difficult to study the nature of neuronal histamine. So a critical point in this study was whether the histamine detected was of neuronal origin.

Histamine release increased in response to electrical stimulation of the tuberomammillary nucleus, the region in which histaminergic cell bodies are located, and also in response to perfusion of the anterior hypothalamic area with high K^+ CSF (Fig. 2). The evoked release of histamine were prevented completely by removal of Ca^{2+} from the perfusion fluid (Fig. 3), and the basal release of histamine was also suppressed by infusion of TTX into the anterior hypothalamic area (Fig. 4). These characteristics of histamine release are similar to those of dopamine release in the striatum (Imperato and Di Chiara 1984; Westerink et al. 1987; Zetterström et al. 1988) and acetylcholine release in the striatum and the cerebral cortex (Damsma et al. 1987; Kurosawa et al. 1989). However, they are different from those of histamine release from mast cells. Mast cells are devoid of voltage-sensitive calcium channels (Penner et al. 1988) and then depolarization stimuli do not induce histamine release from them (Schwartz 1975). In some unphysiological conditions, such as general administration of compound 48/80, a very potent mast cell degranulator, histamine release from mast cells may contribute to the extracellular concentration of histamine measured by microdialysis (Russell et al. 1990). However, present results clearly indicate that both the basal and evoked release of histamine we observed in a physiological condition were of neuronal origin.

The basal rate of release of histamine in the anterior hypothalamic area of anaesthetized rats, 4.4 ± 0.6 fmol/min, was similar to that of conscious and freely moving rats observed during the light-period (15:00–17:30, 4.7 ± 0.4 fmol/min; Mochizuki et al. to be published), indicating that urethane anaesthesia did not affect in vivo histamine release appreciably. Assuming that the relative recovery of histamine through the membrane in in vivo dialysis conditions is the same with that in in vitro conditions (39.2%), the extracellular concentration of histamine can be estimated as 11.2 nM. Very recently, Russell et al. (1990) reported that the basal concentration of extracellular histamine in the hypothalamus of chloral hydrate-anaesthetized rat was 8.5 nM as measured by microdialysis combined with radioenzymatic assay. These two values are in good accord.

The basal release of histamine did not decrease on removal of the extracellular Ca^{2+}, just like the basal release of acetylcholine (Westerink et al. 1988). These findings may have been due to difficulty in removing sufficient extracellular Ca^{2+} to decrease the basal release of neurotransmitters.

The release of dopamine from the striatum measured by microdialysis was reported to increase to about 5–18 times the basal value on the high K^+ perfusion (Imperato and Di Chiara 1984; Zetterström et al. 1988; Westerink et al. 1989). The release of neuronal serotonin was also increased to about 8–21 times by high K^+ perfusion (Kalén et al. 1988). However, the release of histamine increased only 1.5- to 2-fold over the basal release (Fig. 2). In a push-pull perfusion study, the maximal rate of evoked histamine release observed in the hypothalamus of anaesthetized cats was also reported to be about 3-fold the basal release (Prast et al. 1989) and a similar value was obtained by microdialysis (Russell et al. 1990). The relatively high basal release and relatively low evoked release might be characteristic features of the histaminergic neuron system.

FMH is a potent and specific inhibitor of HDC. Its in vivo administration depletes the pool of histamine with rapid turnover, i.e., neuronal histamine (Garbarg et al. 1980; Maeyama et al. 1982, 1983) and so it has been widely used in physiological and pharmacological studies (Watanabe et al. 1990). In this work, we found that the release of histamine in the anterior hypothalamic area decreased to less than 20% of the control level 2 h after i.p. injection of FMH and remained low for the rest of the observation period (Fig. 5). These results indicate

that neuronal histamine has a very rapid turnover rate and that the activity of the histaminergic neuron is dependent on HDC activity.

Arrang et al. (1987), using slice preparations, obtained evidence for a local feedback mechanism regulating the release and synthesis of histamine through a presynaptic autoreceptor designated as H_3-receptor, and showed that thioperamide was a specific antagonist of the receptor. Garbarg et al. (1989) and Oishi et al. (1989) reported that thioperamide elicited prolonged increase of histamine turnover indicated by changes in the contents of histamine and N^{τ}-methylhistamine in the cortex of rats. In this study, we demonstrated the increase in endogenous histamine release in living brain after injection of thioperamide (Fig. 6). This increase was greater than those elicited by electrical stimulation of the tuberomammillary nucleus or high K^+ perfusion of the anterior hypothalamic area, suggesting that presynaptic control mediated through the H_3-autoreceptor constitutes a major regulatory mechanism of histaminergic neuron activity (Garbarg et al. 1989).

The in vivo release of histamine has been examined by a push-pull perfusion technique. Philippu et al. (1982) observed delayed effects of depolarization stimuli on histamine release in anaesthetized cats, and concluded that depolarization of the superfused region led to the release of other neurotransmitters, which in turn enhanced histamine release. Prast et al. (1988, 1989) found that the rate of histamine release in anaesthetized cats was dependent on the activity of other histaminergic or non-histaminergic neurons which may be localized in remote brain areas. Furthermore, in vitro studies on hypothalamic or cortical slices and synaptosomes of rats demonstrated that the neuronal histamine release was modulated through NMDA-, GABA- (Kishino et al. 1989), α_2- (Hill and Straw 1988), muscarinic (Gulat-Marnay et al. 1989) and nicotinic (Ono et al. 1990) receptors. The present microdialysis method will be useful in analyzing these regulatory mechanisms of release of endogenous neuronal histamine in vivo.

In this work, we monitored the endogenous release of histamine in rat brain successfully using a combination of a microdialysis technique and a highly sensitive HPLC-fluorometric method. We confirmed that this histamine was of neuronal origin by several types of experiments. We also demonstrated the importance of HDC activity and presynaptic H_3-receptor in regulating the activity of histaminergic neurons.

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