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Effect of Unilateral Vestibular Stimulation on Histamine Release From the Hypothalamus of Rats In Vivo

A. HORII, N. TAKEDA, T. MATSUNAGA, A. YAMATODANI, T. MOCHIZUKI, K. OKAKURA-MOCHIZUKI, AND H. WADA
Departments of Otolaryngology, Molecular Physiology, and Pharmacology II, Osaka University Medical School, Suita 565, Japan.

SUMMARY AND CONCLUSIONS

1. We investigated the effect of unilateral vestibular stimulation on histamine release from the anterior hypothalamic area of urethan-anesthetized rats in vivo, using a brain microdialysis method coupled with high-performance liquid chromatography fluorometry.

2. The histamine release was increased to ~180% of the basal release by the electrical stimulation of the inner ear with 1 Hz, 500 μA, and 200 ms for 20 min. This effect was dependent on the current intensity.

3. Activation of the unilateral horizontal semicircular canal by middle ear irrigation for 15 min with 45°C water increased the histamine release to ~200% of the basal release.

4. Irrigation of the middle ear with ice water for 15 min increased the histamine release to ~190% of the basal release.

5. The histamine release was not changed by the irrigation of the middle ear with 37°C water and the irrigation of the auricle with ice water, which suggests that neither somatosensory stimulation to the middle ear nor nonspecific cold stress affects the histamine release.

6. All these findings suggest that the sensory mismatch signals induced by caloric stimulation and unilateral electrical vestibular stimulation activate the histaminergic neuron system in the brain.

INTRODUCTION

Acute vestibular disorders, such as a sudden change in the resting discharge of vestibular afferents in Ménière's disease and the unilateral loss of vestibular end organs as a result of labyrinthectomy, cause vertigo. The acute vestibular disorders are frequently associated with such autonomic reactions as nausea and vomiting, and these symptoms can be relieved by histamine H_1 blockers (Cohen and deJong 1972). The vestibular system participates in the development of motion sickness in humans (Money 1970), and the efficacy of H_1 blockers on preventing motion sickness is widely accepted (Wood and Graybiel 1970). Therefore the involvement of the histaminergic neuron system in the brain is suggested in vestibuloautonomic process. Recently, the highest density of the fibers of the histaminergic neuron system was found in the hypothalamic nuclei (Inagaki et al. 1990; Watanabe et al. 1984). Brain histamine was suggested to be involved in hypothalamic regulation of the autonomic nervous system (Yamatodani et al. 1991). Both studies also support histaminergic involvement in vestibuloautonomic reaction.

The in vivo neurotransmitter levels in the extracellular fluid in the CNS have been successfully determined by a microdialysis technique (Ungerstedt 1991). Recently, using this technique coupled with a highly sensitive high-performance liquid chromatography (HPLC) assay method, Mochizuki et al. (1991, 1992) succeeded in determining neuronal histamine release from the anterior hypothalamic area (AHy) of rats and found that the extracellular levels of histamine showed a clear circadian rhythm and that the histamine release was regulated by presynaptic *N*-methyl-D-aspartate receptors (Okakura et al. 1992).

In the present study we attempt to clarify the possible vestibular influence on histaminergic neuronal activity. We examine the effect of electrical stimulation of the inner ear through the round window as well as the effect of caloric stimulation on the histamine release from the AHy of rats in vivo using the microdialysis method.

METHODS

The animal experiments in this study were conducted under the guidelines approved by the Animal Care Committee of Osaka University Medical School.

Microdialysis methods and histamine analysis

Male Wistar strain rats weighing 180–300 g were anesthetized with urethan (1.2 g/kg ip). A microdialysis probe (CMA/10, membrane length 2 mm, Carnegie Medicine, Stockholm, Sweden) was stereotaxically inserted into the right AHy according to the atlas of Paxinos and Watson (1986). The probe was perfused with artificial cerebrospinal fluid (ACSF) 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 the dialysates were collected every 20 min. The composition of the ACSF was (in mM) 140 NaCl, 3 KCl, 2.5 $CaCl_2$, and 5 glucose, pH adjusted to 7.4. In each experiment, the rectal temperature was monitored and maintained at 37°C using a temperature controller (CMA/150, Carnegie Medicine). After each experiment, the brains were removed and cut into 50-μm coronal sections in a cryostat to confirm the location of the probe.

The histamine concentration of the dialysate was determined by a sensitive HPLC fluorometric method (Yamatodani et al. 1985) with slight modification (Mochizuki et al. 1991). After sampling, perchloric acid was added to the dialysate to a final concentration of 2% and 20 μl of the mixture were injected into a column (4 mm ID × 50 mm) packed with a cation exchanger, TSKgel SP2SW (Tosoh, Tokyo; particle size 5 μm). Histamine was eluted with 0.25 M KH_2PO_4 at a flow of 0.6 ml/min and derivatized by an on-line automated Shore's *o*-phthalaldehyde method. The fluorescence intensity was measured at 450 nm with excitation at 360 nm. The detection limit was 0.01 pmol per injection.

In each experiment, the mean of the first three fractions was

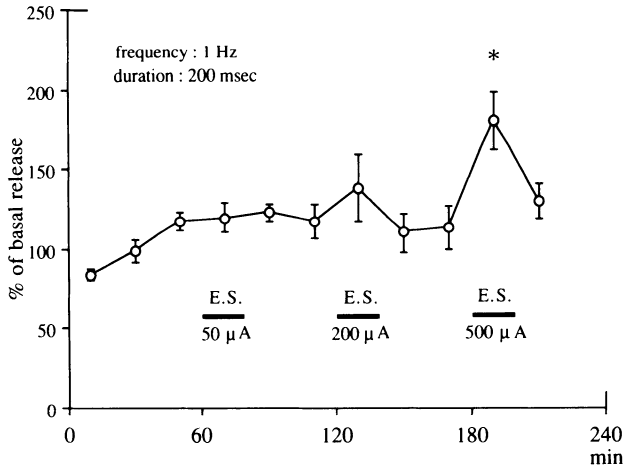

FIG. 1. Effect of electrical stimulation of the inner ear on histamine release from the anterior hypothalamic area (AHy). Intensity was changed from 50 to 500 μA at intervals of 40 min. Results were means ± SE ($n = 7$). Periods of electrical stimulation are indicated by horizontal bars. Asterisk: $P < 0.01$ vs. the release immediately before the evoked release.

defined as the mean basal release and the following fractions were expressed as a percentage of this mean basal release. The differences between the evoked release and the release immediately before the evoked release were examined with a paired two-tailed t test.

Electrical stimulation

Seven animals were used in this experiment. The bulla tympani of the right ear was opened by a retroauricular surgical approach under urethan anesthesia (1.2 g/kg). A stainless steel wire insulated except for 2 mm at the tip was placed on the round window as a stimulating electrode and another one placed on a cervical muscle served as a reference electrode. The round window was stimulated with negative square-wave pulses (1 Hz, 200 ms, 50–500 μA) during a collection period of 20 min at 40-min intervals. The electrical stimulation was delivered by a constant current stimulator (DPS-160B, Dia Medical System, Tokyo). The eye movements that occurred during the electrical stimulations were observed.

Caloric stimulation

Eleven animals were used in this experiment. Caloric vestibular stimulation was induced through the middle ear. Under urethan anesthesia (1.2 g/kg) the bulla tympani of the right ear was opened and a Teflon tube (outer diameter 0.965 mm) was inserted into the middle ear. Through this tube the middle ear was irrigated with water. In all irrigation the flow rate was fixed at 5 ml/min with a peristaltic pump, and each of the irrigation periods lasted for 15 min. In the first group of five animals, we measured their histamine release during ice-water irrigation of the auricle, irrigation of the middle ear with hot water (45°C), and irrigation of the middle ear with ice water at 40-min intervals. In the second group of three animals, the middle ear was irrigated with water at body temperature (37°C) and with ice water at an interval of 40 min. The eye movements that occurred during caloric stimulation were observed.

In another experiment, we examined caloric nystagmus in unanesthetized animals. Rats ($n = 3$) were anesthetized with pentobarbital sodium (40 mg/kg ip). The bulla tympani was opened for a Tefrone tube (0.965 mm OD) to be inserted. After recovering from the anesthesia the animals were injected with pentazocine (10 mg/kg sc) to avoid possible pain (Blane 1967) induced by the caloric stimulation. Then animals were placed in a prone position in individual restraining cages and caloric stimulation was applied to the middle ear through the tube. Caloric nystagmus was observed during the ice-water irrigation of the auricle and the irrigation of the middle ear with water at 37, 45, and 0°C each for 15 min at an interval of 40 min. The flow rate of the irrigations was fixed at 5 ml/min with peristaltic pump.

RESULTS

Electrical stimulation

Figure 1 shows the effect of the electrical stimulation of the inner ear on histamine release from the AHy. The basal histamine release was 0.047 ± 0.006 pmol per 20 min (mean ± SE, $n = 7$). The histamine release was not changed by 50-μA electrical stimulation; however, with 200- and 500-μA stimulation it was increased to 138 and 181% ($P < 0.01$) of the basal release, respectively. No eye deviation was induced by the 50-μA electrical stimulation. An upward shift of the right (ipsilateral) eye and a downward shift of the left eye were observed during the electrical stimulation of 200 and 500 μA.

Caloric stimulation

Figures 2 and 3 show the effect of the caloric stimulation on histamine release from the AHy. The histamine release was not affected by the 15-min ice-water irrigation of the auricle. Both hot (45°C) and ice-water irrigation of the middle ear for 15 min increased the histamine release to 196% ($P < 0.05$) and 194% ($P < 0.05$) of the basal release, respectively (Fig. 2). The middle ear irrigation with 37°C water did not affect the histamine release, even though it had been increased significantly by ice-water irrigation in the same preparation (Fig. 3). Slight eye deviation, but no caloric nystagmus, was induced by the caloric stimulation under urethan anesthesia.

In unanesthetized rats, the hot-water (45°C) irrigation of the right middle ear induced horizontal nystagmus toward the right side, and the ice-water irrigation of the right middle ear induced it toward the left side. No nystagmus was

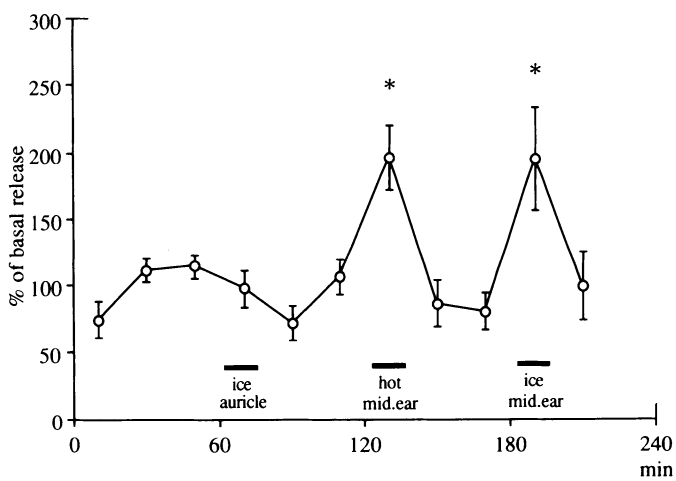

FIG. 2. Effect of caloric stimulation on histamine release from the AHy. Irrigation with ice water of the auricle, with hot water of the middle ear (mid. ear), and with ice water of the middle ear was carried out during the periods indicated by horizontal bars. Results were means ± SE ($n = 5$). Asterisk: $P < 0.05$ vs. the release immediately before the evoked release.

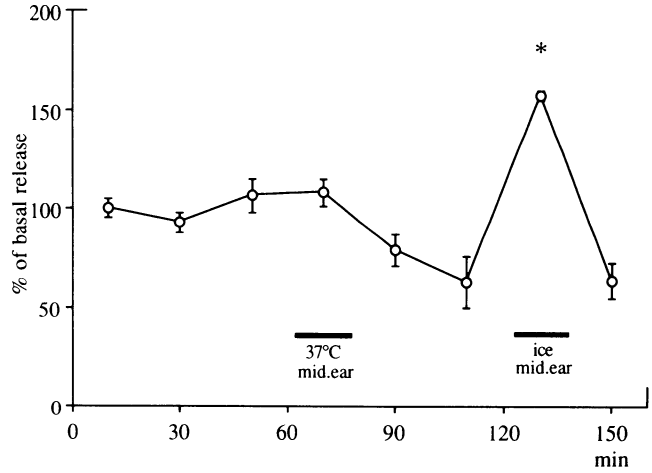

FIG. 3. Effect of caloric stimulation on histamine release from the AHy. Irrigation of the middle ear (mid. ear) with 37°C water and with ice water was carried out during the periods indicated by horizontal bars. Results were means ± SE ($n = 3$). Asterisk: $P < 0.01$ vs. the release immediately before the evoked release.

induced by the ice-water irrigation of the auricle or by the middle ear irrigation with 37°C water.

DISCUSSION

We have observed neither changes in the histamine release from the AHy nor the eye deviation during 50 μA of electrical stimulation to the round window. However, when 200 and 500 μA of electrical stimulation were applied, the histamine release was increased to ~140 and 180% ($P < 0.01$) of the basal release, respectively, and vertical eye deviation was observed. Goldberg et al. (1984) reported that electrical stimulation to the perilymphatic space of the vestibule modulated the firing rates of vestibular primary afferent nerves, presumably because the currents acted directly on the primary afferent nerves. We could assume that the vertical eye deviation in this study was probably caused by the stimulation to the vestibular nerve. These findings suggest that hypothalamic histamine release was evoked by electrical stimulation of the vestibular nerve.

The electrical stimulation applied to the round window not only activated the vestibular afferents but also may have affected the cochlea or adjacent brain. Because the effect of the electrical stimulation was not confined to the vestibular system, we next examined the effect of caloric stimulation, which was known to be specific to the vestibular labyrinth. According to the endolymphatic convection current theory, caloric stimulation is most effective when the horizontal semicircular canal is in vertical position. In our preparations, animals were placed on a David Kopf stereotaxic frame so that the horizontal semicircular canal was not horizontal but was tilted 30° up from the horizontal plane. The caloric nystagmus was not observed in urethan-anesthetized rats. This is presumably because the fast phase of nystagmus was suppressed by the anesthesia (Collins 1974). In unanesthetized rats, nystagmus to the same side as the stimulated ear was observed during the hot-water irrigation, which suggests that our hot-water caloric procedure induced an ampullopetal endolymphatic flow in the horizontal semicircular canal. This observation concurs with Ewald's law (Bárány 1906; Honrubia et al. 1981), which states that the ampullopetal deviation of the cupula induced by hot-water irrigation increases impulses from the ipsilateral horizontal semicircular canal, and as a result the nystagmus was directed toward the stimulated side. The middle ear irrigation with hot water increased the histamine release from the AHy to ~200% of the basal release, which suggests that an increase of afferent impulses from the unilateral horizontal semicircular canal evoked the histamine release from the AHy.

The middle ear irrigation with cold water also increased the histamine release from the AHy to ~190% of the basal release. A decrease of afferent impulses from the unilateral horizontal semicircular canal could also evoke histamine release from the AHy, because the cold-water irrigation induced nystagmus contralaterally to the stimulated ear in unanesthetized rats. These findings suggest that the histaminergic neuron system in the brain was activated by an increase and a decrease of vestibular afferent impulses.

On the other hand, the ice-water irrigation to the auricle or the 37°C water irrigation to the middle ear did not affect the histamine release, and neither caused endolymphatic flow. These findings indicate that neither nonspecific cold stress nor somatosensory stimulation to the middle ear caused an increase in the histamine release. The possibility that the measured effect was due to a change of arousal state still remains. If the caloric stimulus caused a change of arousal state, nystagmus should be observed. Because the caloric nystagmus was not observed in the urethan-anesthetized rats, the stimulus did not cause changes in the arousal state. Therefore this possibility could be denied.

Borison and Wang (1953) evoked vomiting by electrical stimulation of the brain stem and concluded that the effective loci were concentrated in the parvicellular reticular formation (PCRF). Mehler (1983) clarified the nerve fiber connection between PCRF and several brain stem nuclei and areas, and identified the nucleus tractus solitarii, the dorsal motor nucleus of the vagus, and the nucleus ambiguus as the nuclei that constituted integral functional components of various visceral pathways and actual emetic circuits. It was suggested that the vomiting center was characterized by the neural interactions between these nuclei and PCRF. Immunohistochemical studies with anti-histidine decarboxylase antibody demonstrated that the histaminergic fibers were distributed in PCRF, the nucleus tractus solitarii, and the dorsal motor nucleus of the vagus (Inagaki et al. 1988). In autoradiographic studies in which [^{3}H]-mepyramine was used, H_1 receptors were located in PCRF, the nucleus tractus solitarii, the dorsal motor nucleus of the vagus nerve, and the nucleus ambiguus (Palacios et al. 1981). These studies indicate that both the histaminergic fibers and H_1 receptors are located in the vomiting center. There were several studies reported on the relationship between histamine and vomiting. Bhargava et al. (1982) reported that intracerebroventricular administration of histamine caused vomiting in dogs. We demonstrated that the double rotation around two axes that produced motion sickness in rats increased histamine content in the hypothalamus and the medulla oblongata, whereas single rotation around one axis produced neither motion sickness nor increased histamine content (Takeda et al. 1986). We also

reported that α-fluoromethylhistidine, which depletes the neuronal component of brain histamine, prevented motion sickness in rats (Takeda et al. 1989) and cats (Lucot and Takeda 1992). Clinically, emesis associated with acute vestibular disorders or motion sickness is inhibited by histamine H_1 blockers (Cohen and deJong 1972; Wood and Graybiel 1970). These findings suggest that the central histaminergic neuron system plays a physiologically significant role in vomiting in vertigo and motion sickness.

Housley et al. (1988) reported that histamine (0.001–0.1 mM) increased the firing rate of afferent ampullar nerves of frog, whereas both histamine H_1 and H_2 antagonists (0.01–0.05 mM) inhibited the ampullar nerve activity. This report suggested that histamine might have acted as a hair cell transmitter in frog, and the action site of H_1 antagonists that were used to treat vertigo and motion sickness was in such a peripheral location as the semicircular canal. In contrast, Bledsoe et al. (1989) reported that histamine (0.002–2.0 mM) had no effect on the spontaneous activity of frog's ampullar nerve, whereas pyrilamine (0.01–0.05 mM), an H_1 antagonist, suppressed the spontaneous activity. Because histamine (2.0 mM) failed to block the actions of pyrilamine (0.1 mM), they concluded that the action of pyrilamine was nonspecific, possibly because of blockade of voltage-dependent sodium channels. Kohl et al. (1987) reported that astemizole, an H_1 antagonist that does not cross the blood-brain barrier, had no effect on controlling motion sickness in humans that was induced through cross-coupled accelerative semicircular canal stimulation in a rotating chair. Furthermore, our immunohistochemical study using anti-histidine decarboxylase antibody failed to find histidine decarboxylase-reactive sites in rat labyrinth (unpublished data). These findings strongly suggest that the sites for H_1 blocker may be in central rather than peripheral locations.

Physiological vertigo (motion sickness) and pathological vertigo (peripheral or central vestibular lesions) are generated by an acute sensory mismatch between the expected sensory patterns and the converging inputs from the labyrinth, the eyes, or somatosensory receptors (Brandt 1991). The sensory mismatch signals cause vertigo by disturbing the cortical spatial orientation and vomiting by activating the vomiting center in the medulla oblongata. The autonomic reaction associated with the caloric stimulation induced by both cold and hot water is caused by the canal-otolith mismatch (Benson 1984). An acute unilateral labyrinthine dysfunction causes vertigo because the sensation of self-motion induced by the vestibular imbalance contradicts the vision and the somatosensors (Brandt 1991). Unilateral electrical stimulation to the round window may also cause the intervestibular imbalance. The canal-otolith mismatch induced by the caloric stimulation and the intervestibular imbalance induced by the unilateral electrical vestibular stimulation cause the sensory mismatch to induce the autonomic reaction. Examining our results together with the reports by others, we could conclude that the histaminergic neuron system was activated by the sensory mismatch signals induced by the caloric stimulation and unilateral electrical vestibular stimulation.

The physiological and clinical vertigo syndromes are commonly characterized by a combination of phenomena involving perceptual, ocular motor, postural, and vegetative manifestations; their symptoms are vertigo, nystagmus, ataxia, and nausea. Although such autonomic reactions as nausea and vomiting are related to activation of the vomiting center, the pathways or receptors involved in the vestibuloautonomic reflex have not been identified. On the basis of our findings in this study, we are able to propose a pathway from vestibular inputs to hypothalamic histaminergic neurons as a neuronal circuit that is involved in the vestibuloautonomic reflex. Although no monosynaptic innervation from the vestibular nuclei to the histaminergic neurons in the hypothalamic tuberomammillary nucleus has been shown in morphological studies (Ericson et al. 1991), the neurons in the lateral hypothalamic area have responded to electrical stimulation of the lateral vestibular nucleus in both extracellular and intracellular recordings, and this response was considered to be polysynaptic because the latencies were shortened by stimulation of higher current (Katafuchi et al. 1987). Several indirect pathways from the vestibular nuclei to the hypothalamus have been reported. Ericson et al. (1991) identified an afferent connection to the hypothalamic tuberomammillary nucleus from the nucleus prepositus hypoglossi, which is known to connect with the vestibular nuclei. Pompeiano (1977) reported that the reticular neurons responded to ampullar or macular stimulation. Brodal (1972) demonstrated a pathway from the vestibular nuclei to the reticular formation using degeneration techniques. Another degeneration study has shown the existence of a reticulohypothalamic pathway (Wolf and Dicara 1971). It is possible that the vestibular inputs were transmitted polysynaptically to the hypothalamus via the reticular formation utilizing its ascending projections to the forebrain. There are studies that indicate that the vestibular system has strong connections with the fastigial nucleus of the cerebellum and that report possible pathways through which the vestibular information may reach the hypothalamus, i.e., through fastigioreticular (Walberg et al. 1962) and fastigiohypothalamic (Harper and Heath 1973) pathways. Because sensory mismatch signals create stress as a warning signal for the body to withdraw from unusual situations (Brandt 1991), the stress generated by sensory mismatch signals may activate the histaminergic neuron system.

The histaminergic hypothesis may also explain oliguria associated with acute vestibular disorders and motion sickness. The plasma vasopressin level was increased in those individuals who suffered from motion sickness (Eversmann et al. 1978). It was reported that some histaminergic fibers innervate the paraventricular nucleus, a nucleus containing vasopressinergic neurons (Inagaki et al. 1988). Vasopressin release can be increased by intracerebroventricular administration of histamine, utilizing H_1 receptors (Dogterom et al. 1976; Tuomisto et al. 1984). These reports indicate that histaminergic inputs to the paraventricular nucleus might aid in the development of oliguria in acute vestibular disorders and motion sickness.

In conclusion, our findings in the present study suggest that the sensory mismatch signals generated by caloric stimulation and unilateral electrical vestibular stimulation activate the histaminergic neuron system and that histaminergic activation is involved in autonomic reactions including

nausea, vomiting, and oliguria with acute vestibular disorders and motion sickness.

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Address for reprint requests: A. Horii, Dept. of Otolaryngology, Osaka University Medical School, 2-2 Yamadaoka, Suita, Osaka 565, Japan.

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