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Alleviation of ischemic neuronal damage by histamine H_2 receptor stimulation in the rat striatum

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Abstract

Transient ischemia was produced for 15 min by occlusion of the middle cerebral artery in halothane-anesthetized rats, and changes in the extracellular concentrations of neurotransmitter monoamines and amino acids were examined in the striatum. The occlusion produced marked increases in the extracellular concentrations of both dopamine and glutamate in the striatum in the saline-injected control group, the peak values being 148 and 5.2 times those before ischemia, respectively. Preischemic administration of histamine (200 nmol, i.c.v.) suppressed the increase in dopamine and glutamate levels during ischemia, the peak values being 38% and 40% of those in the control group, respectively. Neither the dopamine nor glutamate level was affected by 6-[2-(4-imidazolyl)ethylamino]-*N*-(trifluoromethylphenyl)heptanecarboxamide (HTMT), an H_1 agonist (100 nmol, i.c.v.). However, dimaprit, an H_2 agonist (100 nmol, i.c.v.) suppressed the peak values to 42% and 32%, respectively. Most neurons were degenerated 7 days after ischemia in control animals. Histologic outcome was alleviated by either histamine or dimaprit treatment, whereas HTMT did not affect the outcome. Although postischemic administration of mepyramine, an H_1 antagonist (5 nmol, i.c.v.), did not affect the histologic alleviation caused by preischemic treatment with histamine, ranitidine, an H_2 antagonist (30 nmol, i.c.v.), partly abolished the improvement caused by histamine. These results suggest that suppression of ischemic release of excitatory neurotransmitters by histamine H_2 action is a contributing factor in alleviation of histologic outcome.

Keywords: Cerebral ischemia; Dimaprit; Dopamine; Glutamate; Histamine; Striatum

1. Introduction

Histamine has been shown to possess neurotransmitter properties in the mammalian brain (Schwartz et al., 1986), regulating arousal level and memory retention by stimulating specific receptors on target cells in the brain (De Almeida and Izquierdo, 1986; Kalivas, 1982; Lin et al., 1988). The histaminergic system is widely distributed throughout the entire brain from cell bodies present in the tuberomammillary nucleus of the posterior basal hypothalamus (Watanabe et al., 1984), modulating the release of neurotransmitters from other neuronal systems, such as the dopaminergic, noradrenergic, and cholinergic systems (Philippu et al., 1984; Prast et al., 1999). In our previous studies, blockade of histamine H_2 receptors facilitated the ischemia-induced release of glutamate and dopamine, and also aggravated ischemic neuronal damage (Adachi et al., 2001, 2002). These findings imply the possibility that the elevation of the central histamine level protects neurons against ischemia through histamine H_2 receptors. In the present study, therefore, we examined the effects of histamine, 6-[2-(4-imidazolyl)ethylamino]-*N*-(trifluoromethylphenyl)heptanecarboxamide (HTMT), an H_1 agonist, and dimaprit, an H_2 agonist, on ischemia-induced release of dopamine, 5-hydroxytryptamine (5-HT), aspartate, glutamate, and glycine. For these purposes, we employed an animal model of middle cerebral artery occlusion, which provokes cerebral infarction in the striatum. To further clarify the causal relationship between neurotransmitter release and histologic outcome, the effects of postischemic administration of mepyramine, an H_1 antagonist, and ranitidine, an H_2 antagonist, were evaluated in histamine-treated animals.

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2. Materials and methods

2.1. Animals

This study was approved by the Committee on Animal Experimentation at Ehime University School of Medicine, Ehime, Japan. All animals received humane care in compliance with the Principles of Laboratory Animal Care formulated by Ehime University School of Medicine. Male Wistar rats (Charles River, Yokohama, Japan) weighing approximately 300 g were kept in groups in a room controlled at 23 ± 2 °C, maintained under an alternating 12-h light and 12-h dark cycle (lights on at 6:00 a.m.). The animals were deprived of food for at least 6 h because of the influence of preischemic plasma glucose concentration on the neurologic outcome.

2.2. Experiment 1: effects of histamine agonists

The effects of histamine-related agents on ischemia-induced release of neurotransmitters and histologic outcome were examined. Thirty-one rats were divided into four groups; saline-treated group ($n = 10$), histamine-treated group ($n = 7$), HTMT-treated group ($n = 6$), and dimaprit-treated group ($n = 8$).

The rats were anesthetized with 2% halothane in balanced 50% oxygen and 50% nitrous oxide, and were kept under spontaneous ventilation. After the animals were placed in a stereotaxic apparatus (David Kopf, Tujunga, CA, USA) in the prone position, the skull was exposed and two small burr holes were drilled: one in the left hemisphere (0.8 mm posterior and 1.5 mm lateral to the bregma) for drug administration, and the other in the right hemisphere (0.3 mm posterior and 4.0 mm lateral to the bregma) for the insertion of a microdialysis probe. Saline, histamine (200 nmol), HTMT (100 nmol), or dimaprit (100 nmol) was administered in a constant volume of 20 μl into the lateral ventricle through the burr hole via a 27-gauge needle at a depth of 5.0 mm below the brain surface, according to doses shown previously (Bugajski et al., 2000; Puebla and Arilla, 1996). An I-shaped microdialysis probe (A-I-8-01; Eicom, Kyoto, Japan) was then inserted into the right striatum through the burr hole, its tip positioned 6.0 mm below the brain surface. After the probe was fixed on the skull with dental cement, the probe was perfused with Ringer's solution at 2 μl/min.

After a stabilization period for 60 min, brain perfusates were collected every 15 min into microtubes on ice and stored at −80 °C until analysis. After the collection of the first microdialysate sample, surgery was started. With the rats in a supine position, the skin was incised along the median line of the neck, and the right carotid artery was exposed. After injection with heparin (100 units, i.p.), the root of the right middle cerebral artery was occluded by inserting a silicone-coated 4-0 nylon thread from the bifurcation of the internal and external carotid arteries. The tip of the thread was placed 18 mm distal from the bifurcation. After 15 min of ischemia, the thread was pulled by 5 mm to restore the blood flow. Before induction of ischemia, two microdialysate fractions were collected. Then, the collection of the third microdialysate fraction was started immediately after the insertion of the thread. Seven microdialysate fractions were collected after reperfusion of the blood flow. During the collection of the dialysates, the temporal muscle temperature was maintained at 37.5 ± 0.2 °C with a heating lamp. After collecting perfusates, all surgical incisions were sutured. The animals were allowed to recover from anesthesia, and the rectal temperature was kept at 37–38 °C. The animals were brought to their cages in a room maintained at constant temperature and allowed access to food and water ad libitum. The concentrations of dopamine, 3,4-dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA), 5-HT, and 5-hydroxyindoleacetic acid (5-HIAA) in dialysates were determined using a high-performance liquid chromatography system with electrochemical detection (Mitsuyo et al., 2003). The concentrations of amino acids were determined using a cation-exchange high-performance liquid chromatography system coupled with postcolumn fluorescent derivatization (Adachi et al., 2001).

Seven days after this transient ischemia, the animals were anesthetized with an intraperitoneal injection of sodium pentobarbital (50 mg/kg). Their brains were then dissected and frozen at −15 °C. Brain slices, 6 μm thick, were cut with a cryostat along the coronal planes at the optic chiasma and stained with hematoxylin and eosin. The number of preserved neurons in a constant area (1 mm^2) in the striatum on each hemisphere was counted in a single-blinded manner.

2.3. Experiment 2: effects of histamine antagonists

To evaluate the relationship between changes in the extracellular concentrations of neurotransmitters and histologic outcome, the effects of postischemic administration of mepyramine, an H_1 antagonist, and ranitidine, an H_2 antagonist, on histologic outcome were examined in histamine-pretreated rats. Twenty rats were allocated to one of three groups; the control group, the mepyramine group, and the ranitidine group. After induction of anesthesia, all animals were stereotaxically injected with histamine (200 nmol, i.c.v.) and subjected to middle cerebral artery occlusion for 15 min, according to the procedure described above. Immediately after reperfusion, saline (20 μl, i.c.v.), mepyramine (5 nmol, i.c.v.), or ranitidine (30 nmol, i.c.v.) was injected into the animals of each corresponding group. The animals were allowed to recover from anesthesia and kept in a room at constant temperature. After 7 days, the striatum of the animals were observed by light microscopy by the procedure described in Experiment 1.

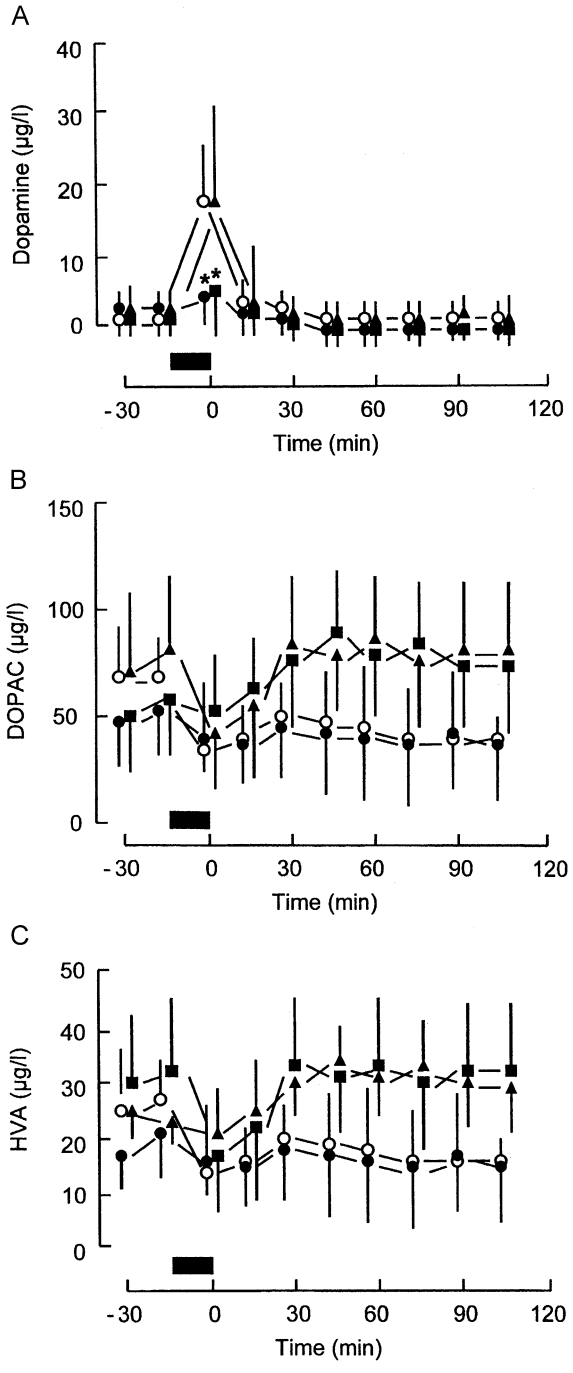

Fig. 1. The effects of histamine-related agents on ischemic changes in the concentrations of dopamine (A), DOPAC (B), and HVA (C) in dialysates from the striatum. Solid rectangles designate the duration of ischemia (15 min) produced by occlusion of the middle cerebral artery. Saline-injected group ($n=10$) (○), histamine (200 nmol, i.c.v.)-injected group ($n=7$) (●), HTMT (100 nmol, i.c.v.)-injected group ($n=6$) (▲), and dimaprit (100 nmol, i.c.v.)-injected group ($n=8$) (■). Each value represents the mean ± S.D. *$P<0.05$ as compared with each corresponding value in the saline group. DOPAC, 3,4-dihydroxyphenylacetic acid; HVA, homovanillic acid; HTMT, 6-[2-(4-imidazolyl)ethylamino]-*N*-(trifluoromethylphenyl)-heptanecarboxamide.

2.4. Statistical analysis

The data from the microdialysis experiments were analyzed using repeated-measures analysis of variance to detect differences among groups. When differences were found, the Scheffé test was used post hoc to compare each fractional value with that of the corresponding control group. The data from histology were analyzed using analysis of variance with the Scheffé test.

3. Results

3.1. Experiment 1: effects of histamine agonists

3.1.1. Monoamines and their metabolites

The concentration of dopamine in dialysates did not differ among the saline, histamine, HTMT, and dimaprit groups before induction of ischemia (Fig. 1). Cerebral

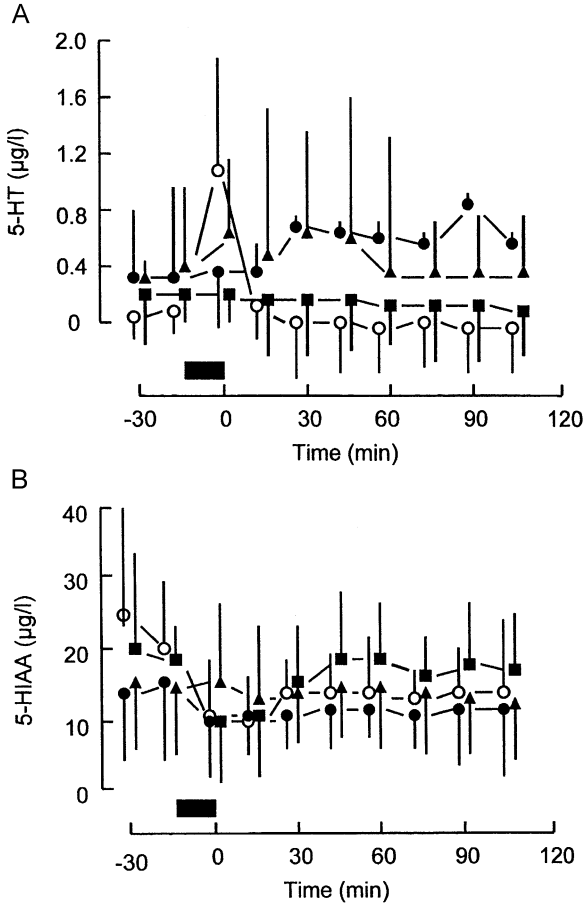

Fig. 2. The effects of histamine-related agents on ischemic changes in the concentrations of 5-HT (A) and 5-HIAA (B) in dialysates from the striatum. Solid rectangles designate the duration of ischemia (15 min) produced by occlusion of the middle cerebral artery. Saline-injected group ($n=10$) (○), histamine (200 nmol, i.c.v.)-injected group ($n=7$) (●), HTMT (100 nmol, i.c.v.)-injected group ($n=6$) (▲), and dimaprit (100 nmol, i.c.v.)-injected group ($n=8$) (■). Each value represents the mean ± S.D. 5-HT, 5-hydroxytryptamine; 5-HIAA, 5-hydroxyindoleacetic acid.

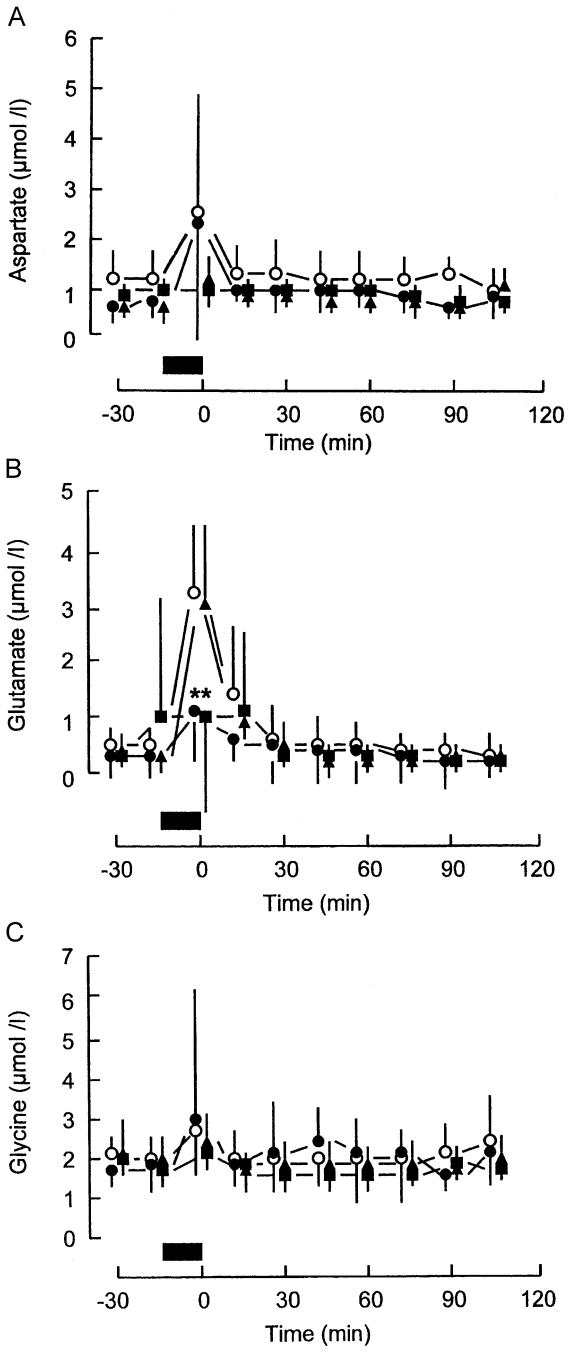

Fig. 3. The effects of histamine-related agents on ischemic changes in the concentrations of aspartate (A), glutamate (B), and glycine (C) in dialysates from the striatum. Solid rectangles designate the duration of ischemia (15 min) produced by occlusion of the middle cerebral artery. Saline-injected group ($n=10$) (○), histamine (200 nmol, i.c.v.)-injected group ($n=7$) (●), HTMT (100 nmol, i.c.v.)-injected group ($n=6$) (▲), and dimaprit (100 nmol, i.c.v.)-injected group ($n=8$) (■). Each value represents the mean ± S.D. *$P<0.05$ as compared with each corresponding value in the saline group.

ischemia produced a marked increase in the dopamine level in the saline group, the peak value being 148 times that before ischemia. The preischemic administration of histamine suppressed the increase in the dopamine level during ischemia, and the peak value was 38% of that in the saline group. The preischemic administration of HTMT did not affect the increase in the dopamine level during ischemia. The treatment with dimaprit, however, suppressed the peak value to 42% of that in the saline group. After reperfusion, the dopamine levels in the four groups returned to basal levels. DOPAC and HVA levels tended to decrease during ischemia and returned to basal levels after reperfusion in all groups. Nevertheless, there were no differences in the corresponding values of dopamine metabolites among the four groups.

Similar to the dopamine concentration, the basal levels of 5-HT and 5-HIAA did not differ among the groups before induction of ischemia (Fig. 2). The concentration of 5-HT was increased by transient ischemia in the control group, although the magnitude of the elevation was not so large compared to that of the dopamine level. The ischemia-induced increase in the level of 5-HT tended to be suppressed by both histamine and dimaprit, although effects were not significant due to large variations. No remarkable changes were observed in the 5-HIAA level among the four groups.

3.1.2. Amino acids

The basal levels of aspartate, glutamate, and glycine did not differ among the groups before induction of ischemia (Fig. 3). Occlusion of the middle cerebral artery produced a marked increase in the glutamate level in the control group, the peak value being 5.2 times that before ischemia. The preischemic administration of either histamine or dimaprit suppressed the increase in the glutamate level during ischemia. The peak values in the histamine and dimaprit groups

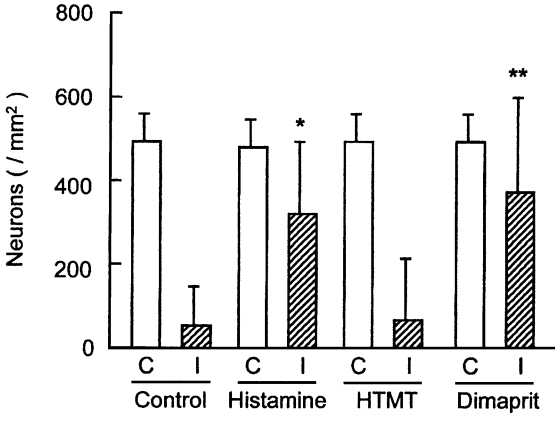

Fig. 4. The effects of preischemic administration of histamine-related agents on ischemic neuronal damage in the striatum. Saline, histamine (200 nmol, i.c.v.), HTMT (100 nmol, i.c.v.), or dimaprit (100 nmol, i.c.v.) were administered, and transient ischemia was induced for 15 min by occluding the middle cerebral artery. The number of preserved neurons (/mm^2) was counted 7 days after ischemia on the contralateral (nonischemic) side (C) and ipsilateral (ischemic) side (I) in the saline ($n=10$), histamine ($n=7$), HTMT ($n=6$), and dimaprit ($n=8$) groups. Each value represents the mean ± S.D. *$P<0.05$, **$P<0.01$ as compared with each corresponding value in the saline group.

were 40% and 32% of that in the saline group, respectively. The preischemic administration of HTMT did not affect the increase in the glutamate level during ischemia.

There were no remarkable changes in the aspartate and glycine levels during ischemia. Changes in the concentrations of aspartate and glycine were smaller than that of the glutamate concentration, and there were no remarkable differences among the four groups.

3.1.3. Histologic outcome

All animals regained consciousness and the righting reflex within 30 min after halothane anesthesia was stopped. No seizures were noted in any of the animals in the 7-day period between ischemia and death. Upon histological evaluation 7 days after ischemia, transient ischemia for 15 min provoked severe neuronal damage in the control group (Fig. 4). The number of striatal neurons in the control group was reduced to 10% of that on the nonischemic side. The preischemic treatment with histamine alleviated the ischemic damage, and the percentage of preserved neurons in the histamine group was 60% of that on the nonischemic side. The HTMT treatment did not show beneficial effects on striatal neurons against ischemia. However, dimaprit preserved striatal neurons, and the percentage of preserved neurons in the dimaprit group was similar to that of the histamine group. No agents exerted morphological influences on the neurons in the nonischemic side.

3.2. Experiment 2: effects of histamine antagonists

The number of preserved neurons in animals which received histamine before ischemia was 94% of that on the nonischemic side (Fig. 5). In the animals that received histamine before ischemia, the postischemic treatment with mepyramine did not affect the number of preserved neurons. The postischemic treatment with ranitidine, however, reduced the number of striatal neurons in animals pretreated with histamine. The number of preserved neurons was 55% of that on the nonischemic side. Neither antagonist affected the number of neurons on the nonischemic side.

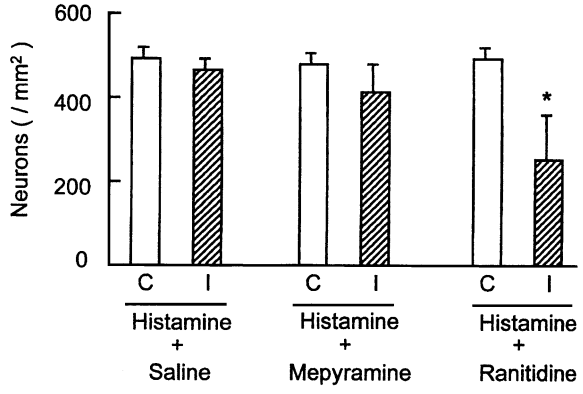

Fig. 5. The effects of postischemic administration of mepyramine and ranitidine on ischemic neuronal damage in the striatum in histamine-pretreated rats. All animals were injected with histamine (200 nmol, i.c.v.), and transient ischemia was induced for 15 min by occluding the middle cerebral artery. After reperfusion, saline, mepyramine (5 nmol, i.c.v.), or ranitidine (30 nmol, i.c.v.) was injected. The number of preserved neurons (/mm^2) was counted 7 days after ischemia on the contralateral (nonischemic) side (C) and ipsilateral (ischemic) side (I) in the saline ($n=6$), mepyramine ($n=7$), and ranitidine ($n=7$) groups. Each value represents the mean ± S.D. *$P<0.05$ as compared with each corresponding value in the saline group.

4. Discussion

The preischemic administration of both histamine and dimaprit suppressed ischemia-induced increases in the dopamine and glutamate levels during ischemia and alleviated histologic outcome after 7 days, whereas HTMT affected neither neurotransmitter release nor histologic outcome.

There are several reports that suggest the detrimental effects of dopamine in cerebral ischemia (Clemens and Phebus, 1988; Globus et al., 1987) most probably due to generation of reactive oxygen species (Hyslop et al., 1995). Reactive oxygen species may be formed via two mechanisms: one is oxidation by monoamine oxidase to produce hydrogen peroxide and DOPAC (Maker et al., 1981), and the other is the spontaneous and enzymatic oxidation of the catechol ring to form hydrogen peroxide (Hastings, 1995). In our previous study, blockade of histamine H_2 receptors facilitated the ischemia-induced release of dopamine, and aggravated ischemic neuronal damage (Adachi et al., 2002). In contrast, the blocking of dopaminergic innervation by lesioning the substantia nigra resumed the damage induced by histamine H_2 blockade (Otsuka et al., 2003). The suppression of ischemic release of dopamine by histamine H_2 receptor stimulation found in the present study is a likely mechanism responsible for the improvement in histologic outcome.

In this study, the ischemia-induced increase in the 5-HT level tended to be suppressed by the histamine and the dimaprit treatment, no remarkable change being observed in the 5-HIAA level. Some reports suggest that increased activity in the serotonergic system has a beneficial effect on ischemic damage. The increase in the 5-HT concentration in the synaptic cleft resulting from blockade of the reuptake mechanism has been shown to be neuroprotective against cerebral ischemia, whereas the depletion of 5-HT from the neuron has been reported to aggravate ischemic neuronal injury (Oishi et al., 1989; Prehn et al., 1993). Since the relationship between changes in the metabolism of 5-HT and histologic outcome was not elucidated in the present study, it is unlikely that serotonergic activity contributes to the improvement by histamine H_2 action.

With respect to neurotransmitter amino acids, the preischemic administration of either histamine or dimaprit suppressed the increase in the ischemic release of glutamate, whereas preischemic administration of HTMT did not affect it. In cerebral ischemia, an excessive amount of glutamate is released from nerve endings, and a large

amount of Ca^{2+} enters the postsynaptic neurons, provoking the enzymatic process leading to irreversible neuronal injury (Benveniste et al., 1984; Rothman and Olney, 1995). Similar to the changes in dopamine release induced by histamine H_2 blockade, ranitidine facilitated ischemic increase in the extracellular concentration of glutamate and aggravated neuronal damage in our previous study (Adachi et al., 2001). As a result, the suppression of glutamate release by histamine H_2 receptor stimulation observed in the present study may be a factor in the alleviation of histologic outcome. Although aspartate has a role as an excitatory neurotransmitter in the brain, no remarkable changes in the aspartate level were observed in the present study. Glycine has been shown to potentiate *N*-methyl-D-aspartate responses by increasing the frequency of channel opening (Johnson and Ascher, 1987). However, the histamine receptor agonists did not affect the glycine level.

The progression of ischemic neuronal damage involves edema formation, inflammatory cell infiltration, and reactions of cytokines and adhesion molecules during the reperfusion phase, as well as reactions related to an excess release of excitatory neurotransmitters. Inflammatory reactions are particularly suggested to play an important role in the development of tissue damage (Jean et al., 1998; Liao et al., 2001), since the suppression of leukocyte function by antibodies against interleukin-1 has been demonstrated to alleviate reperfusion injury (Garcia et al., 1995). On the other hand, histamine H_2 action has been reported to suppress inflammatory reactions in the late phase of inflammation in various animal models, although histamine H_1 receptor stimulation provokes anaphylactic reactions in the early phase (Hirasawa et al., 1987; Dohlsten et al., 1986, 1988). The administration of histamine or dimaprit, therefore, might have alleviated the histologic outcome by activating anti-inflammatory reactions through histamine H_2 receptors.

In the present study, alleviation of the histologic outcome by preischemic treatment with histamine was partly abolished by the postischemic administration of ranitidine. This finding seems to explain the beneficial effects of histamine H_2 action against reperfusion injury. Alleviation of reperfusion injury might be a factor in the improvement by histamine as well as suppression of neurotransmitter release. However, since the half-life of histamine has been reported to be shorter than that of dopamine and 5-HT (Prell and Green, 1994), it is unlikely that it exerted an influence on reperfusion injury around 24 h after ischemic events. The partial abolishment of the histologic outcome by ranitidine in histamine-treated animals may be caused by the blockade of histamine H_2 action by endogenous histamine, since the basal release of histamine in the physiologic state is higher than that of other neurotransmitters (Itoh et al., 1991; Mochizuki et al., 1991).

The histaminergic system has been demonstrated to innervate the cerebral microvasculature (Takagi et al., 1986), and several reports indicate the regulation of blood–brain permeability by brain histamine. Carotid artery infusion of histamine has been shown to increase blood–brain permeability (Dux and Joo, 1982), and histamine H_2 antagonists attenuate brain edema induced by cerebral ischemia or systemic administration of kainate (Tosaki et al., 1994; Sztriha et al., 1987). These findings suggest that histamine H_2 action facilitates brain edema, which results in the aggravation of neuronal damage. Despite these effects of histamine H_2 action on the cerebral microvasculature, histamine and dimaprit alleviated the histologic outcome.

Taken together, suppression of the ischemia-induced release of dopamine and glutamate via histamine H_2 receptors is a contributing factor in the alleviation of ischemic neuronal damage by histamine.

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