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Review

Cerebral ischemia and brain histamine

Naoto Adachi*

Department of Anesthesiology and Resuscitology, Ehime University School of Medicine, Shitsukawa, Touon-shi, Ehime 791-0295, Japan
Medical Division, Mabuchi Clinic, Kakimoto-cho 590-4, Kuromon-dori Gojo-agaru, Shimogyo-ku, Kyoto-shi, Kyoto 600-8357, Japan

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Abstract

Cerebral ischemia induces excess release of glutamate and an increase in the intracellular Ca^{2+} concentration in neurons, which provokes enzymatic process leading to irreversible neuronal injury. Histamine plays a role as a neurotransmitter in the mammalian brain, and histamine release from nerve endings is enhanced in ischemia by facilitation of histaminergic activity. Dissimilar to ischemia-induced release of glutamate, histamine release is gradual and long lasting. The enhancement may contribute to neuroprotection against ischemic damage, because suppression of histaminergic activity aggravates the histologic outcome caused by ischemia. Preischemic administration of histamine (i.c.v.) suppresses ischemic release of glutamate and ameliorates neuronal damage, whereas blockade of central histamine H_2 receptors aggravates ischemic injury. These suggest that histamine provides beneficial effects against ischemic damage through histamine H_2 receptors, when administered before induction of ischemia. Postischemic loading with histidine, a precursor of histamine, alleviates both brain infarction and delayed neuronal death. Since the alleviation is abolished by blockade of central histamine H_2 receptors, facilitation of central histamine H_2 action caused by histidine may prevent reperfusion injury after ischemic events. Because the ischemia-induced increase in the glutamate level rapidly resumes after reperfusion of cerebral blood flow, beneficial effects caused by postischemic loading with histidine may be due to other mechanisms besides suppression of excitatory neurotransmitter release. Anti-inflammatory action by histamine H_2 receptor stimulation is a likely mechanism responsible for the improvement.

Theme: Disorders of the nervous system
Topic: Ischemia

Keywords: Brain infarction; Cerebral ischemia; Delayed neuronal death; Dopamine; Glutamate; Histamine; Histidine

Contents

* Fax: +81 89 960 5386.
E-mail address: nadachi@m.ehime-u.ac.jp.

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1. Introduction

The human brain has about 10,000,000,000 neurons, each of which makes about 1000 synaptic contacts with other neurons. To maintain physiologic function of the neuronal network, the brain requires much energy. Although the weight of the brain in humans is only about 2% of the body weight, cerebral blood flow is 50 mL/100 g/min, which is 12–15% of cardiac output. Oxygen consumption is 3.5 mL/100 g/min, which is 20% of oxygen consumption of the whole body. However, since the brain contains virtually no reserve supply of oxygen and only small stores of glucose or energy-rich compounds, the brain is exquisitely vulnerable to ischemic injury. When the duration of ischemia is sufficiently long, acute necrosis occurs in glia and endothelial cells as well as neurons, and there is no room to apply therapies for degenerated neurons. Despite successful reperfusion of cerebral blood flow, there are several factors that harm neurons during reperfusion. Even when cerebral blood flow is resumed within a few minutes, morphological and functional damage is observed after several days, which is called delayed neuronal death [50,62]. Although recent studies have demonstrated biochemical mechanisms for delayed neuronal death, the prevention of delayed neuronal death is difficult. Thus, the brain once exposed to ischemia can be treated only in a short period in the early phase of reperfusion.

Histamine is a biogenic amine that plays an important role in inducing anaphylactic responses, such as bronchospasm, an increase in vascular permeability, and hypotensive shock in peripheral organs in various species of mammalians. These actions are mediated by histamine H_1 receptor stimulation [12,25]. In contrast, histamine has been shown to depress immunological processes by suppressing lymphocyte proliferation, cytokine production, and neutrophil accumulation [38]. These immunosuppressive actions are involved in histamine H_2 receptor stimulation [22,23,49,97]. Besides roles as a mediator of immune responses and gastric acid secretion in peripheral organs, histamine exists in the brain and possesses neurotransmitter properties [85,93].

In this review, the experimental evidence for the role of central histamine on cerebral ischemia was highlighted by concentrating on data related to experimental procedures using animal models of cerebral ischemia.

2. Histamine in the CNS

Histamine is formed from L-histidine and has a role as a neurotransmitter in the mammalian brain (Fig. 1) [93]. Histaminergic fibers are distributed widely in the entire brain from cell bodies present in the tuberomammillary nucleus of the posterior basal hypothalamus, which is typical of the patterns characteristic of other aminergic systems [98,99]. They regulate the release of non-histaminergic neurotransmitters through histamine heteroreceptors located on the non-histaminergic nerve endings (Fig. 2) [74,75]. Thus, the histaminergic system forms a part of the neuronal network by modulating other neuronal systems, such as catecholaminergic and cholinergic systems [74,75]. While histamine in the peripheral tissue is mainly converted to imidazoleacetic acid by diamine oxidase, histamine in the brain is metabolized by histamine-*N*-methyltransferase to form *tele*-methylhistamine (Fig. 1). Most of the *tele*-methylhistamine formed is converted by monoamine oxidase B to *tele*-methylimidazoleacetic acid.

The role of the histaminergic system has been determined by i.c.v. administration of histamine and its antagonists, since histamine is not transported to the brain across the blood–brain barrier. The histaminergic system regulates

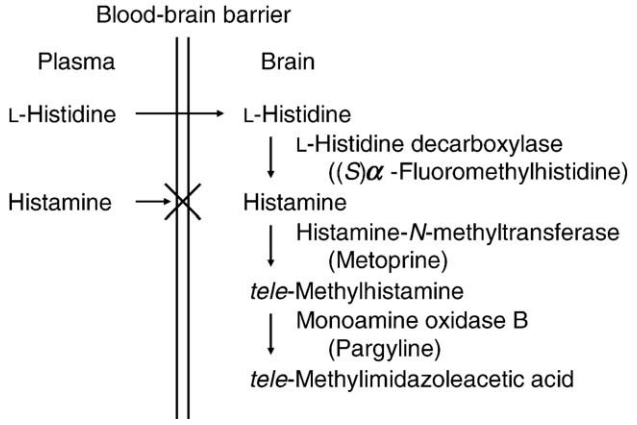

Fig. 1. Biosynthesis and metabolism of brain histamine. Histamine in the brain is not transported from plasma, but is formed from L-histidine by a specific enzyme, L-histidine decarboxylase. There are two major pathways of histamine metabolism; ring methylation and oxidative deamination by diamine oxidase. In the brain, most of histamine is catalized by histamine-*N*-methyltransferase to form *tele*-methylhistamine, which is converted by monoamine oxidase B to *tele*-methylimidazoleacetic acid. Inhibitors are shown in parentheses.