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The roles of histamine and its receptor ligands in central nervous system disorders: An update

Weiwei Hu, Zhong Chen *

Department of Pharmacology, Key Laboratory of Medical Neurobiology of the Ministry of Health of China, School of Basic Medical Sciences, College of Pharmaceutical Sciences, School of Medicine, Zhejiang University, Hangzhou, Zhejiang 310058, PR China

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ABSTRACT

The neurotransmitter histamine receives less attention compared with other biogenic amines, because of its moderate action in the central nervous system (CNS). However, recent evidence suggests that histamine plays an important role in multiple CNS disorders including insomnia, narcolepsy, Parkinson's diseases, schizophrenia, Alzheimer's disease, and cerebral ischemia. New insights are emerging into the potential roles of histamine receptors as targets for the treatment of these diseases. Although some histamine related agents have failed in clinical trials, current preclinical studies suggest that this neurotransmitter may still have extensive applications in treating CNS disorders, however, advanced studies are warranted. This review summarizes findings from animal models and clinical research on the role of histamine and its receptor ligands in the brain for treatment of CNS disorders. The development of novel histamine receptor ligands and gaining an in-depth understanding of their potential mechanisms are necessary stepping stones to unlock their wide-ranging applications in the clinical arena.

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1. Introduction

In contrast with other biogenic amines, histamine has garnered less attention in the context of neuroscience. This is likely due to its relatively moderate action to fine tune other principal neurotransmitters, such as excitatory glutamate and inhibitory GABA. The direct regulation of those excitatory and inhibitory neurotransmitters in cerebral disorders may elicit severe side effects, which impede their extensive

Abbreviations: AD, Alzheimer's disease; Arch, aerhodopsin; BBB, brain blood barrier; cAMP, cyclic adenosine monophosphate; CBF, cerebral blood flow; ChR2, channelrhodopsin-2; CREB, cAMP response element-binding protein; CSF, cerebrospinal fluid; CNS, central nervous system; GPe, globus pallidus; GPi, internal segments of the globus pallidus; GS, glutamine synthetase; HCRT, hypocretin; HDC, histidine decarboxylase; HNMT, histamine *N*-methyltransferase; IP3, inositol trisphosphate; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; MCAO, occlusion of the middle cerebral artery; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MSNs, medium-spiny projection neurons; NMDA, *N*-methyl-D-aspartate; NSCs, neural stem cells; 6-OHDA, 6-hydroxydopamine; PD, Parkinson's disease; PFC, prefrontal cortex; PI3K, phosphatidylinositol 3-kinase; PKA, protein kinase A; PLA2, phospholipase A2; rCBF, regional cerebral blood flow; rtPA, recombinant tissue plasminogen activator; SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticulata; STN, subthalamic nucleus; SVZ, subventricular zone; TMN, tuberomammillary nucleus; VLPO, ventrolateral preoptic nucleus.

* Corresponding author.
E-mail address: chenzhong@zju.edu.cn (Z. Chen).

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use for medical applications. Therefore, the pharmacological application of histamine related agents may bring forth new prospects for the therapy of several CNS disorders. Taken together, it is imperative to expand our knowledge regarding the role of histamine in the central nervous system. In this review, we provide an overview of the action of histamine and its receptor ligands in animal studies and clinical trials of several CNS disorders, with a focus on cerebral ischemia, which receives less attention. This review also summarizes the prospects of further preclinical studies in this field.

2. Histamine in the brain

Histamine is produced in peripheral tissues by mast cells and basophils found in nearby connective tissues to participate in allergic and inflammatory responses. Another important site of histamine storage and release is the enterochromaffin-like cells in the stomach, which control gastric acid release. The presence of histamine in the brain was first mentioned by Kwiatkowski in 1943 (Kwiatkowski, 1943), and was one of the last organs where histamine receptors were identified. The histaminergic neuron is the main source of histamine production in the brain, the soma of which is located in the tuberomammillary nucleus (TMN) of the hypothalamus (Haas & Panula, 2003). Approximately 64,000 histaminergic neurons are found in the tuberomammillary nucleus in humans (Airaksinen et al., 1991), while only 4600 are localized in the brains of rats (Ericson, Watanabe, & Kohler, 1987). Although the location of histaminergic cell body is limited to a small area, its projections are widely spread throughout the brain, including the cerebrum, cerebellum, posterior pituitary, and the spinal cord. The synthesis of histamine relies on the action of histidine decarboxylase (HDC), an enzyme that catalyzes the oxidative decarboxylation of L-histidine. HDC knockout mice are often used to study the role of histamine in the brain (Watanabe & Yanai, 2001). The newly generated HDC-Cre mice have provided a superior approach to selectively modulate histaminergic neurons through cross-breeding with conditional knockout mice or by conditional expression of channelrhodopsin-2 (ChR2) to activate specific neurons (Williams et al., 2014; Yanovsky et al., 2012). The synthesized histamine is carried into vesicles by the vesticular monoamine-transporter VMAT-2. After release, histamine is metabolized by histamine *N*-methyltransferase (HNMT) into inactive telemethylhistamine in the postsynapses or glia. The turnover rate for neuronal histamine is rapid (half-life <1 h); therefore histamine levels in brain tissue can be used as good approximations of the release of neuronal histamine. However, the turnover rate may be altered under certain conditions (Schwartz, Arrang, Garbarg, Pollard, & Ruat, 1991), so direct measurement of extracelluar histamine levels by microdialysis is a more precise method to detect the status of its release. Mast cells also contain a significant amount of brain-derived histamine (Grzanna & Shultz, 1982), but are limitedly distributed in the thalamus, hypothalamus, dura mater, leptomenings, and choroid plexus (Ibrahim, 1974). Other possible sources of histamine in the brain may include microglia and microvascular endothelial cells (Katoh et al., 2001; Yamakami et al., 2000). However, the action of nonneuronal histamine remains elusive.

3. Histamine receptors and ligands

Four types of histamine receptors have been identified in the brain. Histamine H1 and H2 receptors (H1R and H2R) are found postsynaptically in all parts of the brain, including the cortex, hippocampus, striatum, and hypothalamus. The H1R (486–491 amino-acids) is coupled to the Gq/11 protein and phospholipase C, which is known to promote inositol trisphosphate (IP3)-dependent Ca^{2+} release from intracellular Ca^{2+}-stores, and is also directly involved in diacylglycerol formation. The latter, in turn, activates protein kinase C, which phosphorylates intracellular proteins. H1R also activates AMP-kinase, nuclear factor kappa B, nitric oxide synthases, and phospholipase A2 (PLA2), which induces arachidonic acid formation (Haas, Sergeeva, & Selbach, 2008). H2R (359 amino-acids) is coupled to Gs and stimulates adenylylcyclase, thereby increasing intracellular cyclic adenosine monophosphate (cAMP), which in turn activates protein kinase A (PKA) and the transcription factor cAMP response element-binding protein (CREB). H2R activation also blocks Ca^{2+}-activated potassium conductance and inhibits both PLA2 and the release of arachidonic acid. Although the expression levels and location of H1R and H2R are comparable in the brain (Haas & Panula, 2003), H1R is the predominant histamine receptor in the brain in terms of function, leading to many open questions for researchers.

The histamine H3 receptor (H3R; 326–445 amino-acids) is located on histaminergic neuron somata, dendrites and axon varicosities, as well as on the axon varicosities and somata of other neurons, providing negative feedback to inhibit histamine synthesis and the release of histamine or other transmitters, including glutamate, acetylcholine, and GABA. However, vast majority of H3Rs are postsynaptically present in the basal ganglia and especially within the dorsal and ventral striatum. H3R is coupled to Gi/o to inhibit adenylyl cyclase and the high voltage activated Ca^{2+} channels that are responsible for regulation of histamine synthesis and the neurotransmitter release. Other signaling pathways have been reported to be involved in H3R activation, such as the inhibition of the Na^+/H^+ exchanger (Karmazyn, 1999), the enhancement of G protein-gated inwardly rectifying K^+ channels (Sahlholm, Nilsson, Marcellino, Fuxe, & Arhem, 2012), phospholipase C activation (Coge et al., 2001), the mitogen-activated protein kinase (MAPK) pathway (Drutel et al., 2001), and the phosphatidylinositol 3-kinase (PI3K) pathway (Bongers et al., 2007).

The histamine H4 receptor (H4R) was recently discovered, and is predominantly expressed in immune cells, including mast cells, eosinphils and dendritic cells. In the brain, H4R is present in microglia besides mast cells, however its function in these cells remains mysterious. Thus far, there has been no convincing evidence confirming the expression of H4R in neurons, which is due to flawed methods used for detection (Schneider & Seifert, 2016). Further studies from independent research groups will be necessary with more robust techniques including the use of monoclonal anti-H4R antibodies, qPCR experiments, and concentration dependent stimulation of H4R by agonists. H4R shares ~40% homology with H3R, and belongs to the class of Gi/Go-coupled GPCRs that function to reduce cAMP accumulation. In addition, activation of the H4 receptor has also been shown to increase Ca^{2+} mobilization and activate kinases (ERK, PI3K, and MAPK) and transcription factor activating protein-1 (Dong et al., 2014; Jemima, Prema, & Thangam, 2014).

Despite their importance, H1R or H2R agonists have not been directly applied in clinic due to their broad and largely undesirable peripheral action. The first generation of H1R antagonists, including diphenhydramine, promethazine, tripelennamine, and chlorphenamine, have been shown to penetrate the brain blood barrier (BBB), and often show strong sedative effects. Also, anticholinergic activities were often found in first generation histamine H1R antagonists. The second generation of H1R antagonists (cetirizine, terfanadine, astemizole, and loratadine, et al.) has displayed long-term action, but showed weak sedative and anticholinergic effects with a relatively poor capacity for BBB penetration (Yanai et al., 1995a, 1995b). Among these second generation antagonists, terfenadine and astemizole have both been withdrawn from the market due to their cardiotoxicity. Third generation H1R antagonists are active enantiomers (levocetirizine) and metabolites (desloratadine and fexofenadine) of the second generation H1R antagonists. Fexofenadine has been associated with a decreased risk of cardiac arrhythmia compared to terfenadine. In contrast, there is almost no advantage of levocetirizine or desloratadine, compared to cetirizine or loratadine, respectively, so the term "third generation" should be used with caution (Camelo-Nunes, 2006; Kalpaklioglu & Baccioglu, 2012). The sedative effects of H1R antagonists were initially recognized as side effects for the treatment of allergic rhinitis, but such action is responsible for the use of the induction of sleep. Due to blockage of H1R