Chapter 10

Histamine in Neurotransmission and Brain Diseases

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Abstract

Apart from its central role in the mediation of allergic reactions, gastric acid secretion and inflammation in the periphery, histamine serves an important function as a neurotransmitter in the central nervous system. The histaminergic neurons originate from the tuberomamillary nucleus of the posterior hypothalamus and send projections to most parts of the brain. The central histamine system is involved in many brain functions such as arousal, control of pituitary hormone secretion, suppression of eating and cognitive functions. The effects of neuronal histamine are mediated via G-protein-coupled H_1-H_4 receptors. The prominent role of histamine as a wake-promoting substance has drawn interest to treat sleep-wake disorders, especially narcolepsy, via modulation of H_3 receptor function. Post mortem studies have revealed alterations in histaminergic system in neurological and psychiatric diseases. Brain histamine levels are decreased in Alzheimer's disease patients whereas abnormally high histamine concentrations are found in the brains of Parkinson's disease and schizophrenic patients. Low histamine levels are associated with convulsions and seizures. The release of histamine is altered in response to different types of brain injury: e.g. increased release of histamine in an ischemic brain trauma might have a role in the recovery from neuronal damage. Neuronal histamine is also involved in the pain perception. Drugs that increase brain and spinal histamine concentrations have antinociceptive properties. Histaminergic drugs, most importantly histamine H_3 receptors ligands, have shown efficacy in many animal models of the above-mentioned disorders. Ongoing clinical trials will reveal the efficacy and safety of these drugs in the treatment of human patients.

Histaminergic Neurons

The first findings of histamine in the brain date back to 1919 when John J. Abel isolated histamine from the pituitary.[1] However, histamine's role as a neurotransmitter became evident only several decades later when lesions of the lateral hypothalamic area were found to decrease the activity of histamine synthetizing enzyme, L-histidine decarboxylase (HDC).[2] Another decade went by before methods became available to directly demonstrate the localization of the histaminergic neurons in the brain.[3,4] Cell bodies of histaminergic neurons are localized in the tuberomamillary nucleus (TMN) of the posterior hypothalamus from where they send projections to essentially all areas of the central nervous system similar to other amines (Fig. 1).[5] The number of histamine-containing neurons is about 4000 in the rat[6] whereas in human brain histaminergic neurons are more numerous (>64,000).[7]

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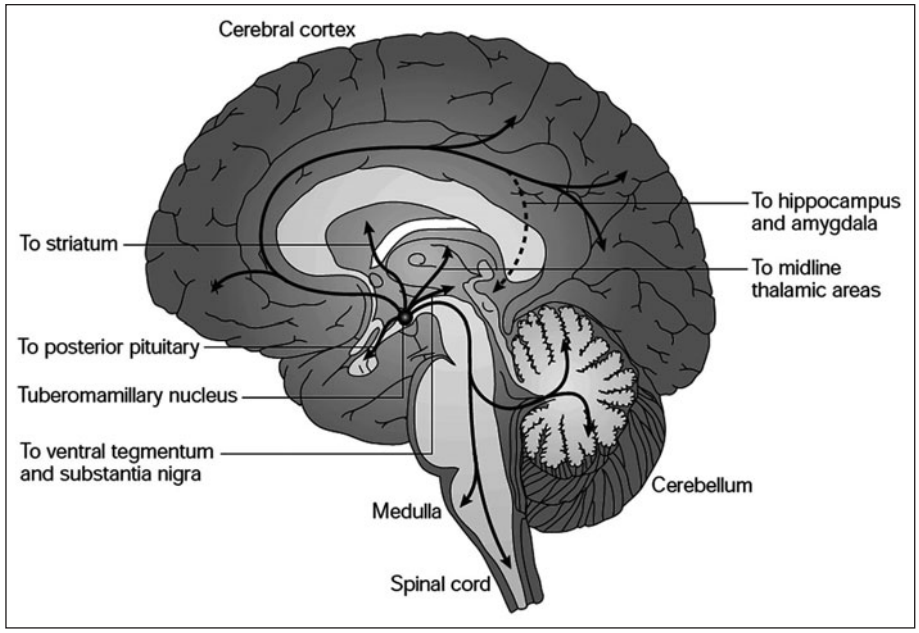

Figure 1. Histaminergic neurons and main projections in the human brain. Reprinted from: Haas H, Panula P. Nat Rev Neurosci 2003; 4:121-130.[5]

In addition to neurons, mast cells can produce histamine in the brain.[8] Indications of histamine synthesis in microglial cells also exists, but in vivo evidence of histamine produced by microglia is still missing.[9] It is noteworthy that brain ependymal cells also express HDC and can potentially synthesize histamine.[10] The role of this histamine is unknown, but it may be involved in regulation of stem cells located underneath the ependymal layer. Neural stem cells in vitro respond to both H_1R and H_2R receptor ligands.[11] Nonneuronal histamine has an important role in immune responses in the periphery and in the CNS and is covered elsewhere in this book. However, it should be noted that the source of brain histamine in some cases is difficult to detect. It is thus possible that both neuronal and nonneuronal histamine might regulate certain brain functions such as neuroinflammation.

Histamine Synthesis, Storage, Release and Catabolism

Histamine penetrates the brain poorly from blood, which protects the brain from many effects of blood-borne histamine. Histamine is synthetized from amino acid histidine by the specific histidine decarboxylase (HDC) enzyme in the brain.[2] The activity of HDC is highest in the hypothalamus where the histaminergic cell bodies are located, but HDC is also active in histaminergic nerve terminals.[3] The rate-limiting factor for histamine synthesis is the bioavailability of its precursor, histidine. Histamine is stored in vesicles in cell somata and especially in axon varicosities distinct from those containing GABA in the same cells.[12-14] Vesicular monoamine transporter 2 (VMAT-2) is responsible for the transport of histamine to the intracellular vesicles.[5] Upon arrival of action potentials histamine is released in a Ca^{2+}-dependent manner from the storage vesicles. In contrast to other amines, histaminergic synapses are rarely found in vertebrate nervous tissue and most histaminergic endings (varicosities) do not make close contact with postsynaptic sites.

Inactivation of histamine in the brain begins with a methylation reaction by histamine-N-methyltransferase.[15] Tele-methylhistamine undergoes oxidative deamination by monoamine oxidase B

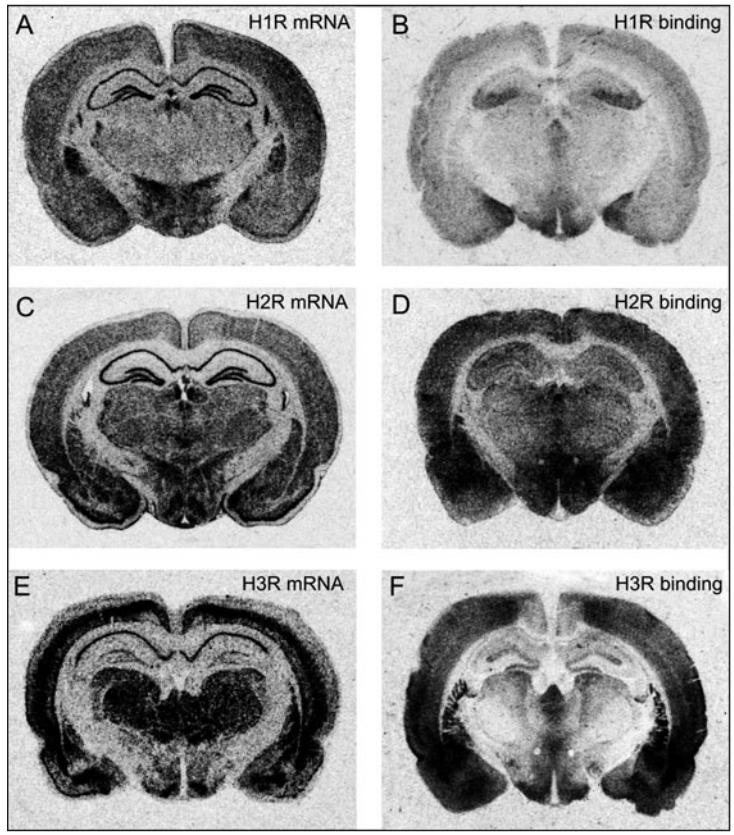

Figure 2. Distribution of histamine receptors in rat brain. Coronal sections at the level of the medial hypothalamus showing mRNA in situ hybridization and specific radioligand binding of H_1R (A, B), H_2R (C, D) and H_3R (E, F) receptors. Modified from: Haas H, Panula P. Nat Rev Neurosci 2003; 4:121-130.[5]

(MAO-B) into *t*-methyl-imidazolacetic acid.[16] Diamine oxidase (DAO) is the main histamine metabolizing enzyme in the peripheral tissues, but its activity in the brain is considerably low in basal conditions. However, it can be activated under conditions where methylation is inhibited.[17]

Histamine Receptors in the Brain

The actions of histamine in the brain are mediated through four G protein-coupled receptors, H_1R-H_4R (Fig. 2). H_1R and H_2R are postsynaptic and mediate mostly excitatory actions on neurons or potentiate excitatory inputs.[5] H_3R are located on histaminergic and other neurons on their somata, dendrites and axons.[18] On presynaptic sites H_3 autoreceptors inhibit the synthesis and release of histamine and H_3 heteroreceptors inhibit the release of other neurotransmitters.[19,20] The importance of postsynaptic H_3R on somata of neurons other than histaminergic neurons is not fully understood, but a recent study demonstrated that in striatum they are able to couple to dopamine D2 receptors and this interaction decreases the affinity of D2 receptors for its agonists.[21] An interesting property of H_3R is the high constitutive activity, which means spontaneous activity in the absence of histamine.[22] The constitutive activity has a potential regulatory role in the brain and several inverse agonists that are able to block this activity are currently in clinical trials to prove their efficacy in disorders such as Alzheimer's disease, schizophrenia, epilepsy, narcolepsy and obesity.[23,24] Another particular feature of

H_3R is the existence of multiple isoforms[25,26] derived from a single gene[27] by alternative splicing. The distribution of H_1R-H_3R is widespread in the brain as characterized by mRNA in situ hybridization and specific radioligand binding studies (Fig. 2). H_4R were first thought to be expressed only in the periphery, but recent studies suggest that H_4R is also expressed both in human and rat brain with highest levels of H_4R mRNA detected in the spinal cord.[28]

Histamine neurons are pacemakers that display a regular spontaneous firing with low frequency (1-4 Hz). When waking up, the firing of histaminergic neurons is increased.[5] During slow wave sleep the firing is low and no firing can be detected during rapid-eye-movement (REM) sleep. The inhibition of histaminergic neurons during sleep is mediated via GABAergic control from the ventrolateral preoptic area (VLPO).[29]

Physiological Role of Neuronal Histamine

Brain histamine is implicated in brain homeostasis and control of several neuroendocrine functions. Histamine has an important role in the control of behavioral state, biological rhythms, body weight, energy metabolism, thermoregulation, fluid balance, stress and reproduction.[5] In addition, histamine is implicated in higher brain functions such as sensory and motor functions, mood state, reward, learning and memory.

Arousal

Histamine has a prominent role in the control of arousal. The first cues of histamine as a waking substance came from the unwanted sedative side-effects of the first generation antihistamines that were able to cross the blood brain barrier. EEG recordings have shown that tuberomammillary neurons fire during wakefulness, but not during sleep.[30,31] In agreement, manipulation of the histaminergic system by H_3R antagonists to activate histaminergic neurons,[32] inhibition of histamine synthesis by alpha-fluoromethylhistidine[33] or histidine decarboxylase gene deletion (HDC knockout mice) leads to disturbances in sleep and waking state.[34]

Control of Pituitary Hormone Secretion

The role of histamine in the regulation of various endocrine functions is due to the effects of histamine on secretion of pituitary hormones.[35] This function is also in agreement with abundant expression of H_1R-H_3R in the hypothalamus (Fig. 2). Histamine regulates fluid balance via activation of H_1R localized on the neurons of supraoptic nucleus, which causes the release of vasopressin[36,37] and in turn induces antidiuresis.[38,39] Histaminergic neurons are also activated during parturition and lactation regulating the release of oxytocin and prolactin.[35,40,41] In addition, certain subgroups of histaminergic neurons are activated in response to stressful stimuli and control the release of adrenocorticotropic hormone.[42] Histamine also participates in the regulation of the release of growth hormone and thyrotropin-releasing hormone.[35]

Appetite and Body Weight

A large body of evidence links neuronal histamine to the regulation of appetite and body weight. First indications came from the appetite stimulating and weight increasing side-effects of first generation antipsychotics and antidepressants that had strong H_1R antagonist properties.[43] Later, several studies have demonstrated that histamine acts as an anorexigenic agent via stimulation of H_1R.[44] Histamine mediates the inhibitory effect of leptin on appetite via H_1R[45] confirmed by the complete absence of leptin-induced feeding suppression in H_1R knockout mice.[46,47] The effects of histamine on appetite are linked to various other neuroendocrine peptides such as orexins, neuropeptide Y, peptide YY and bombesin.[48] In addition to control of appetite, neuronal histamine affects metabolism by increasing lipolysis.[49,50] H_3R are promising targets to treat obesity since blockade of H_3R seems to be beneficial in decreasing energy intake, body weight and plasma triglycerides.[23] However, based on inconsistent results in H_3R antagonist studies, further investigations are needed to prove the potential of these drugs in the treatment of obesity and weight gain.

Histamine in Brain Diseases

Even though no pathological states have been selectively connected to deficits in the brain histamine system, alterations in histaminergic neurotransmission have been found in many neurological and psychiatric diseases such as sleep disorders, disorders of mood and cognition (schizophrenia, depression, Alzheimer's disease), movement disorders (Parkinson's disease), epilepsy, eating disorders, pain, neuroinflammation and addiction.[48] In the following parts of this chapter the role of histamine in some selected important brain diseases will be reviewed.

Sleep-Wake Disorders

Narcolepsy is a rare sleep disorder which is characterized by excessive daytime sleepiness that can be accompanied by manifestation of sudden loss of muscle tone triggered by emotional factors, referred to as cataplexy.[51] Pathophysiological studies have shown that narcolepsy is caused by the early loss of orexinergic neurons in the hypothalamus. Histaminergic neurons remain active during cataplexy whereas norepinephrine neurons stop firing and serotonin neurons lose much of their activity.[52] H_3R antagonists reduce sleepiness and cataplexy in animal models, probably due to the blockade of autoreceptors on histaminergic neurons resulting in increased release of histamine. Several compounds are being investigated in Phase II clinical trials for the treatment of narcolepsy.[23]

Due to the central role of histamine in the control of arousal and wake state, histamine receptors are potential targets for treatment of other types of sleep and wakefulness disorders as well. Doxepin is a tricyclic antidepressant that displays antagonistic effects on H_1R/H_2R in addition to the inhibitory action on norepinephrine and serotonin reuptake. The most common side-effect of doxepin is sedation and it has been shown to improve sleep quality in elderly patients suffering from insomnia.[53] Hypersomnia, on the other hand, could be treated by enhancing histaminergic activity. H_3R control histaminergic activity and histamine release and thus are promising targets to treat hypersomnia.

Alzheimer's Disease

Neuropathological studies have demonstrated deficits in the histaminergic system of Alzheimer's disease (AD) patients. Histamine and histidine decarboxylase levels are decreased in some key areas for cognition such as frontal cortex and hippocampus (Table 1).[54,55] Furthermore, numerous neurofibrillary tangles are found in the tuberomammillary nucleus of the AD brain and the number of large neurons in TMN is decreased, which may at least partly cause the histaminergic dysfunction in AD brain.[56,57] The number of H_1R ligand binding sites is decreased in the AD brain,[58] but interestingly H_3R levels seem to remain normal.[59] It is possible that decreased histaminergic activity may participate in the cognitive impairments of AD based on the ability of histamine to activate septohippocampal GABAergic neurons through both direct and indirect (cholinergic) mechanisms, which contribute to maintenance of hippocampal theta rhythm and thus cognition and memory.[60] A potentially important target for cognitive effects of H_3R ligands is also the thalamocortical system since the H_3R is expressed at particularly high levels in both the rat[61] and human[62] thalamus and cerebral cortex. Interestingly in the mouse, the H_3R expression is significantly lower, which may render studies with mice less relevant for modeling of human disease processes than those with rats.

Novel H_3R antagonists increase acetylcholine levels in cortical areas and hippocampus and improve performance in different cognition paradigms in experimental animals.[59,63-65] Ongoing clinical trials will show whether these compounds are effective in patients as well. In addition to memory-improving effects, H_3R antagonists show efficacy in attention and impulsivity, which makes them attractive candidates for the treatment of attention deficit hyperactivity disorder (ADHD) and cognitive deficits in schizophrenia (see below).

Table 1. Changes in histamine concentrations in different brain areas of Parkinson's disease and Alzheimer's disease patients

	Parkinson's Disease	Alzheimer's Disease
Caudate	+**28***	±0
Putamen	+**59***	–60
Substantia nigra pars compacta	+**101***	–27
Substantia nigra pars reticulata	+64	–23
Globus pallidus internum	+**134***	–
Globus pallidus externum	+**100***	–
Hypothalamus	+47	**–58***
Hippocampus	+16	**–57***
Frontal cortex	+17	–33
Temporal cortex	–5	**–47***
Occipital cortex	–18	–25

Data are expressed as a percentage change in histamine concentration from corresponding control brains. Asterisks refer to statistically significant differences from controls. Modified from Panula et al[54] and Rinne et al.[78]

Schizophrenia

Studies in humans and models in rodents support a role for histamine in the pathophysiology of schizophrenia. The levels of histamine's major metabolite, N-tele-methylhistamine, are elevated in the cerebrospinal fluid of schizophrenics[66] whereas the H_1R binding sites are decreased.[67,68] In agreement, repeated administration of methamphetamine which results in behavioral sensitization to dopamine agonists, a cardinal feature of schizophrenia, is accompanied by enhanced histamine release in rat brain.[69] Similar increases in histamine release are found in mice treated with phencyclidine.[70] Histamine H_3R radioligand binding is significantly increased postmortem in the prefrontal cortex of schizophrenics as compared to normal control, bipolar or depressive subjects.[71] Although this may be a consequence of drug treatment, lack of such differences in the temporal cortex of the same subjects suggests that increased H_3R radioligand binding may be directly related to the disease process. H_3R may play important roles in regulation of the thalamocortical system, which is essential for sensory systems and cognitive functions. H_3R mRNA is expressed at very high level in the dorsal thalamic nuclei of the human brain[72] and in layers IV and V of different subregions of the prefrontal cortex.[62]

Based on the alterations in the histaminergic system in schizophrenic patients, histaminergic drugs might be useful in the treatment of schizophrenia. Indeed, in preclinical studies, H_3R antagonists display antipsychotic effects by improving the deficits in sensomotoric gating in a prepulse inhibition of startle model and by reducing the hyperactivity induced by methamphetamine.[73] Some new H_3R antagonists also increase the release of dopamine in rat prefrontal cortex[59,63] which is regarded as beneficial since hypodopaminergic function in prefrontal cortex is associated with negative symptoms and cognitive deficits of schizophrenia.[74] Tiprolisant (BF2.649) is a novel H_3R antagonist that has an antipsychotic profile in animal models and shows efficacy in patients suffering from antipsychotic-induced weight gain. The effect of tiprolisant on cognitive functions is currently being investigated in clinical trials.[23] Interestingly several open studies have shown that the H_2R antagonist famotidine reduces negative symptoms in schizophrenics,[75,76] a finding that needs to be confirmed in controlled studies.

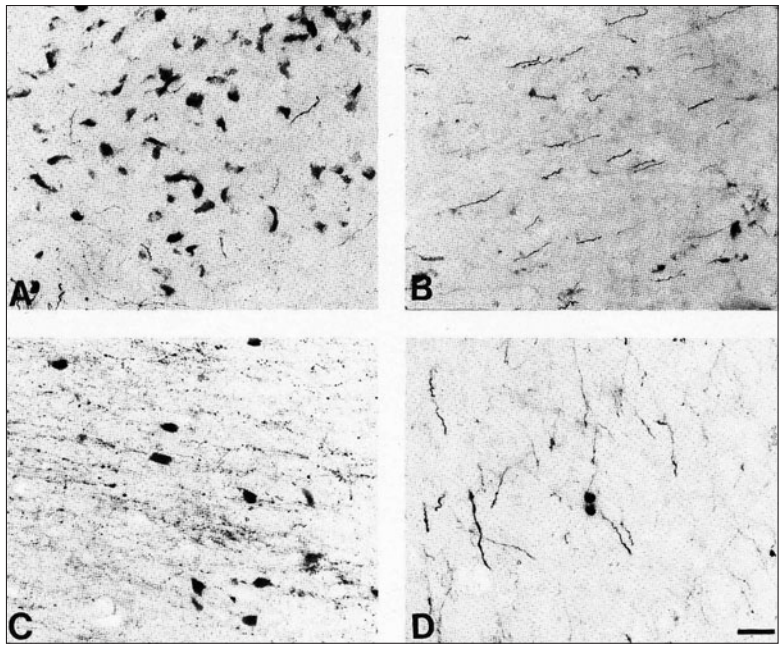

Figure 3. Histaminergic fibers in the substantia nigra of normal and Parkinson's disease brain. A,B) Histamine-immunoreactive fibers in normal brain substantia nigra pars compacta (A) and pars reticulata (B). C,D) Histaminergic fibers in Parkinson's disease brain substantia nigra pars compacta (C) and pars reticulata (D). Reproduced with permission from: Anichtchik OV et al. Exp Neurol 2000; 163:20-30,[77] ©2000 Elsevier.

Parkinson's Disease

Morphological changes and an increase in histaminergic fibers in the substantia nigra have been detected in Parkinson's disease (PD) patients (Fig. 3).[77] Also the histamine levels in the brains of Parkinson patients are increased in areas that regulate motor behavior such as the putamen, substantia nigra and globus pallidus (Table 1).[78] Polymorphism of Thr105Ile histamine-N-methyltransferase that leads to increased turnover of histamine is associated with PD risk.[79] Furthermore, H_3R ligand binding levels are increased[80] or unchanged[81] in PD patients. The H_3R binding is also increased in an animal model of PD where dopaminergic neurons are destroyed by a neurotoxic agent 6-OHDA.[82,83] H_3R regulate the release of GABA[84] and serotonin[85] in the direct and indirect striato-nigral movement pathways and might thus serve as possible drug targets in the treatment of Parkinson's disease and other movement disorders. H_3R antagonists improved motor coordination in 6-OHDA-lesioned rats.[86] In contrast, the H_3R agonist immepip, co-administered with L-dopa, decreased dyskinesia in nonhuman primate model of PD, whereas it increased parkinsonian disability when given alone.[87]

Since 1988[88] it has been known that inflammation and microglia may play important roles in PD. Both in animal models of PD and in PD patients, many characteristic features of neuroinflammation have been found.[89] An alteration of blood-brain barrier (BBB) function, characterized by increased permeability to both FITC-labeled albumin and horseradish peroxidase and neovascularization, follows an experimental lesion induced by intracerebral 6-OHDA.[90] Endothelial proliferation has also been found in human PD patients[91] and this seems to be associated with dysfunction of the BBB in PD patients as evidenced by uptake of (^{11}C)verapamil.[92] The alteration of BBB function may be a secondary phenomenon, since in experimental animals

it is observed ipsilaterally to the 6-OHDA lesion.[90] Whether the alteration of BBB function is primary or secondary in PD, it is potentially important as dysfunctional BBB may allow entry of blood-borne toxins in the affected areas. Similarly, entrance of histidine might increase leading to larger than normal amounts of substrate available for HDC present in the nerve fibers. Histamine synthesis is largely regulated by substrate availability and unusually high histidine levels following, e.g., portacaval anastomosis are associated with very high brain histamine levels.[93] Alternatively, increased histamine in PD may be associated with neovascularization.

Epilepsy

Animal models and clinical observations have revealed that the brain histaminergic system has an inhibitory effect on seizures.[5] H_1R antihistamines show pro-convulsant effects particularly in children[94] and suppression of histaminergic activity promotes seizures in animal models.[95-98] In addition, development of epileptic behavior by kindling of the amygdala is increased in HDC- and H_1R-knockout mice.[99] Histamine levels in cerebrospinal fluid of children with febrile convulsions are significantly lower than those in the febrile children without convulsions.[100] Low histamine levels have also been detected in Krushinski-Molodkina rats that are prone to epilepsy.[101] In addition to its anti-convulsive effects, histamine has neuroprotective properties[102,103] and inhibits excitotoxic effects of glutamate.[103] H_3R antagonists have shown beneficial effects in different seizure models, such as electrically induced convulsions,[104,105] kindling[106] and pentylenetetrazole-induced seizures.[107]

Brain Injury

Involvement of histamine in the pathophysiology of brain injuries has been demonstrated in hypoxia,[108] trauma,[109,110] ischemia and stroke[111] or neoplasms.[112] For example, in rat brain, trauma leads to increased histamine levels both in the plasma and in the traumatized hemisphere.[110] In another study, fluid-percussion-evoked brain trauma caused changes in H_3R regulation demonstrated by receptor binding and mRNA in situ hybridization experiments.[109] In ischemic brain damage, histamine is released gradually over a long time frame.[113] Since preischemic administration of alpha-fluoromethylhistidine completely abolishes the ischemia-induced increase in the brain histamine, the source of histamine in cerebral ischemia is regarded to be neuronal.[113,114] An increased level of brain histamine may contribute to the amelioration of ischemic neuronal damage.[115] Thus, the emergence of neuronal injuries after ischemic events could be decreased by increasing brain histamine levels by histidine loading or H_3R blockade.

Pain

The descending histaminergic neurons originating from TMN project to areas related to pain perception[116] such as the dorsal raphe nucleus, periaqueductal gray region and dorsal horn of the spinal cord.[4,117,118] Several studies have demonstrated that histamine applied directly into CNS induces antinociception.[119-123] In line with this, brain histamine level reduction by alpha-fuoromethylhistidine or H_3R agonists enhances nociception.[123,124] Studies using histaminergic ligands[121] or mice lacking either H_1R or H_2R[125] suggest that H_1R and H_2R are responsible for the mediation of histamine's effects on pain perception.

Spinal H_3R have been also linked to antinociception based on studies with H_3R knockout mice and H_3R antagonists.[126,127] Interestingly, activation of H_3R seems to inhibit only certain types of pain such as pain induced by mechanical low-intensity stimulation.[128] The antinociceptive properties of novel H_4R antagonists[129] and recently described expression of H_4R in spinal cord[28] suggest a role for neuronal H_4R in pain perception as well.

Conclusion

The brain histaminergic system participates in the regulation of various brain functions, including sleep-wake cycle, energy and endocrine homeostasis and cognition. The effects of histamine in the brain are mediated via four histamine receptors (H_1R-H_4R), of which H_1R-H_3R are highly expressed. Changes in the neuronal histaminergic system are found in various brain

disorders such as Alzheimer's disease, Parkinson's disease and schizophrenia, making histamine receptors promising targets for future drug therapies.

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