



The Effect of Central and Peripheral Histamine on Brain Development

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Abstract

During embryogenesis, brain histamine has both central and peripheral origins and plays a crucial role in neurogenesis in animals and humans. Central histamine influences the proliferation, migration, and differentiation of stem cells in the developing brain, regulates the number of orexinergic neurons during embryogenesis, protects the developing brain from damage, and is involved in the regulation of spermine biosynthesis. Histamine's widespread distribution in the body allows it to participate in many processes of fetal development.

Keywords: Histamine, Histaminergic neurons, Development, Brain

Abbreviations: FoxP2: Forkhead box protein P2; GABA: Gamma-aminobutyric acid; HDC: Histidine decarboxylase; Ngn1: Neurogenin 1; SVZ: Subventricular zone; TM: Tuberomammillary; VMAT-2: Vesicular monoamine transporter type 2.

Introduction

Histamine is a biogenic diamine, widely distributed in animal and human tissues. It is a biologically active compound involved in the transmission of intercellular signals, including in the nervous system, where it functions as a neurotransmitter. In the brain, histamine is formed mainly in histaminergic neurons; a small amount is synthesized in mast cells of the meninges and layers of loose connective tissue, as well as in ependymocytes of the cerebral ventricles and choroid plexuses. The histaminergic neural system of the brain plays an important role in the regulation of many physiological functions, systems, and reactions of the body: the neuroendocrine and cardiovascular systems, cerebral blood flow, body temperature, sleep and wakefulness, eating and drinking behavior, memory and learning, as well as in the pathogenesis

of many diseases [1-7]. The action of histamine is mediated by several receptors: postsynaptic (H1 and H2), presynaptic (H3), and another receptor, which is mainly present in the immune system (H4). All receptors belong to the family of rhodopsin-like receptors of class A associated with guanine nucleotide-binding proteins (G proteins) [3,5].

Histaminergic neurons are first detected on the 13th day of embryogenesis at the junction of the midbrain and hindbrain. Their number increases here until the 16th day, forming a temporary, transient histaminergic system, where histamine colocalizes with serotonin. Then, histamine and the enzyme that synthesizes it, histidine decarboxylase (HDC), gradually disappear from these neurons, and they become purely serotonergic. From the 16th to

the 20th day of prenatal development, a permanent, definitive histaminergic system is formed in the tuberomammillary (TM) region of the posterior hypothalamus. This system will subsequently contain five neuronal clusters (E1-E5), which make up the histaminergic neuronal system of adult vertebrates [8].

However, the role of histamine in animal and human neurogenesis remains poorly understood and controversial. The purpose of this review is to analyze the literature on this issue.

The Role of Histaminergic Neurons in the Brain in Neurogenesis

Early brain development is driven by growth factors, neuropeptides, and small molecules such as biogenic amines, the most prominent of which in brain embryogenesis are histamine, dopamine, norepinephrine, and serotonin [25]. Histamine is one of the first neurotransmitters to appear in embryogenesis and reaches its maximum concentration simultaneously with the development of histaminergic neurons in the brain. This suggests its important role in neurogenesis. Histamine affects brain stem cells during both prenatal and postnatal ontogenesis [5,10]. In rat and mouse cerebral cortex stem cells, histamine increases the expression of the transcription factors Ngn1 (neurogenin 1) and FoxP2 (forkhead box protein P2), which are necessary for the development of deep layers of the cortex [11,12]. The most obvious source of histamine in this case are the projections of neurons of the TM region of the hypothalamus [13]. It has been shown that histamine induces the proliferation of neural stem cells *in vitro* through H2 receptors and promotes neuronal differentiation through H1 receptors [14]. Until now, there has been no evidence of a role for histamine H3 receptors in the proliferation and differentiation of stem cells, although the gene encoding these receptors is expressed in neural stem cells [10].

L. Bernardino, et al. described the unique role of histamine in the proliferation, survival, and differentiation of subventricular zone (SVZ) cells, as well as the underlying molecular mechanisms [15]. In the experiment, SVZ cells were treated with histamine for 7 days. Then, to phenotypically assess neuronal differentiation, an immunocytochemical reaction was performed with antibodies against NeuN (a marker of mature neurons [16,17]), which showed that histamine significantly increases the percentage of NeuN-positive neurons compared to control cultures. Moreover, histamine, through activation of the H1 receptor, induces functional differentiation of subventricular zone cells without affecting their proliferation or survival. Moreover, incubation of SVZ cells with 100 μ M histamine for 72 hours causes a significant increase in their mRNA levels proneurogenic genes Mash1, Dlx2 and Ngn1, compared with control samples.

The results of the study conducted by L. Bernardino, et al. also showed that histamine is actively involved in the reduction of the pool of immature cells in relation to neuronal commitment (the acquisition by the cell of structural and functional characteristics of the terminal stage of differentiation). It is worth noting that

the immunoreactivity of P-JNK (stress-activated protein kinase) induced by histamine is associated with Tau, a microtubule-associated protein that promotes the binding and stabilization of axonal microtubules of both immature and mature neurons. These data indicate that histamine promotes axonogenesis and maturation of neurons [15]. It induces proliferation of neural stem cells and neuronal differentiation due to the activation of various histamine receptors [14,18].

In adult mammals, there are several areas of the brain where neurogenesis occurs: the olfactory bulb [19], the subventricular zone [20], the SVZ in the hippocampus [21,22] and the hypothalamus [23,24]. In mammals, histamine can regulate stem cells in the subventricular zone [9]. The peak in the number of transitional histaminergic neurons in the brain and the peak of neurogenesis coincide on the 14th day of embryonic development in rats, leading to the belief that histamine is an important regulator of embryonic brain development [18].

During embryogenesis, histamine regulates the number of brain neurons that produce orexin (hypocretin), which in turn can regulate the number of histaminergic neurons themselves. Orexinergic neurons are located in the posterolateral hypothalamus and perifornical area, in close proximity to histaminergic neurons. Both nuclei partially overlap and form a functional unity [9]. In zebrafish *rerio* in suppression of HDC mRNA translation, as the amount of mRNA both orexin and the number of orexinergic neurons are reduced, while overexpression of HDC mRNA increases the number of orexinergic neurons), indicating that histamine regulates the development of these cells. In zebrafish, this regulation involves histamine H1 receptors [25]. An earlier study in rodents showed that mice with H1 receptor blockade had decreased orexin levels in the brain [26].

Interestingly, histaminergic neurons protect the developing hippocampus from kainic acid-induced injury by regulating neuronal survival at least in part through H1 and H3 receptors. In kainic acid-treated hippocampal slices, the histamine H3 receptor antagonist thioperamide enhanced the neuroprotective effect of histaminergic neurons, whereas the H1 receptor antagonists triprolidine and mepipramine dose-dependently reduced neuroprotection in hippocampus cultured with posterior hypothalamic slices containing histaminergic neurons [27].

Medium spiny neurons and GABAergic interneurons (GABA - gamma-aminobutyric acid) of the striatum and substantia nigra of the midbrain are known to be important for proper movement modulation. The presence of disturbances in their development or connections between them underlies the manifestation of Gilles de la Tourette syndrome - chronic physical and/or motor tics [9,28]. A mutation in the gene encoding HDC (nonsense mutation W317X) is associated with Tourette syndrome, which is inherited in an autosomal dominant manner. Histamine may play a significant role in the early development of both GABAergic interneurons and medium spiny neurons of the striatum [9].

Little is known about the effects of histamine on cell migration in the developing brain. However, cimetidine (a histamine H₂ receptor antagonist) has been shown to induce migration of cells obtained *in vitro* from human brain tumors, while histamine inhibits it [29].

The peak in histamine concentration during brain development is accompanied by a peak in spermine concentration (an aliphatic polyamine associated with nucleic acids and thought to be involved in stabilizing their helical structure, a possible modulator of ionotropic glutamate receptors and potassium channels, formed from spermidine [30]) with a visible 24-48-hour lag [31]. In the brain of adult rats, astrocytic glia is the major cell type that exhibit immunoreactivity to spermine/spermidine [30]. Therefore, it is possible that central histamine is involved in the regulation of the synthesis of this substance in astrocytes containing histamine receptors. There is also direct evidence that histamine stimulates ornithine decarboxylase (a key enzyme in spermine biosynthesis) in the rat brain via H₂ receptors [31].

Interestingly, with age, the levels of central histamine and its metabolites, but not the expression of HDC, increase, while the density of receptors decreases. This may contribute to the development of brain pathology and neuronal dysfunction in the elderly [5].

Histamine of Mast Cells and Ependymocytes of the Brain

It should be noted that on the 18th day of embryogenesis, the rat brain is also populated by histamine-immunoreactive mast cells [28,32,33]. Their number increases until the 4th day of postnatal development, after which it gradually begins to decrease [28]. The main location of these HDC- and histamine-containing tissue basophils is in the intermediate velum between the developing thalamus and hippocampus. In addition, they are also found in the meninges, choroid plexus, layers of loose connective tissue of the thalamus and around the fimbria of the hippocampus. Later, in adulthood, the perivascular space of the dorsal thalamus and the median eminence of the hypothalamus are the best-known localization sites of mast cells [9]. The role of mast cell histamine in the brain is unclear, although in early postnatal development these cells are responsible for the formation of a significant portion of the total brain histamine pool [28].

Transitional populations of neurons and mast cells mediate two distinct (embryonic and postnatal, respectively) short-term peaks in central histamine levels in the developing rat brain [34]. The first peak occurs on day 16 of prenatal development, when the transitional population of histaminergic neurons reaches its maximum development in the brainstem (raphe). The highest histamine concentrations are found in the pons, as well as in the midbrain and medulla oblongata. Histamine immunoreactivity then gradually declines by day 20 of embryogenesis, after which only serotonin remains in this region [35]. The second peak of

histamine concentration in the brain, occurring on day 5 after birth [33], can be explained by the increase in the number of mast cells [36]. Total central histamine levels then gradually decline to adult levels at approximately 2 weeks of postnatal development and correlate with the maturation of histaminergic neurons in the posterior hypothalamus [9].

From day 14 of embryogenesis, ependymal cells of the brain ventricles and choroid plexus also express HDC and contain histamine, which can be secreted in significant quantities in the absence of vesicular monoamine transporter type 2 (VMAT-2), which is required for histamine storage in neurons of the posterior hypothalamus [9,37]. Histamine synthesized by ependymal cells of the brain may be involved in the regulation of the formation of subventricular stem cells located beneath the ependymal layer [38]. Notably, a positive signal obtained by *in situ* hybridization *In situ*, when studying HDC mRNA, is not restricted to areas containing histamine nerve fibers, indicating that in some areas, such as the cerebral cortex, histamine originates from sources other than neurons [35,36].

The Role of Peripheral Histamine in Embryogenesis

Brain histamine in embryogenesis may also have a peripheral origin. During prenatal development, the liver and stomach produce histamine in high concentrations, and the blood-brain barrier is not yet functioning properly [39], which allows peripheral histamine to penetrate into the brain [20]. The presence of a histamine uptake mechanism in developing raphe neurons or in histamine-immunoreactive fibers of the transient histaminergic system has not yet been established, but such a mechanism may explain the discrepancy between high histamine concentrations and low activity of the histamine-synthesizing enzyme in the embryonic brain [40].

In the mouse embryo, histamine is present in cells of the salivary glands, spleen, kidneys, insulin-producing islet cells of the pancreas, enterochromaffin-like cells of the stomach, in the osteogenic zone of developing bones, in neurons of the peripheral nervous system, and in mast cells [39]. During the embryonic period, there are some fundamental differences in the patterns of HDC expression in mice and rats. For example, in rats, this enzyme is highly expressed in the liver, whereas in mice, it is expressed in the skin and renal tubules.

The widespread distribution of histamine in the fetus allows it to participate in many developmental processes. The absence of histamine in mice lacking HDC is associated with a decrease in the number of mast cells (with the remaining mast cells characterized by a small number of granules, hypergastrinemia, an increase in the number of enterochromaffin-like and parietal cells in the thickened gastric wall, an increase in bone mass, and a high rate of carcinogenesis of the skin and colon. Despite all of the above, mice lacking HDC are externally indistinguishable from their peers and reproduce normally [9].

Conclusion

Thus, histamine, particularly of central origin, plays a crucial role in animal and human neurogenesis. During fetal brain development in mammals, histamine is produced by neurons of the transitional histaminergic system of the midbrain and hindbrain, ependymal cells, mast cells, and, toward the end of embryogenesis, by neurons of the posterior hypothalamus. Central histamine influences the proliferation, migration, and differentiation of stem cells in the developing brain, regulates the number of orexinergic neurons during embryogenesis, protects the developing brain from damage, and is involved in the regulation of spermine biosynthesis. Peripheral histamine also plays an important role in embryogenesis.

Author Contributions

All authors made the same contribution to the preparation of the article.

Conflict of Interest

Authors declare that they have no financial or personal conflicts of interest that could inappropriately influence the writing of this review article.

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