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Review Article

Disorders in the Ontogenesis of The Brain Histaminergic System Under Various Experimental Influences

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Abstract

The purpose of the review is to analyze the literature and summarize the results of world studies of disorders of the individual development of the histaminergic system of the brain under various experimental influences.

The review describes disturbances in the ontogenesis of the histaminergic system of the brain in such pathological conditions as diabetes mellitus and diabetes insipidus, hypo- and hyperthyroidism, autism spectrum disorders, changes in dopaminergic signaling and the amount of dopamine, alcohol intoxication, demonstrating the role of glucose, vasopressin, thyroid hormones, valproic acid, dopamine and other factors in the development of the histaminergic system.

Analysis of literature data allows us to conclude that the histaminergic system of the brain is highly sensitive to various endogenous and exogenous factors.

Keywords: Histaminergic system, Brain, Ontogenesis

Abbreviations: DI: Diabetes Insipidus; HDC: Histidine Decarboxylase; HZ: Heterozygous; L-DOPA: L-3,4-dihydroxyphenylalanine; LE: Long Evans; MANF: Mesencephalic Astrocyte-Derived Neurotrophic Factor; th: tyrosine hydroxylase; TM: Tuberomammillary; VPA: Valproic Acid.

Introduction

Histamine is a biologically active compound involved in the transmission of intercellular signals, including in the brain, where it functions as a neurotransmitter. There are two relatively independent pools in the body: peripheral and central. Central histamine is synthesized from the amino acid L-histidine by the enzyme histidine decarboxylase (HDC) in a limited population of histaminergic neurons located in the tuberomammillary (TM) nucleus of the posterior hypothalamus. The bodies of these neurons form five clusters - nuclei (E1-E5), and their axons extend to all parts of the brain. Histaminergic neurons are located in the TM region of the posterior hypothalamus in all vertebrates [1]. Even in the fish Danio rerio, which is widely used for neurogenetic research, both histaminergic neurons and histamine receptors are very similar to those of mammals.

Histaminergic neurons of the brain realize their action through four types of receptors: H1-H4, which are widely and heterogeneously distributed in the brain and belong to the family of G-protein coupled receptors. A high distribution density of all three types of histamine receptors has been shown in the cerebral cortex, hippocampus, amygdala and hypothalamus. In general, histamine H1 and H2 receptors have primarily excitatory effects on brain neurons or potentiate excitatory input. On the contrary, activation of

histamine H3 receptors causes autoinhibition of TM neurons and inhibits the release of neurotransmitters [1,2]. H4 receptors are not as widely represented in the central nervous system as other histamine receptors. They are mainly found in the cerebellum, thalamus, hippocampus and deep layers of the cerebral cortex. This type of receptor plays an important role in immune defense [3].

The development of the histaminergic system of the brain has been studied in most detail in the rat. It has been established that from the 13th to the 16th days of embryogenesis, a temporary transient histaminergic system is formed in the midbrain and hindbrain of the rat, in which histamine colocalizes with serotonin. Then the histamine and HDC in these neurons disappear and they become purely serotonergic. On 16-20th days of embryogenesis, another histaminergic system, characteristic of adult vertebrates, is formed in the posterior hypothalamus [4-6].

Histamine plays an important role in brain development, participating in many physiological and pathological processes. The participation of central histamine in the pathogenesis of many pathological conditions and diseases has been studied: muscle hypotonia, Alzheimer's disease, Parkinson's disease, epilepsy, morphine addiction, alcoholism, autism, etc. [1]. However, there is little data in the literature on the influence of various factors on the development of the histaminergic system itself. In this review, we describe disturbances in the ontogenesis of the histaminergic system in pathological conditions such as diabetes mellitus and diabetes insipidus, hypo- and hyperthyroidism, autism spectrum disorders, changes in dopaminergic signaling and the amount of dopamine, thereby showing the role of glucose, vasopressin, thyroid hormones, valproic acid, dopamine and other factors in the development of the histaminergic system of the brain.

Experimental Diabetes Mellitus

Solis and colleagues (*Solis KH, et al.* 2017) examined changes in histamine levels and H1 histamine receptor expression in the brain of fetal diabetic rats on the 12th, 14th, 16th, 18th and 20th day of intrauterine development. Diabetes in pregnant females was modeled by intraperitoneal administration of streptozotocin on the 5th day of pregnancy at the rate of 50 mg/kg body weight. A significant increase (3.5 times) in the concentration of histamine in the neuroepithelium of the cerebral cortex of embryos on the 14th day of prenatal development in experimental animals was revealed. Based on the assumption that the main source of embryonic histamine on the 12th and 14th days of embryogenesis are transient histaminergic neurons [6], we measured the level of expression of HDC mRNA, the amount of HDC and the activity of this enzyme in the ventral region of the midbrain and primary hindbrain, the location localization of the transitional histaminergic system. The results showed lower levels of HDC mRNA in the fetuses of the experimental group on the 12th (3.8 times) and 14th (2.1 times) days, which was accompanied by a decrease in the amount of its protein on the 14th day (1 .8 times) compared to control values. Thus, the increased level of telencephalic histamine on the 14th day of embryogenesis in the diabetic group is not explained by fetal HDC mRNA, the level or activity of this enzyme in the brain. It was noted that the concentration of histamine in maternal serum from the experimental group was lower compared to the control. A comparison of the amount of H1 receptor mRNA showed that in embryos obtained from rats with diabetes, this indicator increases on the 12th (2 times) and 20th (2.9 times) days, and on the 16th and 18th days On the 1st day, lower values are observed compared to the control group (5.5 times and 1.3 times, respectively). However, in the telencephalon of embryos of the experimental group, the levels of H1 receptor protein significantly increase on the 12th (1.6 times) and 16th (1.7 times) days compared to the control group [7].

Vasopressin Deficiency and Diabetes Insipidus

To determine whether the absence of vasopressin affects the development of the histaminergic system in the hypothalamus, studies were conducted to examine changes in brain histamine concentrations in diabetic rat pups aged 2-38th days from birth with diabetes insipidus. To conduct the experiment, we used homozygous Brattleboro rats (hereinafter referred to as DI - diabetes insipidus) - a laboratory line of red rats incapable of producing vasopressin, that is, mutant in the antidiuretic hormone gene, which phenotypically manifests itself in the form of diabetes insipidus (in particular, water consumption and urine output increase 10 times or more). This mutation is a frameshift mutation, in which a single nitrogenous base is deleted, guanine. In addition to homozygous DI animals , the brains of normal LongEvans (LE) rats, from which the mutant strain arose, and heterozygous (HZ) Brattleboro rats were examined, as they have lower plasma vasopressin concentrations than control LE rats.

It was found that in animals of all three genotypes, the concentration of histamine in the hypothalamus during the first 6 postnatal days does not differ. However, in HZ and LE rats, histamine concentrations increase rapidly from 10th to 22th days. In DI rats, the period of most rapid increase in histamine levels occurs much later, between days 14 and 26 [8].

At the same time, a 2.5-fold increase in the concentration of histamine is observed in some nuclei of the hypothalamus of 9-week-old Brattleboro rats, especially in the supraoptic, suprachiasmatic, paraventricular nuclei and in the retrochiasmatic region, which is part of the mediobasal hypothalamus, which regulates neuroendocrine connections [9]. No such difference was found in the rest of the brain. In contrast, histamine concentrations are characterized by relatively high values during the first 10 days of life, especially in DI rat pups. After the 14th day, no significant differences were found between control and experimental animals. It is believed that in the absence of the ability to synthesize vasopressin, magnocellular neurons of the supraoptic and paraventricular nuclei are impaired in their ability to regulate the development of histamine-containing nerve endings, which they presumably possess [8].

Thyroid hormones, hyper- and hypothyroidism

Thyroid hormones have been shown to influence the rate of brain maturation [10]. At the same time, they have a significant effect on the synthesis of histamine. In turn, imbalances in neurotransmitter function may play an important role in the devel-

opment of mental disorders caused by thyroid dysfunction during critical periods of postnatal development [11]. There is evidence that thyroidectomy causes a significant increase in HDC activity (about 100%) in the rabbit hypothalamus [12]. In newborn rat pups, the concentration of histamine in the brain increases with hypothyroidism, and decreases with hyperthyroidism [13].

Direct labeling of H1 receptors made it possible to establish that the age-related increase in their content is significantly accelerated in rats born with experimental hyperthyroidism and decreases in hypothyroidism. While in hyperthyroid animals the density of H1 histamine receptors characteristic of a normal adult rat is achieved at the age of 21 days, in rats with thyroid hormone deficiency the density and total content of H1 receptors remain significantly reduced even by the 30th day, compared with control animals, in which by this time these indicators correspond to an adult organism. In a sexually mature animal, experimentally induced hypothyroidism causes a decrease in both the density and total content of H1 receptors. In the case of hyperthyroidism, the density of receptors increases, but their number per unit area remains unchanged [11]. A decrease in the number of H1 receptors in hypothyroid rat pups may be associated with impaired growth and arborization of neurons, as well as a decrease in synaptic density [11], since similar phenomena were noted earlier when studying the effect of thyroid hormone deficiency on brain development [14,15]. It is believed that thyroid hormone deficiency directly affects receptor protein synthesis. On the other hand, stimulation of neuronal protein synthesis and structural and biochemical differentiation induced by excess thyroid hormone may explain the accelerated formation of H1 receptors in hyperthyroid pups [11]. Thus, the results of the presented study show that thyroid hormones regulate the density and total content of histamine H1 receptors in the brain, as a result of which thyroid dysfunction in early and adulthood can cause disorders of the histaminergic system.

Dopamine

To study the role of dopamine in the development of histaminergic neurons, we inhibited the translation of two non-allic forms of the enzyme involved in the synthesis of dopamine, tyrosine hydroxylase (th1 and th2), and used dopamine receptor ligands to change dopaminergic signaling in fish larvae of Danio rerio [16]. It has been shown that at 5 days after fertilization, histaminergic neurons surround th2 - expressing neurons in the hypothalamus. Knockdown of the th2 gene increases the number of histidine decarboxylase-containing neurons and histamine levels, while increased dopaminergic signaling using the dopamine precursor L-DOPA (L-3,4-dihydroxyphenylalanine) or dopamine receptor agonists reduces the number of histaminergic neurons. At the same time, an increase in the number of the latter is accompanied by a comparable increase in the number of neurons expressing orexin/hypocretin, confirming the observation that histamine stimulates the development of orexinergic neurons [17]. It was found that the Wnt signaling pathway and the neurotrophic factor MANF (mesencephalic astrocyte-derived neurotrophic factor), which regulate the formation of the dopaminergic system [16,18-20], also influence the development of histaminergic neurons in the brain [16]. However, it is worth noting that the potential regulatory role of dopamine in the development of histaminergic neurons is difficult to study in mammals, since mice lacking tyrosine hydroxylase do not survive [16, 21,22]. It has been suggested that dopamine paracrinely regulates the terminal differentiation of histamine-producing neurons during embryonic neurogenesis [16].

Valproate

Recently, increasing attention has been paid to valproic acid (VPA, valproate), which is a simple branched-chain fatty acid widely used to treat epilepsy and bipolar disorder. It is being investigated as a treatment for HIV infection and various types of cancer because, as an inhibitor of histone deacetylase, it induces acetylation of histone and non-histone proteins associated with nucleosome remodeling and gene transcription [23]. However, when taken during pregnancy, valproate increases the risk of autism spectrum disorder in the offspring, which is characterized by persistent deficits in the ability to initiate and maintain social interactions and social connections, as well as restricted interests and highly repetitive behaviors [24].

Of note, brain samples (dorsolateral prefrontal cortex) from individuals with this neuropsychiatric disorder show altered expression of histamine receptors [25]. Animal experiments in which VPA was used to recapitulate the core symptoms of this disorder demonstrated that ciproxifan, an inverse agonist of the histamine H3 receptor, was able to partially restore the impaired communication seen in mice pre-exposed to valproate [26].

A study was conducted to study the embryonic effect of valproic acid on the histaminergic system and social behavior of Danio rerio fish. The main objective of the study was to evaluate the state of the histaminergic system in larval and adult zebrafish exposed to VPA from late gastrulation until neural tube formation. Communication skills, reactions to alternating periods of "light-dark" and motor activity of animals were also studied. Embryos treated with 25μmol/L valproate were observed for morphological abnormalities every day until day 5 of development. During the experiment, it was discovered that about 27% of the embryos in the experimental group died or acquired obvious developmental defects. In the remaining larvae, there is a significant decrease in the number of histamine-immunoreactive neurons compared to the control [27]. In Danio fish, valproic acid leads to a decrease in the proliferation of telencephalon cells without causing their apoptosis [28], however, in the presented study, differences in the level of mRNA expression of proliferating cell nuclear antigen) was not detected in the posterior hypothalamus between the compared groups of animals [27].

On the 5th day of development, zebrafish larvae treated with VPA showed a decrease in histamine concentration, as well as the levels of expression of HDC and transcripts of histamine H1, H2, H3 receptors compared to the control group. The decreases observed in the expression of HDC and H3 receptor mRNA were also noted in adulthood, although the histamine level in experimental animals had already normalized by this time. Zebrafish larvae exposed to

VPA under normal lighting conditions exhibit a decrease in locomotor activity (by approximately 75%) and also demonstrate a weakened response to alternating light-dark periods. This may be due to a significant decrease in histamine content, since these disorders are characteristic of Danio rerio larvae, deprived of the ability to synthesize histamine due to inhibition of translation of the gene encoding HDC [39]. Adult animals exposed to VPA also exhibit impaired social behavior [27].

In summary, significant molecular and neurochemical changes occur in the histaminergic system of zebrafish exposed to valproate for a short period during early development. It is important to note that some of these changes persist into adulthood, despite the good regenerative capacity of zebrafish [29].

Presenilin 1 and γ-secretase

was studied using psen1 mutant zebrafish [20]. Presenilins are a family of transmembrane proteins that form part of the γ-secretase protease complex [30]. Mutations in genes carrying information about presenilins lead to early onset of Alzheimer's disease [31]. Unlike psen1 knockout mice, which die at birth [32], psen1 -/- mutant Danio rerio are completely viable [20], despite the fact that inhibition of presenilin 1 function induces defective brain development in them [33]. In Danio fish lacking psen1, the histaminergic system changes throughout life [20]. Thus, in psen1 -/- Danio rerio at the age of seven days from the moment of fertilization, the number of histamine-producing neurons is reduced compared to the wild type, while increased activation of caspase-3, usually observed in the presence of apoptosis, was not noted. At the age of 2 months, the number of histaminergic neurons is at the same level as in normal fish. In one-year-old psen1 -/- Danio fish, the number of histamine neurons is increased compared to fish of the original type, and by one and a half years it exceeds the norm by an average of 50%. The observed effect is specific to the histaminergic neurotransmitter system and does not affect other neurotransmitter systems.

Such changes in the number of histaminergic neurons are accompanied by histamine-mediated behavioral changes in both larval and adult Danio rerio [34]. The mediation of the identified changes in the behavioral reactions of fish from the experimental group by histamine is confirmed by previously conducted studies, which show that histamine is a factor stimulating the state of wakefulness, a mediator of vigilance and cognitive ability [1,2,17].

The γ-secretase complex regulates the development of histaminergic neurons through Notch1a signaling [20]. The intracellular domain of Notch functions as a transcription factor and is of great importance in the early stages of embryogenesis, since it controls the proliferation and choice of differentiation pathways of stem cells [35]. In addition, it is the best known substrate of presenilins [20]. Notch1a mRNA was detected along the midline of the rostrocaudal axis in the hypothalamus, cerebellum and ventricular zone of the telencephalon of Danio rerio fish at the age of 7, 14 and 28 days after fertilization. The listed areas are neurogenic and proliferative in the brain of Danio fish [36,37]. In psen1 −/− Danio fish, Notch1a mRNA expression in such zones is significantly reduced by day 7 postfertilization. This indicates a change in the processes of neurogenesis and proliferation, which, in turn, may affect histaminergic neurons.

It should be noted that the increase in the number of histaminergic neurons in adult Danio fish lacking psen1 indicates long-term plasticity of the histaminergic system. It has been suggested that new histaminergic neurons may arise if local stem cells are induced to differentiate, or this phenomenon may be associated with phenotypic plasticity, that is, a change in the neurochemical phenotype of neurons adjacent to histaminergic neurons [20]. This phenotypic switch occurs in the transient histaminergic system during rodent development [38] and can even be observed in adult animals, allowing homeostatic plasticity [39].

Alcohol

During the experiment, females consumed a balanced liquid diet Sustacal throughout pregnancy, containing either sucrose (control group) or ethanol (experimental group) in a volume ratio of 6%. Newborns were nursed by mothers who ate a similar diet. A study found that ethanol consumption by females during pregnancy resulted in a significant increase in brain histamine levels in their fetuses. An increase in histamine concentration is also observed in newborn rat pups whose mothers receive ethanol during lactation, compared with the corresponding control groups. It should be noted that when ethanol is replaced with sucrose in the diet of lactating rats, histamine levels in the brain structures of newborns are restored to control values within one week [40].

However, exposure to alcohol during pregnancy and lactation does not significantly affect the activity of histidine decarboxylase in the brain structures of the fetus and newborn. These data indicate that the increase in histamine levels with prolonged ethanol consumption is not mediated by changes in HDC activity and may either be a direct effect of ethanol metabolism leading to histamine release or reflect peripheral changes in maternal histamine levels [40]. The blood-brain barrier in the fetus does not yet function properly [41], which allows peripheral histamine to enter the brain [42]. It is likely that an increase in the level of histamine in the mother's blood can affect the fetal brain. The increase in brain histamine levels in rat pups whose mothers consumed ethanol during lactation suggests that ethanol supplied through milk to the newborns is capable of inducing these changes in them [40], as it was previously reported that, although the level of ethanol in the mother's blood is not completely same as the level of alcohol appearing in milk, there is a direct correlation between the two [43].

Conclusion

Histaminergic neurons, histamine and its receptors appear in the brain of animals and humans in the early stages of embryogenesis. During its development, the histaminergic system is under strict control of other aminergic systems, such as the dopaminergic and orexinergic systems. Thus, a decrease in the content of dopamine and orexin leads to an increase in the number of histaminergic neurons. At the same time, according to some scientists, dopamine during embryonic neurogenesis can paracrinely regulate the terminal differentiation of histamine-producing neurons.

In addition, many experimental influences (administration of valproic acid, alcohol intoxication, etc.) and some pathological conditions (diabetes mellitus and diabetes insipidus, hypo- and hyperthyroidism) affect the development of the histaminergic system of the brain.

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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