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Visions & Reflections (Minireview)

Histamine receptor-mediated signaling during development and brain function in adulthood

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Abstract. Histamine might have an important role in brain development. However, most studies have focused on short-term effects of histamine receptor-mediated signaling on brain function in adulthood. Little is known about the potential long-term effects of histamine receptor-mediated signaling during development on brain function in adulthood. We hypothesize that increased postsynaptic histamine receptor-mediated signaling during development has detrimental effects on brain function in adulthood. Our data support this hypothesis. In the developing mouse brain, histamine H3 receptor blockade, which increases histamine release, has detrimental sex-dependent effects on object recognition, spatial learning in the water maze, and pre-pulse inhibition in adulthood. Our data also support the hypothesis that histamine mediates the detrimental long-term sex-dependent effects of methamphetamine exposure early in life on these brain functions in adulthood. Therefore, increased efforts are warranted to carefully evaluate the effects of drugs that directly or indirectly affect histamine receptor-mediated signaling during development on cognitive function later in life.

Keywords. Histamine, development, cognition, schizophrenia, sex.

Histamine receptors

In the central nervous system (CNS), synthesis of L-histidine into histamine (HA) by L-histidine decarboxylase takes place in a restricted population of neurons located in the tuberomammillary nucleus (TM) of the posterior hypothalamus. From the TM, histaminergic neurons project to virtually the entire brain, and, in the CNS, HA is involved in many important physiological processes, including the release of stress hormones such as corticotropin-releasing factor (CRF) and arginine vasopressin (AVP) (for a review see [1]). Four distinct HA receptors, which are all G-protein-coupled receptors (GPCRs), have been identified.

H1 receptors, which couple to $G_{q/11}$ proteins, are expressed in the CNS, especially in the thalamus, hippocampus, cortex, amygdala, and in the basal forebrain. In the periphery, H1 receptors are widely expressed in tissue such as ileum, smooth muscle and heart. Mobilization of calcium from intracellular Ca^{2+} stores is the main action of H1 receptors. Besides increasing inositol phosphate accumulation that further increases calcium flow, Ca^{2+} is, among other things, also responsible for the induction of nitric oxide production, leading to relaxation of the endothelium [2, 3].

H2 receptors, expressed in the periphery and in the CNS, couple to G_s proteins. In the periphery, the main role of the H2 receptor is the regulation of gastric acid

secretion in the parietal cells in the endothelium. Furthermore, the H2 receptor mediates relaxation of airway and vascular smooth muscle. In the CNS, the H2 receptor is widely expressed with particularly high receptor density in the basal ganglia, the hippocampus and amygdala. High expression is also found in pyramidal cells, raphe nuclei and the substantia nigra. In the CNS, H2 receptor activation is associated with excitation through a blocking effect of Ca^{2+} and K^+ channels, regulation of fluid balance, and regulation of hormonal secretion.

The H3 receptor enables HA to inhibit its own release [4–7]. Thus, stimulation of H3 receptors by H3 agonists inhibits HA synthesis and release, while inhibition of H3 receptors by H3 receptor antagonists increases HA release [4, 8]. Endogenous release of HA in brain is mainly regulated by H3 receptors. In the CNS, H3 receptors are widely expressed as presynaptic autoreceptors. High densities have been found in nucleus accumbens, striatum, olfactory tubercles, substantia nigra and the amygdala. Lower receptor densities have been detected in the hypothalamus. The H3 receptor is a constitutively active receptor [9] that mediates its effects through the $G_{i/o}$ class of G-proteins [10]. In addition to HA, H3 receptor-mediated signaling also affect other neurotransmitters such as dopamine [11], serotonin [12, 13], GABA [14], norepinephrine [15], and various peptides [16].

The H4 receptor [17] is not as widely expressed as other HA receptors. H4 receptors have been found mainly in medullary and peripheral hematopoietic cells such as eosinophils, neutrophils and $CD4^+$ T cells [18–20], suggesting an important role for the H4 receptor in the immune system. In the CNS, H4 receptors are mainly found in the cerebellum and at much lower levels in the hippocampus [18].

HA, HA receptors, and the developing brain

HA might have an important role in brain development. HA is one of the first neurotransmitters to appear and the concentration of HA in prenatal brain is fivefold that of adult levels. HA concentrations are high at embryonic day 13 (E13), stay elevated from E14 to E18, and gradually decrease toward birth [21, 22]. The first histaminergic nerve fibers reach the frontal and parietal cortex at E15 [23, 24] and adult-like distribution of HA-immunoreactive nerve fibers in the developing brain is reached by postnatal (P) 14 [24]. HA-containing mast cells start to appear at E18, continue postnatally, and result in another peak in brain HA concentration on P5. Subsequently, HA concentrations decrease to that of adult levels during the first postnatal weeks.

Fetal rodent brain express H1 [25], H2, [26] and H3 [26] receptors. At E15, HA is transiently produced in a subgroup of neurons in the raphe nucleus [22] and H1, H2, and H3 receptors are expressed in the ventricular neuroepithelium in the midbrain and medulla [25, 26]. At E16, H3 receptor mRNA is strongly expressed in thalamus, hypothalamus, midbrain, and cortex [26], which are target areas for developing raphe neurons whose fibers contain HA [22] and later in development for developing HA neurons from the tuberomammillary area of the hypothalamus [23]. At E19 and at birth, H3 receptor mRNA is expressed in the cortical plate, cortical layer 6b, and nucleus accumbens [26].

Studies with [^{3}H]mepyramine and [^{3}H]Rα-methylhistamine have been performed to evaluate the postnatal development profile of H1 and H3 receptors, respectively. H1 receptors were detected first at P2. In contrast, H3 receptors were detected first at P9. H1 receptors are detected at higher levels in the hypothalamus, hippocampus, and amygdala, while lower levels are detected in cortex, striatum, thalamus, and substantia nigra [27]. Resembling the changes in neuronal HA, H1 receptor binding increased (an increase in binding sites without changes in affinity) from birth to adult levels at P25–P30 [28, 29].

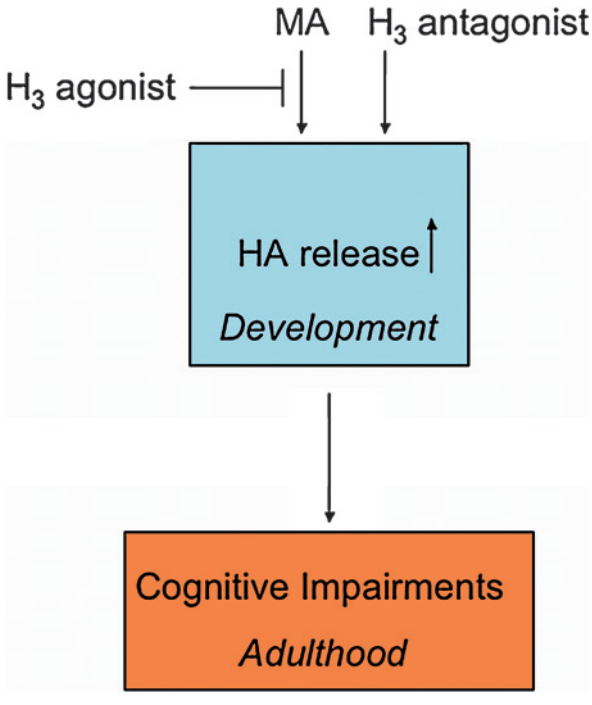

Figure 1. Hypothesis of role of histamine (HA) in detrimental long-term effects of methamphetamine (MA) during development on cognitive function in adulthood.

HA-receptor-mediated signaling during development and brain function in adulthood

Most studies have focused on short-term effects of HA receptor-mediated signaling on brain function, including effects on measures of anxiety, depression, and learning and memory. For example, in adulthood both positive and negative effects of neuronal HA on cognitive function have been reported. H3 receptor stimulation improved memory retention in the water maze [30] and H3 receptor blockade impaired social memory [31] and object recognition [32]. Similarly, H3 receptor blockade, histamine, or histidine, decreased social investigation time, while H3 receptor stimulation or inhibition of HA synthesis increased social investigation time [31]. Further, mice lacking H1 receptors showed less social isolation stress-induced impairments in cognition than wild-type mice [33]. Finally, bilateral lesion of the TMs improved learning and memory in adult and aged animals [34]. In contrast, H3 receptor blockade might be beneficial under condition of cognitive impairments caused by cholinergic dysfunction [35–37]. Also, while immediate post-training intracerebroventricular administration of HA facilitated retention of inhibitory avoidance behavior [38] and improved memory deficits in active avoidance following hippocampal lesions [39], HA depletion impaired the acquisition of active avoidance behavior [40]. Further, H3 receptor blockade improved social interaction in adults [41]. During development, acute H3 receptor blockade might also be beneficial for retention of animals to avoid a footshock in a repeated acquisition avoidance model [42]. However, little is known about the potential long-term effects of HA receptor-mediated signaling during development on brain function in adulthood. The role of HA in brain function has been studied in mice lacking the enzyme required to generate HA from L-histidine, histidine decarboxylase (HDC). The effects of HDC deficiency on cognitive performance are sex dependent and might relate to the anxiety levels of the mice [43–45]. While object recognition is impaired in male HDC-deficient male mice [43], this is not seen in female HDC-deficient mice [44]. In contrast, while male HDC-deficient mice showed enhanced spatial learning and memory in the water maze [45], female HDC-deficient mice showed impaired spatial learning and memory in the water maze [44]. Female HDC-deficient mice showed enhanced passive avoidance memory retention [44], suggesting that the effects of HDC deficiency on cognitive function might be brain region dependent. These effects of HDC deficiency on cognitive function in adulthood could involve acute, chronic, and/or long-term effects of HDC deficiency.

We hypothesize that increased postsynaptic HA receptor-mediated signaling during development has detrimental effects on brain function in adulthood. To start testing this hypothesis, neonatal mice were administered the H3 receptor antagonist thioperamide (5 mg/kg), which in turn would cause an increase in HA release, or saline, once daily, from P11 to P20. This time period was selected as it can be used to model the human third trimester, as granule cells of the dentate gyrus of the hippocampus are developing in humans and rodents in these respective time periods [46, 47]. The mice were tested at 3 months of age. The results of this study are as described in detail in [48] and summarized below. There were no effects of thioperamide on body weight, exploratory behavior, measures of anxiety, or sensorimotor function. Next, the mice were tested in complex novel location and novel object recognition tests [49, 50]. The novel location recognition test assesses the ability of mice to recognize a novel spatial arrangement of familiar objects and is sensitive to hippocampal damage [51]. The novel object recognition test assesses the ability to recognize a novel object in the environment and is unaffected by hippocampal lesions [52]. When a familiar object was moved to a novel location, saline-treated female and male mice spent more time exploring the object in the novel than familiar location. In contrast, thioperamide-treated females showed impairments in novel location recognition and did not spend significantly more time exploring the object in the novel location. In contrast to females, thioperamide-treated male mice showed novel location recognition, indicating that females might be more susceptible to the effects of thioperamide on novel location recognition.

When a familiar object was replaced by a novel one, thioperamide-treated female and male mice spent significantly less time exploring it than saline-treated male mice and did not explore the novel object more than the two familiar objects.

Next, a modified Morris water maze was used to assess spatial learning and memory [53]. Mice were trained to swim to a submerged platform in order to escape from the water. First they were trained with the platform clearly marked by a beacon on the visible platform component (non-spatial training, days 1 and 2), and then they were trained with the beacon removed in the hidden platform component (spatial training, days 3–5) during which the mice had to navigate using the available spatial cues in the room. There were two daily sessions 3.5 h apart, each consisting of three 60-s trials (with 10–15-min intertrail intervals). During the visible platform training, the platform was moved to a different quadrant of the pool for each session. The hidden platform location

was the same as the location in the first visible platform session.

During the sessions with the visible platform, thioperamide- and saline-treated female and male mice performed equally well in the time required to reach the platform (latency). The latency measure could be used as the swim speeds during the visible sessions were similar in the groups. In female mice, compared to neonatal saline treatment, neonatal thioperamide treatment caused impairments in ability to locate the hidden platform. In contrast to females, neonatal thioperamide treatment did not impair the ability of male mice to locate the platform during the hidden water maze sessions.

The probe trial was designed to examine the extent of spatial discrimination learning (spatial bias) 1 h following the last session of hidden platform training. In the probe trial, saline- and thioperamide-treated female mice spent more time in the target quadrant than in any other quadrant, indicating spatial memory retention. A higher dose of thioperamine might have caused impairments in the hidden sessions and probe trial of the water maze. As novel location recognition and spatial learning in the water maze is hippocampus-dependent, these data indicate that female mice might be more susceptible to the detrimental effects of increased histaminergic neurotransmission early in life on hippocampus-dependent learning and memory in adulthood.

Lastly, pre-pulse inhibition was used to assess sensorimotor gating. Pre-pulse inhibition is measured by the change in startle response following a pre-pulse. Potential differences in hearing sensitivity might affect performance in the pre-pulse inhibition test. Therefore, the acoustic startle threshold was assessed first. There were no effects of thioperamide on acoustic startle threshold. Compared to sex-matched saline-treated mice, thioperamide-treated mice showed impaired pre-pulse inhibition. This effect was more pronounced in male than female mice. This sex difference might be related to the fact that following neonatal administration of saline the pre-pulse inhibition was lower in female than male mice.

HA as mediator of detrimental long-term effects of methamphetamine on brain function in adulthood

In addition to the long-term effects of increased HA-mediated neurotransmission during development on brain function in adulthood being important in their own right, HA may also mediate the long-term effects of methamphetamine on brain function. Our data indicate that neonatal administration of methamphetamine (5 mg/kg, once daily, P11–P20) mimics neonatal administration of thioperamide in its effects on novel location recognition, spatial learning, and pre-pulse inhibition. If HA mediates the effects of neonatal methamphetamine administration early in life, inhibiting HA release should antagonize these effects. Indeed, our data indicate that in neonates the H3 receptor agonist immepip inhibits the long-term detrimental effects of methamphetamine on object recognition, spatial learning, and pre-pulse inhibition (Fig. 1). The link between HA and methamphetamine is not limited to development [54–56]. In adulthood, HA and its precursor L-histidine inhibit methamphetamine-induced stereotyped behavior and behavioral sensitization to methamphetamine, and these effects are blocked in the presence of H1 or H2 receptor antagonists [57]. Similarly, behavioral sensitization to methamphetamine is also enhanced in mice lacking HDC (for review see [58]). In contrast, in adult rodents, methamphetamine induces HA release in various brain regions and chronic methamphetamine administration increased cortical HA levels [55]. In addition, H3 receptor antagonists potentiate methamphetamine self-administration and methamphetamine-induced accumbal dopamine release [59], as well as the discriminative-stimulus effects of methamphetamine [60, 61].

Conclusions and perspectives

In humans, the short-term effects of HA receptor-mediated signaling in the adult brain are well studied. In contrast, little is known about the potential long-term effects of increased HA receptor-mediated signaling in the developing brain. H3 receptor antagonists were suggested as potential targets for pain, sleep disorders, attention-deficit hyperactivity disorder, cognitive disorders such as Alzheimer's disease, myocardial ischemia, migraine, and inflammatory diseases (for reviews see [62, 63]) and even suggested as potential future 'wonder drugs', being effective anti-obesity drugs while at the same time enhancing cognitive performance ('get smart and get slim') [62]. Based on the effects of H3 receptor antagonists thioperamide and ciproxifan on pre-pulse inhibition in 5–7-week-old C57BL/6 and DBA/2 mice, H3 receptor antagonists were suggested as potential candidates for treatment of schizophrenia [64]. However, our data support the hypothesis that in the developing mouse brain H3 receptor blockade has detrimental effects on object recognition, spatial learning in the water maze, and pre-pulse inhibition. Impairments in pre-pulse inhibition following H3 receptor blockade early in life are important in the context of the proposed role of brain HA in schizo-

phrenia and animal models of schizophrenia, such as methamphetamine-induced behavioral sensitization and phencyclidine, which both enhance HA release [56].

Besides the detrimental long-term effects of drugs that directly increase HA release in the developing brain, our data also support the hypothesis that HA mediates the detrimental long-term effects of methamphetamine exposure early in life on object recognition, spatial learning and memory, and pre-pulse inhibition in adulthood. This is very concerning, especially in the context of the rise in methamphetamine use among women of childbearing age [65], and the data supporting detrimental short- and long-term effects of methamphetamine exposure on the developing human brain. In humans, following methamphetamine exposure of the developing brain, retarded growth *in utero*, reductions in head circumference at birth, increased morbidity, and impairments in hippocampus-dependent visual recognition memory during the first year of life have been reported [66–71]. In addition, methamphetamine exposure of the human brain may result in long-term cognitive deficits [72], including impairments in hippocampus-dependent spatial learning and memory [73]. Using magnetic resonance imaging combined with volumetric analysis of selected brain regions, the cognitive changes in methamphetamine-exposed children were shown to be associated with reduced volumes of several brain structures, including the hippocampus [73].

Because of the ethical issues involved, potential long-term effects of increased HA receptor-mediated signaling are difficult to study in humans in controlled experiments. Therefore, increased efforts are warranted to carefully evaluate the effects of drugs that directly or indirectly affect HA receptor-mediated signaling during development in animal models that allow controlled assessments of the potential effects of increased HA receptor-mediated signaling on cognitive function later in life. As these effects might be sex-dependent, there is a need to study these effects in both females and males.

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