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Review

Modulation of behavior by the histaminergic system: Lessons from HDC-, H_3R- and H_4R-deficient mice

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ABSTRACT

Histamine, which is synthesized by histidine decarboxylase (HDC), does not only modulate the immune system, but is also acting as a neurotransmitter. Histaminergic neurons project from the tuberomamillary nucleus to numerous brain regions. Activation of presynaptic H_3R inhibits the release of histamine and of non-histaminergic neurotransmitters. The phenotypes of *Hdc*$^{-/-}$- and *Hrh3*$^{-/-}$ mice comprise behaviors related to locomotor activity, memory, cognition, anxiety, circadian rhythm, pain perception, food intake and addiction. We critically discuss these phenotypes that are probably caused by global changes of the histaminergic tone rather than by an altered stimulation of a single histamine receptor subtype. Constitutive H_3R activity may add another layer of complexity by causing "histamine-independent histaminergic" processes, e.g. in *Hdc*$^{-/-}$ mice. We also discuss the clinical relevance of H_3R- and HDC-deficient mice, e.g. the role of HDC in Tourette's syndrome. Finally, this review summarizes current knowledge on possible central H_4R functions. Neuronal expression of H_4R, however, is discussed controversially and a systematic behavioral characterization of *Hrh4*$^{-/-}$ mice is still missing.

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1. Introduction

Decarboxylation of the amino acid L-histidine by histidine decarboxylase (HDC) yields the biogenic amine histamine (Fig. 1). Histamine is an agonist at four G protein-coupled receptors, H_1R, H_2R, H_3R and H_4R (Bongers et al., 2010; Walter and Stark, 2012; Seifert et al., 2013; Strasser et al., 2013). Peripheral histamine is produced by mast cells, basophils and gastric enterochromaffine-like cells. The histamine H_1R couples preferentially to $G\alpha_q$ proteins, and its stimulation results in pruritus or increased vascular permeability. This leads to the symptoms typically associated with immediate-type (type I) allergies, like erythema and edema (Hill et al., 1997). The H_2R activates mainly $G\alpha_s$ proteins, stimulates gastric acid secretion and increases inotropy of the heart (Hill et al., 1997; Shin et al., 2008). Histamine is a key player in immunological processes, and H_1R, H_2R as well as the $G\alpha_{i/o}$-coupled H_4R modulate Th1/Th2 balance and regulate chemotaxis and degranulation of immune cells (Jutel et al., 2009; Neumann et al., 2014).

In addition to its peripheral functions, histamine also acts as a neurotransmitter (Fig. 1). All neuronal histamine originates from the tuberomamillary nucleus (TM), which is located in the posterior hypothalamus and sends histaminergic projections to a multitude of brain regions, including cerebral cortex, hippocampus, amygdala, striatum and areas of the brain stem (Haas et al., 2008; Schneider et al., 2014). The H_1R, H_2R and H_3R as well as the histamine-synthesizing enzyme HDC are neuronally expressed (Fig. 1). Due to serious problems with histamine H_4R antibody specificity (Beermann et al., 2012), detection of neuronal H_4R on the protein level is still subject to controversy.

As we have already discussed in our recent review article about the behavioral phenotype of the corresponding knockout mice (Schneider et al., 2014), H_1R modulates numerous voluntary and involuntary behaviors like locomotor activity, emotional states, cognition, sleep, circadian rhythm, pain perception, energy homeostasis, respiration and susceptibility to seizures. This can be explained by the expression profile of H_1R, which is found in brain regions like hypothalamus, thalamus, cortex and brainstem as well as on glia cells (Haas et al., 2008). While central H_1R function was extensively studied in *Hrh1*$^{-/-}$ mice, there are surprisingly few data available on the behavior of *Hrh2*$^{-/-}$ mice. The results suggest that H_1R and H_2R share similar functions in several cases (Schneider et al., 2014). In fact, H_2R is colocalized with H_1R in some areas, indicating potential synergism of the two receptors (Haas et al., 2008).

This review intends to complete the overview of behavioral phenotypes of mice lacking components of the histaminergic system. We will summarize the available data on HDC-, H_3R- and H_4R-deficient mice and compare their phenotypes with the behavior of *Hrh1*$^{-/-}$- and *Hrh2*$^{-/-}$ mice (cf. summary in Table 3). HDC is responsible for the synthesis of histamine, and therefore, HDC-deficiency should result in depletion of central and peripheral histamine. The histamine H_3R couples to $G\alpha_{i/o}$ proteins and acts as a presynaptic auto- and heteroreceptor that negatively regulates the release of histamine and other neurotransmitters (Haas et al., 2008). Thus, knockouts of both HDC and H_3R are expected to exhibit altered concentrations of neuronal histamine or other neurotransmitters (Fig. 1). This should yield rather unspecific effects via enhanced or reduced stimulation of any of the four histamine receptor subtypes. Since there are only few data available on the central function of the H_4R and on the behavior of the corresponding knockout mice, we will mainly focus on HDC and H_3R in this review.

2. Behavioral phenotype of *Hdc*$^{-/-}$, *Hrh3*$^{-/-}$ and *Hrh4*$^{-/-}$ mice

Hdc$^{-/-}$ mice were generated in 2001 and initially characterized with regard to abundance and morphology of mast cells (Ohtsu et al., 2001). HDC-deficiency resulted in the virtual absence of histamine in plasma and organs like skin, stomach, spleen and kidney of mice kept on a low histamine diet (0.6 nmol/g). Unexpectedly, however, there was still a considerable concentration of histamine detectable in the brain, which amounts to about 30% of the histamine content of wild-type controls (Ohtsu et al., 2001). This may originate from residual dietary histamine (despite the use of a low-histamine diet) or from the brain-specific expression of another HDC-like enzyme that continues to work in *Hdc*$^{-/-}$ mice (Ohtsu et al., 2001). For the behavioral characterization of HDC-deficient animals it is most important to clarify if this residual brain histamine is neuronal histamine. Parmentier et al. (2002) assume that the brain histamine of *Hdc*$^{-/-}$ mice is extraneuronal, because dietary histamine hardly crosses the blood brain barrier (Schwartz et al., 1991). This was confirmed by the absence of central effects after peripheral injection of histamine (Parmentier et al., 2002). Moreover, it is unlikely that another histamine-synthesizing enzyme exists in the brain, because no histaminergic cells were detected in the TM or other regions of the *Hdc*$^{-/-}$ brain by histamine immunohistochemistry (Parmentier et al., 2002). Nevertheless, this potential histamine source should be kept in mind when behavioral data from *Hdc*$^{-/-}$ mice are interpreted, and all *Hdc*$^{-/-}$ experiments should be performed with mice kept on a strictly histamine-free diet. An overview of the results obtained with *Hdc*$^{-/-}$ mice is shown in Table 1, which also provides the available information on the dietary conditions.

Except for a hyperplasia of ependymal cells of the ventricles (Palkovits et al., 2007), HDC-deficiency was not associated with major changes in brain morphology and *Hdc*$^{-/-}$ mice developed normally (Parmentier et al., 2002). Even the neuronal structure of the TM was preserved (Parmentier et al., 2002). Analysis of mRNA expression showed only a non-significant trend toward increased H_1R- and H_2R expression in the hippocampus of *Hdc*$^{-/-}$ mice (Chepkova et al., 2012). By contrast, another study reports that H_2R mRNA was reduced in the brain of *Hdc*$^{-/-}$ mice (Fitzsimons et al., 2001). However, this result was not reflected on protein level, since binding experiments with [^{3}H]tiotidine yielded a similar number of binding sites in the brains of wild-type and *Hdc*$^{-/-}$ mice (Fitzsimons et al., 2001). H_3R mRNA was also decreased in the hippocampus and increased in the TM of *Hdc*$^{-/-}$ mice (Chepkova et al., 2012).

Hrh3$^{-/-}$ mice were generated more than a decade ago independently by two groups (Takahashi et al., 2002; Toyota et al., 2002). Compared to wild-type mice, *Hrh3*$^{-/-}$ mice show increased concentrations of the histamine metabolite *tele*-methylhistamine, specifically in the region of hypothalamus and thalamus (Takahashi et al., 2002), which points to increased histaminergic neurotransmission and is the logical consequence of deficiency in a histamine-stimulated presynaptic autoreceptor. Total histamine levels were decreased in hypothalamus and thalamus (Takahashi et al., 2002) or cortex (Toyota et al., 2002) of *Hrh3*$^{-/-}$ mice. This may be a result of excessive histamine release that leads to a reduction