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Histamine receptors

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Editorial

Histamine receptors

Histamine and its receptors in the nervous system received recognition late in comparison to the other aminergic transmitters, after the detection of histaminergic neurons in the posterior hypothalamus (Panula et al., 1984; Watanabe et al., 1984). Four G-protein coupled receptors have been identified in vertebrates (Panula et al., 2015), at least 3 of which fulfill important functions in the brain. H_1Rs mediate mostly neuronal excitation and are blocked by the classical antihistamines causing sedation, H_2R activation also excites certain neurons, H_2R-antagonists revolutionized stomach ulcer treatment and H_3Rs are inhibitory autoreceptors and heteroreceptors with complex pre- and postsynaptic functions. For the most recently described H_4R mediation of neural actions are so far uncertain. In this issue a number of specific functions in the nervous system are reviewed or presented by authors using different approaches and methods from molecules to mind, from synapse to behavior. Whereas the cloning of the H_3R (Lovenberg et al., 1999) transformed the drug development for this target, the H_1R and H_2R are still being investigated as important postsynaptic histamine receptors in the brain. For example, the metabolic side effects of antipsychotics are largely due to H_1R antagonism in the hypothalamus. In this issue Provensi et al. 2016 review feeding disorders and therapeutic opportunities to prevent obesity and metabolic syndrome. Tabarean (2016) treats the role of histamine receptors in the hypothalamic energy homeostasis. Parmentier et al. (2016) demonstrate the prominent role of the H_1R in cortical activation. J-C Schwartz (2016) who made major discoveries in the field since almost half a century, detected the H_3R and, together with J-M Lecomte developed the first H_3R antagonist/inverse agonist drug that just entered the market (Wakix).

There is evidence from clinical studies that H_2R antagonists may be useful in schizophrenia, but no new brain-penetrating drugs have been developed. The potential of H_3R antagonists in brain disorders is still evident, although their capacity to improve cognition has not been shown in clinical studies. They are being used to treat sleep/wakefulness disorders. Animal studies from several laboratories have shown that H_3R antagonists inhibit alcohol drinking, alcohol-induced place preference and cue-induced reinstatement of alcohol seeking. However, clinical studies have not been carried out. Several histamine H_3R antagonists have been developed over the last decade but only one has been filed so far (Dauvilliers et al., 2013). Hudkins et al. (2016) and Sadek et al. (2016) describe the production, development and testing of new H_3R antagonists. Furthermore Sadek and Stark (2016) compare the affinity, selectivity and efficacy of typical ligands for all histamine receptors.

Bolam and Ellender (2016) review the complex mechanisms by which histamine regulates striatal functions through H_1R, H_2R and H_3R. Keeping in mind that many other parts of the motor system, including the thalamus and cortex, also are regulated by histamine, the complexity of this system is evident. Histamine interacts with many other neurotransmitter systems. An important finding was that lack of histamine synthesis due to a mutation in the synthesizing enzyme histidine decarboxylase is associated with Gilles de la Tourette syndrome (Ercan-Sencicek et al., 2010). Subsequently, histaminergic regulation of the striatum has become an important field (Rapanelli and Pittenger, 2016). In the striatal areas, including the nucleus caudatus and accumbens, interactions with dopamine are particularly important (Aquino-Miranda et al., 2016). DeLuca et al. (2016) report a dopaminergic neuron group in the tuberomamillary nucleus and revisit the H_3R autoreceptor function.

A role of the H_4R in brain has not been conclusively shown: some studies have suggested the presence of this receptor in neurons, whereas others have not found evidence of neuronal expression. Some of the early experimental H_3R drugs have later proven to be good ligands at H_4R as well, which may complicate interpretation of pharmacological studies. There is evidence of H_4R expression in non-neuronal cells in the brain. The importance of the tools used to assess the role of histamine receptors in the brain is emphasized in the review by Schneider et al. (2016). They conclude that there is no evidence so far for H_4R expression and function in nervous tissue. Petri et al. (2016) investigated the presynaptic interaction of H_3R and H_4R on four peripheral tissues and one brain tissue model in vitro. Only H_3R activation reduced the release of other transmitters, none of the synaptic sites displayed H_4R mediated effects.

Zlomuzica et al. (2016) review the role of histamine and its receptors in cognition and possible prevention of cognitive decline in Alzheimer's dementia. Yeung et al. (2016) show ventral hippocampal infusions of histamine causing anxiolysis and an increase in theta activity, whereas the anxiolytic diazepam reduces theta. These results question the functional role of theta frequency depression in the hippocampus for anxiolysis. Nuutinen et al. (2016) report the effects of H_3R antagonism on motivational aspects of alcohol reinforcement and suggest a therapeutic strategy to reduce craving and to prevent relapse.

The histaminergic system in brain is recognized now as a major player in the ascending activation of the forebrain, the hypothalamic homeostasis and the endocrine system (Haas et al., 2008) and histamine receptors are still actively explored on a wide range of therapeutic targets. This motivated us to assemble a number of reviews and research papers in this special issue.

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