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Focus Paper

FOCUS PAPER

Histamine Receptors in the Cross-Talk between Periphery and Brain

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The histamine system, as all modulatory neurotransmitters, is a pleiotropic system. Histamine plays a major role in the regulation of autonomic functions, including energy balance, sleep, and regulation of body temperature. In addition, histamine is crucial in controlling arousal and cognition. The large array of functions regulated by histamine is mirrored by the widespread projections of histaminergic neurons, which are localized in the tuberomamillary nucleus in the hypothalamus and project widely throughout the brain (Haas and Panula, 2003). Despite its important functions, the histaminergic system is much less studied compared with the more famous monoamine systems: noradrenaline, serotonin, and dopamine. This may have historical reasons; the Falck-Hillarp method that visualizes catecholamine (Carlsson et al., 1961) and initiated the study of monoamines did not label histamine. Thus, the investigation of the histamine system lagged behind, and the study of histamine in the brain did not take until the development of an antibody against the synthesizing enzyme L-histidine decarboxylase (Watanabe and Ohtsu, 2002).

Another factor hampering the interest in the development of histaminergic drugs can be traced to histamine's regulation of sleep and the use of antihistamines to treat allergies. As everyone who used the old-generation antihistamine knows, these drugs make you drowsy, whereas stimulating the histamine system to improve, for example, cognition can entail sleep disturbances. Nevertheless, histamine has a great and underexplored potential to provide targets for many CNS disorders. The last years have seen an increase in the proposed use of histaminergic drugs beyond the homeostatic functions such as sleep and energy balance. The histamine system has been suggested as a possible target for the treatment of psychiatric disorders, and drugs that modulate this system have been especially proposed as cognitive enhancers (Tiligada et al., 2011). An increased understanding of the histamine system should be of great use for the development of new, much-needed pharmacological treatments for psychiatric disorders.

The authors of a paper presented in this issue of IJNP previously showed that part of the hypophagic effect induced by oleoylethanolamide (OEA) is mediated by the histamine system (Provensi et al., 2014). OEA is released by the enterocytes in response to high fat intake and is known to reduce eating. OEA has also been shown to affect memory consolidation (Campolongo et al., 2009), and the authors therefore asked the question whether histamine was also involved in this effect. Indeed, they showed that the administration of either H_1 or H_2 receptor antagonists in the amygdala blocked the effect of OEA in contextual fear conditioning.

There are 4 known histamine receptors expressed in the CNS, all of them G-protein coupled. The H_1 and H_2 receptors (Gq- and Gs-coupled, respectively) are classically considered postsynaptic receptors, whereas the H_1 receptor activates the phospholipase C-phosphokinase C pathway and the H_2 receptor activates the phosphokinase A pathway (Haas and Panula, 2016). The H_3 receptor is Gi-coupled and localized pre- and postsynaptically, whereas it has predominantly been studied as an autoreceptor. Blocking of the H_3 receptor enhances histamine release that in turn modulates neuronal function and plasticity (Doreulee et al., 2000; Andersson et al., 2010; Femenia et al., 2015) and has been proposed as a treatment of mental disorders (Schlicker and Kathmann, 2016). The histamine H_4 receptor was only recently discovered; it seems to have mainly immunological functions, and its distribution and function in the CNS are still somewhat debated (Schneider and Seifert, 2016).

The fact that the effect of OEA on fear conditioning is completely abolished by blocking either the H_1 or the H_2 receptor in the amygdala is interesting. The overlapping effect of these 2 receptors has been seen in other areas and behaviors. Blocking either the H_1 and H_2 receptor in the lateral septum decreases anxiety (Chee and Menard, 2013), and both the H_1 and H_2 receptor knockout mice show enhanced emotional learning but reduced spatial learning (Dai et al., 2007). In other experiments, however, only the H_1 receptor antagonist reduces anxiety,

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whereas the H_2 receptor antagonist has no effect (Gianlorenco et al., 2014). In the hippocampus, a H_2 receptor antagonist, but not a H_1 antagonist, improve learning (Taati et al., 2014). The latter finding is at variance with the results of our study, where we needed to block both the H_1 and the H_2 receptor in the hippocampus to get an antidepressant effect in the forced swim test (Femenia et al., 2015). As Provensi et al. (2014) discuss in their paper, there are many factors that can explain these differences, including differential expression of the H_1 and H_2 receptors in different areas, interaction with other neurotransmitter systems, and different roles of the H_1 and H_2 receptor in different behaviors. Their finding underscores our need to better understand the fundamental function of the H_1 and H_2 receptors in different areas in the central nervous system. Both the H_1 and H_2 receptors affect the excitability of neurons (Yanovsky and Haas, 1998; Selbach et al., 1997), and the H_1 receptor can cause either membrane depolarization by reduction of leak potassium conductance or membrane hyperpolarization by intracellular calcium signaling and activation of calcium-activated potassium (K_{Ca}) channels (Haas 1981; Weiger 1997). The H_2 receptor, on the other hand, inhibits the K_{Ca} channels that underlie afterhyperpolarization and affect firing pattern (Haas and Greene, 1986; Pedarzani and Storm, 1993). Preliminary data from our laboratory (manuscript in preparation) show that evoked synaptic transmission is affected neither by neither the H_1 nor the H_2 receptor in the hippocampus, but that postsynaptic histamine receptors can affect spontaneous release of glutamate.

Taken in a larger perspective, the work of Provensi et al. (2014) is also a reminder that we cannot consider the brain in isolation. The brain is in itself a complex organ, where several neurotransmitters interact, such as the noradrenergic and histaminergic systems, as shown by the authors. In addition, we need to consider the interaction between the brain and the periphery. Since it is well known that our body-state affects our behavior and cognition, it is promising that we now start to identify the signaling pathways from the periphery to the central nervous system. The work from Provensi et al. (2014), together with others (Piomelli, 2013), is an important contribution to this endeavor, where they identify that OEA released from enterocytes activates the vagus nerve, the trigeminal tract, which in turn affects several neuromodulatory systems, including histamine (Provensi et al., 2014). In the ongoing work on peripheral signals affecting higher cognitive functions, such as memory, we have a lot to learn from the work already done in studies of autonomic functions (Sestan-Pesa and Horvath, 2016).

The identification of signaling pathways connecting the periphery with the central nervous system is fascinating and holds great promise for the development of new therapeutics, since the periphery is much more accessible for pharmaceutical treatment compared with the brain.

Statement of Interest

None.

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