Histaminergic neurons partake in the gut-brain axis to modulate appetite and memory

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The central nervous system and viscera constitute a functional ensemble, the gut-brain axis, that allows bidirectional information flow that contributes to the control of feeding behaviour appetite, memory and response to stress and pain. Recent research on the gut-brain axis has reviled the contribution of extensive neuronal networks and chemical factors among which a lipid compound synthesised in the intestine upon ingestion of dietary fat, the anandamide monounsatured analogue, oleoylethanolamide (OEA). Using different behavioural settings, we show that the cognitive and homeostatic effects of OEA are at least in part mediated by interaction with the central and/or peripheral histaminergic system. We demonstrated that OEA produces a hypophagic effect that is significantly attenuated in brain histamine deprived mice (Provensi et al., 2014). In the periphery, fasting stimulates a histamine H1 receptor-dependent signaling that promotes OEA mobilisation in the liver and subsequently OEA-dependent lipolysis and fatty acid oxidation. We found that OEA generates an exaggerated emotional response in an aversively motivated task, the contextual fear conditioning paradigm and that this effect is abrogated by the inhibition of histaminergic neurotransmission or the local blockade of either H1 or H2 receptors in the BLA (Provensi et al., 2017). Furthermore, OEA induces antidepressant-related responses by recruiting the histaminergic neurotransmission. We also analysed the effect of acute brain histamine depletion on the temporal organization of motor sequences of mice behaviour in the open-field with a dedicated software. We found that histamine deficiency is correlated to a general enhancement of behavioural pattern complexity, suggesting a putative involvement of histamine in the pathophysiology of tics and related disorders. Systemic OEA reverted the effects of histamine depletion, to the same extent as the D2/D3 antagonist sulpiride (3) suggesting a potential role for OEA in the treatment of such diseases.

In conclusion, we are beginning to unravel unsuspected functions of both central and peripheral histaminergic systems as part of the complex gut-brain axis.

1. Provensi et al. (2014) PNAS 111, 11527-11532

2. Provensi et al. (2017) Int J Neuropsychopharmacol. doi: 10.1093/ijnp/pyw11.

3. Santangelo et al. (2017) Neuropharmacology 113, 533-542