Key role of the brain histaminergic system at the crossroad of eating behaviour, weight gain and emotional memory: preclinical and clinical evidence.

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The last few decades have witnessed an increasing interest for, and knowledge of the neurobiology of histamine. An ever-growing number of publications demonstrate the physiological role of brain histamine in the regulation of homeostatic functions and behaviours such as wakefulness, appetite, memory consolidation and extinction. Dysregulation of histamine synthesis or neurotransmission has been associated with human brain disorders, whereas histamine receptor ligands have been proposed for the treatment of CNS diseases.

In our laboratory, we have extensively studied in animal models the involvement of the histaminergic system in learning and storing aversive, as well as emotionally neutral information. By using behavioral tests such as contextual fear conditioning, inhibitory avoidance and object recognition in association with systemic or intracerebral administration of selective histaminergic ligands, and in-vivo microdialysis, we described how activation of different histaminergic receptors (H_1, H_2 and H_3) in selected brain regions exerts promnesic or amnesic effects. We also demonstrated in animal models, that the efficacy of compounds commonly used in the treatment of human brain disorders require the integrity of the neuronal histaminergic system to exert their behavioral and neurochemical effects.

More recently, we focused our attention on brain histamine as a neurotransmitter regulating feeding behaviour. Hunger and satiety are key factors driving eating behaviour. They are controlled by a complex interplay of central neurotransmitter systems and peripheral endocrine stimuli. Brain histamine is released during the appetitive phase to provide a high level of arousal preparatory to feeding, and mediates satiety. The relevance of the brain histaminergic system in the control of eating behaviour and energy expenditure is being re-evaluated in light of recent clinical studies that report the beneficial effects of histamine ligands in the prevention of obesity and dysmetabolic disorders associated with antipsychotic treatments. In this regard, we recently found that the lipid-derived messenger oleoylethanolamide (OEA) secreted by the intestine and that signals satiety to hypothalamic nuclei, requires the integrity of the brain histamine system to fully exert its hypophagic effect. Furthermore, OEA activates only selective histaminergic pathways in the hypothalamus devoted to the control of food intake.

In our understanding, brain histamine serves as a relay station integrating peripheral signals and central functions to influence the emotional value of different experiences and to control energy expenditure and eating behaviour. In conclusion, we believe that our studies may contribute to the development of more effective pharmacotherapy for the management of cognitive and eating disorders and ameliorate the safety profile of centrally acting drugs.