Satiety factor oleoylethanolamide recruits the brain histaminergic system to inhibit food intake

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Key factors driving eating behavior are hunger and satiety, which are controlled by a complex interplay of central neurotransmitter systems and peripheral stimuli. The lipid-derived messenger oleoylethanolamide (OEA) is released by enterocytes in response to fat intake and indirectly signals satiety to hypothalamic nuclei. Brain histamine is released during the appetitive phase to provide a high level of arousal in anticipation of feeding, and mediates satiety. However, despite the possible functional overlap of satiety signals, it is not known whether histamine participates in OEA-induced hypophagia. Using different experimental settings and diets, we report that the anorexiant effect of OEA is significantly attenuated in mice deficient in the histamine-synthesizing enzyme histidine decarboxylase (HDC-KO) or acutely depleted of histamine via interocerebroventricular infusion of the HDC blocker α-fluoromethylhistidine (α-FMH). α-FMH abolished OEA-induced early occurrence of satiety onset while increasing histamine release in the CNS with an H_3 receptor antagonist-increased hypophagia. OEA augmented histamine release in the cortex of fasted mice within a time window compatible to its anorexic effects. OEA also increased c-Fos expression in the oxytocin neurons of the paraventricular nuclei of WT but not HDC-KO mice. The density of c-Fos immunoreactive neurons in other brain regions that receive histaminergic innervation and participate in the expression of feeding behavior was comparable in OEA-treated WT and HDC-KO mice. Our results demonstrate that OEA requires the integrity of the brain histamine system to fully exert its hypophagic effect and that the oxytocin neuron-rich nuclei are the likely hypothalamic area where brain histamine influences the central effects of OEA.