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From Gut to Brain: *a pas de deux* between oleoylethanolamide and neuronal histamine

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Summary
Brain responses to feeding start before consumption, since seeing, smelling or just think about food may elicit exocrine and endocrine secretions in the gut and stimulate appetite. On the other hand, food intake initiates a cascade of hormonal responses by the gastrointestinal system that are integrated in the central nervous system inducing satiety. This complex communication between the periphery and the CNS is called gut/brain axis. Many gut- and adipose tissue-derived peptides and neurotransmitters are recruited to orchestrate feeding behavior, including the lipid-derived satiety factor oleoylethanolamide and the neuronal histamine. In this review the main findings regarding the role of these two systems in the control of food consumption are presented. The evidence of their interaction along with the putative underlying mechanisms as well we the impact on food intake, memory and mood are reviewed.

The pas de deux is one of the most characteristic and significant moments in classical ballet pieces, not surprisingly it is present in many well-known ballets. As the French term suggests (literally "step of two") it consists of a duet executed by two dancers, usually a danseur and a ballerina, who perform a particular choreography together. The classical grand pas de deux, which often served as the climax of a scene or an entire performance, is usually structured in five parts: an entrée which serves as a short prelude, an adagio featuring graceful and elaborate movement by the dancing pair, then there are two variations consisting of virtuosic solos for each dancer alone followed by a final coda where the duet dance again ending with a grand musical climax. In this review, the scientific data obtained in our laboratory in Florence will be presented with a sort of "artistic license" following the pas de deux structure. The following paragraph explaining the concept representing the entrée, will be followed by a brief adagio about the gut-brain axis. Then we will have the variations in two sessions in which we will present our danseurs (oleoylethanolamide and neuronal histamine) and describe their role in regulation of food consumption. Finally, a coda where our data regarding the interaction of these actuators in the control of food intake, memory and mood will be discussed.

The role of gut/brain axis in modulating food intake

Body weight is tightly regulated by complex homeostatic mechanisms controlling the balance between food intake and energy expenditure, even subtle mismatches (less than 0.5%) in this balance are sufficient to cause weight gain (1). Thus, obesity can be defined as a state in which energy intake chronically exceeds energy expenditure. Obesity is widely recognized as a largest and fastest growing public health problem in developed and developing world. The World Health Organization created the neologism "globesity" to define a growing global epidemic of overweight and obesity. Research efforts done in the last decades in order to fight such obesity epidemic resulted in remarkable growth in our knowledge regarding appetite and satiety mechanisms (2). A key role in this process is played by a complex system regulating energy homeostasis called the gut-brain axis. The axis refers to a neurohumoral communication network comprising the central nervous system (CNS), the enteric nervous system (ENS), the autonomic nervous system (ANS), neuroendocrine and immunological systems, in addition to the gut microbiota (3).

The communication across the axis occurs via local, paracrine and or/endocrine mechanisms involving gut- and adipose tissue- derived peptides. Neural networks, such as the enteric nervous system (ENS) and vagus nerve also convey information within the gut-brain axis. In addition to their peripheral effects, gut hormones play a pivotal role relaying information about the nutritional status to important appetite controlling centers within the CNS, which integrates this peripheral information with higher brain centers regulating reward and mood and contribute to modulate feelings of hunger and satiety (4,5). In the last years the gut microbiota has emerged as one of the key regulators of gut-brain communication and has led to the appreciation of the importance of a microbiota gut-brain axis. Many factors can influence microbiota composition and vice-versa diferential microbial composition may influence weight-gain through several inter-dependent pathways including energy harvesting, short-chain fatty-acids (SCFA) signaling, behaviour modifications, controlling satiety and modulating inflammatory responses within the host (6).

Oleoylethanolamide: a lipid-derived satiety factor

While consuming fat has been stigmatized in our society for causing obesity, it has long been known that direct infusion of lipid emulsions into the small intestine rapidly and potently suppresses food intake in mammalian species, including humans. A link between fat ingestion and reduced food intake was identified in 2001 when Daniele Piomelli's group demonstrated that the fatty acid oleoylethanolamide (OEA) suppresses food intake in rodents. OEA, as other N-acyletanolamides, are found in various tissues including brain, lungs, immune cells, adipocytes, etc. In the small intestine (duodenum and jejunum), the levels of OEA change according to the nutrient status: they decrease during food deprivation and increase upon refeeding (7–9). Duodenal infusion of individual nutrients evidenced that fat, in particular oleic acid, is a potent stimulus for OEA synthesis, whereas sugar and protein do not alter OEA levels (10). However, more recent studies demonstrated that prolonged consumption of a high-fat diet even for short periods of time (one week) is sufficient to suppress jejunal OEA mobilization (11), raising the possibility that fat enriched diets might promote overeating, at least in part, by suppressing the satiating effects of gut-derived OEA (12,13).

Following a seminal work by Rodriguez de Fonseca and coworkers (7) showing that exogenous (ip) administered OEA elicited a sustained inhibition of food intake in rats, subsequent studies demonstrated that OEA-induced hypophagic effect is dependent of the feeding state of the animals. In free-fed animals, detailed analysis of the meal pattern revealed that OEA delayed eating onset and decreased meal frequency without change in meal size suggesting that the hypophagic effect is related to a prolonga-

tion of satiety, that is the state of fullness after eating. On the other hand, in food-restricted animals, OEA not only increased the latency to eat but also reduced meal size, suggesting that, in a situation when larger meals are consumed (as occurs after food deprivation) OEA can also induce satiation, that is meal termination (14,15). Importantly, OEA administration did not induce taste aversion, visceral pain, fear or anxiety-like behaviours and did not alter plasma corticosterone levels. Therefore, the hypophagic action cannot be attribute to states of stress or malaise (7,16).

OEA is a shorter, monounsaturated analogue of the endocannabinoid anandamide, but unlike anandamide it acts independently of the cannabinoid pathway. Several lines of evidence (reviewed in (12,13) indicate that OEA-induced hypophagic action is mediated by the activation of peroxisome proliferator-activated receptor-α (PPAR-α), a nuclear receptor acting as a major transcriptional regulator of lipid metabolism and energy balance. OEA-induced hypophagia was mimicked by two synthetic PPAR-α agonists WY-14643 and GW-7647 and was abolished in mice lacking PPAR-α (17,18). Beyond binding to PPAR-α, OEA activates other two receptors with moderate potency: the capsaicin receptor transient receptor potential vanilloid-1 (TRPV1) and the G protein-coupled receptor 119 (GPR119). However, genetic deletion of TRPV1 or GPR119 did not affected eating reduction induced by OEA (19,20), strongly arguing against a direct involvement of these receptors in OEA-induced satiety.

Similarly to other anorexigenic gut-derived signals, peripherally administered OEA stimulates c-Fos expression (a marker of neuronal activation) in the nucleus tractus solitarius (NTS) in the brainstem suggesting the involvement of brain circuits in OEA's actions. However, when directly infused into the lateral ventricles OEA had no effect on food consumption (7). Indeed, current evidence supports a model whereby OEA promotes satiety via PPAR-α-mediated activation of afferent vagal fibers from the small intestine to the brain: total subdiaphragmatic vagotomy prevents the anorexiant effect induced by systemic OEA injections and a similar failure was observed in animals treated with neurotoxic doses of capsaicin, which deprive the animals of peripheral vagal and non-vagal sensory fibers (7). A recent study challenged this hypothesis since it was demonstrated that subdiaphragmatic vagal deafferentation, which selectively eliminates all abdominal vagal afferents while retaining about half of the vagal efferents intact, does not affect OEA-induced hypophagia (Azari et al., 2014).

Within the brain, in addition to activation of the NTS, OEA systemic injection also increased c-Fos expression in the in oxytocin-immunoreactive neurons in the paraventricular (PVN) and supraoptic nuclei (SON) of the hypothalamus (21–23). This activation is paralleled by increased oxytocin neurosecretion and elevated circulating levels gaetani (21,24). Moreover, pharmacological blockade of brain oxytocin receptors abrogates the hypophagic effects of OEA without blocking c-Fos activation on NTS suggesting that PVN involvement is downstream to NTS activation (21). More recently it was demonstrated that a noradrenergic pathway from the NTS to the hypothalamus seems to mediate OEA effects on feeding behavior and on hypothalamic oxytocin increase, as demonstrated in rats with chemical lesions of hindbrain noradrenergic neurons (25). Accordingly, peripheral administration of OEA in rats increased hypothalamic noradrenaline concentrations (26). These findings suggest that noradrenergic NTS-PVN projections are involved in the activation of the hypothalamic oxytocinergic system, which mediates OEA's pro-satiety action.

The role of Central Histaminergic System in regulation of food consumption

The observation that first generation antihistamines have a sedative effect suggested that histamine had relevant actions in the central nervous system. However, the failure to demonstrate its localization in the brain greatly limited the acceptance of this

amine as a neurotransmitter (27). However, in the early 1980s two discoveries were a real breakthrough in the field: first, the identification of new histaminergic receptor (the H3R autoreceptor) in neurons (28) and second, the development of antibodies to identify histaminergic neurons system and the determination of their localization in the posterior hypothalamus (29,30).

These findings were received with great enthusiasm by the scientific community and many anatomical, neurochemical and behavioural studies ensued and it soon became clear that brain histamine regulates several brain functions.

Nowadays, we know that histaminergic neurons are found in several species which nearly 64000 neurons in human brain (31). In mammals, all histaminergic cell bodies are localized solely in the tuberomamillary nucleus (TMN) of the posterior hypothalamus from where they project widely through ascending and descending pathways, therefore virtually all brain regions contain some histaminergic fibers (32). Within these cells, histamine is synthesized by a one-step decarboxylation of the amino-acid L-histidine catalyzed by the enzyme histidine decarboxylase (HDC) and then stored in vesicles ready to be released via voltage- and calcium-dependent mechanisms (32). Once released, histamine activates specific pre- and postsynaptic receptors that mediate its physiological actions. So far four different histaminergic receptors have been identified, namely H1R, H2R, H3R and H4R. They are all metabotropic receptors and are expressed in the central nervous system with different densities across different brain areas (33). Therefore, given such widespread distribution, is not surprising that brain histamine is involved in the regulation of numerous physiological functions and behaviors, such as thermoregulation, circadian rhythms, neuroendocrine secretion, food and drink intake, locomotion, aggressiveness, learning and memory, emotionality (34,35).

The first report of histamine-induced anorexiant actions dates back to 1973, when a significant long-term suppression of food intake was observed following histamine infusion into cats' lateral ventricles (36). A similar reduction was observed after histamine acute infusion into the lateral ventricles (37) or continuous infusion into the suprachiasmatic nucleus of the hypothalamus (38) of rats. Consistently, hypophagia was also observed after administration of L-histidine (39) or metoprine (40), a histamine precursor and an inhibitor of its metabolism, respectively. Subsequent studies demonstrated that H1R activation in the hypothalamic PVN and ventromedial nucleus (VMH) induced satiety. The blockade of brain H3R autoreceptors, resulting in increase of histamine release, also reduced food intake. On the contrary, other studies indicate that the H2R does not participate in feeding regulation. Detailed review of the effects of histaminergic ligands in animal feeding behaviour studies can be found in (41).

In humans, it has long been known that the administration of antihistamines can cause weight gain. In fact, one antihistamine, cyproheptadine, has actually been used in malnourished and/or underweight patients with a variety of health conditions, such as cancer, HIV, anorexia nervosa with the purpose of increasing appetite and weight gain (42). Moreover, a relationship between the use of H1R antagonists (i.e. cetirizine, fexofenadine and desloratadine) and an increased risk of obesity using data available from the National Health Examination Survey has been described (43). The authors found that adult users of H1R antihistamines had significantly greater weight, body mass index, waist circumference, and insulin levels as compared with age and gender-matched, healthy controls.

Further evidence of the association between histamine and food intake emerged by the relationship of second generation antipsychotics-induced weight gain and their potency as H1R antagonists (44). Among these, olanzapine and clozapine that are associated with the greatest weight gain and metabolic impairments shows the highest affinity for the H1R (45).

The weight gain associated with antipsychotics treat ment is considered a major public health concern, due to its impact on drug compliance and exposure of patients to risks of co-morbidities due to metabolic consequences. In these regard a series of studies demonstratdc the efficacy of betahistine, a mixed H1R partial agonist and H3R antagonist clinically used for the treatment of Meniere's disease (46), in mitigating olanzapine-associated weight gain and somnolence without affecting olanzapine effects on positive and negative syndrome scales (47–50).

Interaction between brain histamine and OEA on food consumption

When we started our studies, we knew that exogenous administration of OEA suppressed food intake by activating PPAR-α and engaging oxytocin neurotransmission through a mechanism mediated by the vagus nerve. Since OEA does not readily cross the blood brain barrier (at least in the doses used in the preclinical studies) we ask whether OEA recruits other neurotransmitter systems in the brain to reduce food intake. As extensive evidence suggested an important role for neuronal histamine in feeding behaviour, our hypothesis was that peripherally administered OEA might engage histamine signaling in the brain to fully exert its hypophagic effect. To test this concept, we used different experimental sets as described in the next paragraphs.

First we tested the effects of a single OEA injection in mice unable to synthetize histamine due to targeted disruption of the histidine decarboxylase gene (HDC-/-) and in normal mice (HDC+/+). As expected, a significant reduction in food consumption was observed in HDC+/+ animals receiving OEA injections with respect to vehicle-treated littermates. On the other hand, the hypophagic effect of OEA was significantly decreased in HDC-/- mice. Such attenuated effect was not related with a possible hyperphagic phenotype due to histamine deficiency, since vehicle-treated animals from both genotypes consumed comparable amounts of food (22). Indeed, previous reports already demonstrated that HDC-/- mice are not hyperphagic nor obese at least up to 12 week of age (51).

The generation of genetically engineered mice overexpressing or lacking specific genes contributed enormously to our understanding of neurophysiology. Is important to note though, that when studying adult phenotypes, the potential confounding effects due to developmental compensation are allways present (52). Hence, to avoid any bias relative to possible compensatory mechanisms in HDC-/- mice, we also measured food consumption in mice pharmacologically deprived of both basal and releasable brain histamine by means of an infusion into the lateral ventricles of the HDC irreversible inhibitor α-fluoromethylhistidine (α-FMH) (22,53). The results obtained mirrored those observed using genetically modified mice: OEA caused a profound reduction in the total amount of food consumed by mice with normal histaminergic transmission, whereas such effect was significantly less prominent in α-FMH-treated mice (22).

At this point we argued that, if OEA-induced effects were attenuated by histamine-deficiency, boosting histamine release should potentiate it. To test our hypothesis, we evaluated food intake in normal mice treated with a combination of OEA and ABT-239, an H3R antagonist that increases histamine release by blocking H3 autoreceptors (54).

Each compound dose-dependently decreased food consumption and, in keeping with our prediction, wen coadministered a further reduction of feeding was observed. Furthermore, the interaction index $\gamma=1.03y$, obtained from the isobolographic analysis revealed an addictive interaction between these compounds (22), meaning that the two compounds, acting together produced a combined effect that is consistent with their individual potencies, that usually happens with drugs acting via the same or similar mechanism (55). These results further support a role for histaminergic transmission on OEA-induced effects. It is noteworthy that OEA hypopha-

gic action in normal mice was not completely reversed but just attenuated in histamine-deprived mice.
Therefore, other mechanisms not involving the histaminergic transmission might contribute to OEA's effects. Nonetheless, the use of different experimental settings gave comparable results, supporting our view that OEA requires the integrity of the central histaminergic system to fully exert its hypophagic effect.

Histaminergic transmission is required for OEA-induced procognitive effects

The ability to remember contextual cues associated with food sources, including their exact location and safety of access, is clearly advantageous to animals foraging in the wild (12). Moreover, emotional arousal due to aversive and rewarding experiences enhance memory consolidation (56). These concepts raised the hypothesis that hormonal and neural signals elicited by feeding might also enhance the consolidation of recent experiences. To test this idea, Campolongo and colleagues evaluated the effects of OEA on memory consolidation using two classical animal models: the inhibitory avoidance and the Morris water maze test, to evaluate emotional and spatial memory, respectively. They found that systemically post-training administration of OEA improved animals' performance in both tests. The procognitive effects of OEA were mimicked by PPAR-α agonists and lost in PPAR-α null mice. Moreover, OEA's effect was blocked by lidocaine infusions into the NTS or the beta-adrenergic antagonist propranolol into the basolateral amygdala (BLA) suggesting that peripheral OEA reach the brain via the afferent vagus and improves memory consolidation by stimulating noradrenergic activity in the BLA (57).The concept of several neurotransmitter systems contributing to emotional memory consolidation within the same brain region is indisputable (58,59). The role of neuronal histamine as a modulator of several types of memories is well established (reviewed in 60,61). We then speculated that OEA might modulate emotional memory by engaging the histaminergic neurotransmission in the BLA. Our findings confirmed and expanded Campolongo's observations as we demonstrated that OEA increases memory expression of another aversively motivated task, contextual fear conditioning. Moreover, depletion of releasable histamine in the brain by α-FMH infusion into the lateral ventricles or intra-BLA infusion pyrilamine or zolantidine, an H1R and an H2R antagonist, respectively, prevented the freezing-enhancing effects of OEA. Microdialysis experiments further strengthened our hypothesis as OEA significantly increased histamine release from the BLA when systemically administered at the same dose that improved animals' memory (62).
Taken together these data suggest that OEA produced in the gut by a rich-fat meal initiates an integrated response presumably via the vagus nerve that reaches the brain where satiety (mediated by histaminergic, noradrenergic e and oxytocinergic transmission in the hypothalamus) coincides temporarily with increased consolidation of information about the spatial and emotional context in which the meal was consumed (mediated by histaminergic and noradrenergic transmission in the BLA).

Histamine-deficient mice do not respond to OEA-induced antidepressant-like effects

The first intuition that OEA may have antidepressant-like properties dates back to findings described by Bortolato and colleagues showing that chronic administration of URB597, a well-known fatty acid amide hydrolase (FAAH) inhibitor, dose-dependently prevented behavioural alterations induced by the chronic mild stress, a validated animal model of depression. This treatment also increased midbrain levels of the endocannabinoid anandamide, but also the non-cannabinoid lipid amides palmitoylethanolamide (PEA) and OEA (63). Following this insight, the effects of OEA chronic treatment were determined in two predictive depression models, the tail suspension test (TST) (64)

and the unpredictable chronic mild stress (65). OEA was found to ameliorate depressive symptoms associated to either lipopolysaccharides (LPS) administration (66) or to acute alcohol exposure (67). It has been proposed that neurobiological basis of the potential antidepressant actions of OEA involved serotonin/noradrenaline (64) and/or oxytocin (21,68) release.

The role of histamine and its receptors in depression has been much less explored as compared with other monoamines. Nonetheless, human studies showed reduced H1R density in the brain of depressed patients that positively correlated with the severity of clinical symptoms (69,70) and preclinical characterization of different H3R antagonists revealed antidepressant activities in different animal models (71–74). We reported that the selective serotonin reuptake inhibitors (SSRIs) citalopram and paroxetine required the integrity of the central histaminergic system to reduce immobility in the TST (75). Therefore, we decided to investigate if OEA as well engaged histaminergic neurotransmission to exert its antidepressant-like effect. Using the TST, we confirmed previous findings reporting a significant reduction in the immobility time in normal mice treated with OEA. However, such effect was not observed following either acute (α-FMH-treated mice) or chronic (HDC-/-) histamine deprivation. Accordingly, OEA-induced increase in hippocampal and cortical CREB phosphorylation was not observed in HDC-/- mice. On the other hand, the classical tricyclic antidepressant imipramine increased CREB phosphorylation and reduced immobility time in both normal and histamine-deficient mice (76). Given the important role of the transcription factor CREB in signaling pathways relevant for pathogenesis and therapy of depression (77) we believe that disruption of CREB activation may be responsible, at least in part, for the inefficacy of OEA in histamine-deprived mice. Our data also highlighted the role of PPAR-α in mediating OEA-antidepressant effects since both the behavioural and neurochemical actions of OEA were absent in PPAR-α null mice (76).

Neural underpinnings of the functional interaction between OEA and histamine

As brain histaminergic transmission seems to be involved in the effects of OEA, we expected OEA to influence histamine extra neuronal levels. Indeed, systemic administration of OEA, at the same dose effective in suppressing food intake, augmented histamine release from the prefrontal cortex of fasted but not satiated mice. The increase was fast and transient, reaching a maximum within 30 min after OEA administration (22). As expected, also the H3R antagonist ABT-239 augmented cortical histamine release. As stated before, we hypothesized that the hypophagic effects of OEA and ABT-239 converge onto a common pathway, as strongly suggested by the isobolographic analysis of feeding behavior. In keeping with this prediction, we observed a further increase in histamine release following ABT-239 and OEA co-administration with respect to the compounds given alone (22). Moreover, OEA systemic administration induced c-Fos expression in a subgroup of TMN neurons, further supporting a role for histaminergic neurons on OEA-induced effects (22).

In order to investigate the brain sites where histamine and OEA signaling converge, we compared the pattern of c-Fos expression in feeding related brain areas of HDC+/+ and HDC-/- mice treated with OEA or vehicle systemic injections. First of all, we confirmed previous findings of augmented c-Fos expression in oxytocinergic neurons in the paraventricular (PVN) and supraoptic (SON) nuclei and augmented oxytocin immune-density in the neurohypophysis following OEA systemic administration. All these effects were absent in HDC-/- mice (22,23).

As pharmacological blockade of oxytocin receptors in the brain prevents OEA anorexic effects (21), reduced oxytocic neuronal activation observed in histamine-deprived animals is probably responsible for the attenuated behavioural effects observed in these animals.

Histaminergic neurons may also induce hypophagia by targeting other brain regions such as the lateral (LH) or ventromedial (VMH) hypothalamus and (41). However, these circuits seem not to participate in OEA effects, as no differences in c-Fos expression were observed in OEA-treated compared to vehicle-treated animals of both genotypes (23). Surprisingly, we found increased c-Fos expression in a small number of cells of the actuate nucleus (ARC) of HDC+/+ but not HDC-/- mice treated with OEA (23), yet the role ARC activation in OEA-induced hypophagic effect was not further studied. We also found that OEA decreased neuronal activation within the nucleus accumbens in both normal and histamine-deprived mice (22). A prudent interpretation could be that OEA may reduce feeding also by affecting the reward value of food consumption. Interestingly, OEA increased c-Fos expression in the amygdalar complex, both in the central (CeA) and the basolateral (BLA). The activation of these nuclei required the histaminergic neurotransmission (23). Since CeA activation is observed also following other anorexic stimuli, including GLP-1 and glucagon, we suggest that this nucleus may take part in the circuitry mediating the hypophagic effects of OEA. On the contrary, the significance of OEA-induced BLA activation in terms of food intake is less clear. However, it fits well with the increase of histamine release observed in microdialysis experiments and the facilitation of aversive memory consolidation through noradrenergic and histaminergic transmission within this nucleus (57,62). Finally, similar levels of c-Fos were found in the NST in mice from both genotypes (23).

As the NST is a primary brainstem area activated by vagal afferents relaying OEA signaling from the periphery, it strongly suggests that OEA-induced NST activation precedes the stimulation of the histaminergic system.

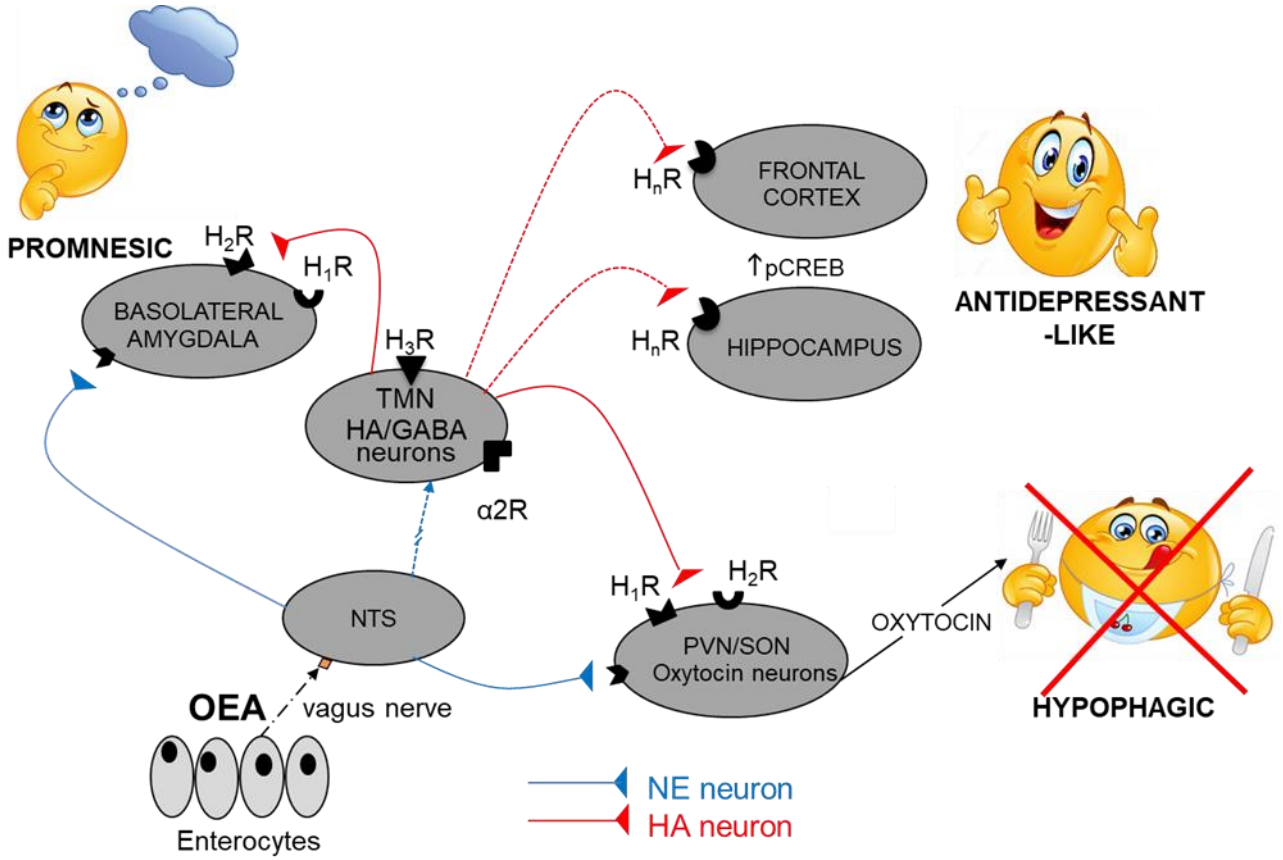
It is clear that all these findings strongly support the role of histaminergic transmission mediating OEA central effects, but how can we organize all these pieces and solve the puzzle? In the last years we demonstrated that HA neurons in the TMN compose a are heterogeneous population, organized in distinct circuits and differently regulated (78,79). Therefore, we believe that the TMN serves as a neuronal gateway that integrates peripheral hormonal, interoceptive, and environmental signals to coordinate the adequate behavioral responses. In our model, represented in **figure 1**, OEA produced by the enterocites or exogenously administred activates PPAR-α in the gut and send information to the NTS trough the vagus nerve. It was recently shown that noradrenergic NTS–PVN projections are involved in the activation of the hypothalamic oxytocin system (25) and in the TMN, α2A adrenoreceptors inhibit GABAergic transmission to TMN neurons (80). Therefore, it is conceivable that NTS adrenergic fibers projecting to the TMN disinhibit histaminergic neurons that in turn facilitate oxytocin release from the PVN to mediate OEA's prosatiety effect. In keeping with this hypothesis, it was demonstrated that intranuclear and systemic release of oxytocin in response to suckling is controlled by H1R and H2R within the PVN (81). Both, NTS adrenergic fibers and TMN histaminergic fibers projecting to the BLA contribute mediate OEA-induced procognitive effects by activation of H1R, H2R and β adrenergic receptors. The circuitry underlying the effecs of OEA on mood are not clear, but we can hypothetize that direct or indirect histaminergic pathways projecting to the cortex and hippocampus is responsible for the antidepressant-like responses observed following OEA chronic treatment through activation of CREB intracellular pathway.

Concluding remarks and perspectives

Both OEA and neuronal histamine have been described in several species as molecules modulating a wide of biological functions. The evidences reviewed here strongly support the hypothesis that these two ancient systems converge and interact at several levels. However, it is clear that further work

is required to clarify all the mediators and to completely describe the neuronal circuitry involved in this pas de deux. Currently we are expanding the study of this interaction to other OEA-induced effects, particularly in the periphery. In this regard we have recently published a very interesting study describing the role for histamine presumably releases by intestinal mast-cells that triggered OEA formation in the liver, which in turn stimulates ketogenesis in the liver, a vital process for survival, because ketone bodies keep the brain and muscles active during a prolonged fast or intense physical exercise (82).

Figure 1. Schematic drawing of the putative circuitry underpinning interactions between the peripheral satiety factor OEA and the central histaminergic system.



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