Eating disorders: from bench to bedside and back

Silvana Gaetani,* Adele Romano,* Gustavo Provensi,† Valdo Ricca,† Thomas Lutz‡§ and Maria Beatrice Passani¶

*Department of Physiology and Pharmacology “V. Erspamer”, Sapienza University of Rome, Rome, Italy
†Department of Neuroscience, Psychology, Drug Discovery and Child Health (NEUROFARBA), University of Florence, Florence, Italy
‡Institute of Veterinary Physiology, Vetsuisse Faculty University of Zurich, Zurich, Switzerland
§Center of Integrative Human Physiology, University of Zurich, Zurich, Switzerland
¶Department of Science Health, University of Florence, Florence, Italy

Abstract
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 behavior based not only on the homeostatic, but also on the hedonic aspects of food intake. The prevalence of eating disorders, such as anorexia nervosa, binge eating and obesity, poses an enormous clinical burden, and involves an ever-growing percentage of the population worldwide. Clinical and preclinical research is constantly adding new information to the field and orienting further studies with the aim of providing a foundation for developing more specific and effective treatment approaches to pathological conditions. A recent symposium at the XVI Congress of the Società Italiana di Neuroscienze (SINS, 2015) ‘Eating disorders: from bench to bedside and back’ brought together basic scientists and clinicians with the objective of presenting novel perspectives in the neurobiology of eating disorders. Clinical studies presented by V. Ricca illustrated some genetic aspects of the psychopathology of anorexia nervosa. Preclinical studies addressed different issues ranging from the description of animal models that mimic human pathologies such as anorexia nervosa, diet-induced obesity, and binge eating disorders (T. Lutz), to novel interactions between peripheral signals and central circuits that govern food intake, mood and stress (A. Romano and G. Provensi). The gut–brain axis has received increasing attention in the recent years as preclinical studies are demonstrating that the brain and visceral organs such as the liver and guts, but also the microbiota are constantly engaged in processes of reciprocal communication, with unexpected physiological and pathological implications. Eating is controlled by a plethora of factors; genetic predisposition, early life adverse conditions, peripheral gastrointestinal hormones that act directly or indirectly on the central nervous system, all are receiving attention as they presumably contribute to the development of eating disorders.

Keywords: animal models of eating disorders, central neurotransmitter systems, food consumption, gut–brain axis, obesity.

J. Neurochem. (2016) 139, 691–699.
activated glucocorticoid receptors (GR), leading to lack of negative feedback regulation and thus to partial glucocorticoid resistance, frequently observed in depressed patients. Considering the GR role in the HPA axis control and integration of the stress response, the GR receptor genes appear to be one of the main candidates to explain individual differences in stress responsiveness and sensitivity of HPA axis (Cellini et al. 2010). The BclI restriction fragment length polymorphism (rs41423247) – the most widely studied polymorphisms associated with glucocorticoid receptor expression – is located in intron 2 of the GR gene (located on chromosome 5q31) and involves a C-to-G conversion, with a frequency of 35% (Kumsta et al. 2007; Slof-Op’t Landt et al. 2014). This polymorphism is considered a moderator of stress-induced effects, as it is believed to modulate inhibitory feedback within the HPA axis and, in this fashion, to contribute to variability in stress reactivity (Wust et al. 2004; Kumsta et al. 2007). In a preliminary study, the group of Ricca tested whether the BclI receptor gene polymorphism is associated with different psychopathological manifestations of AN. In particular, the distribution of the functional polymorphism of the intronic BclI (rs41423247) was evaluated in a series of Italian EDs patients referring to the outpatient clinic for EDs of Florence (Italy), and in an age and sex matched group of 102 AN patients. Patients were compared with a group of 101 Caucasian unrelated controls, consecutively recruited through local advertisements directed toward students attending the Florence University School of Medicine. The controls were carefully interviewed in order to exclude any history of an ED, any actual psychiatric axis I disorder or the presence of a first-degree relative suffering from an ED. Patients were evaluated by means of the Structured Clinical Interview for the diagnostic and statistical manual of mental disorders (DSM-IV), and other self-reported questionnaires, at the first day of admission to the clinic. Childhood abuse was evaluated by means of a clinical interview. No association between the BclI polymorphism and presence of AN diagnosis was found, while G allele carrier patients (GG, GC genotype) showed a more frequent depressive disorder co-morbidity ($p < 0.05$), and purging behaviors ($p < 0.05$), as compared with CC genotype patients. A significant gene-environment interaction was detected, as G allele carriers reporting a history of childhood abuse showed a higher frequency of purging behaviors and subjective binge eating (all $p < 0.05$), as compared to subjects without this condition, while within patients with CC genotypes, this difference was not detected. The experimental approach adopted in this study provides an integrative perspective based on the assumption that EDs are caused by a sequence or combination of risk factors rather than a single influence. Our results suggested that the BclI polymorphism moderates the association between childhood adversities and eating psychopathology. Accordingly, the results of Ricca and colleagues support the observation that even though the new criteria for EDs included in the DSM 5 represents an undoubted progress for reliability and communication between clinicians and researchers, diagnostic categories included in the current nosological systems barely correlate with etiological factors. These results also stress the relevance of childhood abuse for individual vulnerability to AN. A clinical implication of this study is the need for treatment approaches based on accurate psychopathological evaluation.

Furthermore, current treatments for obesity and eating disorders lack sufficient efficacy (Table 1) and are complicated by high relapse rates and a wide range of side effects, thus highlighting the need to identify novel pharmacological targets for the development of more effective and safer therapies.

### Animal models of eating disorders

The incidence of obesity, AN, binge eating and other eating disorders continues to climb worldwide, making it imperative that animal models sharing characteristics of human obesity and its co-morbidities be developed in the quest for novel preventions or treatments (Lutz and Woods 2012; Table 1).

#### Models of AN

As previously mentioned, AN is a serious disease in people with a higher prevalence in women than in men. Many characteristics of AN patients can be mimicked in a rat model of combined food restriction and increased physical activity. Female rats show a cyclic decrease in eating. This effect can also be seen in female rats that have access to a running wheel; total food intake is higher in these animals, but the pattern of eating is undisturbed. Interestingly, when these rats are food restricted, they increase their running wheel activity to a degree that seriously impairs their physical health. Food restricted rats exhibiting this hyperactivity stop cycling while food restriction alone does not lead to an interruption of the rats’ sexual cycle. Low leptin levels seem to contribute to the phenotype of these AN rats because hyperactivity can be reduced and the sexual cycle can be restored by leptin supplementation (Dixon et al. 2003; Hebebrand et al. 2003).

#### Hormonal and diet-induced obesity in rat

Sex differences in the occurrence of some eating disorders may depend on estrogen’s modulation of eating controls. Estradiol (E2) exerts an inhibitory effect on eating. Sexually intact female rats cyclically decrease eating on the day of estrous, i.e. the day after the peak in circulating E2. Removal of E2 action by ovariotomy (OVX) in female rats increases their body weight that is associated with an increase in eating, including a lack of the cyclic decreases in eating. Hence, the OVX rat mimics some aspects of obesity in women after menopause, and OVX rats receiving cyclic E2
| Eating disorders         | Preclinical studies                  | Clinical studies                           | Effect                  | References |
|-------------------------|--------------------------------------|--------------------------------------------|-------------------------|------------|
| **Obesity**             | Lutz and Bueter 2014                 | Bray et al. 2016                           | Body weight loss        |            |
|                         |                                      | Surgical procedure: adjustable gastric banding, sleeve gastrectomy, Roux-en-Y gastric bypass | Body weight loss        |            |
|                         |                                      | Bray et al. 2016                           | Orlistat, lorcaserin, phentermine, topiramate, naltrexone, liraglutide, metformin |            |
|                         | Piomelli 2013; Romano et al. 2015    | Body weight loss                           |                         |            |
|                         | Kageyama et al. 2016                 | Body weight loss                           |                         |            |
|                         | Hay et al. 2015                      | Decreased feeding                          |                         |            |
|                         | Romano et al. 2015; Finelli et al. 2014 | Decreased feeding                        |                         |            |
|                         | Arora and Anubhuti 2006;             | Decreased feeding                          |                         |            |
| **Anorexia nervosa**    | Hillebrand et al. 2005               | APA; Treasure et al. 2010                  | Weak reduction          |            |
|                         | Olanzapine                           | Cognitive therapy; behavioral counseling; interpersonal psychotherapy | Weak reduction          |            |
|                         | Leptin                               | APA; Treasure et al. 2010                  | Fluoxetine, imipramine  |            |
| **Bulimia nervosa**     | Selective 5-HT reuptake inhibitors (SSRI) | APA; Treasure et al. 2010                  | Strong reduction        |            |
|                         | Attenuated obsessive consumatory behavior | APA; Treasure et al. 2010                  | Behavioral counseling; interpersonal psychotherapy |            |
|                         | APA; Treasure et al. 2010            | Cognitive therapy                          | Moderate reduction      |            |
|                         | Behavioral counseling; interpersonal psychotherapy | APA; Treasure et al. 2010                  | Fluoxetine, imipramine, topiramate |            |
| **Binge eating disorders** | Statnick et al. 2016                | Inhibited excessive feeding behavior       | APA; Treasure et al. 2010 | Moderate reduction |
|                         | Micioni Di Bonaventura et al. 2014   | Decreased frustration stress-induced binge eating | APA; Treasure et al. 2010 | Inconsistent results |
|                         | Bocarsly et al. 2014                 | Suppressed binge eating of palatable food  | APA; Treasure et al. 2010 | Strong reduction |
|                         |                                      | McElroy et al. 2015                        | Lisdexamphetamine       |            |

APA, American Psychiatric Association; CART, cocaine- and amphetamine-regulated transcript; CCK, cholecystokinin; CRF, corticotropin releasing factor; POMC, proopiomelanocortin.
replacement allow a direct comparison with intact rats. The effect of E2 on eating is mainly mediated by increasing the action of satiation signals like cholecystokinin or glucagon-like peptide-1. Interestingly, the body weight lowering and eating inhibitory effect of Roux-en-Y gastric bypass surgery is more pronounced in female OVX rats that receive cyclic E2 replacement compared to OVX control rats (Asarian and Geary 2013). Outbred Sprague–Dawley rats have been used as a polygenic model of obesity that shares many characteristics with the common form of human obesity. These rats become obese on a high-energy diet (diet-induced obese) while part of the animals remains lean (diet-resistant). The diet-induced obese rats show distinct abnormalities of glucose metabolism, and they are insulin and leptin resistant at an early age, before the onset of overt obesity (Levin et al. 2003; Bouret et al. 2008).

Model of binge eating disorders
Growing attention has been attracted by stress-induced food-reward behaviors, which seem to be crucial in the development of eating disorders. Binge eating disorders (BED) also seems to be more prevalent in women than in men. The group of C. Cifani (Università di Camerino) developed a rat model of BED that combines the use of intermittent food restriction with frustration stress (Micioni Di Bonaventura et al. 2014). When access to appropriate diets is given, these animals show massive binges of eating, similar to human patients. BED in women also seems to differ across the sexual cycle and we recently showed that E2 can in fact reduce the number of BE episodes in our rat model (Asarian and Geary 2013).

Study of reward driven mechanisms
Food intake is not only controlled by physiological ‘homeostatic’ but also by hedonic factors that affect the reward areas in the brain. On the other hand, reward-driven processes are influenced by gastrointestinal hormones that can overcome the homeostatic controls of eating under certain conditions. Centrally, reward driven mechanisms are mediated by the mesolimbic system including the ventral tegmental area and the nucleus accumbens. The neurotransmitter dopamine acts as a mediator of reward stimuli in these areas. Most rat strains can be used to study reward driven mechanisms; these studies may, e.g. involve progressive ratio tests where animals have to ‘work’ for food (e.g. by lever pressing for the release of food pellets), and they will typically work more for palatable food sources. Further, rats whose dopamine synthesis or dopamine receptor signaling is disturbed can be used to study reward deficit syndromes. A technique that allows the assessment of the influence of various stimuli on the reward system involves the direct analysis of dopamine release with a high temporal resolution is the fast-scan cyclic voltammetry (Mietlicki-Baase et al. 2015).

Amylin derived amyloid may link neurodegeneration, obesity, and diabetes
Amylin (islet amyloid polypeptide; IAPP) is a pancreatic satiation hormone that reduces eating by direct central nervous system (CNS) actions. Unrelated to this hormonal action, amylin-derived islet amyloid deposits are a typical characteristic in type II diabetic humans. Because rodent amylin has a slightly different amino acid sequence, rodent amylin does not form amyloid deposits, but transgenic rats expressing human amylin (hIAPP) have been generated to study islet amyloid associated phenomena (Butler et al. 2004; Matveyenko et al. 2009). Epidemiological studies established a clear association between neurodegenerative diseases like Alzheimer’s disease and type II diabetes. Further, beta amyloid shows striking biochemical similarities to amylin derived amyloid, and amylin’s propensity to form amyloid plaques is not restricted to pancreatic islet cells but can also be seen in the brain. Amylin-derived amyloid has been found to co-localize with beta amyloid plaques in some Alzheimer’s disease patients, and beta amyloid seems to bind preferentially to a subtype of the amylin receptor. Hence, the hIAPP rats allow studying the contribution of amylin or hIAPP derived amyloid to the development of neurodegenerative diseases (Lutz and Meyer 2015).

In summary, a wide range of eating disorders and related diseases can be investigated by the use of specific animal models that mimic at least some major aspects of the respective diseases.

The ‘gut-to-brain axis’: possible implications for the treatment of eating disorders and obesity
A great deal of effort has been devoted to research on the role that different kind of endogenous molecules such as lipids, peptides hormones and neurotransmitters play in the regulation of the energy balance. These signals highly integrated in a complex and redundant network involving the CNS and many peripheral organs, respond to both homeostatic and non-homeostatic (hedonic) factors of feeding behavior and energy balance (Matias et al. 2006; Diéguez et al. 2011; Ghourab et al. 2011; Lateef et al. 2011; Parker and Bloom 2012; Tsuneki et al. 2012; Woods and Begg 2015) (Fig. 1). The so-called ‘gut-to-brain-axis’ is a two-way system based on neural and hormonal signals released upon the ingestion of nutrients that allows the communication between the gastrointestinal-tract and the regulatory appetite centers of the CNS. Although recent research on the gut–brain axis has pinpointed the contribution of several mechanisms, here we focused our attention on the role of a lipid compound, the anandamide monounsatured analog, oleoylethanolamide (OEA) that acts mainly as a mediator of satiety.

Within the gut, OEA is synthesized upon the ingestion of dietary fat, when free oleic acid is absorbed by the enterocytes; this step requires the activation of the cell-
membrane protein CD36 that acts as a biosensor of food derived oleic acid (Guijarro et al. 2010). Although OEA is similar to the endocannabinoid anandamide for its structure and metabolism, opposite to anandamide, the exogenous administration of OEA causes a decrease in food intake in rats and mice (Rodríguez de Fonseca et al. 2001; Fu et al. 2003; Gaetani et al. 2003; Nielsen et al. 2004; Oveisi et al. 2004; Astarita et al. 2006) in a structurally and behaviorally selective fashion. Such effect is not mediated by cannabinoid receptors, for which OEA has no affinity, but rather it requires the expression of the peroxisome proliferator-activated receptor-alpha (PPAR-alpha) (Fu et al. 2003). The intraperitoneal administration of OEA analogs does not reduce food intake (oleic acid) or is less potent than OEA (palmitoylethanolamide; Rodríguez de Fonseca et al. 2001). OEA induces a specific inhibitory effect on eating, by prolonging the latency of eating onset (Gaetani et al. 2003; Romano et al. 2014a) or the inter-meal interval (Oveisi et al. 2004) without affecting the amount of food eaten during a meal (meal size) and without inducing visceral illness or anxiety (Piomelli 2013).

OEA controls the energy status of the organism not only by regulating the energy intake, but also the energy expenditure, as suggested by the observation that OEA administration is able to stimulate lipolysis and reduce body weight gain in both lean and obese rats and mice (Guzmán et al. 2004). Several lines of evidence demonstrated that OEA effects are mediated by the activation of PPAR-alpha receptors (Fu et al. 2003), largely expressed in the duodenum and jejunum. From the periphery, the signal triggered by OEA reaches the CNS, where it activates brain areas involved in the control of food intake, such as the nucleus of the solitary tract (NST), the area postrema (AP), and the hypothalamic paraventricular nucleus (TMN) and supraoptic nuclei (SON). This activation was suggested by the increase of c-fos mRNA observed in rats and mice systemically treated with OEA. Oxytocin released from neurons of PVN and SON can act centrally to modulate feeding behavior and can be released into the blood stream from the neurohypophysis. The histaminergic system mediates, at least in part, the cognitive and antidepressant-like effects of OEA.

Fig. 1 Schematic drawing illustrating the putative interactions between oleoylethanolamide (OEA) central brain structures. OEA triggers a signal that reaches the brainstem, in the nucleus of solitary tract (NST) and area postrema (AP). Noradrenergic neurons within the NST convey information directly to oxytocinergic neurons of the paraventricular nucleus (PVN) and supraoptic nucleus (SON), or via the histaminergic tuberomamillary nucleus (TMN), and stimulates oxytocin expression and release. Oxytocin released from neurons of PVN and SON can act centrally to modulate feeding behavior and can be released into the blood stream from the neurohypophysis. The histaminergic system mediates, at least in part, the cognitive and antidepressant-like effects of OEA.
OXY neurons within the PVN and SON receive a direct excitatory input originating from the A2 noradrenergic cell group in the NST (Rinaman et al. 1995), and it was demonstrated that these noradrenergic projections represent an essential component of the circuit responsible for the activation of OXY neurons within the hypothalamus, which sustain the inhibition of feeding produced by the peripheral administration of OEA (Romano et al. 2013b).

The NST is the first CNS area that receives a large multiplicity of signals arising from the gastrointestinal tract (mechanical, chemical, nutrient), and in turn projects by noradrenergic and peptidergic neurotransmission to other brain regions involved in the control of energy balance, including the hypothalamic and limbic forebrain nuclei (Rinaman 2010).

The mechanism by which the peripheral administration of OEA induces neuronal activation within the NST remains poorly understood; however, previous evidence suggested that visceral afferent fibers play a crucial role in the behavioral effect of OEA (Piomelli 2013). This observation is supported by several studies demonstrating that the anorexigenic effect of OEA is abolished in rats subjected to a total subdiaphragmatic vagotomy or treated with the neurotoxin capsaicin (Rodríguez de Fonseca et al. 2001; Fu et al. 2003) although contrasting novel findings (Azari et al. 2014) led us to hypothesize that the signal triggered by peripheral OEA reaches the CNS through an alternative pathway. This pathway might implicate the activation of neurons of the AP, a region of the hindbrain that by the absence of a functional blood–brain barrier and the presence of fenestrated capillaries may be reached by circulating signals (Lutz et al. 1998).

In keeping with this latter hypothesis, very recent preliminary data from our laboratory suggest that the anorexigenic effect of OEA is abolished in rats subjected to a surgical lesion of the AP (Romano et al. in preparation). Moreover, we observed that the lesion of the AP prevents OEA-induced c-Fos and dopamine beta hydroxylase (enzyme involved in the biosynthesis of the noradrenaline) expression in the NST, as well as prevents in both PVN and SON the increase of OXY expression (Romano et al. in preparation). Overall, we hypothesize that AP neurons play a crucial role in the activation of brainstem noradrenergic neurons, which in turn leads to the activation of the hypothalamic OXY system (Romano et al. 2013b) that is involved in OEA’s pro-satiety action (Fig. 1).

The central neurotransmitter systems recruited by peripheral OEA to inhibit food intake include also the brain histaminergic neurons. Histamine-containing neurons are restricted to discrete cell clusters in the TMN of the posterior hypothalamus (Watanabe et al. 1983; Panula et al. 1984) and send axons to the entire CNS (Inagaki et al. 1988; Airaksinen et al. 1989; Fig. 1). Histamine neurons send projections within the CNS that are organized in functionally distinct circuits impinging on different brain regions (Blandina et al. 2012). By activating four metabotropic receptors (H1–H4), histamine affects a variety of homeostatic functions such as circadian rhythms, neuroendocrine secretion, food intake and drinking, and also more complex brain functions such as arousal, emotionality and cognition (Haas et al. 2008; Panula et al. 2015). Alterations in the central histaminergic system were found in several brain disorders such as depression, schizophrenia, Alzheimer’s and Parkinson’s diseases, Tourette syndrome (Panula and Nuutinen 2013). The first evidence of the inverse relationship between brain histaminergic activity and appetite dates back to the seminal paper by Clineschmidt and Lotti (1973) who administered histamine into the lateral ventricle of cats and observed a long-term suppression of food intake. Nowadays, evidence indicates that histamine plays a critical role also in the regulation of body weight as elevation of histamine levels in the brain decreases food intake and body weight (reviewed in Provensi et al. 2015). Using different behavioral settings, we observed that OEA induced a hypophagic effect that was significantly attenuated in mice lacking the gene encoding for histidine decarboxylase (HDC-KO) or acutely depleted of histamine through i.c.v. infusions of the HDC blocker α-fluoromethylhistidine (α-FMHs) (Provensi et al. 2014). Conversely, increased histamine release elicited by the treatment with the H3 receptor (H3R) antagonist ABT-239 potentiated OEA-induced hypophagia. OEA also increased c-Fos expression in a subgroup of TMN neurons and augmented histamine release from the cortex of hungry mice. Furthermore, OEA induced activation of oxytocin neurons in the PVN, a histaminergic projection area, and this effect was blunted in histamine-deficient mice, an observation that could account for the inefficacy of OEA in these animals (Provensi et al. 2014; Fig. 1).

Novelty-induced attention and arousal have a major impact on feeding behavior, both for food searching and consumption, as well as the ability to remember the context associated with food availability or palatability (DiPatrizio and Piomelli 2016). In this regard, OEA systemic injection increased memory retention in the inhibitory avoidance and the Morris water maze tests (Campolongo et al. 2009). The authors suggested that OEA improved memory consolidation by indirectly stimulating noradrenergic activity in the basolateral amygdala (BLA), as propranolol injected into the NST blocked such effect.

Histaminergic neurotransmission in the BLA modulates emotional memory processes (Benetti et al. 2015). Interestingly, we observed that OEA i.p. injection induced a fast and transient increase of histamine release (up to 125%) from the BLA of freely moving rats at the same dose that augmented the time the animals spent freezing in the contextual fear conditioned paradigm (Provensi et al., submitted). Moreover, i.c.v. infusion of α-FMH or intra-BLA infusion of either pyrilamine or zolantidine (H1R and H2R antagonists, respectively) prevented OEA-induced procognitive effects
(Provensi et al., submitted). Thus, OEA signaling in the gut initiates an integrated response in which satiety induced by a fat-rich meal coincides temporally with enhanced encoding information about the spatial and emotional context in which the meal was consumed and this involves at least both histaminergic and noradrenergic transmission.

In the last year, the positive effects for chronic OEA treatment were demonstrated in animal models predictive of antidepressant efficacy based on behavioral ‘despair’ (Yu et al. 2015) or chronic stress (Jin et al. 2015). Although the role of neuronal histamine in depression is not completely understood, positron emission tomography studies showed reduced H1R density in the brain of depressed patients that positively correlated with the severity of clinical profile (Kano et al. 2004). We recently demonstrated that the integrity of the central histaminergic system is required for the behavioral and neurochemical effects elicited by selective 5-HT reuptake inhibitors (Munari et al. 2015). Preliminary results in our laboratory using the tail suspension test (TST, a behavioral model widely used to test drug antidepressant-like efficacy), showed that OEA-induced antidepressant-like effect was abolished in mice unable to synthesize histamine (both HDC-KO and α-FMHis-treated). Disruption of histamine neurotransmission affected not only behavioral responses, but also the activation of intracellular pathways elicited by OEA such as cAMP-response element binding protein phosphorylation in the frontal cortex and hippocampus. Of relevance, such effects are not associated with compensatory mechanisms of genetically modified animals, as administration of imipramine, a classical tricyclic antidepressant, or 8-bromoadenosine 3’-5’-cyclic monophosphate, a long-acting protein kinase A activator, increased hippocampal cAMP-response element binding protein phosphorylation and reduced immobility time in the tail suspension test in mice of both genotypes (Munari et al. 2015). Taken together, these results indicate that the histaminergic system contributes not only to OEA-induced hypophagic effect, but also to other PPAR-alpha-mediated effects such as antidepressant-like and procognitive actions, suggesting that both systems are attractive targets for the development of innovative drugs.

Although there are several questions that remain unanswered, the evidence collected so far on the signaling triggered by OEA suggest that the histaminergic system may be a key element of the gut-to-brain axis which monitors and modulates the dietary fat intake, whose dysfunction might, perhaps, contribute to obesity. We maintain that understanding the actions of hypothalamic neuronal histamine and peripheral signaling factors such as OEA may provide strategies for further research of neuronal circuit that regulates feeding behavior and to the development of new pharmacotherapeutic approaches to treat eating disorders. Furthermore, a recent study suggested that OEA signaling has a crucial role for hedonic regulation of food craving and obesity in humans (Grosshans et al. 2014), and a previous report showed how this signal is altered in the blood and cerebrospinal fluid of women who suffered from bulimia and anorexia nervosa (Gaetani et al. 2008). Therefore, OEA should be considered a valid target for developing novel drugs for the treatment of obesity and/or eating disorders.

Concluding remarks

Food consumption and body weight are controlled by very complex and integrated mechanisms. Hunger and satiety are key factors that drive feeding behavior and that are under the influence of several central and peripheral neuroendocrine systems, environmental factors, the behavioral state, and circadian rhythm. All these factors concur to alter homeostatic aspects of appetite and energy expenditure, and deregulation of any such component may contribute significantly to the onset of obesity and or metabolic disorders. For instance, obesity is a risk factor for diabetes, hyperlipidemia, hypertension, all of which are associated with an increased risk of cardiovascular disease and mortality. Unfortunately, current medications for the long-term treatment of eating disorders are moderately effective at best. Therefore, research focusing on compounds that affect energy balance through novel mechanisms is warranted. In this respect, the symposium met the interest not only of the academia, but also of industry and stimulated interesting discussion.

Acknowledgments and conflict of interest disclosure

This Review has been solicited at the symposium ‘Eating disorders – from bench to bedside and return’ at the XVI Congress of the Società Italiana di Neuroscienze (SINS, 2016), financially supported by the International Society for Neurochemistry (ISN). The authors have no conflict of interest to declare.

All experiments were conducted in compliance with the ARRIVE guidelines.

References

Airaksinen M. S., Fluge G., Fuchs E. and Panula P. (1989) Histaminergic system in the tree shrew brain. J. Comp. Neurol. 286, 289–310.

American Psychiatric Association (2013) Diagnostic and statistical manual of mental disorders, 5th edn. American Psychiatric Association, Washington, DC.

Arora S. and Anubhuti. (2006) Role of neuropeptides in appetite regulation and obesity—a review. Neuropeptides 40, 375–401.

Asarian L. and Geary N. (2013) Sex differences in the physiology of eating. Am. J. Physiol. Regul. Integr. Comp. Physiol. 305, R1215–R1267.

Astarita G., Di Giacomo B., Gaetani S., Oveis F., Compton T. R., Rivara S., Tarzia G., Mor M. and Piomelli D. (2006) Pharmacological characterization of hydrolysis-resistant analogs of oleoylthanolamide with potent anorexiant properties. J. Pharmacol. Exp. Ther. 318, 563–570.
Lutz T. A. and Woods S. C. (2012) Overview of animal models of obesity. Curr. Protoc. Pharmacol. 58, 1–18, chapter 5, Unit 5.61.

Lutz T. A., Senn M., Althaus J., Del Prete E., Ehrensperger F. and Scharrer E. (1998) Lesion of the area postrema/nucleus of the solitary tract (AP/NTS) attenuates the anorectic effects of amylin and calcitonin gene-related peptide (CGRP) in rats. Peptides 19, 309–317.

Matias I., Bisogno T. and Di Marzo V. (2006) Endogenous cannabinoids in the brain and peripheral tissues: regulation of their levels and control of food intake. Int. J. Obes. 30(Suppl 1), S7–S12.

Matveenko A. V., Gurlo T., Daval M., Butler A. E. and Butler P. C. (2012) Tablets or liposomes reduced food intake in rats. Am. J. Physiol. 302, E151–E157.

Mathur M., Kaur S., Ganguly S., and Desai R. (2012) Oleoylethanolamide and C18:2n6 are effective anti-obesity agents: role of the hypothalamic orexigenic neuropeptide Y. Curr. Pharm. Des. 18, 736–747.

Munari L., Provensi G., Passani M. B., Galeotti N., Cassano T., Benetti et al. (2009) Successful versus failed adaptation to high-fat diet-induced insulin resistance: the role of IAPP-induced beta-cell endoplasmic reticulum stress. Diabetes 58, 906–916.

McElroy S. L., Hudson J. L., Mitchell J. E., Willeby D., Ferreira-Cornwell M. C., Gao J., Wang J., Whitaker T., Jonas J. and Gasior M. (2015) Efficacy and safety of lisdexamfetamine for treatment of adults with moderate to severe binge eating disorder; a randomized clinical trial. JAMA Psychiatry 72, 235–246.

Micioni Di Bonaventura M. V., Cicciocippo R., Romano A. et al. (2014) Role of bed nucleus of the stria terminalis corticotropin-releasing factor receptors in frustration stress-induced binge-like palatable food consumption in female rats with a history of food restriction. J. Neurosci. 34, 11316–11324.

Mietlicki-Baase E. G., Reiner D. J., Cone J. J., Olivos D. R., McGrath L. et al. (1999) Synthesis and oral administration of 19:4n6,15–18,20-diacylglycerol: potential implications for obesity, diabetes, and atherosclerosis. J. Lipid Res. 40, 372–385.

Munari L., Provensi G., Passani M. B., Galeotti N., Cassano T., Benetti F., Corradetti R. and Blandina P. (2015) Brain histamine is crucial for selective serotonin reuptake inhibitors’ behavioral and neurochemical effects. Int. J. Neuropsychopharmacol. 18, pyv045.

Nielsen M. J., Petersen G., Astrup A. and Hansen H. S. (2004) Food intake is inhibited by oral oleoylethanolamide. J. Lipid Res. 45, 1027–1029.

Oveisi F., Gaetani S., Eng K. T. and Piomelli D. (2004) Oleoylethanolamide inhibits food intake in free-feeding rats after oral administration. Pharmacol. Res. 49, 461–466.

Panula P. and Nuutinen S. (2013) The histaminergic network in the brain: basic organization and role in disease. Nat. Rev. Neurosci. 14, 472–487.

Panula P., Yang H. Y. and Costa E. (1984) Histamine-containing neurons in the rat hypothalamus. Proc. Natl Acad. Sci. USA 81, 2572–2576.

Panula P., Chazot P. L., Cowart M., Gutzmer R., Leurs R., Liu W. L., Stark H., Thurmond R. L. and Haas H. S. (2015) A central mechanism regulating food intake in the mouse. J. Neurochem. 133, 166–181.

Parker J. A. and Bloom S. R. (2012) Hypothalamic neuropeptides and the regulation of food intake. Curr. Top. Behav. Neurosci. 38, 69–83.

Piomelli D. (2013) A fatty gut feeling. Nat. Rev. Neurosci. 14, 347–358.

Rodríguez de Fonseca F., Navarro M., Gómez R. et al. (2001) An anorexic lipid mediator regulated by feeding. Nature 414, 209–212.

Romano A., Cassano T., Tempesta B., Cianci S., Dipasquale P., Coccorello R., Cuomo V. and Gaetani S. (2013a) The satiety signal oleoylethanolamide stimulates oxytocin neurosecretion from rat hypothalamic neurons. Peptides 49, 21–26.

Romano A., Potes C. S., Tempesta B., Cassano T., Cuomo V., Lutz T. and Gaetani S. (2013b) Hindbrain noradrenergic input to the hypothalamic PVN mediates the activation of oxytocinergic neurons induced by the satiety factor oleoylethanolamide. Am. J. Physiol. Endocrinol. Metab. 305, E1266–E1273.

Romano A., Coccorello R., Giacovazzo G., Bedse G., Moles A. and Gaetani S. (2014a) Oleoylethanolamide: a novel potential pharmacological alternative to cannabinoid antagonists for the control of appetite. Biomed Res. Int. 2014, 203425.

Romano A., Karimian Azari E., Tempesta B., Mansouri A., Micioni Di Bonaventura M. V., Ramachandran D., Lutz T. A., Bedse G., Langhans W. and Gaetani S. (2014b) High dietary fat intake influences the activation of specific hindbrain and hypothalamic nuclei by the satiety factor oleoylethanolamide. Physiol. Behav. 136, 55–62.

Romano A., Tempesta B., Provensi G., Passani M. B. and Gaetani S. (2015) Central mechanisms mediating the hypogastic effects of oleoylethanolamide and N-acylphosphatidylethanolamines: different lipid signals? Front Pharmacol. 6, 137.

Slof-Op’t Landt M. C., DeRijk R. H., van Son G. E., Suchiman H. E., Meulenbelt I., Slagboom P. E. and Van Furfth E. F. (2014) A common mineralocorticoid receptor polymorphism (1180V) interacts with life events in relation to perfectionism in eating disorders: a pilot study. Eur. Eat. Disord. Rev. 22, 423–429.

Statnick M. A., Chen Y., Ansonoff M. et al. (2016) A novel nociceptin receptor antagonist LY2940094 inhibits excessive feeding behavior in rodents: a possible mechanism for the treatment of binge eating disorder. J. Pharmacol. Exp. Ther. 356, 493–502.

Taksande B. G., Chopde C. T., Umekar M. J. and Kotagale N. R. (2015) Agmatine attenuates hyperactivity and weight loss associated with activity-based anorexia in female rats. Pharmacol. Biochem. Behav. 132, 136–141.

Trexleury J., Claudino A. M. and Zucker N. (2010) Eating disorders. Lancet 375, 583–593.

Tsuneki H., Wada T. and Sasaoka T. (2012) Role of orexin in the central regulation of glucose and energy homeostasis. Endocr. J. 59, 365–374.

Verhagen L. A., Luijendijk M. C. and Adan R. A. (2011) Leptin reduces hyperactivity and food intake in mice models of behavior despair. Brain Res. 1371, 49–60.

Watanabe T., Taguchi Y., Hayashi H., Tanaka J., Shiosaka S., Tohyama M., Kubota H., Terano Y. and Wada H. (1983) Evidence for the presence of a histaminergic neuron system in the rat brain: an immunohistochemical analysis. Neurosci. Lett. 39, 249–254.

Woods S. C. and Begg D. P. (2015) Regulation of the motivation to eat. Curr. Top. Behav. Neurosci. 27, 15–34.

Wust S., Federenko I. S., van Rossum E. F., Koper J. W., Kumsta R., Entinger S. and Hellhammer D. H. (2004) A psychobiological perspective on genetic determinants of hypothalamic and pituitary-adrenal axis activity. Ann. N. Y. Acad. Sci. 1032, 52–62.

Yü H. L., Sun L. P., Li M. M. and Quan Z. S. (2015) Involvement of norepinephrine and serotonin system in antidepressant-like effects of oleoylethanolamide in the mice models of behavior despair. Neurosci. Lett. 593, 24–28.