European Journal of Pharmacology 660 (2011) 28–42

Contents lists available at ScienceDirect

European Journal of Pharmacology

journal homepage: www.elsevier.com/locate/ejphar

Review

Neurobiology of overeating and obesity: The role of melanocortins and beyond

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ARTICLE INFO

Article history:
Received 28 September 2010
Received in revised form 10 January 2011
Accepted 13 January 2011
Available online 2 February 2011

Keywords:
Obesity
Leptin resistance
Addiction
Craving
Melanocortin

ABSTRACT

The alarming increase in the incidence of obesity and obesity-associated disorders makes the etiology of obesity a widely studied topic today. As opposed to 'homeostatic feeding', where food intake is restricted to satisfy one's biological needs, the term 'non-homeostatic' feeding refers to eating for pleasure or the trend to over-consume (palatable) food. Overconsumption is considered a crucial factor in the development of obesity. Exaggerated consumption of (palatable) food, coupled to a loss of control over food intake despite awareness of its negative consequences, suggests that overeating may be a form of addiction. At a molecular level, insulin and leptin resistance are hallmarks of obesity. In this review, we specifically address the question how leptin resistance contributes to enhanced craving for (palatable) food. Since dopamine is a key player in the motivation for food, the interconnection between dopamine, leptin and neuropeptides related to feeding will be discussed. Understanding the mechanisms by which these neuropeptidergic systems hijack the homeostatic feeding mechanisms, thus leading to overeating and obesity is the primary aim of this review. The melanocortin system, one of the crucial neuropeptidergic systems modulating feeding behavior will be extensively discussed. The inter-relationship between neuronal populations in the arcuate nucleus and other areas regulating energy homeostasis (lateral hypothalamus, paraventricular nucleus, ventromedial hypothalamus etc.) and reward circuitry (the ventral tegmental area and nucleus accumbens) will be evaluated and scrutinized.

Contents

1. Introduction

The rapid urbanization throughout the globe in the past few decades, marks the rise in the incidence of many chronic illnesses, including obesity and diabetes (Fry and Finley, 2005). Recent data from Europe and The United States shows a high incidence of obesity in the general population, 20% and 34%, respectively (Fry and Finley, 2005; Nguyen and El-Serag, 2010). Interestingly, only in an insignificant subset, obesity is a result of single mutation in genes involving energy homeostasis. A majority of cases of obesity results from a combination of genetic, behavioral and environmental factors. The

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doi:10.1016/j.ejphar.2011.01.034

improvements in food availability and alterations in dietary patterns with a prevalence of energy-dense fat and sweet foods are crucial environmental factors in today's obesity epidemic. Distinguished from 'homeostatic feeding', where food intake is restricted to satisfy one's biological needs, this kind of 'non-homeostatic feeding' or 'feeding for pleasure' has gained a special place in our society and overeating, food craving and compulsive eating are important deleterious factors culminating in obesity.

The increased attraction towards pleasurable feeding and the loss of control over food intake have been compared to addictive behavior. Studies on animals and humans have demonstrated activation of the brain reward system when subjects are exposed to palatable food. Thus, homeostatic control of feeding, where the brain maintains a temporal control on the amounts of food ingested involves the hypothalamus and the brainstem, whereas the reward circuit, encompassing brain areas such as the ventral striatum, prefrontal cortex and amygdala is sensitive to the hedonic aspects of food. Interestingly, the systems involved in homeostatic and non-homeostatic feeding are not entirely separated, as multiple connections between these two systems exist (Lutter and Nestler, 2009). Additionally, in a situation of hunger even non-palatable foods will be rewarding. This suggests the existence of a distributed neural network that controls different aspects of feeding behavior, with rostral limbic and cortical brain areas being more important for pleasure feeling and caudal parts for controlling meal size (Adan et al, 2008). Overconsumption in this paper will be studied in the light of two contributing factors: (a) increase in meal size, i.e. animals consume bigger amounts of food due to defective satiation and/or augmented desire for certain foods (Fulton, 2010) and (b) increase in meal frequency. We aim to understand the neural mechanisms by which the hedonic signals interact and hijack the homeostatic regulation of food intake. Although at first glance, hijacking of the homeostatic regulatory mechanisms by its hedonic counterpart may seem conflicting, it should be borne in mind that during evolution, humans have lived in an environment where food availability was restricted and uncertain (e.g. hunter–gatherers) and the biological system has been 'hard-wired' to maximize energy stores (Schwartz et al, 2003).

2. Homeostatic control of food intake

The question concerning the regulation of food intake has intrigued scientists for several decades. The actual shift from the earlier 'peripheral' theories, where hunger and satiation were considered to be a unique property of the stomach, to the more 'central' theories, involving the brain in feeding control, did not occur until the 1950s. Correspondingly, the glucostat theory of Mayer and the lipostat theory of Kennedy suggested the role of carbohydrate and fat as major components regulating energy balance (Kennedy, 1953; Mayer, 1955). Lesion experiments during this period also identified the ventromedial hypothalamus and the lateral hypothalamus as the brain 'satiety' and 'feeding' center, respectively (Mayer and Thomas, 1967). These observations, although somewhat preliminary, laid the foundation for further elucidation of the complex neuronal networks influencing feeding and satiation. A major breakthrough in obesity research came through studying spontaneously obese mice, the ob/ob (obese) and the db/db (diabetic) mice being the forerunners (Speakman et al., 2007). Using surgical vascular-anastomosis between these strains and normal mice, it was shown that the ob/ob and the db/db mice had a dysfunctional 'satiety factor' and 'satiety center', respectively (Coleman, 1973). Later, with the advent of better molecular cloning techniques, this satiety factor was identified in 1994 as circulating leptin, which appeared to be absent in the ob/ob mouse, while a dysfunctional long form of leptin receptor (see below) was identified as the cause of obesity in the db/db mouse (Zhang et al., 1994; Tartaglia et al., 1995).

Leptin is perhaps the most widely studied biological factor controlling food intake. Secreted primarily from the adipose tissue, leptin is a 146 amino acid protein circulating in the blood. It accomplishes a biochemical communication between adipose tissue and the brain areas involved in energy homeostasis, updating the latter on the degree of peripheral adiposity (Margetic et al., 2002). The action of leptin in the brain is mediated by the leptin receptor, which belongs to the class-I cytokine receptor family (Tartaglia, 1997). Three principal forms of leptin-receptor have been found in mammals: the secreted (leptin receptor-c), the long (leptin receptor-b) and short intracellular domain (leptin receptor-a) leptin receptor. Each carries the same extracellular domain but differs in the length of the cytoplasmic domain (Myers et al., 2008; Ahima and Osei, 2004). The leptin receptor-b is vital for the physiological action of leptin in the hypothalamus. The arcuate nucleus, dorsomedial hypothalamus, ventromedial hypothalamus and lateral hypothalamus express this form of leptin receptor (Elmquist et al., 1998). Similar to other cytokine receptors, the leptin receptor lacks an intrinsic enzymatic activity and is dependent on the Jak-2 kinases for signal transduction. Fig. 1 indicates the principal components of the leptin-signaling pathway.

2.1. Leptin resistance

The amount of circulating leptin is proportional to the degree of peripheral adiposity (Considine et al., 1996). Intriguingly, enhanced (and prolonged) increase in the circulating levels of leptin, does not further enhance the leptin receptor-b signaling cascade (Myers et al., 2008). Analogous to the concept of insulin resistance, where augmented amounts of insulin fail to decrease plasma glucose levels, leptin resistance implies a clinical condition associated with obesity, where the anorectic action of leptin is blunted despite its high circulating amounts in the periphery (Munzberg et al., 2005).

Being one of the central issues in understanding obesity, several explanations have been put forward to explain the phenomenon of leptin resistance. First, studies comparing the db/db mouse, which lacks only leptin receptor-b and mouse mutants devoid of all isoforms of leptin receptor, showed that the soluble and short isoforms of leptin receptor may be responsible for leptin's transport across the blood brain barrier (Shimizu et al., 2007). Deficiencies in the peripheral levels of these isoforms in obese conditions indicate their potential role in leptin resistance (Ogier et al., 2002). Second, the inability of leptin to reach its target can be also due to other factors, like the high levels of circulating triglycerides in obesity, which hinder leptin transport across the blood brain barrier (Banks et al., 2004). Third, intracellular mechanisms activated by the leptin signaling cascade also modulate the action of leptin receptor by negatively regulating its own receptor activity. One such mechanism is suppressor of cytokine signaling-3 (SOCS-3) activation. Signal transducer activator of transcription-3 (STAT-3) protein activated upon phosphorylation of leptin receptor-b, further activates SOCS-3 protein, which in turn suppresses the activity of the leptin receptor by acting at the level of Jak-2 kinase and Tyr 985 residue of the leptin receptor. Neuronal SOCS-3 deficient mice show enhanced STAT-3 protein phosphorylation together with a leaner phenotype (Mori et al., 2004). Focusing on the dose-related effect of leptin on its receptor to explain leptin resistance, Munzberg et al. (2005) hypothesized that under baseline levels, small increments in leptin concentrations would result in enhancement of leptin signaling, whereas elevated amounts of leptin as encountered in obesity, would lead to higher expression of SOCS-3, thereby dampening leptin signaling. The increase of SOCS-3 expression in obesity may also occur irrespective of blunted STAT3 activation, indicating the involvement of an alternative pathway (Tups, 2009). Lastly, the tyrosine phosphatase protein 1B has shown to negatively regulate the activity of the Jak-2 kinase (Cheng et al., 2002; Zabolotny et al., 2002). Single nucleotide polymorphisms (SNP) in the gene have been associated with obesity and diabetes mellitus type II (Bento et al., 2004; Cheyssac et al., 2006). Thus, current evidence indicates the involvement of multiple simultaneous

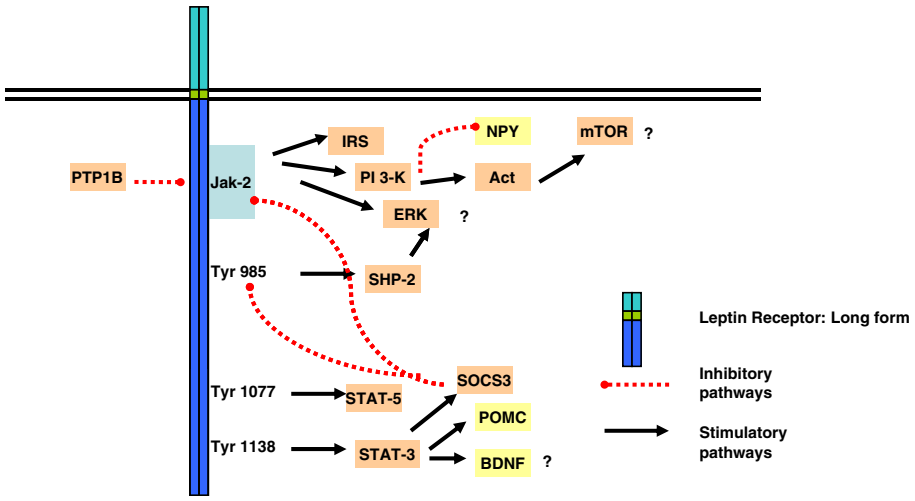

Fig. 1. Leptin receptor signaling cascade. Binding of leptin to the extracellular domain of its receptor leads to the activation of janus kinase-2 (Kloek et al., 2002), which in turn induces the phosphorylation of three downstream tyrosine residues (Try 985, Tyr 1077 and Try 1138) (Myers et al., 2008). Jak-2 autophosphorylation further activates several downstream proteins like the insulin receptor substrate (IRS), extracellular signal regulated kinases (Jansen et al., 2003; Rahmouni et al., 2009) and the phosphor inositid 3-kinases (PI3-K) (Sahu, 2003). It is through the PI3-K kinase pathway by which Neuropeptide Y (NPY) levels are downregulated in the arcuate nucleus upon leptin action. Furthermore, active PI3-K leads to the stimulation of the mammalian target of rapamycin (mTOR) pathway via Protein Kinase B (Act) (Kahn and Myers, 2006). Tryosine phosphatase protein 1B (PTP1B) acts as a negative modulator of JAK-2 kinase (Sahu, 2003). Tyr 1138 phosphorylation activates the signal transducer activator of transcription-3 (STAT-3) protein which thereby promotes propoiomelanocortin (POMC) expression (Hakansson and Meister, 1998), suppressor of cytokine signaling 3 (SOCS3) synthesis (Bjorbaek et al., 1999; Bjorbaek et al., 2000) and possibly brain-derived neurotrophic factor (BDNF) (Komori et al., 2006). SOCS-3 negatively influences the activity of the Try 985 and Jak-2 proteins (Munzberg et al., 2005; Shimizu et al., 2007). At the Try 985 residue, phosphorylation commences the activity of the SHP-2 protein, which competes with SOCS-3 to bind to Try 985 and further promote ERK activity (Bjorbaek et al., 2001). The function of active signal transducer activator of transcription-5 (STAT-5), at the Try1077 still needs to be clarified (Hekerman et al., 2005).

mechanisms in leptin resistance. Therefore, targeting a single process to combat this phenomenon is not likely to be successful. Additionally, leptin resistance itself and the presence of a feedback loop within the leptin signaling cascade draws our attention to its evolutionary perspective where increased adiposity may be beneficial (e.g. seasonal animals and pregnancy) (Tups, 2009). Keeping this evolutionary bias towards weight gain in mind, Leibel (2005) in his studies on obese and non-obese human subjects reported that a 10% decrease in body weight in either group, resulted in the decrease in non-resting energy expenditure of up to 20%, enough for recidivating obesity. This effect may be partially due to the dose–response curve of leptin. When leptin levels are below a particular 'threshold', a decrease in catabolic expenditure with simultaneous enhancement in feeding occurs. Conversely, high-circulating levels of leptin (as seen in obesity) have no pronounced effect on metabolism and feeding. This 'threshold' is in turn defined as a neurobiological correlate that is influenced by genetic, internal and external environmental factors. Interestingly, chronically elevated levels of leptin can also alter this 'threshold'. It has been hypothesized that a rightward-shift in the 'threshold' can be encountered in obese subjects, i.e. even small dips in leptin levels will lead to increased activation of anabolic mechanisms culminating in pronounced weight gain (Leibel, 2005). Fig. 2 summarizes the above-mentioned mechanisms of leptin resistance.

2.2. Hypothalamic control of feeding

The hypothalamus is a prime relay station controlling feeding behavior and the distinct roles of the various hypothalamic sub-nuclei with respect to food intake have been studied in great detail. After crossing the blood brain barrier, circulating leptin reaches the arcuate nucleus, which contains two principal neuronal populations: the neuropeptide Y/agouti related peptide (AGRP) and the pro-opio melanocortin (POMC)/cocaine and amphetamine related transcript (CART) neurons (Schwartz et al., 2000). Both populations express the leptin receptor, project to other hypothalamic nuclei and have an opposing action on energy balance (Schwartz et al., 1996; Cheung et al., 1997). The action of leptin on these neurons is also contrasting. Intracerebroventricular (i.c.v.) administration of leptin decreases neuropeptide Y/AGRP expression (Morrison et al., 2005) while enhancing the activity of the POMC neurons (Cowley et al., 2000). A sub-population of the neuropeptide Y neurons contains γ-aminobutyric acid (GABA) and sends inhibitory projections to the POMC neurons within the arcuate nucleus (Cowley et al., 2000; Horvath et al., 1997). Furthermore, i.c.v. administration of neuropeptide Y has been shown to increase feeding (Hulsey et al., 1995). Likewise, states of negative energy balance such as fasting result in increased neuropeptide Y levels in the arcuate nucleus, indicating the anabolic effect of this neuropeptide (Schwartz and Seeley, 1997; Arora and Anubhuti, 2006). The POMC neurons, on the other hand, secrete α-melanocyte stimulating hormone (α-MSH) and promote anorexia, an effect mediated by second order neurons primarily in the paraventricular nucleus and ventromedial hypothalamus expressing the melanocortin 3 or 4 receptor (MC_3 receptor and MC_4 receptor). In contrast, AGRP, a protein co-secreted by the neuropeptide Y neurons of the arcuate nucleus, is a potent and long lasting orexinergic agent that has an inverse agonistic action on the MC_4 receptor (Adan et al., 2008; Schwartz et al., 2000). Both neuropeptide Y and POMC neurons project to different hypothalamic second order neurons in various hypothalamic areas (e.g. paraventricular nucleus, lateral hypothalamus and ventromedial hypothalamus) that further regulate anabolic or catabolic events. Within the paraventricular nucleus, several target neurons of the POMC/CART and neuropeptide Y/AGRP have been identified: thyrotropin releasing hormone, oxytocin and corticotropin releasing hormone neurons, all well-known catabolic modulators (Kim et al., 2002; Lu et al., 2003; Schwartz et al., 2000).

Another hypothalamic nucleus, the lateral hypothalamus, contains neurons that produce two orexinergic neuropeptides, i.e. orexin and melanin concentrating hormone. I.c.v. infusion of both elicits a robust feeding response (Griffond and Risold, 2009; Rossi et al., 1997). The orexins (orexins A and B) are alternative splice forms of the orexin precursor protein. From the lateral hypothalamus, the orexin-containing neurons project to various brain areas regulating feeding and arousal. Furthermore, orexinergic fibers also project to the neuropeptide Y/AGRP and POMC/CART neurons of the arcuate

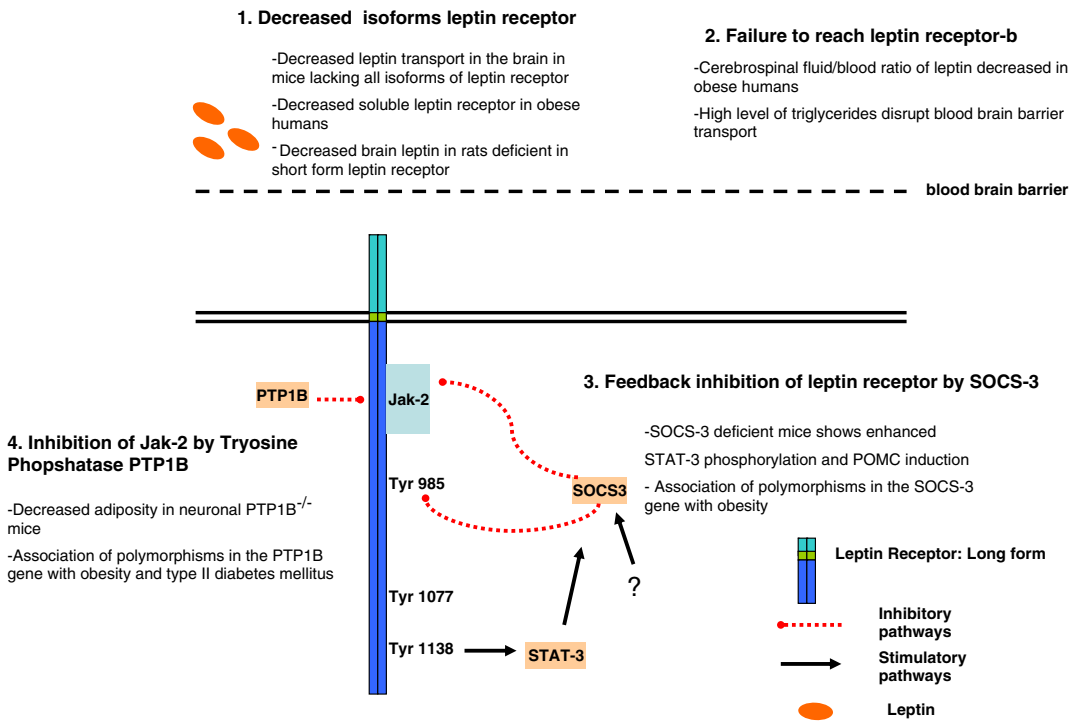

Fig. 2. Leptin resistance. The possible mechanisms of leptin resistance in obesity. For references see text. Additional references (Caro et al., 1996; Kastin et al., 1999; Talbert et al., 2009; Bence et al., 2006).

nucleus, thus activating the former and inhibiting the latter cell-populations via orexin 1 and 2 receptors (OX_1 receptor and OX_2 receptor), respectively (Willie et al., 2001). The underlying mechanisms by which orexins and melanin concentrating hormone control feeding are poorly understood, but the projections to the brain reward centers may play an important role (Cason et al., 2010; Griffond and Risold, 2009). Finally, the ventromedial hypothalamus, an important hypothalamic site containing brain derived neurotropic factor (BDNF) neurons, receives connections from neuropeptide Y/AGRP and POMC/CART neurons. Recent studies have shown BDNF to be a downstream target of MC_4 receptor, and BDNF also acts as a direct effector for leptin-mediated anorexia (Komori et al., 2006; Nicholson et al., 2007). The downstream targets of BDNF mediating feeding remain to be elucidated. The importance of the MC_4 receptor and BDNF for human body weight regulation has been recently shown in genome wide association studies, where allelic variants in these loci contribute to the variance of body mass index observed in human population (see Fig. 3) (Loos et al., 2008).

3. Hedonic control of food intake

It is important to note that not only hunger elicits feeding. Humans, for example, tend to 'finish their plate' and cue-induced feeding in a satiated state has been shown in both rats and humans (Jansen et al., 2003; Weingarten, 1983). This phenomenon of enhanced food consumption beyond one's nutritional need relates to the fact that food is a natural reward. Food has been shown to be reinforcing in the similar manner as drugs are, although this does not necessarily mean that food is addictive, as animals will work for a variety of natural rewards that benefit survival, such as water and sex (Corsica and Pelchat, 2010; Koob, 1992; Wilson, 2010). When trying to relate drug addiction to overeating, it is important that we define terms like: 'liking', 'wanting' and 'compulsion', because they are often used to describe components of the addiction syndrome (Everitt and Robbins, 2005; Berridge et al., 2009; Koob and Volkow, 2010). 'Liking' refers to the pleasurable feeling associated with the receipt and consumption of a reward, while 'wanting' is considered a subjective desire that induces a goal-directed behavior to obtain a reward (Corsica and Pelchat, 2010; Finlayson et al., 2007). The neural substrates of 'wanting' and 'liking' have been widely discussed. Berridge has described that the neural substrate of 'liking' is a combination of several brain nuclei. Starting from deep brainstem structures which act as an initial gateway for sensory perception, it includes higher order centers like the nucleus accumbens, ventral pallidum and the orbitofrontal cortex, involving GABAergic, opioid, and endocannabinoid neurotransmission (Berridge, 2009). 'Wanting', which is often considered to be closely related to motivational influences on behavior, has been associated with dopamine signaling in the mesolimbic system, as well as its connections with the prefrontal cortex and amygdala (Barbano and Cador, 2007; Berridge, 2009; Berridge and Robinson, 1998; Salamone et al., 2009). 'Compulsion' refers to behavior that is continued or repeated, while being dissociated from an apparent goal, or in the light of adverse consequences. It is important to realize that 'compulsion' (rather than 'wanting' or 'liking') is a key term in the definition of addiction (American Psychiatric Association and American Psychiatric Association, Task Force on DSM-IV, 2000; Koob and Volkow, 2010). In fact, it has been observed that certain addicts no longer 'like' but rather 'need' drugs of abuse, although the reductions in the hedonic properties of drugs ('liking') in addiction strongly depend on the type of drug used (Lambert et al., 2006). The behavior of drug addicts is no longer primarily mediated by the outcome of their actions (action — outcome behavior), as the neural circuits underlying reward and motivation have been altered by prolonged drug abuse, so that exposure to drug-associated stimuli leads to automatic, habitual patterns of drug seeking, that are no longer voluntary or goal-directed (stimulus — response behavior) (Everitt and Robbins, 2005). The neural substrates of compulsive drug seeking constitute involvement of dorsal striatal regions that mediate habitual behavior, together with a breakdown of cognitive control over behavior, mediated by the prefrontal cortex (Everitt and Robbins, 2005; Porrino et al., 2004). In addition, prolonged drug abuse engages brain stress systems, and

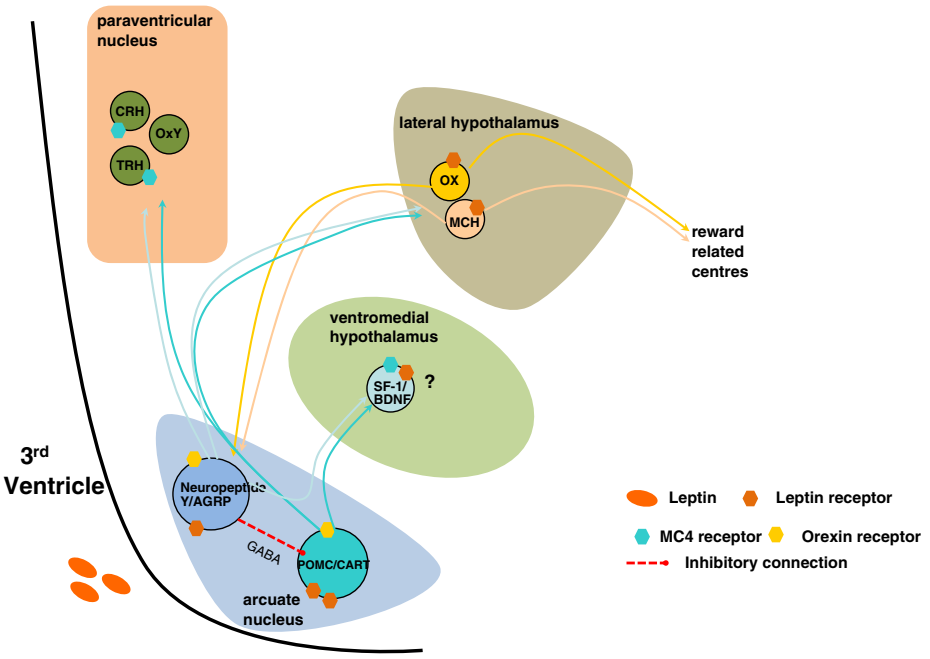

Fig. 3. Neuroanatomy of energy homeostasis: Schematic representation the principle hypothalamic sub-nuclei involved in feeding behavior. MCH: melanocyte concentrating hormone, CRH: corticoitropin releasing hormone TRH: thyrotropin releasing hormone OxY: Oxytocin SF-1: orphan nuclear receptor SF-1 (for references see text).

dysregulates neural substrates of motivation (Robinson and Berridge, 1993; Koob and Volkow, 2010). The ability of food to induce compulsive behavior, like drugs of abuse do, has (in our view) not convincingly been shown. It has, however, been shown that food has a very high motivational value and may sometimes even be preferred over drugs (Lenoir et al., 2007). In fact, although obesity may or may not be explained as a 'food addiction', certain similarities between overconsumption and addiction (e.g. both relate to a 'loss of control' over intake) are worth mentioning. The following sections will elaborate more on this and the interaction of the dopaminergic system with leptin and other (feeding) neuropeptides (melanocortin system, orexins, BDNF, and opioids) with respect to overeating will be discussed in detail.

3.1. Dopamine and overeating

Drugs of abuse increase dopamine levels in the nucleus accumbens, activating postsynaptic dopamine 1 and 2 receptors (D_1 receptor and D_2 receptor) on the target neurons (Di Chiara and Imperato, 1988; Koob, 1992). These elevated dopamine levels may enhance the association of primary rewards with environmental cues and initiate goal-directed behavior (Berridge and Robinson, 1998; Hyman et al., 2006). The mechanism by which this elevation of dopamine is achieved differs for the various substances of abuse (See Fig. 4) (Hyman et al., 2006; Ritz et al., 1987; Sulzer et al., 2005; Trigo et al., 2010).

Similarities between drug addiction and obesity come from multiple studies. First, involvement of the brain reward circuitries during feeding comes from in-vivo microdialysis studies in rodents, where increased levels of dopamine were detected in the brain reward regions in response to eating and drinking (Yoshida et al., 1992), analogous to receipt of other rewards (Schultz et al., 1993), although it should be borne in mind that the magnitude of the dopamine response to food is much smaller than the dopamine response to drugs. In addition, activation of comparable brain areas (hippocampus, insula, caudate nucleus, and the ventral striatum) in response to food and drug cravings has also been shown (Kilts et al., 2001; Pelchat, 2009; Pelchat et al., 2004; Rolls and McCabe, 2007). The mesolimbic dopaminergic system, projecting from the ventral tegmental area to the nucleus accumbens and the frontal cortex, is one of the major pathways implicated in addictive behavior, and is therefore a focus in this review.

It has been shown that drugs of abuse increase extra-synaptic levels of dopamine in the nucleus accumbens, either directly or indirectly (Koob and Volkow, 2010). The repeated increase in dopamine in response to prolonged abuse of addictive substances, in the long run leads to a reduced D_2 receptor density in the striatum (Volkow et al., 2002). Interestingly, D_2 receptor levels in the striatum of obese subjects are also decreased (Wang et al., 2001), possibly affecting the cortico-striatal top-down inhibitory mechanisms (Volkow et al., 2008). Conversely, D_2 receptor levels are upregulated in previously obese subjects who underwent gastric bypass surgery to combat excessive adiposity (Steele et al., 2010). Decreased D_2 receptor levels have been simultaneously noted in some rodent models of obesity (Hamdi et al., 1992), and this reduction in D_2 receptor levels in these animals is reversed if animals are placed on a restricted feeding schedule. This data suggests that overeating may be a compensatory mechanism to adjust for decreased dopamine activity. This process, referred to as the 'reward deficiency syndrome', is often used as a model to explain compulsive behavior in an addictive state. It hypothesizes that the initial use of drugs of abuse leads to exaggerated amounts of synaptic dopamine in the nucleus accumbens leading to excessive stimulation of the post-synaptic dopaminergic receptors (Koob and Le Moal, 2001). This chronic receptor stimulation ultimately results in a decreased post-synaptic receptor density. Due to this de-sensitization to increased dopaminergic stimulation, some of the effects of a fixed drug dose wane over time, resulting in tolerance to these effects. This may be reflected by the decreased thresholds for electrical self-stimulation in rats given extended access to cocaine. These rats become insensitive to low electrical currents and only self-stimulate when the reward (stimulation intensity) is substantially increased (Ahmed et al., 2002). Consistent with this notion, Wang et al. (2002) have proposed the dopaminergic hypofunction theory of overeating, where overeating is an adjustment of the obese brain to compensate for low extracellular dopamine levels (Stice et al., 2009. Indeed, it was recently shown that obese rats fed on high-fat diet for a span of 40 days display an increase in the threshold for rewarding self-stimulation (Johnson and Kenny, 2010). In addition, using a lenti-viral approach, Johnson and Kenny

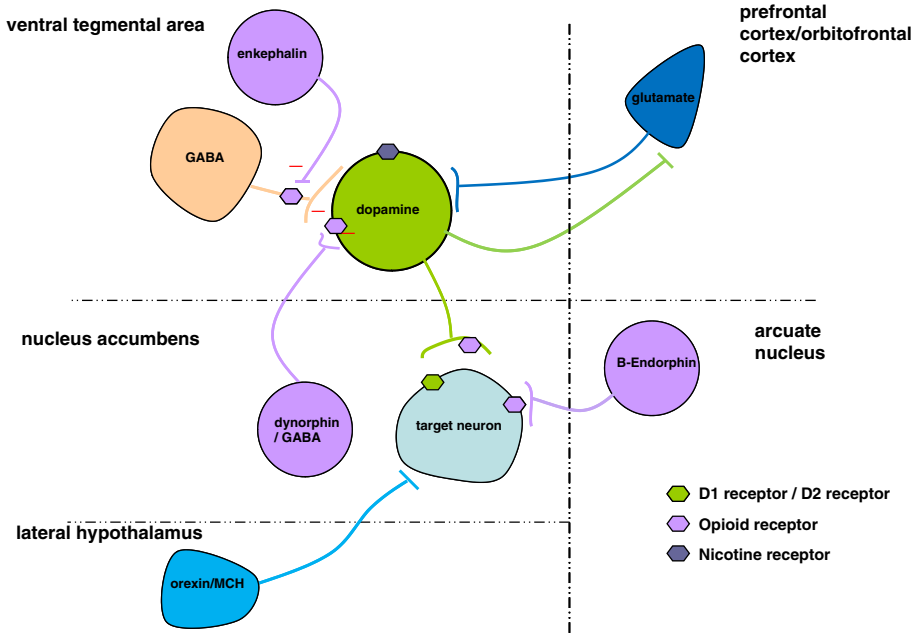

Fig. 4. The interaction of the dopaminergic, endogenous opioid and GABAergic systems in brain reward circuitry. Dopaminergic neurons in the ventral tegmental area send afferent fibers to the nucleus accumbens, prefrontal cortex, orbitofrontal cortex and the amygdala (not shown). The prefrontal cortex and the orbitofrontal cortex are essential sites for the cognitive control of reward-associated behavior, which send glutamergic projections to i.e. the nucleus accumbens and amygdala. The role of these neocortical structures has been widely studied with respect to addiction. Lateral hypothalamus sends orexinergic signals to the nucleus accumbens, details of which will be discussed in one of the following sections. The nucleus accumbens also receives synaptic inputs from several brainstem nuclei (parabrachial nucleus and nucleus of solitary tract: not shown), carrying gustatory and satiety signals. The opioid system (arcuate nucleus, nucleus accumbens, and ventral tegmental area) forms a part of both feed forward and feedback loop, to modulate activity within the reward circuitry. (Adan et al., 2008; Trigo et al., 2010).

(2010) demonstrated that knocking down striatal D_2 receptors resulted in compulsive eating in rats exposed to high caloric diet (Johnson and Kenny, 2010). However, whether the decreased D_2 receptors levels are a cause or a consequence of addiction is not clear. Studies have shown that humans with the Taq1A allele near the D_2 receptor gene have lower number of these receptors and are also more prone to addiction (Blum et al., 2008; Pohjalainen et al., 1998). In addition, as the dopaminergic system is involved in the motivational aspects of reward, decreased dopamine and D_2 receptor levels in various addictive states and obesity have been hypothesized to lead to an increased motivation for drugs and palatable food (Wang et al., 2002). Consistently, animals exposed to high fat high sucrose choice diet show an increased motivation for a sucrose reward when tested under a progressive ratio schedule of reinforcement (la Fleur et al., 2007). However, it still needs to be elucidated how chronically reduced dopaminergic neurotransmission in the nucleus accumbens induces increased motivation for rewards in addiction and obesity, as reduced dopaminergic transmission in the nucleus accumbens is well known to reduce the motivation for food and drugs (Barbano and Cador, 2007; Berridge, 2009; Salamone et al., 2009).

The role of opioids with respect to intake of drugs has been well established (Trigo et al., 2010). Opioid infusions in the nucleus accumbens result in enhanced intake of palatable solutions (including ethanol and saccharin solutions) and increased preference for high-fat food (Zhang et al., 1998; Zhang and Kelley, 2002). It has been suggested that opioids do so by increasing the hedonic appreciation of a reward, in other words: by increasing 'liking' (American Psychiatric Association, 2007; Barbano and Cador, 2007, but see: Pecina, 2008), rather than through modulation of the motivation for rewards (which, as mentioned above, depends upon dopaminergic activity). Interestingly, this also works the other way around, as consumption of highly palatable food results in changes in opioid expression (Welch, 1996). Most importantly, when access to a highly palatable diet is discontinued in rats, decreased levels of endogenous opioids are encountered in these animals when compared to animals that were never (or only briefly) exposed to palatable chow (Kelley et al., 2003). This, of course, is also reminiscent of the reward deficiency theory. Furthermore, important interactions between the opioid system and cannabinoids in both addiction and feeding have been identified. Examples include the permissive function that opioids and cannabinoids have on alcohol intake: increased alcohol intake by treatment with morphine is blocked by administration of a cannabinoid receptor antagonist (Rimonabant) and stimulation of alcohol consumption using a cannabinoid receptor 1 agonist is blocked by naloxone (Colombo et al., 2005; Cota et al., 2006).

Although the compulsive aspects of procurement and intake have not been as convincingly shown for food (Johnson and Kenny, 2010), as they have been for drugs (e.g. Deroche-Gamonet et al., 2004; Vanderschuren and Everitt, 2004; Hopf and Bonci, 2010; Lesscher et al., 2010; Vanderschuren and Everitt, 2005), the evidence described above indicated that there definitely is some overlap between overeating and addiction. However, these similarities between overeating/obesity and addiction, still fail to answer the fundamental question as to how the homeostatic mechanisms controlling body weight are overpowered by its hedonic counterpart. One of the answers might lie in the extended role of leptin beyond the hypothalamus and its interaction with the dopaminergic system.

3.2. Leptin, reward circuitry and overeating

The earliest evidence of leptin-induced modulation of the brain reward pathways comes from intracranial self-stimulation studies in rodents (Fulton et al., 2000). The presence of a metabolically active leptin receptor in the dopaminergic neurons of the ventral tegmental area suggests an interaction between brain reward mechanisms and leptin (Figlewicz et al., 2003). Food deprivation decreases circulating leptin levels, and this has been used for many years to study the effect of leptin on the brain reward centers.

Food restriction in rodents has been shown to reduce the threshold for lateral hypothalamus self-stimulation (Abrahamsen et al., 1995)

and central administration of leptin attenuates the effects of food restriction on self-stimulation (Fulton et al., 2000). Moreover, the rewarding properties of heroin are enhanced under food-restricted conditions (Shalev et al., 2001). As food restriction lowers the amount of circulating leptin, Figlewicz and Benoit (2009) have argued that reduced amounts of leptin are thus associated with higher reward sensitivity, whereas increased leptin signaling will dampen this heightened reward sensitivity. Indeed, a functional magnetic resonance imaging study by Farooqi et al. (2007) on two congenital leptin deficient human subjects showed that 7 days of leptin replacement therapy modulated the activity of the ventral striatum together with decrease in total calorie intake and attenuated liking ratings to food images. In line with this finding, it was reported that food-restricted animals demonstrate conditioned place preference for low calorie sucrose pellets that was reversed by peripheral leptin administration (Figlewicz et al., 2001). I.c.v. administration of leptin or insulin blocked the high fat diet-induced conditioned place preference in rats (Figlewicz et al., 2004). Likewise, sucrose self-administration in rats on a progressive ratio schedule of reinforcement was also attenuated by i.c.v. administration of insulin or leptin (Figlewicz et al., 2006). Supported by their studies on food-deprived animals, Figlewicz et al. (2006) and Figlewicz and Benoit (2009) suggest that the rewarding value of food is determined by the nutritional state of the individual at that time. Hence, a hungry individual (with lower leptin levels) will assign a higher rewarding value to food compared to an individual that is satiated. However, does that imply that the obese brain is always 'hungry' and thus assigns a higher value to food?

Based on the concept of cross-sensitization between food and drugs of abuse, Carr (2002) showed that animals that are maintained at 80% of their initial body weight exhibit an augmentation of the rewarding effects of cocaine and amphetamine in an intracranial self-stimulation paradigm. Consistently, prior studies have shown that food-restricted animals consume higher amounts of drugs of abuse (Carroll et al., 1979). An important question addressed by Carr was whether the increased sensitivity for drug reward in food-deprived conditions is a form of sensitization and persisted after cessation of food deprivation (Carr, 2002). In fact, the change to an ad-libitum diet simultaneously reversed the effect of food restriction on amphetamine reward. This indicates that the enhancement of reward sensitivity to drugs during food-restriction might differ from the sensitization due to repeated drug exposure (Carr, 2002), as drug induced behavioral sensitization is known to be persistent (Robinson and Berridge, 1993; Vanderschuren and Kalivas, 2000). However, it is important to note that in the food-restriction paradigm animals are non-satiated. Therefore it is difficult to distinguish whether the witnessed alterations in behavior are due to the homeostatic or hedonic aspects of low leptin levels. Stress is yet another confounding element in these studies, because food-restriction may cause stress and stressed animals are more sensitive to the motivational and rewarding properties of food and drugs (Abrahamsen and Carr, 1996; Shalev et al., 2006; Goeders and Guerin, 1996; Piazza and Le Moal, 1998).

Interestingly, when comparing studies in food-restricted rodents with leptin-resistance/obesity, we notice certain striking similarities. In both situations, attenuated leptin signaling either due to low circulating amounts or due to alterations in the leptin signal transduction pathway, leads to heightened motivation for food rewards. Low leptin levels, occurring during obesity/leptin resistance, may trigger a pathological situation where the body 'thinks' it is in a hungry state and simultaneously enhances motivation for obtaining rewards. This would imply, that normalizing the disrupted leptin signaling cascade in the obese brain may be sufficient to decrease motivation for food reward.

At least two studies have shown activation of the leptin signaling pathway in the dopaminergic neurons of the ventral tegmental area (Fulton et al., 2006; Hommel et al., 2006), but the proposed mechanisms by which leptin regulates the dopaminergic neurons are contrasting. Fulton et al. (2006), based on their studies of the ob/ob mice, showed that decreased dopamine content in the ventral tegmental area and nucleus accumbens encountered in these mice, is reversed by 3-days of leptin administration. In contrast, Hommel et al. (2006) demonstrated that direct administration of leptin into the ventral tegmental area inhibited the firing of dopaminergic neurons and attenuated feeding. Furthermore, a virus-mediated knockdown of the leptin receptor-b led to enhanced feeding and sensitivity to palatable food (Hommel et al., 2006). This discrepancy between the two studies (i.e. opposing effects of leptin on the ventral tegmental area neurons) can be attributed to the fact that total deficiency of leptin during development can result in morphological alterations in the neuronal circuits and synapses resulting in a different behavioral response (Bouret et al., 2004; Louis and Myers, 2007). Interestingly, the decrease in feeding in response to i.c.v. leptin-treatment was also accompanied by lower dopamine levels in the nucleus accumbens (Krugel et al., 2003). An attenuated feeding response was also noted when leptin was directly injected into the ventral tegmental area (Morton et al., 2009). Taken together, it is evident that leptin action is not limited to the homeostatic centers for food intake, but extends to the brain reward circuits. Therefore, conducting further studies as to how leptin resistance contributes to preference for palatable food will be central to the understanding of leptin's role in overeating.

Prolonged exposure to a high fat diet in rodents has shown to induce diet-induced obesity together with leptin resistance (Lin et al., 2000). In a study by Munzberg et al. (2004), it was reported that exposure of animals to a high fat diet results in the development of leptin resistance selectively in the arcuate nucleus (measured by STAT-3 phosphorylation levels), while other brain areas expressing the leptin receptor were spared. Since knocking down the leptin receptor would mimic a leptin-resistant state, the study by Hommel et al. (2006) provides a novel view on the effects of leptin on brain reward circuitry. In addition, Munzberg et al. (2004) detected altered STAT-3 protein levels after 16 weeks of high fat diet consumption. Hence, it is possible that a leptin-resistant condition can develop in brain areas other than the arcuate nucleus, but at a different time-point after exposure to a high fat diet. Again, animals exposed to diet-induced obesity show decreased dopamine levels in the nucleus accumbens combined with an attenuated response to sucrose and amphetamine rewards (Davis et al., 2008). Thus, analogous to chronic substance abuse (Volkow et al., 2002), prolonged exposure to a high fat diet can lead to hypofunction of the dopaminergic system (Davis et al., 2008). Likewise, nucleus accumbens dopamine levels are decreased in obesity-prone animals but not obesity-resistant animals, further underscoring the fact that mesolimbic dopaminergic signaling may be dampened in leptin-resistant conditions. Central leptin administration in lean animals decreases basal and food-invoked dopamine levels in the nucleus accumbens (Krugel et al., 2003) together with a decrease in food intake (Mistry et al., 1997). However, leptin-resistant conditions (as in diet-induced obesity) also dampen mesolimbic dopaminergic signaling (Davis et al., 2008) but simultaneously enhance feeding (Farley et al., 2003). One of the answers to this paradox might be that leptin possibly activates alternative intracellular pathways in the ventral tegmental area and the hypothalamus, exerting differential effects on food intake (Morton et al., 2009). It is also possible that under lean conditions, leptin reduces dopamine levels without altering the dopamine receptor densities, whereas, overeating and obese conditions decrease dopamine and D_2 receptor levels (Huang et al., 2006). Interestingly, it is not only leptin that influences the dopaminergic system; recent findings suggest that the leptin–dopamine interaction is bi-directional and dopamine has been shown to negatively influence leptin action in the hypothalamus (Kim et al., 2010).

3.3. Melanocortin system in feeding

The melanocortin system, comprising the melanocortin receptors, natural agonists and inverse agonists, plays a critical role in the regulation of body weight. Of the five melanocortin receptors, the MC_3

receptor and MC_4 receptor are widely expressed in the brain, and these have been extensively studied with respect to energy balance (Cone, 2005). Studies on C57/BL/6J MC_4 receptor knockout animals have shown that these animals exhibit late-onset obesity, accompanied by enhanced longitudinal growth, hyperphagia, hyperinsulinemia and hyperleptinemia. Male MC_4 receptor knockout mice additionally show a reduction in nocturnal locomotion (Marsh et al., 1999). Thus, weight gain in the MC_4 receptor knockout animals has been conceived as being the result of increased food consumption and low locomotor activity (Adan et al., 2006). The MC_3 receptor knockout animals, on the other hand, display obesity, hyperleptinemia and decreased locomotion without hyperphagia. Weight gain in these animals occurs as a result of increased feeding efficiency (weight gain to food intake ratio) (Chen et al., 2000a,b). Heterozygous MC_4 receptor mice show an intermediate phenotype compared to wild type and MC_4 receptor knockout animals, whereas the heterozygous MC_3 receptor animals do not differ significantly from their wild type littermates (Chen et al., 2000a,b).

α-MSH, the endogenous ligand of the MC_3 receptor and MC_4 receptor is the product of the precursor pro-opio-melanocortin (POMC) protein. As indicated in the preceding section, the POMC neurons of the arcuate nucleus synthesize α-MSH that acts on MC_3 receptor and MC_4 receptor expressing neurons (see Section 2.2). AGRP, co-synthesized in the neuropeptide Y neurons is an inverse agonist at the MC_4 receptor. Downstream targets of the melanocortin system include several neuronal populations in diverse brain areas implicated in food intake, meal choice and satiety (Adan et al., 2006). Immunohistochemical studies show that MC_3 receptors and MC_4 receptors are expressed in the hypothalamus, cortex, amygdala and parts of the brainstem (Kishi et al., 2003). Interestingly, MC_3 receptors are also expressed in the POMC neurons of the arcuate nucleus, establishing a feedback regulatory control over the melanocortin system. Both peripheral and central administration of an MC_3 receptor agonist stimulates feeding, whereas treatment with a low dose of an MC_3 receptor antagonist has an opposite effect (Marks et al., 2006; Lee et al., 2007). The expression of POMC messenger RNA in response to MC_3 receptor agonist treatment has been also shown to decrease, underscoring the autoreceptor role of MC_3 receptor in these neurons (Lee et al., 2007).

Comparable to MC_4 receptor knockout animals, mutations in the MC_4 receptor in humans have been associated with obesity, hyperphagia, tall-stature and hyperinsulinemia, suggesting a similar role of the melanocortin pathway in humans and rodents (Farooqi et al., 2000; Govaerts et al., 2005). Indeed, there is converging evidence to support the association between human MC4 receptor mutation and morbid obesity (Farooqi et al., 2000; Mergen et al., 2001; Vaisse et al., 1998). Mutations in the MC_3 receptor have been also reported in humans (Tao, 2007; Tao and Segaloff, 2003; Lee et al., 2007). These mutations have been associated with obesity, hyperleptinemia and relative hypophagia, features reminiscent of the MC_3 receptor knockout animals (Chen et al., 2000a).

The connection between leptin and the melanocortin system has been well established. Low leptinemic conditions such as fasting increase the amount of AGRP/neuropeptide Y messenger RNA. The levels of POMC messenger RNA correspondingly decrease (Swart et al., 2002). Furthermore, animals with defective leptin signaling, such as the ob/ob and db/db mice, show increased AGRP and attenuated POMC expression, mimicking conditions of fasting (Mizuno et al., 1998). Both POMC and AGRP neurons express the leptin receptor-b and leptin has been shown to increase the firing of the former neurons while inhibiting the latter (Pinto et al., 2004). Thus, there is convincing evidence to suggest that the melanocortin system is crucial in body weight regulation, and a number of mechanisms have been hypothesized by which this regulation is achieved. Compared to wild type mice, peripheral injections of the MC_3 receptor / MC_4 receptor agonist Melatonan II in MC_4 receptor knockout mice failed to decrease food consumption or enhance metabolism. This confirms the notion that the melanocortin system acts by either decreasing the amount of food consumed or by increasing metabolism (Chen et al., 2000a,b). However, leptin does not mediate its anorexic effects exclusively via the melanocortin system; simultaneous catabolic pathways other than melanocortin system exist. Evidence from humans with MC_4 receptor deficiency or leptin deficiency shows that ad-libitum feeding in the former group is less, suggesting the presence of alternative anorexic pathway mediated by leptin (Farooqi et al., 2003). By influencing downstream catabolic modulating neurons, the melanocortin system promotes energy expenditure, presumably via the paraventricular nucleus. Indeed, microinjection of the α-MSH analog Melatonan II into the paraventricular nucleus has been shown to result in reduced feeding. This inhibition of feeding was blocked by a pre-injection of a MC_3 receptor/MC_4 receptor antagonist (Cowley et al., 1999). In contrast, over-expression of the MC_4 receptor inverse agonist agouti in the paraventricular nucleus resulted in hyperphagia and weight gain (Kas et al., 2004). Among the second order neurons populating the paraventricular nucleus, thyrotropin releasing hormone and corticotropin releasing hormone-containing neurons are important targets of the melanocortin system. It has been shown *in vitro* that both leptin and α-MSH enhance the promoter activity of thyrotropin releasing hormone gene, an integral neuropeptide in the hypothalamus–pituitary–thyroid axis that regulates energy expenditure. I.c.v. administration of AGRP suppresses circulating thyrotropin releasing hormone levels in male rats while injection of α-MSH analog has an opposing effect (Kim et al., 2000). Similar to fasting levels of leptin and α-MSH, thyrotropin releasing hormone levels are also decreased during periods of fasting, where energy conservation is the primary goal (Boelen et al., 2008; Hollenberg, 2008). In an analogous fashion, Melatonan II potently increases corticotropin releasing hormone gene transcription in the paraventricular nucleus and subsequently enhances plasma corticosterone levels in rats, thus modulating activity of the hypothalamus–pituitary–adrenal axis (Lu et al., 2003). The exact mechanism by which these second order neurons in the paraventricular nucleus regulate energy balance is unclear. Recent data suggest that the BDNF system may be a downstream target of melanocortin system that mediates anorexia. One of the following sections in the current review specifically focuses on this neuropeptide. We have already mentioned that leptin-resistant conditions like obesity or high fat diet exposure are accompanied by blunted leptin receptor signaling. Interestingly, although decreased leptin signaling in the arcuate nucleus leads to lower α-MSH secretion, the functionality of the melanocortin system downstream of the POMC neurons remains intact. Enriori et al. (2007) demonstrated that when Melatonan II was injected intraperitoneally in diet-induced obesity animals, they showed up to 90% decrease in food intake.

Another mechanism by which the melanocortin system might regulate feeding is by influencing the amount of food consumed during a meal, i.e. the meal size. Meal size is determined by several parameters including gut-associated satiation signals (cholecystokinin, amylin, glucagon, peptideYY (3–36), metabolic signals (leptin and glucose), meal composition and palatability (Kennedy et al., 1994; Moran, 2006). Administration of Melatonan II in the third or fourth ventricle reduces total caloric intake in terms of meal size although the meal frequency and inter-meal intervals remain unaltered (Goldberg, 2010; Zheng et al., 2005). Evidence suggests that during meal consumption, gut-associated peptides relay satiety signals to the brain, either by the afferent fibers of the vagus nerve or through area postrema, which ultimately converge on the nucleus of solitary tract (Moran, 2006; Smith et al., 1985). The nucleus of solitary tract, in turn, is reciprocally connected to brain areas involved in feeding, meal choice and motivation (Fattore et al., 2010). This nucleus serves as a sensory gateway for various visceral signals, and it sends projections to a range of brain areas, including hypothalamic

and extra-hypothalamic sites monitoring food intake (Grill, 2010). Importantly, the brainstem melanocortin system comprises a separate population of POMC neurons in the nucleus of solitary tract (Palkovits et al., 1987), the POMC neuronal projections from the arcuate nucleus that extend to the dorsal vagal complex and the melanocortin receptors in the brainstem (Cone, 2005; Grill et al., 1998). This suggests that the melanocortin system might play a role in the control of feeding by altering meal size. In fact, it was shown that MC_3 receptor/MC_4 receptor agonist or antagonist (SHU9119) administration either into the fourth ventricle or directly to the dorsal vagal complex, elicited a suppression and enhancement in feeding response, respectively (Grill et al., 1998; Williams et al., 2000). Through a series of experiments, Zheng et al., 2005 have stressed the importance of the connection between gastric satiety signal cholecystokinin and the brainstem melanocortin system to induce meal termination. It was shown that brainstem-specific Melatonan II infusion decreases feeding by enhancing the satiating capacity of a given meal, independent of diet type (regular chow Vs high fat diet) (Zheng et al., 2005). Furthermore, Melatonan II and SHU9119 can both modulate ERK 1/2 activity within the cholecystokinin signal transduction pathway, which mediates the cholecystokinin-induced suppression in food intake (Sutton et al., 2004, 2005; Zheng et al., 2005). In addition MC_4 receptor have been identified to modulate presynaptic vagal and non-vagal glutamergic inputs into the nucleus of solitary tract (Wan et al., 2008), which is consistent with the fact that peripheral administration of cholecystokinin decreases food consumption in MC_3 receptor knockout but not MC_4 receptor knockout animals (Rodgers et al., 2002). Thus, the nucleus of the solitary tract is considered to be a neural hub where the peripheral satiety signal cholecystokinin (via dorsal vagal afferents) and melanocortin signaling (via hypothalamic projections or native population) interact to influence downstream second order neurons necessary for meal termination (Cone, 2005; Grill et al., 1998; Kishi et al., 2003; Nicholson et al., 2007; Sutton et al., 2005; Williams et al., 2000). Regardless of the evidence of the involvement of the melanocortin system to influence feeding via a brainstem mechanism, further research is necessary to fully elucidate whether the hyperphagia observed in MC_4 receptor knockout animals is a consequence of defective satiation.

The third mechanism by which the melanocortin system may influence feeding is through reward-related brain structures. A close relationship exists between the MC_3 receptor, MC_4 receptor and dopaminergic neurotransmission in the ventral tegmental area and nucleus accumbens (Adan and Gispen, 1997; Alvaro et al., 1996). Thus, infusion of Melatonan II into the ventral tegmental area increases dopamine release in the nucleus accumbens (Lindblom et al., 2001). Other evidence on the influence of melanocortin system on the reward circuitry comes from studies where animals exposed to various addictive drugs show alterations in hypothalamic POMC transcripts (Bronstein et al., 1990; Le Merrer et al., 2009). Also, central administration of Melatonan II facilitates the threshold-lowering effect of amphetamine in a lateral hypothalamic self-stimulation paradigm (Cabeza de Vaca et al., 2002), i.e. melanocortin receptor stimulation increased the rewarding properties of amphetamine. Consistent results were also reported by Hsu et al. (2005) where the rewarding and psychomotor stimulant effects of cocaine were blocked by intra-nucleus accumbens injection of SHU9119. Furthermore, up and down-regulation of the MC_4 receptor in the striatum has been shown respectively after chronic cocaine or morphine treatment (Alvaro et al., 2003; Hsu et al., 2005). It was also demonstrated that the locomotor activation after cocaine administration was abolished in the MC_4 receptor knockout mice and reduced in heterozygous MC_4 receptor animals (Hsu et al., 2005). The upregulation of striatal MC_4 receptor in animals in response to repeated cocaine administration suggests that the melanocortin system plays a role in drug induced behavioral sensitization. Collectively, these studies suggest that increased melanocortin signaling via the α-MSH pathway enhances the sensitivity to drugs while reduced α-MSH signaling will lead to the opposite. Thus, if we compare drug and food reward, an opposite situation would be expected. As the melanocortin system mediates anorexia and satiation, the reward-enhancing effect of melanocortins appears paradoxical. This discrepancy may be due to the fact that several of the above studies used Melatonan II, which binds to both MC_3 receptor and MC_4 receptor, making it impossible to distinguish the individual roles of these receptors. Second, it is possible that the melanocortin system interacts with other neuropeptidergic systems to influence homeostatic and reward mechanisms, but future studies need to clarify this. Cabeza de Vaca et al. (2002) also suggest that a differential α-MSH tone exists in brain areas responding to food or drug rewards. This results in a differential role of melanocortins in regulating food-intake as opposed to rewarding effects of drugs. Even though several studies have been conducted to study the interrelationship between melanocortins, dopamine and drugs of abuse, there are almost no data on the role of melanocortin signaling in the mesolimbic dopaminergic neurons with respect to food intake.

3.4. Orexins and overeating

The lateral hypothalamus is one of the fundamental sites bridging the gap between the homeostatic and hedonic aspects of feeding. Lesions of the lateral hypothalamus induce anorexia (Bernardis and Bellinger, 1993), underscoring its role in feeding. Evidence of its influence on the brain reward circuit comes from electrical stimulation studies, as electric stimulation of the lateral hypothalamus is highly reinforcing (Carr, 2002; Johnson and Kenny, 2010; Markou and Koob, 1992; Wise, 1996). Studies in rodents have shown connections between the lateral hypothalamus and brain reward areas (the ventral tegmental area and nucleus accumbens) (Balcita-Pedicino and Sesack, 2007; Leinninger et al., 2009; Peyron et al., 1998), and lateral hypothalamic neuronal populations of orexinergic (Borgland et al., 2010), GABAergic (Leinninger et al., 2009) and melanin concentrating hormone-containing neurons (Pissios et al., 2008), have been shown to modulate signaling in the mesolimbic dopamine circuit.

The role of orexins with respect to feeding and addiction has been widely studied. Acute central administration of orexin leads to a robust hyperphagic response in rodents and other vertebrates (Rodgers et al., 2002). Analogous to leptin, orexin also plays a dual role in regulating both homeostatic and hedonic aspects of food intake. It has been suggested that orexin mediates its homeostatic aspect of feeding through its connection with the arcuate nucleus where it has been shown to regulate the neuropeptide Y and POMC neurons (Tsujino and Sakurai, 2009). Leptin hyperpolarizes orexinergic neurons (Yamanaka et al., 2003) and decreases orexin messenger RNA expression (Sahu, 2003). However, administration of an OX_1 receptor antagonist only partially reverses the obese phenotype in ob/ob mice (Haynes et al., 2002). Likewise, leptin only partly ameliorates the orexinergic effect of orexin in rats (Zhu et al., 2002), suggestive of simultaneous neuronal pathways being involved in body weight regulation. A single i.c.v. orexin A administration induced enhanced food intake in satiated animals (Haynes et al., 1999), indicating that orexin A-induced hyperphagia may be mediated by orexin's effect on the brain reward mechanisms. In addition, similar to drugs of abuse, orexin administration in the nucleus accumbens increases locomotor activity with a simultaneous increase in feeding (Thorpe and Kotz, 2005). Likewise, increased c-fos activation in the lateral hypothalamus orexinergic cells was shown in animals that demonstrated a conditioned place preference for cocaine, morphine or food (Harris et al., 2005). In the same paper, it was also shown that systemic injection of an OX_1 receptor antagonist reverses the conditioned place preference for morphine. Furthermore, chemical activation of orexinergic neurons in the lateral hypothalamus reinstated extinguished morphine place preference (Harris et al., 2005). Together, these data indicate an important role for orexins in the modulation of the

reward function and that activation of these neurons is important to couple drug rewards with environmental cues (Harris and Aston-Jones, 2006).

Multiple lines of research also connect orexins to hedonic feeding. Central administration of orexin A increased free feeding of sucrose pellets and also responding for sucrose pellets under fixed ratio and progressive ratio schedules of reinforcement (Thorpe et al., 2005). The increased self-administration of sucrose pellets was decreased by a systemic injection of an OX_1 receptor antagonist (Cason et al., 2010). I.c.v. administration of orexin also augments high fat diet preference (Clegg et al., 2002) and treatment with an OX_1 receptor antagonist decreased self-administration of a high fat diet (Nair et al., 2008), indicating that the approach behavior towards a reward is possibly mediated through the OX_1 receptor. Analogously, animals given i.c.v. orexin show enhanced breakpoints for high fat diet reward under a progressive ratio schedule, and this increase in breakpoints is reversed when an OX_1 receptor antagonist is systemically administered (Choi et al., 2010). In a recent publication, Choi et al. (2010) also showed that systemic administration of an OX_1 receptor antagonist decreased high fat diet consumption in satiated animals, an observation similar to that of Nair et al. (2008). Hence, it may be concluded that orexin signaling is important in overriding homeostatic mechanisms regulating food intake to drive animals towards hedonically determined food consumption. Orexinergic fibers from the lateral hypothalamus project both to the ventral tegmental area and the nucleus accumbens. In the former area, they make extensive connections with dopaminergic cell bodies (Fadel and Deutch, 2002) that express OX_1 receptor and OX_2 receptor (Narita et al., 2006). Indeed, orexin A injections into the ventral tegmental area cause elevated dopamine levels in the nucleus accumbens (Narita et al., 2006) and orexins have been found to increase the firing of dopaminergic neurons in vitro (Korotkova et al., 2003). Since orexins modulate dopaminergic signaling in the nucleus accumbens, it is likely that the effects of orexin on reward processes discussed in the preceding paragraph are mediated via the mesolimbic dopaminergic circuit. Direct effects of orexin A in the nucleus accumbens were also reported by Thorpe and Kotz (2005), who showed that infusion of orexin A into the nucleus accumbens shell was accompanied by heightened locomotion and feeding. It is interesting to note that dopaminergic neurons of the ventral tegmental area project both to the nucleus accumbens shell and neurons from the nucleus accumbens shell project back to the lateral hypothalamus orexin neurons, establishing a feedback loop in this circuitry (Harris and Aston-Jones, 2006).

Recently, it was shown that appetite, meal frequency and length of a meal were also increased after central administration of orexin A (Baird et al., 2009). This suggests that hindbrain satiation mechanisms may be involved in orexin A mediated feeding. In fact, orexin A administration in animals with hindbrain (area postrema, nucleus of solitary tract) lesions, resulted in a decrease in meal size without altering the meal frequency (Baird et al., 2009). In support of this, orexin-immunoreactive fibers and orexin receptors are present in the dorsal vagal complex, a neural hub where peripheral satiety signals interact with neuropeptidergic systems to control satiety (Kirchgessner, 2002). Thus, we can conclude that orexin-mediated hyperphagia may result from enhanced hedonic feeding or altered satiation. However, the exact mechanism of action of orexin demands further investigation.

3.5. Brain derived neurotropic factor and implications in overeating

The ventromedial hypothalamus is another hypothalamic area participating in energy balance. Lesions of this area are associated with enhanced feeding while electrolytic stimulation results in suppression of feeding (King, 2006; Ruffin and Nicolaidis, 1999). Brain derived neurotropic factor (BDNF), a neuronal growth factor, belonging to the neurotropin family (Tapia-Arancibia et al., 2004), is expressed in high levels in the ventromedial hypothalamus (Kernie et al., 2000). More than a decade ago, the importance of BDNF in feeding was established (Pelleymounter et al., 1995; Kernie et al., 2000). It was shown that i.c.v. infusion of BDNF led to weight loss in rodents (Pelleymounter et al., 1995). Mice heterozygous in the BDNF locus showed enhanced adiposity accompanied with increased locomotor activity and leptin resistance (Kernie et al., 2000). Reduction of the BDNF receptor, tyrosine kinase B (TrkB receptor) leads to weight gain and hyperphagia, while stimulation of the receptor is accompanied by weight loss in animals exposed to a diet-induced obesity paradigm (Tsao et al., 2008). Food deprivation has been also shown to reduce BDNF expression in the ventromedial hypothalamus (Xu et al., 2003), highlighting the anorexic role of BDNF. Studies in humans support this anorexic property of this neuropeptide, as mutations in the BDNF gene were accompanied by hyperphagia, obesity and hyperactivity (Gray et al., 2006). Similarly, Yeo and colleagues reported a de-novo missense mutation in the TrkB receptor gene that resulted in overt hyperphagia and obesity (Tamminga, 2010). Genome wide association studies conducted on a European population reported a BDNF locus with a genome wide significance ($p \leq 1.6 \times 10^{-7}$) for obesity (Scherag et al., 2010).

Since BDNF is widely expressed in the ventromedial hypothalamus (Xu et al., 2003), the next step was to understand if the anorexic effects of BDNF were region specific. Indeed, ventromedial hypothalamus-specific depletion of BDNF has been shown to enhance weight gain and hyperphagia (Unger et al., 2007), but the underlying molecular mechanisms governing BDNF effect on feeding remain unclear. One of the hypotheses is that BDNF is a downstream target of the melanocortin system, as MC_4 receptor stimulation enhances BDNF secretion (Nicholson et al., 2007). In keeping with this hypothesis, reduction of MC_4 receptor signaling in the ventromedial hypothalamus is characterized by decreased BDNF messenger RNA, and melanocortin receptor agonist treatment reverses the food deprivation-induced reduction in BDNF messenger RNA in the ventromedial hypothalamus (Xu et al., 2003). While exogenous leptin injection does not revert hyperphagia in diet-induced obesity models, it was shown that BDNF injection in these animals successfully decreased food intake (Nakagawa et al., 2003). This suggests that despite disrupted leptin receptor signaling in obesity, downstream effector pathways (melanocortins, BDNF) are still functional and modulation of these pathways may be helpful in devising new tools to treat obesity. Indeed, it was demonstrated in the same paper that chronic BDNF infusion for 6 days not only decreased food intake and body weight, but also decreased serum leptin concentrations in animals exposed to high fat diet for 4 months. Likewise, fasting insulin levels were also reduced in diet-induced obesity animals repeatedly treated with BDNF (Nakagawa et al., 2003). However, there are also data to suggest that BDNF is directly regulated by leptin on BDNF secreting neurons, since after leptin administration, co-localization of phosphorylated STAT-3 protein positive neurons and BDNF messenger RNA was observed (Komori et al., 2006).

Apart from being a downstream target of the melanocortin system, BDNF can also modulate feeding by influencing the mesolimbic dopaminergic circuit. Alterations BDNF and TrkB receptor messenger RNA levels in the ventral tegmental area are found in animals exposed to a high fat diet paradigm (Cordeira et al., 2010). The connection between BDNF, drugs of abuse and mesolimbic dopaminergic system has been studied to some extent. BDNF knockdown in the ventral tegmental area and nucleus accumbens reduced cocaine place conditioning (Graham et al., 2007). Furthermore, nucleus accumbens-specific TrkB receptor or BDNF deletion decreased cocaine self-administration (Graham et al., 2009). Likewise, cocaine injections elevate BDNF protein and TrkB receptors in the nucleus accumbens. There is evidence to indicate that the ventral tegmental area has its own sub-population of BDNF secreting neurons and recently, it was shown that BDNF knockout animals, were not only hyperphagic, as previously reported (Unger et al., 2007), but also showed increased high fat diet consumption in a restricted access paradigm, simulating binge eating behavior (Cordeira et al., 2010).

Converging evidence further indicates that BDNF increases dopaminergic signaling in the mesolimbic circuitry (Cordeira et al., 2010). Central BDNF depletion was accompanied by blunted dopamine release and diminished D_2 receptor in the nucleus accumbens shell and the dorsal striatum. Furthermore, knocking down the BDNF gene in the ventral tegmental area increased the desire for high fat diet compared to standard chow (Cordeira et al., 2010). Thus, Cordeira et al. (2010) suggest: (1) differential functions of hypothalamic and ventral tegmental area BDNF, the former modulating homeostatic control of feeding and the latter governing its hedonic aspects; and (2) since electrically evoked dopamine release in the dorsal striatum is reduced in BDNF knockout mice, it may be possible that the hyperphagia found in ventral tegmental area BDNF knockout animals is a way to compensate for low dopamine levels.

It is known that hypothalamic BDNF levels are decreased in response to high fat diet consumption in obesity-sensitive mice (Yu et al., 2009), which is in line with the finding that high fat diet induces leptin resistance and directly or indirectly (via the melanocortin system) decreases BDNF secretion. Animals fed on palatable food, show an increase in the TrkB receptor transcript and a decrease in BDNF in the ventral tegmental area 30 and 60 min post high fat diet exposure (Cordeira et al., 2010). However, the effects mentioned above were either in the hypothalamus or transient. Thus, the consequence of leptin resistance for BDNF expression in the ventral tegmental area/nucleus accumbens is yet to be determined. Comparing BDNF effects in the hypothalamus and in the ventral tegmental area, in the former, leptin resistance might induce low levels of BDNF and thus minimize its anorectic effect, while in the latter the situation is more complex. Based on the dopamine hypo functioning theory of addiction (Koob and Volkow, 2010; Volkow et al., 1997), one might expect that decreased leptin receptor signaling, as encountered in obesity, will also decrease BDNF levels, further dampening dopamine release and thereby elevating craving for rewards in order to compensate for lower striatal dopamine levels. However, a detailed analysis of the state of the BDNF system in the mesolimbic circuitry needs to be performed with respect to diet-induced obesity and different stages of leptin resistance, to assess the possible similarities of this system in obesity and addiction.

It has been reported that BDNF might interact with satiety signals in the brainstem to reduce food intake (Bariohay et al., 2005). BDNF immunoreactive fibers and TrkB receptors are found in the dorsal vagal complex (Bariohay et al., 2005). Infusions of BDNF into the dorsal vagal complex have been shown to attenuate food consumption and promote weight loss. Moreover, the amounts of endogenous BDNF in this site were diminished in response to low leptinemic condition as in food restriction whereas they were correspondingly increased after peripheral injections of leptin or satiety hormone cholecystokinin (Bariohay et al., 2005). However, whether this anorexic action of BDNF is mediated by leptin itself or via the melanocortin pathway is uncertain. Therefore, further studies looking into the effect of BDNF on meal size would be helpful.

4. Conclusions

The emerging similarities between obesity and substance abuse disorders, makes us think about the possibility that obesity is a form of addiction where the brain reward system, which responds to natural rewards like food and sex, has been biologically re-programed to enhance 'liking' and/or 'wanting' for food. Several similarities between overeating and drug addiction have been shown. These include highly increased motivation to seek food and lasting neurobiological changes in reward-associated brain regions. However, whereas there is an enormous body of evidence to document the changes in brain and behavior that result from repeated and prolonged exposure to drugs of abuse which may contribute to the development of drug addiction (Vanderschuren and Kalivas, 2000; Hyman et al., 2006; Koob and Volkow, 2010), this kind of research on the neurobiology of obesity is only emerging (Adan et al., 2008).

Therefore, future research must be directed at studying the most pertinent aspects of addiction in the context of obesity, e.g. to compare food and drug seeking behavior under aversive consequences, to elucidate whether overeating indeed has a compulsive element (Deroche-Gamonet et al., 2004; Vanderschuren and Everitt, 2004; Johnson and Kenny, 2010). The link between the hypothalamic sites which integrate metabolic information and the brain reward system becomes increasingly clear (Corsica and Pelchat, 2010; Schwartz et al., 2000; Pelchat, 2009). In the current paper, we specifically focused on the mesolimbic dopaminergic system due to the extensive studies conducted on this system, but it should be borne in mind that other systems like the opioid and the endocannabinoid systems substantially contribute to the brain's response to drug or food rewards as well. Readers are referred to excellent recent reviews on this topic (Fattore et al., 2010; Fulton, 2010; Taha, 2010; Trigo et al., 2010). The present review focused on the homeostatic and hedonic roles of three crucial neuropeptidergic systems: melanocortin system, orexins and BDNF, which act downstream of leptin. Other neuropeptides (e.g. melanin concentrating hormone and Neuropeptide Y) that play a distinct role in overeating have not been discussed here (see Chee and Colmers, 2008; Depoortere, 2009; DiLeone et al., 2003; Griffond and Risold, 2009 for excellent reviews on this topic). It is evident that the function of the peptides involved in feeding regulation is not entirely homeostatic. In fact, the homeostatic and hedonic aspects of feeding are not mutually exclusive and one influences the other.

The melanocortin system is perhaps the principal catabolic modulator of energy balance in animals. α-MSH mediates its anorexic effect by affecting several downstream nuclei: paraventricular nucleus (increasing energy expenditure), lateral hypothalamus (via orexinergic neurons and its connection to the mesolimbic dopaminergic circuit), ventromedial hypothalamus (BDNF and its downstream targets), nucleus of solitary tract/dorsal vagal complex (by interacting with peripheral satiety signal cholecystokinin) and directly influencing the mesolimbic circuit (motivated approach behavior) (Adan et al., 2006; Cone, 2005; Kim et al., 2000, 2002; Kishi et al., 2003; Lindblom et al., 2001; Lu et al., 2003). Overconsumption can be seen as a secondary phenomenon in response to altered neuropeptidergic systems and rewiring of the brain reward circuitry encountered in leptin-resistant states. Hence, understanding the concrete roles of these neuropeptidergic systems with respect to the reward circuitry in both physiological and leptin resistant states will provide more answers to the leptin resistance–overeating link. It is important to note that although several similarities exist between over-eating and addiction, it does not automatically mean that overeating is a form of addiction. Nevertheless, the booming scientific interest on this field together with a rapidly evolving line of research categorically focusing on overeating as a form of addictive behavior may help us resolve the 'missing link' between these two conditions.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgements

The current work has been supported and funded by the NeuroFAST Foundation (the integrated neurobiology of food intake, addiction and stress). NeuroFAST is funded by the European Union Seventh Framework Programme (FP7/2007–2013) under grant agreement n° 245009.

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