

REVIEW

Integration of reward signalling and appetite regulating peptide systems in the control of food-cue responses

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Understanding the neurobiological substrates that encode learning about food-associated cues and how those signals are modulated is of great clinical importance especially in light of the worldwide obesity problem. Inappropriate or maladaptive responses to food-associated cues can promote over-consumption, leading to excessive energy intake and weight gain. Chronic exposure to foods rich in fat and sugar alters the reinforcing value of foods and weakens inhibitory neural control, triggering learned, but maladaptive, associations between environmental cues and food rewards. Thus, responses to food-associated cues can promote cravings and food-seeking by activating mesocorticolimbic dopamine neurocircuitry, and exert physiological effects including salivation. These responses may be analogous to the cravings experienced by abstaining drug addicts that can trigger relapse into drug self-administration. Preventing cue-triggered eating may therefore reduce the over-consumption seen in obesity and binge-eating disorder. In this review we discuss recent research examining how cues associated with palatable foods can promote reward-based feeding behaviours and the potential involvement of appetite-regulating peptides including leptin, ghrelin, orexin and melanin concentrating hormone. These peptide signals interface with mesolimbic dopaminergic regions including the ventral tegmental area to modulate reactivity to cues associated with palatable foods. Thus, a novel target for anti-obesity therapeutics is to reduce non-homeostatic, reward driven eating behaviour, which can be triggered by environmental cues associated with highly palatable, fat and sugar rich foods.

Abbreviations

BMI, body mass index; BOLD, blood oxygenation level dependent signal; CS, conditioned stimulus; fMRI, functional magnetic resonance imaging; GHSR, growth hormone secretagogue receptors; LH, lateral hypothalamus; MCH, melanin concentrating hormone; NAC, nucleus accumbens; NPY, neuropeptide Y; OFC, orbitofrontal cortex; OXR, orexin receptor; PVT, paraventricular nucleus of the thalamus; US, unconditioned stimulus; VTA, ventral tegmental area

Tables of Links

TARGETS

GPCRs

Orexin OX₁ receptors
 Orexin OX₂ receptors
 GHSR, growth hormone secretagogue receptor (ghrelin receptor)
 MCH₁ receptors

LIGANDS

Bupropion	Naltrexone
Dopamine	NPY neuropeptide Y
Flupenthixol	Orexin A
Ghrelin	Orexin B
GW803430	Orlistat
Leptin	Phentermine
Liraglutide	SB334867
Lorcaserin	Topiramate
MCH, melanin concentrating hormone	

These Tables list key protein targets and ligands in this article which are hyperlinked to corresponding entries in <http://www.guidetopharmacology.org>, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Pawson *et al.*, 2014) and are permanently archived in the Concise Guide to PHARMACOLOGY 2013/14 Alexander *et al.*, 2013).

Introduction

Consumption beyond basic homeostatic needs, purely based on the rewarding properties of palatable foods, is proposed to be a central contributor to the current worldwide obesity epidemic (Berthoud, 2012). Until recently, only three anti-obesity medications were approved by the Food and Drug Administration (USA) for the long-term clinical management of obesity and related metabolic syndrome. These medications are orlistat (Xenical) which inhibits intestinal lipases to prevent fat absorption, the selective 5-HT_{2C} receptor agonist lorcaserin (Belviq), which acts by potentiating monoamine signalling in the CNS and the combination of the stimulant phentermine, which suppresses appetite and increases metabolic rate, and extended-release topiramate (Qsymia). In 2014, the combination of the μ -opioid antagonist naltrexone plus the noradrenaline and dopamine re-uptake inhibitor bupropion (both controlled release; Contrave) became the fourth medication approved for long-term weight management in patients with obesity, and in December 2014, liraglutide (Saxenda), a glucagon-like peptide 1 receptor agonist, was also approved (Yanovski and Yanovski, 2015).

With increased knowledge of the pathogenesis of obesity, several other potential anti-obesity agents are being investigated. In humans, cues associated with food powerfully enhance both ratings of appetite and food consumption (Ferriday and Brunstrom, 2008). In particular, improved understanding of the neurocircuitry of appetite and metabolism regulation has provided many potential targets for therapeutic anti-obesity agents that are currently under development. Thus, a novel target is to reduce non-homeostatic, reward driven eating behaviour, which can be triggered by environmental cues associated with highly palatable, fat and sugar rich foods.

Eating is essential for survival and is underpinned by the fundamental physiological need to consume energy. However, people often consume in excess of the basic nutrient and energy requirement needed to maintain physiological homeostasis, particularly when there is an abundance of readily available food and drink. Indeed, eating is more often than not controlled by

external cues and stimuli, the time of the day and social factors, rather than time since the last meal and the need to replenish energy stores. The modern environment is replete with food-associated cues that encourage eating in the absence of metabolic demands. In this review, 'cues' refer to external, environmental cues, such as the sight and smell of particular foods, or locations where certain foods are procured. These cues are capable of generating 'cue-reactivity' – the ability of cues to signal that a reward (or punishment) will be imminently received. Through a process of Pavlovian conditioning, cues that typically predict food intake can trigger cue-reactivity, a motivational state that may evoke expectations of food or be experienced as an urge to eat (Jansen, 1998), considered separate from the interoceptive cues generated by internal states such as hunger or satiety (Schachter, 1968). Cue-specific reactions are proposed to evoke cravings for particular foods (Meule *et al.*, 2012, 2014; Jastreboff *et al.*, 2013) in a manner that can be deemed analogous to cue-evoked cravings in drug addicts (see Perry *et al.*, 2014). People who overeat and have become overweight or obese are thought to develop increased cue-reactivity through disordered learning histories related to food intake. Thus, obesity is proposed to be associated with abnormal reward processing of palatable foods and cues associated with these foods (Rogers and Hill, 1989; Davis and Fox, 2008; Stice *et al.*, 2008, 2011a,b; Stoeckel *et al.*, 2008; Boggiano *et al.*, 2009; Demos *et al.*, 2012; Murdaugh *et al.*, 2012; Yokum *et al.*, 2014; Jensen and Kirwan, 2015). Furthermore, some of these abnormalities in reward processing may predate obesity while others may be a consequence of over-eating (Bello *et al.*, 2002; Yokum *et al.*, 2011; Murdaugh *et al.*, 2012; Burger and Stice, 2013, 2014).

At a neural level, hypothalamic appetite regulating circuits project to the reward related midbrain dopamine neurocircuitry (DiLeone *et al.*, 2003; Lutter and Nestler, 2009; Yeo and Heisler, 2012) providing an anatomical basis by which the regulation of such reward related feeding might occur. Gut and adipose tissue-derived signals including peptides such as neuropeptide Y (NPY), cholecystokinin, leptin, insulin and ghrelin, as well as other physical and hormonal signals conveyed by the vagal

nerves to the brainstem, are critical determinants of both the metabolic responses to food (post-ingestive responses such as satiation) and in the initiation of food intake (Havel, 2001). Thus, neural cross talk between homeostatic and reward-related neurocircuitry permits functional interactions to influence the initiation of ingestive behaviours (Shizgal *et al.*, 2001). This review discusses the behavioural and hormonal correlates of food-associated cue-reactivity that may lead to the over-consumption of foods, and the underlying homeostatic and reward neurocircuitry that interacts to control such reward-driven feeding behaviours. We discuss modulation of appetite regulatory peptides [ghrelin, orexin, leptin and melanin concentrating hormone (MCH)] as potential therapeutic targets for maladaptive eating behaviours and food cravings that may contribute to obesity.

Food is a natural reinforcer

Reward or positive reinforcement describes the positive value allocated to an object, behavioural act or an internal physical state that induces pleasurable effects. Food and sex are considered primary reinforcers, capable of directing behaviours leading to their procurement, and our desire for them is hardwired due to their intrinsic requirement for survival on a species-wide basis. Such reinforcers exert many of their effects on behaviour via activation of mesocorticolimbic neurocircuitry, involving projections from the ventral tegmental area (VTA) to areas of the brain such as the nucleus accumbens (NAc), hypothalamus, hippocampus, frontal cortex and central/basomedial amygdala (Fibiger and Phillips, 1988; Kelley and Berridge, 2002; Rada *et al.*, 2005), resulting in the release of neurotransmitters including dopamine, GABA and opioid peptides. Drugs of abuse such as cocaine, alcohol and opioids also activate this reward neurocircuitry, leading to release of dopamine in the mesolimbic pathway (Berridge and Robinson, 1998). Through appetitive (reward-driven) learning, motivational significance or incentive salience is assigned to cues and responses predictive of rewarding outcomes (Robinson and Berridge, 1993). As such, both food- and drug-associated cues have been shown to activate similar brain regions involved in learning, memory and motivation, including the prefrontal cortex, nucleus accumbens, amygdala, orbitofrontal cortex (OFC) and the striatum (Kalivas, 2000; Vanderschuren and Kalivas, 2000; Hotsenpiller *et al.*, 2001; Kalivas *et al.*, 2005; Tang *et al.*, 2012).

In the addiction literature, a distinction between 'liking' and 'wanting' rewards has been drawn (Robinson and Berridge, 2003). 'Wanting' is the desire to acquire a reward, as opposed to 'liking', which is the hedonic (pleasurable) impact of rewards. These constructs are thought to be grounded in distinct neural substrates (Berridge and Robinson, 1998). The neural substrates underlying liking involve the NAc, ventral pallidum and OFC, and primarily GABAergic, opioid and endocannabinoid neurotransmission (Berridge, 2009). 'Wanting' is related to motivational influences on behaviour and has been associated with dopamine signalling in the mesolimbic region, as well as its connections with the prefrontal cortex and amygdala (Barbano and Cador, 2007; Salamone and Correa, 2009; Mahler and Berridge, 2012a). In rats, elevating NAc dopamine had no effect on hedonic responding for sucrose, but increased lever pressing

for sucrose, indicative of enhanced wanting (Wyvell and Berridge, 2000), supporting the proposal that dopamine can mediate reward-related cues to trigger 'wanting', but not the hedonic appraisal of palatable foods. In contrast, opioid agonists were shown to influence the hedonic appraisal of palatable rewards, but did not alter the motivation to lever press for food rewards (Pecina and Berridge, 2005).

Cues become associated with palatable foods to control behaviour

In Pavlovian conditioning, associations are formed between an initially neutral environmental cue, [the conditioned stimulus (CS)], with a natural reinforcer, such as food, [the unconditioned stimulus (US)]. These associations enable the cue (CS) to promote consumption, even in sated animals, potentially influencing homeostatic signals by increasing feelings of hunger (Weingarten, 1983; Cornell *et al.*, 1989; Petrovich, 2011). Alternatively, cues may override satiety signals (Schachter, 1968; Petrovich *et al.*, 2002), as the food-associated cues have been imbued with incentive salience – the 'wanting' attributed to reward-predicting stimuli (Robinson and Berridge, 1993; Berridge, 2007), which can then direct behaviour to procure food. Dopamine neurons in the VTA show phasic activations to food delivery and food-predicting cues (Schultz, 1998a,b). Thus, cues associated with foods are assigned incentive value, and motivating events are signalled through phasic dopamine release (Schultz, 1998a,b; Brown *et al.*, 2011; Flagel *et al.*, 2011b; McCutcheon *et al.*, 2012).

Through predictive associations with rewarding foods, cues are able to evoke food-seeking behaviours, including the performance of a specific action, such as pressing a lever to get food. Animals will learn that a certain cue signals that a food reward is available in a food hopper, and will direct behaviour to the hopper when this cue is presented (known as goal-tracking). Alternatively, animals may direct their behaviour to the cue that predicts food delivery (sign-tracking). These behaviours typically depend on the relative 'value' of the food reward, which determines how much effort will be expended to obtain the outcome. Thus, performance of associated responses is dependent on the internal motivational state to obtain a particular reward. The motivational properties of a food can be reduced, or devalued, by its consumption (sensory-specific satiety) or by its pairing with toxin-induced sickness (Dickinson and Balleine, 1990; Balleine and Dickinson, 1998). Following the devaluation procedure, animals typically show reduced levels of food-seeking behaviours as the food outcome is no longer valued. This food-value mediated behavioural control enables animals to adapt to changing environmental conditions. The brain regions involved in the attribution of incentive value to cues predictive of food rewards include the basolateral amygdala, OFC and NAc. Excitotoxic lesions to these regions in rats that had learnt to associate particular cues with foods resulted in an inability to control food-seeking responses according to the value of a food following its devaluation (Pickens *et al.*, 2003, 2005; Ostlund and Balleine, 2007a,b; Johnson *et al.*, 2009). Our recent research has demonstrated that rats exposed to palatable high fat/high sugar foods were impaired at controlling food-seeking responses to palatable food-associated cues following devaluation by sensory-specific satiety

(Reichelt *et al.*, 2014). This indicates that excessive consumption of obesogenic diets can impair responding to cues associated with palatable foods based on their current value, suggesting that these diets cause changes to reward systems in the brain.

Neural systems involved in cue-triggered food-seeking behaviour

Dopamine signalling is crucial in the formation of associations between cues and food rewards (Bassareo and Di Chiara, 1999a,b). In Pavlovian conditioning, delivery of food is not contingent on behaviour; nevertheless, animals, such as rats, typically approach and contact a cue that is paired with the palatable food (Davey and Cleland, 1982). These cue-directed behaviours (also known as sign-tracking; Flagel *et al.*, 2011a) are thought to reflect the cue acquiring incentive salience (motivational value) as a result of its pairing with the food (Berridge, 2004). During Pavlovian conditioning, cue-directed sign-tracking behaviours and food directed goal-tracking behaviours (e.g. approaches to the food hopper location) can be expressed differentially within a group of animals, some animals showing more sign-tracking and others more goal-tracking behaviours. Pronounced sign-tracking behaviour is assumed to index a greater incentive value to the outcome predictive cue. Substance abuse and addiction are associated with increased sensitivity to drug-related cues, perhaps resulting from sensitization of midbrain dopamine neurons in response to drugs that imbues the drug-related stimuli with excessive incentive salience (Robinson and Berridge, 1993, 2001). Recently, a study demonstrated that rats that showed greatest sensitivity to food-related cues in the form of sign-tracking and goal-tracking responses to a sucrose-paired cue gained more weight when exposed to a palatable junk food diet (Robinson *et al.*, 2015). The greater levels of cue-triggered attraction to sucrose-associated stimuli during Pavlovian conditioning indicated enhanced incentive motivation in rats that became obese, as opposed to rats that were obesity resistant. Thus, those rats that attributed greater incentive value to the sucrose predicting cue were more likely to become obese (Robinson *et al.*, 2015).

Sign-tracking has been shown to be mediated by the NAc and its dopaminergic inputs from the VTA (Flagel *et al.*, 2011a; Saunders and Robinson, 2012; Lopez *et al.*, 2015). Injection of the dopamine receptor antagonist flupenthixol into the NAc core markedly impaired the expression of a sign-tracking conditioned response, but not a goal-tracking conditioned response (Saunders and Robinson, 2012). Thus, dopamine signalling in the NAc core appears particularly important for attributing incentive salience to reward-predicting cues. Lesions of the NAc in rats, via 6-OHDA induced dopamine depletion, impaired both acquisition and expression of a cue-food association, as demonstrated by cue elicited approach behaviour to a food hopper in the form of goal-tracking (Cardinal *et al.*, 2002). Furthermore, a recent study by Darvas *et al.* (2014) showed that *Slc6a3Cre/+;Th* knock-out mice with severe depletion of striatal dopamine (only ~5% of wild type levels, but sufficient dopamine for normal feeding behaviour and locomotion), were impaired in the acquisition of a goal-tracking conditioned food-seeking response to the food hopper when a food cue was presented. *Slc6a3Cre/+;Th* knock-out mice with 30% of wild-type dopamine levels were

able to perform the task comparably to wild type controls (Darvas *et al.*, 2014). This implicates dopamine in the acquisition of a conditioned food-seeking response; however these observations indicate that dopamine in the accumbens and striatum may play different roles in the mechanisms of acquisition versus expression of food-seeking responses.

Cue-potentiated feeding. A range of animal studies has demonstrated that food-associated cues are capable of promoting eating in the absence of metabolic requirements (Weingarten, 1983; Petrovich, 2005, 2007; Reppucci and Petrovich, 2012). Hungry rats (or mice) are first trained to associate a cue such as a sound or a distinct context with deliveries of a palatable food. The rats are then permitted to freely feed on chow in their home cages until their body weights have returned to normal. To test for cue-potentiated feeding, rats are returned to the training chambers and undergo explicit satiation on the trained food outcome (Petrovich *et al.* 2005, 2007), and then tested for cue-induced feeding by being exposed to the discrete cue in the presence of the palatable food, or they are tested with that food in its associated context. Such rats eat more of the palatable food when the cue is presented compared to no cue, or in a neutral context (Petrovich *et al.*, 2005, 2007; Reppucci and Petrovich, 2012). The cue does not potentiate feeding by promoting conditioned approach behaviours to the food hopper where the food was delivered during training; rats were shown to also overeat when the food was available in a different location in the test chamber (Holland and Gallagher, 2003).

Food-associated cues can promote eating behaviours in humans. Cues predictive of food availability are powerful modulators of appetite. Food-related cues generate expectancy of reward delivery through phasic activation of mesocorticolimbic dopaminergic signalling (Schultz, 1998a; Schultz, 1998b), leading to cravings for foods even when sated (Blum *et al.*, 2011). In humans, normal weight participants ate pizza or ice cream, despite reporting satiety after previously consuming these foods to satiety (Cornell *et al.*, 1989). The mere presence of these palatable foods enhanced the reported desire for them and the amount consumed correlated with the reported desire for the food (Cornell *et al.*, 1989) indicating that the wide availability of palatable foods is likely to promote over-consumption. In pre-school children, discrete audio-visual cues (a light and a song) presented immediately prior to the delivery of snack foods in a particular classroom evoked greater consumption than unpaired cues in a different classroom (Birch *et al.*, 1989). More recently, Grenard *et al.* (2013) reported that food cues increased snacking in adolescents, as did social cues such as being with friends. Moreover, the presence of palatable foods attracted attention and increased craving in adult women with no eating behaviour issues. However, the size of these effects was greatly increased in adults with a history of sub-clinical binge-eating behaviours (Sobik *et al.*, 2005), and greater responsiveness to food cues in adult restrained eaters correlated with ratings of cravings and increased consumption of desired foods (Fedoroff *et al.*, 1997; van Koningsbruggen *et al.*, 2012).

Neuroimaging studies indicate differential responsiveness to food-associated cues in obese and obesity-prone individuals. Hyper-responsiveness to food cues may be

underpinned by the assignment of an increased incentive value to highly palatable, energy dense foods, driving over-consumption through augmented reward neurocircuitry (Dagher, 2009; Volkow *et al.*, 2012; Stice *et al.*, 2013). Studies in humans utilizing functional magnetic resonance imaging (fMRI) have enabled monitoring of effects of food-associated cues on a correlate of neuronal activity (BOLD response) in reward-related brain regions, allowing investigations into whether obesity modulates measures of brain activation. Increased BOLD responses on presentation of food cues have been observed in obese individuals in reward processing brain regions and in brain regions involved in control over motivated behaviours, such as the insula and ventrolateral prefrontal cortex, indicating hyper-responsiveness (Rothmund *et al.*, 2007; Stice *et al.*, 2008; Davids *et al.*, 2010; Martin *et al.*, 2010; Gearhardt *et al.*, 2011). Weaker striatal activation was observed during food intake, suggesting that activity in brain regions capable of overriding cue-induced cravings is also decreased by obesity, potentially permitting overeating (Stice *et al.*, 2008). Obese individuals exhibited increased corticolimbic-striatal activation in response to food cues that correlated with reports of increased cravings (Jastreboff *et al.*, 2013) and mesolimbic activity following the presentation of food cues positively correlated with BMI (Loeber *et al.*, 2012). Presentation of high-calorie food cues increased the mesolimbic BOLD response in obese women in comparison to normal weight controls (Rothmund *et al.*, 2007), suggesting obesity changes food cue-reactivity. However, recent research has indicated that the propensity for learning associations between cues paired with food rewards was predictive of future weight gain (Burger and Stice, 2014). This research thus provides evidence that individuals who show increased neural responsiveness to food cues are more vulnerable to excess weight gain. Similarly, rats who showed greater sign-tracking responses to sucrose-paired cues were most likely to gain excessive weight when fed an energy rich junk food diet (Robinson *et al.*, 2015).

Summary: Reward systems in cue-triggered food-seeking behaviour

Consumption in response to food-associated cues in the absence of metabolic need can be viewed in terms of the distinction between 'wanting' and 'liking' (Robinson and Berridge, 2000), and some comparison may be drawn to the concept of incentive salience in drug addiction. Incentive salience theory suggests that repeated exposure to drugs of abuse alters the neural mechanisms of reward signalling and that natural reinforcers may have similar effects. It has, however, not yet been demonstrated whether abnormal responding to food cues is due to the repeated exposure prior to the onset of obesity or as a result of obesity. Studies suggest that there are differences in food reward processing between overweight and lean individuals and the way they respond to food-associated cues (Volkow *et al.*, 2008, 2012). Thus maladaptive responses to cues present in the environment may promote consumption and increase food-cue-reactivity, driving over-consumption (Davidson and Swithers, 2004). Importantly cues can become associated with the sensory as well as the affective/motivational properties of the food (Parkinson *et al.*, 2001) and

so can direct behaviour in a specific manner. As shown in Figure 1, over-consumption may be due to a shift to increased wanting following repeated exposure to palatable foods and cues predictive of delivery of food reward. This is perhaps analogous to the cue-reactivity experienced by abstaining drug addicts when presented with drug associated cues (Tiffany, 1990), and in dietary-restraining individuals (Green *et al.*, 2000).

Role of appetite regulating hormones in the control of reward-driven feeding

Hunger enhances attention to food-associated stimuli (Stockburger *et al.*, 2009). Exposure to palatable foods stimulates consummatory reflexes such as salivation, enhances reported hunger sensations and the desire for food in people (Hill *et al.*, 1984; Hardman *et al.*, 2014) and increases the release of dopamine in the dorsal striatum (Volkow *et al.*, 2002). Thus, reward-driven feeding behaviours and regulation of energy homeostasis are intrinsically linked. In the following sections the roles of peripheral (ghrelin, leptin) and central (orexin, MCH) signalling with respect to cue-induced stimulation of feeding behaviours will be discussed.

Both human and animal studies demonstrate that environments containing food-associated cues can generate eating in the absence of metabolic requirements. Homeostatic control of eating is co-ordinated by a network of appetite-controlling peptides that link peripheral (gastrointestinal) and central (neural) components of behaviour. The appetite-controlling system (Schwartz *et al.*, 2000) includes peripherally secreted hormones that stimulate feeding such as ghrelin, and the 'adipostat' hormones insulin and leptin, as well as centrally released orexigenic mediators NPY, orexins (hypocretins) and MCH. In the brain, the hypothalamus is thought to function as an energy sensing system interfacing with the reward-related mesocorticolimbic dopamine system via secretion of hypothalamic neuropeptides including orexins and NPY (Cone *et al.*, 2014). However, despite NPY's potent stimulatory effect on feeding (Hansen and Morris, 2002; Israel *et al.*, 2005; Kohno and Yada, 2012), NPY has no observed excitatory effect on midbrain dopamine neurons (Quarta and Smolders, 2014), and there is no evidence currently that food-associated cues modulate NPY release.

The interplay with mesolimbic reward-associated pathways and lateral hypothalamic (LH) regulation of energy homeostasis by endocrine feedback signals has not yet been widely investigated. However, cue-stimulated peptide release may have modulatory effects on the hedonic system. In particular, the neuropeptides MCH and orexin interact with mesolimbic dopamine transmission to promote phasic dopamine release during food consumption, and ghrelin-evoked stimulation of the VTA increases the motivation to procure food rewards (Patyal *et al.*, 2012; Cone *et al.*, 2014). Furthermore, leptin has been shown to interact with reward systems and influence drug seeking behaviour including craving induced through alcohol withdrawal (Kiefer *et al.*, 2001). This cue-stimulated peptide regulation of the activity of the mesolimbic dopamine pathway may represent a potential mechanism for regulating food craving and non-homeostatic feeding.

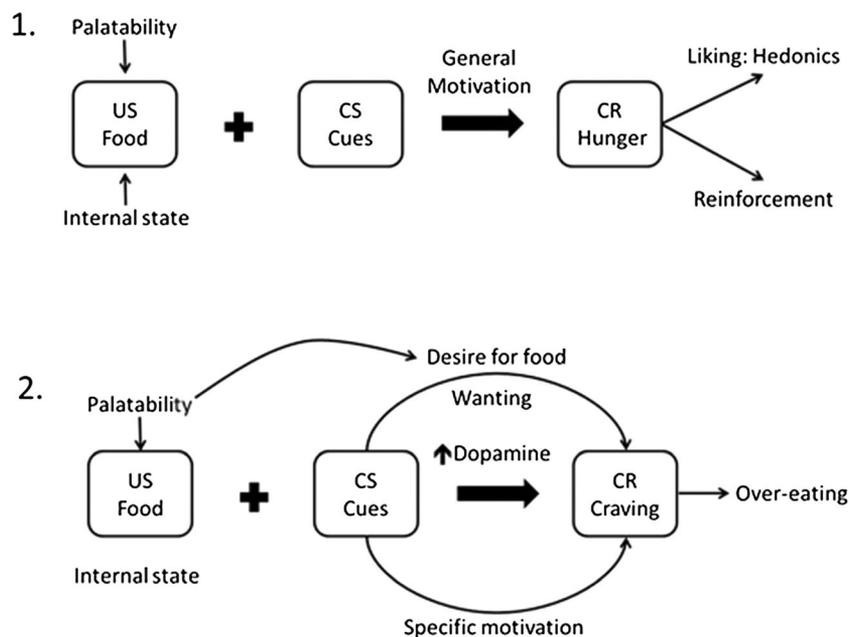


Figure 1

Development of cue-induced control of non-homeostatic feeding behaviour that may underpin over-eating based on incentive salience. 1. Food acts as an US due to its naturally reinforcing capacity. The internal rewarding properties of the food-reward are influenced by the palatability (hedonics) of the food and also by internal homeostatic state, which is modulated by levels of hunger and motivation to evoke a *general* motivated state. Pairings of food (US) with a conditioned stimulus (CS = external cue) leads to the stimulation of a conditioned response (CR), in this case hunger, which generates hedonic appraisal of the event and reinforcement. 2. Following repeated pairings with highly palatable and intrinsically rewarding foods, presentation of cues induce phasic dopamine release (Schultz, 1998a) that is capable of generating wanting for the food in the absence of internal homeostatic demands. Cues are therefore able to generate a specific motivational drive in the absence of homeostatic or metabolic demands. This motivational state induces cravings, which can promote food-seeking behaviours and over-eating that can lead to obesity.

Leptin signalling controls satiety and reward-driven feeding

Leptin, a hormone secreted by fat cells, suppresses food intake and promotes weight loss. Leptin is generally thought to control appetite by activation of receptors in the arcuate nucleus that inhibit release of orexigens such as NPY and agouti releasing peptide, while stimulating the release of anorexigens such as pro-opiomelanocortin. As obese individuals commonly exhibit increased serum levels of leptin, hyperphagia in obesity is attributed to insensitivity to circulating leptin and disruption of leptin signalling in the hypothalamus (El-Haschimi *et al.*, 2000; Munzberg *et al.*, 2004; Enriori *et al.*, 2007). Leptin also binds to specific leptin receptors on dopaminergic neurons in the VTA, inhibiting dopamine signalling in the NAc (Figlewicz *et al.*, 2003; Hommel *et al.*, 2006; Trinko *et al.*, 2011) and the central nucleus of the amygdala (Leshan *et al.*, 2010), providing a regulatory link between energy homeostasis and reward-related behaviour (Fulton *et al.*, 2006).

Although leptin acts as a satiety signal (Trinko *et al.*, 2011; Kanoski *et al.*, 2012), it has also been shown that intraventricular leptin reduces the self-administration of sucrose (Figlewicz *et al.*, 2003; Hommel *et al.*, 2006) and decreased the rewarding effects of drugs of abuse such as opioids (Lim *et al.*, 2014). Furthermore, intracerebral infusion of leptin has been found to attenuate the reward value of intracranial

self-stimulation in rats (Fulton *et al.*, 2000). However, leptin is not released in response to discrete cues associated with palatable foods, but may modulate cue-reactivity, providing a potential pharmacological mechanism to reduce cue-evoked food-seeking. Plasma leptin concentrations have been shown to positively correlate with reports of withdrawal-induced craving for alcohol in alcoholic subjects (Kiefer *et al.*, 2001) and nicotine in withdrawn tobacco smokers (von der Goltz *et al.*, 2010), strengthening the hypothesis that leptin interacts with mesolimbic reward pathways. Furthermore, leptin resistance in the VTA might be an important factor in the development of dietary induced obesity; high fat diet fed rats that became obese were less sensitive to the physiological effects of leptin in the VTA than high fat diet fed rats that were resistant to obesity (Bruijnzeel *et al.*, 2013). Thus, leptin resistance in the VTA could be a risk factor for uncontrolled eating, bingeing and food cravings that potentiate the development of obesity (Bruijnzeel *et al.*, 2013). A recent neuroimaging study demonstrated a significant positive correlation between plasma leptin concentration, BMI and the ventral striatal fMRI BOLD response during visual food cue presentations (Loeber *et al.*, 2012). However, this provides only correlational evidence to suggest food cue-reactivity may be associated with leptin, and increased leptin would typically promote satiety under physiological conditions.

Ghrelin signalling acts as an interface between physiological and reward signalling

Ghrelin is associated with the regulation of appetite and feeding behaviour; in particular, it acts as a hunger signal. Ghrelin is synthesized primarily in the gastrointestinal system and binds to growth hormone secretagogue receptors (GHSRs) that are expressed throughout the brain and also in adipose tissue (Zigman *et al.*, 2006). Systemic administration of ghrelin increases food intake and shifts preference toward diets rich in fat (Egecioglu *et al.*, 2010; Perello *et al.*, 2010). Recent research has demonstrated that ghrelin acts as a key interface between VTA dopamine signalling and physiological (hunger) signals emanating from the LH, provoking food-seeking behaviour (Cone *et al.*, 2014). Ghrelin controls motivation to eat via its interaction with the mesolimbic dopamine circuitry (Abizaid *et al.*, 2006; Overduin *et al.*, 2012), while leaving the hedonic value of the food eaten unaffected, as measured by analysis of licking microstructure (initial lick rates or lick-cluster size) (Overduin *et al.*, 2012). GHSRs are expressed throughout the midbrain dopamine system (Guan *et al.*, 1997; Zigman *et al.*, 2006). This suggests that ghrelin may have a role in reward regulation, perhaps via activation of a projection from the laterodorsal tegmental area onto the dopaminergic VTA neurons that project to the NAc (Naleid *et al.*, 2005), thereby affecting the reinforcing properties of both natural rewards and addictive drugs (Engel and Jerlhag, 2014).

Ghrelin mediates the ability of food-associated cues to evoke feeding behaviours, as blockade of ghrelin signalling through GHSRs by antagonist administration in mice disrupted cue-potentiated feeding behaviour (Walker *et al.*, 2012). Intriguingly, GHSR knock out mice exhibited cue-potentiated feeding, indicating that compensatory mechanisms may control motivated food-cue associations in the absence of ghrelin signalling (Walker *et al.*, 2012). Furthermore, both food-associated cues and the systemic administration of ghrelin activated dorso- and ventromedial hypothalamic nuclei in rats, evoking stereotypical locomotor hyperactivity defined as 'food anticipatory activity' (van der Plasse *et al.*, 2013), indicating recruitment of the same medial hypothalamic neuronal circuitry. Recently, it was demonstrated that following acquisition of a Pavlovian discrimination in which one cue predicted the delivery of rewarding food (CS+) and a second cue predicted nothing (CS-), infusion of ghrelin into the lateral ventricle augmented both phasic dopamine measured by voltammetry and phasic increases in the activity of NAc neurons measured by electrophysiology evoked by the presentation of the CS+, but not the CS- (Cone *et al.*, 2015). This indicates that centrally administered ghrelin is able to increase mesolimbic signalling evoked by motivationally significant stimuli (Cone *et al.*, 2014).

Orexinergic signalling modulates cue-driven food-seeking responses

Orexins are neuropeptides that stimulate feeding behaviours (Clegg *et al.*, 2002; Barson *et al.*, 2013) and underpin the performance of instrumental behaviours aimed at procurement of both food and drugs (Lawrence *et al.*, 2006; Harris *et al.*, 2007; Choi *et al.*, 2010; Mahler *et al.*, 2014). The lateral hypothalamic orexin/hypocretin system is therefore another candidate in the modulation of reward-based feeding behaviour (Kay *et al.*, 2014; Williams, 2014). There are two known forms of orexin –

orexin A and orexin B, and two known receptors, OX₁ and OX₂. The OX₁ receptor is predominantly involved in reward and feeding behaviours and orexin A has a high affinity for this receptor subtype.

Cue triggered reinstatement of reward seeking following extinction of responding involves activity of VTA dopamine neurons (Mahler and Aston-Jones, 2012b). This dopaminergic activity is modulated by simultaneous orexin and glutamate transmission in VTA to promote cue-triggered reinstatement of drug seeking (Mahler *et al.*, 2013). Orexin antagonists reduce cue-induced reinstatement of nicotine (Plaza-Zabala *et al.*, 2013), cocaine (Mahler *et al.*, 2013) and heroin seeking behaviours (Smith *et al.*, 2012) but not of ethanol seeking (Brown *et al.*, 2013). Effects of orexin antagonists on sucrose-seeking have been less clear; systemic OX₁ receptor antagonists prevent cue-induced sucrose seeking when rats are food deprived and therefore are highly motivated to procure food rewards, but had little effect on rats fed *ad libitum* (Cason *et al.*, 2013). Orexin A promotes motivation for salient reinforcers as antagonism of OX₁ receptors reduced responding when high levels of effort were required for seeking cocaine or high fat pellets in self-administration protocols as opposed to during a less effortful schedule (Borgland *et al.*, 2009).

Orexinergic activity in the LH is induced by a discrete cue associated with food delivery in the absence of food or physiological hunger (Reppucci *et al.*, 2012). This indicates that orexinergic neurons are activated by both hunger and cues that induce feeding in the absence of hunger. Orexin-secreting neurons in the LH project to the paraventricular nucleus of the thalamus (PVT). The PVT acts as a relay between LH controlled feeding behaviour and reward-related feeding controlled by the mesolimbic system (Kirouac *et al.*, 2005; Parsons *et al.*, 2007) and the striatum (Martin-Fardon and Boutrel, 2012). Cues associated with palatable food activate LH orexin neurons that project to the PVT inducing striatal NAc dopamine release and food-seeking behaviour (Choi *et al.*, 2010). The orexin system appears to drive compulsive consumption of a rewarding stimulus, and binge-like consumption (Alcaraz-Iborra and Cubero, 2015). Thus, taken together, the capacity of orexin to regulate the drive to procure food rewards suggests that the orexin system may be a novel target for suppression of feeding behaviour driven by reward-related cues.

Melanocortin hormone signalling and the control of cue-evoked food-seeking behaviour

Subsets of orexin neurons in the LH also secrete the neuropeptide MCH, which, like orexins, innervates a range of structures involved in feeding (Broberger *et al.*, 1998; Hanada *et al.*, 2000). Orexin and MCH both promote palatable food intake and their release is stimulated by food ingestion. However, the ingestive action of orexins and MCH occurs through different, albeit complementary effects on behaviour (Barson *et al.*, 2013; Nishimura *et al.*, 2014), with orexins promoting food-seeking and motivation to procure palatable foods, indicated by orexin neuron activity in anticipation of feeding (Mizushige *et al.*, 2006), and MCH release occurring once food intake has occurred, so promoting ongoing food intake (Petrovich *et al.*, 2012).

MCH is also capable of promoting food-seeking behaviours and appears to have a role in the control of reward-driven feeding. MCH secreting neurons located in the LH have input to

reward areas, including the NAc (Georgescu *et al.*, 2005; Sears *et al.*, 2010), where MCH is thought to modulate the rewarding aspects of feeding. By enhancing activity in the NAc, MCH neurons may play a unique role in enhancing the hedonic value of food, and by receiving inputs from the NAc, MCH neurons may participate in a self-reinforcing circuit that can support feeding (Saper *et al.*, 2002). MCH receptors are important in the motivation to perform food reinforced instrumental responses. However, the role of MCH receptors in cue-induced reinstatement of food-seeking following extinction is unclear (Nair *et al.*, 2009). MCH₁ receptor knock-out mice are able to acquire an appetitive Pavlovian discrimination, but showed no preference for responding on a novel nosepoke response for presentations of the cue paired with food rewards (Sherwood *et al.*, 2012). This impairment in conditioned reinforcement was also observed in mice treated with MCH₁ receptor antagonists before the same conditioned reinforcement test procedure (Sherwood *et al.*, 2012). These results suggest an important role for MCH in controlling behaviour based on the conditioned reinforcing value of a cue associated with a food reward. However, in a cue-potentiated feeding setting, very few MCH neurones in the LH showed cFos co-activation in comparison to orexin neurons, indicating that MCH signalling in the LH may not be activated by food-associated cues (Reppucci *et al.*, 2012).

Summary – Food cues can influence aspects of appetite-regulating peptide signalling

Food-associated cues exert powerful influences on ingestive behaviours; they elicit the desire to procure hedonically attractive foods, overpower homeostatic signals of satiety and

even generate hunger, leading to eating outside of basic physiological requirements and promoting over-consumption. Moreover, evidence indicates that eating in response to such cues leaves intact the eating that occurs in the animal's home cage (Petrovich *et al.*, 2007). However, it is not yet known whether acute responding to food cues can cause long-term over-eating and obesity. As shown in Figure 2, food-associated cues are capable of influencing dopaminergic reward neurocircuitry, and the hypothalamus acts as a critical relay centre to provide an interface between homeostatic signals and mesolimbic dopamine activity.

Appetite-regulating hormones as potential therapeutic strategies to reduce cue-related feeding

Environments containing food-associated cues can generate eating in the absence of metabolic requirements. Reducing this non-homeostatic, reward driven consumption may provide a novel therapeutic strategy for obesity. Neuroendocrine signals such as leptin, insulin, MCH, orexins and ghrelin are involved in hunger and satiety signalling as well as reward-related neurocircuitry including mesolimbic dopamine transmission. Neuroimaging studies have shown alterations in neuronal activation when food-associated cues are presented; these changes in neuronal activity correlate with observed levels of leptin and insulin due to increased energy intake, adipose deposits and obesity. Furthermore, Kroemer *et al.* (2013) reported that fasting ghrelin levels correlated positively with BOLD responses to food cues in the hypothalamus and midbrain reward

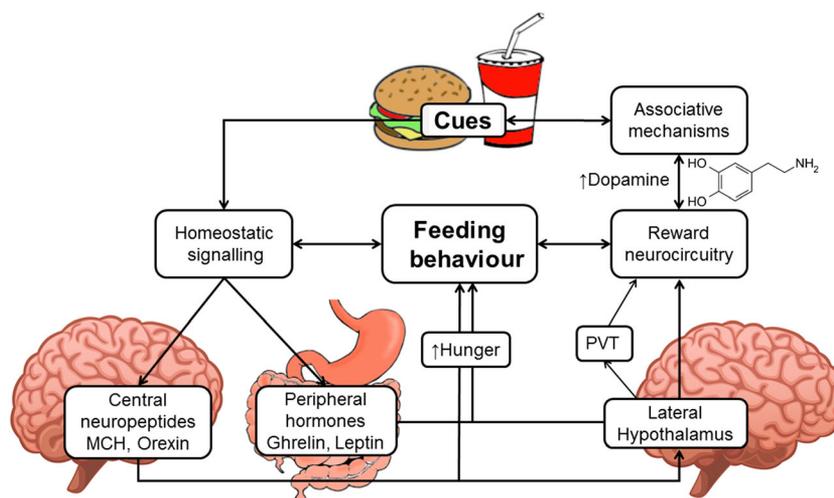


Figure 2

Food-associated cues evoke feeding behaviours via effects on both homeostatic appetite regulating signals and reward neurocircuitry. Palatable food-associated cues are assigned incentive salience and are capable of activating reward neurocircuitry (in particular, the mesolimbic dopamine system) leading to cravings and promotion of feeding behaviour in absence of metabolic demands. Appetite-regulating peptides including ghrelin, orexin and MCH are capable of promoting hunger and evoke feeding behaviour; leptin and insulin signal satiety, and these signals interface with reward neurocircuitry via the lateral hypothalamus and through specific receptors located in the VTA. Satiety promoting hormones leptin and insulin may promote abnormal responsiveness to food cues by enhancing learning about sources of palatable food following ingestion, via specific hippocampal receptors and these are also influenced by orexigenic peptides. However, obesity induces insensitivity to insulin and leptin and little evidence indicates their cue-conditioned anticipatory release. Food-associated cues therefore may be capable of influencing appetite promoting peptide signals that are able to interface with reward neurocircuitry.

associated areas. Ghrelin also correlated with reports of subjective appetite during presentation of food cues, suggesting that it may enhance subjective craving elicited by such cues (Kroemer *et al.*, 2013). The ensuing physiological and neural changes in obesity may therefore lead to a vicious cycle of high energy food consumption, augmenting weight gain and adiposity. The synergistic relationship between homeostatic hormonal signalling may further promote dysregulation of dopamine, increasing cue-reactivity. Furthermore, hypoactivity in inhibitory brain regions influencing top-down behavioural control (Stice *et al.*, 2008) may further promote craving via exposure to food-associated cues leading to a vicious cycle of unrestrained eating.

Studies that have investigated reductions in cue-evoked feeding using peptide and non-peptide antagonists have reported conflicting results, and differences in stability and tissue penetration may account for this discrepancy. Blockade of peripheral GHSRs is currently a pharmacological target for treatment of excessive adiposity in obesity, based on their involvement in regulating fat metabolism (Patterson *et al.*, 2011). Blockade of central GHSRs with non-peptide antagonists may also be useful in reducing reward-driven consumption by decreasing subjective craving when confronted with palatable food-associated cues. Preclinical trials have provided evidence that antagonism of GHSRs with orally administered Compound 26 (also known as LXG-9342) blocked cue potentiated feeding in satiated mice (Walker *et al.*, 2012), suggesting that GHSR antagonists may reduce this aspect of cue-evoked eating behaviours.

Antagonism of orexin signalling is currently being investigated as a potential therapeutic target for drug addiction. Orexin antagonists prevent cue-induced reinstatement of heroin seeking (Smith and Aston-Jones, 2012), and there is some evidence that the OX_1 receptor antagonist SB334867 attenuates cue-induced reinstatement of sucrose seeking in male rats (Cason and Aston-Jones, 2013). However, SB334867 failed to reduce cue-induced reinstatement of sucrose seeking in female rats, suggesting that food-seeking induced by cues engages the orexin system differentially in males and females, and sex-hormone signalling may further mediate cue-evoked food-seeking (Cason and Aston-Jones, 2014).

The peptide MCH_1 receptor antagonist PMC-3881-PI decreases conditioned responding to food-associated cues (Sherwood *et al.*, 2012), and systemic injections of the non-peptide MCH_1 receptor antagonist, GW803430, decreased cue-induced reinstatement of sucrose seeking in rats provided with free access to chow (Karlsson *et al.*, 2012). However, systemic injections of the non-peptide MCH_1 receptor antagonist SNAP 94847 reduced the motivation to lever presses for food pellets, but had no effect on cue induced reinstatement of high fat food-seeking following extinction of operant responding (Nair *et al.*, 2009). Thus, further studies should investigate the efficacy of different peptide and non-peptide antagonists as potential therapeutic strategies.

Conclusions

The manner by which food-associated cues stimulate seeking and eating food involves both reward driven and neuroendocrine mechanisms. From this standpoint, the interaction of

homeostatic and reward-related pathways in the regulation of feeding behaviours should be considered an integrated functional system, and therefore regulation of appetite mediating peptides may provide an alternative approach to the treatment of obesity. However, whether there are alterations in sensitivity between homeostatic mechanisms for sensing energy deficiencies in those who overeat and have become obese compared to those who eat to maintain energy homeostasis presents a significant obstacle to the treatment of obesity through pharmacological approaches. This question poses an additional level of complexity in the modulation of cue-induced eating behaviour as both underlying reward processing and homeostatic systems are altered in obesity. The satiety promoting peptide leptin also has important roles in feeding behaviour and reward driven behaviours. However, leptin resistance develops in obesity due to receptor insensitivity or down regulation. Thus treatment strategies focusing on leptin as a target have been less successful. From the research presented in this review, modulation of ghrelin, MCH and orexin signalling appears to be critically linked with cue-driven responsiveness of reward neurocircuitry and thus may provide a novel way of suppressing reward-driven feeding behaviours in responses to environmental cues. Interventions that target reward systems and appetite-regulating systems in combination may therefore prove more effective in the treatment of obesity and disordered eating by diminishing the impact of food-associated cues that can promote overconsumption.

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Conflict of interest

Authors declare that they have not any conflict of interest.

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