TOPICAL REVIEW

Gut peptide regulation of food intake – evidence for the modulation of hedonic feeding

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Abstract  The number of people living with obesity has tripled worldwide since 1975 with serious implications for public health, as obesity is linked to a significantly higher chance of early death from associated comorbidities (metabolic syndrome, type 2 diabetes, cardiovascular disease and cancer). As obesity is a consequence of food intake exceeding the demands of energy expenditure, efforts are being made to better understand the homeostatic and hedonic mechanisms governing food intake. Gastrointestinal peptides are secreted from enteroendocrine cells in response to nutrient and energy intake, and modulate food intake either via afferent nerves, including the vagus nerve, or directly within the central nervous system, predominantly gaining access at circumventricular organs. Enteroendocrine hormones modulate homeostatic control centres at hypothalamic nuclei and the doro-vagal complex. Additional roles of these peptides in modulating hedonic food intake and/or preference via the neural systems of reward are starting to be elucidated, with both peripheral and central peptide sources potentially contributing to central receptor activation. Pharmacological interventions and gastric bypass surgery for the treatment of type 2 diabetes and obesity elevate enteroendocrine hormone levels and also alter food preference. Hence, understanding of the hedonic mechanisms mediated by gut peptide action could advance development of potential therapeutic strategies for the treatment of obesity and its comorbidities.

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Abstract figure legend: The gastrointestinal tract produces a range of peptides that regulate appetite and body weight. Key peptides are highlighted here. These gut peptides are secreted from enteroendocrine cells in response to nutrient intake and communicate with the brain directly, via the bloodstream, and indirectly, via the vagus nerve, to alter food intake and reward signaling. Interactions between gut peptides and their receptors in the brainstem, hypothalamus and higher order nuclei lead to downstream neural network activation resulting in changes to appetitive and reward-related behaviour.

Introduction

The number of people living with obesity (body mass index (BMI) > 30 kg/m²) has tripled worldwide since 1975 (to 650 million in 2016), with serious implications for public health, as obesity is linked to a significantly higher chance of serious disease (metabolic syndrome, type 2 diabetes, cardiovascular disease and cancer) and early death (Whitlock et al. 2009; Rodgers et al. 2018). Whilst food availability and intake vary by region, average daily food intake has increased by ~500 kcal per day since the 1970s (Chan & Woo, 2010). Furthermore, our diet contains more energy dense foods, with a greater role for fat, saturated fat and sugars, alongside reduced intake of complex carbohydrates and dietary fibre and reduced fruit and vegetable intake (Chan & Woo, 2010). Changes in lifestyle – including reduced physical activity at work and home – only exacerbate the imbalance of caloric intake and energy expenditure resulting in excess fat accumulation and weight gain (Brock et al. 2009).

The rapidly increasing prevalence of obesity and the associated economic cost have prompted efforts to better understand the physiological control of food intake, key to which is the central nervous system (CNS). The CNS receives information from the periphery regarding energy
balance through metabolic, endocrine and neural signals. Integration of these signals by homeostatic and hedonic, or reward-related, pathways governing food intake results in behavioural changes, and can lead to chronic hyperphagia (Strader & Woods, 2005). Recently there has been increased interest in the communication between the gastrointestinal (GI) system and the CNS in the control of food intake, reward and subsequently body weight. Enteroendocrine cells (EECs) of the GI tract secrete peptides in response to nutrient and energy intake, and these communicate with the brain directly or via the vagus nerve (recently reviewed by Cork, 2018) and alter homeostatic and hedonic circuits.

In addition to a major role in food intake control, gut peptides have gained clinical importance in the treatment of type 2 diabetes and obesity. This is perhaps best exemplified by glucagon-like peptide-1 (GLP-1). GLP-1 receptor (GLP-1R) agonists, such as liraglutide, have been developed and approved for treatment of type 2 diabetes due to their insulinotropic action. However, their effect on food intake and body weight has fuelled interest and led to their approval for the treatment of obesity in non-diabetic patients. Liraglutide treatment is associated with weight loss of 5–10% after 1 year in non-diabetic obese patients and is FDA approved for patients with a BMI > 27 kg/m² and a weight-related comorbidity (O’Neil et al. 2018). Similarly, treatment of overweight or obese individuals with the GLP-1R agonist semaglutide results in drastic weight loss (−15.3 kg body weight change at week 68 compared with −2.6 kg in the placebo group; Wilding et al. 2021). Emerging new treatments targeting multiple gut hormone receptors, for example the combination of GLP-1R agonists with agents targeting the glucose-dependent insulinotropic peptide receptor (GIPR), appear to have even greater efficacy on weight loss (Frias et al. 2018).

It has now become clear that the effect of gut peptide receptor activation extants beyond simple homeostatic food intake control; hedonic mechanisms governing appetite are also modulated. In this review, we summarise current knowledge regarding the physiology of appetite of the GI system and explore the potential role of gut peptides in the neural systems of reward.

**Neuroendocrine regulation of food intake**

EECs, which make up <1% of the total gut epithelium, continuously monitor rates of nutrient absorption to maximise assimilation of nutrients (Furness et al. 2013; Gribble & Reimann, 2019). Approximately 12 different EEC subtypes have been identified, traditionally characterised by their hormonal and staining profiles; however, there is evidence of overlap in hormone expression between different cell types (Egerod et al. 2012; Habib et al. 2012). EECs vary in distribution along the GI tract, from the stomach to the rectum, reflecting the different stimuli and resulting physiological responses at each stage of the GI tract (Latorre et al. 2016). Ingested nutrient signals are mostly detected by G-protein-coupled receptors (GPCRs), transporters and ion channels on EECs in the proximal intestine, while more distally located EECs, which do not receive much direct stimulation from ingested foodstuffs, respond to a range of microbial products (Gribble & Reimann, 2019). In response to these stimuli, more than 20 peptide hormones are secreted which target sites including the CNS to indicate short term nutrient availability. Gut peptides are transported in the circulation and act directly on the brain via the circumventricular organs in the hypothalamus and hindbrain, with evidence that some gut peptides cross the blood–brain barrier (Kastin et al. 2002; Nonaka et al. 2003). Gut peptides also communicate with the brain via GPCRs on vagal afferent fibres which synapse in the nucleus of the solitary tract (NTS) and area postrema (AP) in the hindbrain dorsal vagal complex (DVC) (reviewed by Cork, 2018). Recently the importance of non-vagal, spinal afferent signalling for the detection of ingested glucose, either downstream of gut peptide secretion or by glucose sensors in the hepatic portal vein, has been described, resulting in downregulation of agouti-related peptide (AgRP) neuron activity in the arcuate nucleus (ARC) of the hypothalamus (Goldstein et al. 2021). In addition, many gut peptides are also expressed as neuromodulators/neurotransmitters in the peripheral and central nervous system, either fairly widespread, as in the case of substance P and cholecystokinin, or restricted to relatively rare neuronal populations, such as the preproglucagon (PPG)-expressing neurons found in the NTS, which are the main source of central GLP-1 (Rehfeld, 2017; Holt et al. 2019).

The hypothalamus plays a pivotal role in the control of food intake (Hetherington & Ranson, 1983). The best-characterised hypothalamic regions involved in food intake are the lateral hypothalamus (LH), the ventromedial hypothalamus (VMH), the paraventricular hypothalamus (PVH) and the ARC (Anand & Brobeck, 1951; Cowley et al. 1999; Elmquist et al. 1999). Two distinct populations of neurons in the ARC have been intensely studied as they integrate peripheral cues, including gut peptides, detected due to the leaky blood–brain barrier in the adjacent median eminence. Proopiomelanocortin (POMC)-expressing neurons within the ARC inhibit food intake while neuropeptide Y (NPY)/AgRP co-expressing neurons stimulate food intake via projections to other hypothalamic nuclei and brain regions (Williams et al. 2001). Alongside the ability to sense gut peptides and pancreatic β-cell-derived insulin, thought to reflect recent
food intake and nutrient availability, these neurons are modulated by longer term signals of energy balance, such as adipocyte-derived leptin (Farooqi et al. 2007). While AgRP neurons can be classified as key players in the homeostatic modulation of food intake, evidence that they are at least transiently inhibited by the mere presentation of food, independent of actual consumption, challenges the exclusively homeostatic classification of these neurons (Chen et al. 2015).

The neural reward system

In addition to homeostatic signals, food intake is strongly influenced by memory, food cues and societal factors which promote consumption of palatable foods even when homeostatic requirements have been met (Kenny, 2011). This drive to consume food beyond homeostatic need is coordinated by the hedonic, or reward, system in the brain. It has been suggested that the reward system can be distinguished into two components, ‘liking’ and ‘wanting’, which are regulated by distinct but interwoven circuits. These circuits can be influenced simultaneously or independently by emotional and physiological states, societal norms and repeated food exposure (Robinson et al. 2016; Berthoud et al. 2017). Indeed, reward-related neurocircuitry is complex. Figure 1 highlights key brain regions involved in reward, motivation and food intake. Many of these regions project to, receive projections from, and/or overlap with hypothalamic and hindbrain regions involved in the homeostatic control of food intake.

The corticobulbar system is well established in the emotional, mnemonic and executive processing of food intake (Kelley et al. 2005). Bidirectional communication between the prefrontal cortex (PFC), hippocampus and amygdala is thought to play a role in encoding the reward value of food and in memory formation surrounding food experiences (Björntorp & Rosmond, 2000; la Fleur, 2006). Regions of the corticobulbar system also receive projections from the paraventricular thalamus (PVT), midbrain dopaminergic neurons, hypothalamus and parabrachial nucleus (PBN) and send predominantly glutamatergic projections to the striatum, hypothalamus and motor cortex (Kelley et al. 2005).

The mesolimbic pathway connects the midbrain ventral tegmental area (VTA) and substantia nigra pars compacta (SNc) with the striatum, corticobulbar system and hypothalamus via dopaminergic projections (Nair-Roberts et al. 2008; Ungless & Grace, 2012). This pathway is critical in encoding the incentive salience, or ‘wanting’, of food and conditioned responses to food cues (Salamone et al. 2003; Wise, 2006; Fields et al. 2007; Palmiter, 2007; Narayanan et al. 2010). The VTA is also implicated in food priming whereby synaptic density and excitatory synaptic transmission are increased following brief exposure to a highly palatable foodstuff leading to increased food seeking and consumption for days after the initial exposure (Liu et al. 2016).

The striatum, a key integration site for the reward system, can be broadly divided into the dorsal striatum (DS), comprising the caudate nucleus and putamen, and the ventral striatum (VS), comprising the nucleus accumbens (NAc) core/shell and olfactory tubercle. The dorsal and ventral striatum are distinguished by their anatomical location and distinct inputs and outputs (Sesack & Grace, 2010; Kupchik et al. 2015; Yager et al. 2015). The DS integrates glutamatergic inputs from the PFC, motor cortex and thalamus with dopaminergic inputs from the SNc and sends projections to the globus pallidus of the basal ganglia (Gerfen & Surmeier, 2011). The NAc of the VS integrates glutamatergic inputs from the PFC, hippocampus, amygdala and PVT with dopaminergic inputs from the VTA and hypothalamic inputs, and sends projections to the ventral pallidum (VP), hypothalamus and VTA (Bocklisch et al. 2013; Kupchik et al. 2015; O’Connor et al. 2015). These striatal circuits upon activation or inhibition determine the hedonic value of food and coordinate motivated behavioural responses, with subregions of the NAc and VP, termed ‘hedonic hotspots’, thought to specifically generate ‘liking’ of foods (Söderpalm & Berridge, 2000; Farooqi et al. 2007; Malik et al. 2008; Berridge et al. 2010).

As well as being pivotal in the homeostatic control of food intake, the hypothalamus is a key node in the hedonic circuit. The LH receives inputs from reward-related regions including the PFC, basolateral amygdala, NAc and bed nucleus of the stria terminalis (BNST) (Stuber & Wise, 2016). Projections to the central amygdala (CeA), VTA, PVT and lateral habenula support the classification of the LH as a reward centre (Borgland et al. 2008; Cádiz-Moretti et al. 2017). The LH neurocircuitry alongside studies in rodents suggest the LH integrates homeostatic and hedonic cues to coordinate reward-seeking and motivated behaviour (Harris et al. 2005; Cason & Aston-Jones, 2013). Research demonstrating projections from ARC POMC neurons to the VTA and NAc of the mesolimbic system suggests the ARC is also involved in linking homeostatic cues to reward circuitry (King & Hentges, 2011; Lim et al. 2012). This is further supported by the increase in NAc dopamine levels following α-melanocyte-stimulating hormone (α-MSH) microinjection into the VTA (Lindblom et al. 2001).

Recent research has demonstrated that the neural reward system is influenced by the gut. However, the exact mechanisms by which this occurs are poorly understood. Here we provide a summary of the prominent enteroendocrine hormones (from proximal to distal GI
Gut peptides and the reward system

Ghrelin. Ghrelin, a 28 amino acid peptide, is predominantly found in the stomach, and stimulates food intake via sites including orexigenic NPY- and AgRP-expressing neurons, which co-express the ghrelin receptor (growth hormone secretagogue receptor, GHSR) (Tschöp et al. 2000; Nakazato et al. 2001; Cowley et al. 2003). Secretion of ghrelin is modulated by feeding; plasma ghrelin increases during fasting and surges preprandially, with a drop within 1 h postprandially. These prandial changes in plasma ghrelin are associated with...
changes in hunger score (Cummings et al. 2002, 2004). In addition to its role in short term energy balance, ghrelin circulates in relation to long term energy stores with evidence that its levels correlate inversely with measures of adiposity and are modulated by changes in body weight (Cummings, 2006). Ghrelin also alters glucose metabolism, gut motility and gastric acid secretion, thermogenesis, sleep, stress and anxiety, muscle atrophy, and cardiovascular function (Masuda et al. 2000; Tolle et al. 2002; Date et al. 2002b; Weikel et al. 2003; Yasuda et al. 2003; Lutter et al. 2008; Reed et al. 2008; Chuang et al. 2011; Porporato et al. 2013; Rizzo et al. 2013). Furthermore, ghrelin modulates taste sensation and reward-seeking behaviour (Druce et al. 2005; Jerlhag et al. 2007; Overduin et al. 2012; Skibicka et al. 2012b; Cai et al. 2013).

Ghrelin engages reward pathways including the mesolimbic, dopaminergic pathway. Administered to the VTA or the NAc, ghrelin increases food intake via increased dopamine (Naleid et al. 2005; Jerlhag et al. 2007; Skibicka et al. 2012a). As a result, ghrelin increases an animal’s willingness to work for food by increasing motivation, arousal and foraging, in addition to activity that occurs during food anticipation. For example, in sated rats, intra-VTA infusion of ghrelin significantly increased intake of a high fat diet (HFD), with subsequent body weight gain. Interestingly, in food-deprived rats, ghrelin’s potency to increase HFD intake and subsequent body weight was maintained. These orexigenic effects were attenuated by administration of the ghrelin receptor antagonist d-Lys3-GHRP-6 (d-Lys3) into the VTA (Wei et al. 2015). d-Lys3 was subsequently shown to impair the initiation of cue-potentiated feeding (Dailey et al. 2016). The rewarding effect of ghrelin also extends to alcohol (and other substances of abuse), a consequence of GHSR stimulation in the VTA. This effect was shown to require intact signalling at the dopamine receptors, D1R and D2R, within the NAc (Skibicka et al. 2012a).

In rats offered a choice of palatable foods (sucrose pellets and lar, with standard chow), acute intra-cerebroventricular (i.c.v.) or intra-VTA ghrelin injections increased chow intake of rats with a high baseline intake of lar – a similar result was produced when animals were fasted overnight, when endogenous levels of ghrelin are elevated. These effects were suppressed in ghrelin receptor antagonist-treated rats and ghrelin receptor knock-out (KO, GHSR−/−) mice (Schéle et al. 2016). In rats, the effects of ghrelin on food motivation are not limited to palatable foods but extend to standard chow following i.c.v. ghrelin or an overnight fast (Bake et al. 2019). Furthermore, intra-VTA ghrelin enhances responses to palatable food pellets even after a period of extinction (during which time lever pressing has no programmed consequence – in this case delivery of reward) suggesting that ghrelin signalling facilitates relapse to preferred/palatable foods (St-Onge et al. 2016). However, whilst i.c.v. infusion of ghrelin in rats was shown to increase motivation for food (tested using 5% sucrose), the hedonic value of food, assessed by initial lickometer rates and lick-cluster size, was not altered in this nuanced study (Overduin et al. 2012).

High fat feeding (for 12 weeks) has been shown to induce ghrelin resistance in the hypothalamus, specifically in NPY/AgRP neuronal populations in mice; this resistance occurs after 3 weeks of exposure to a HFD, and is reversed by weight loss (Briggs et al. 2010, 2013, 2014). A HFD, however, does not affect the ability of ghrelin to increase food intake when administered via intra-VTA infusion. In addition, ghrelin signalling increases motivation for HFD in an operant conditioning progressive ratio schedule, a measure of an animal’s willingness to seek a reward (Perello et al. 2010). It was subsequently shown that GHSR signalling is required for the escalation of HFD consumption observed during successive binge eating events (Valdivia et al. 2015). In a palatable scheduled feeding paradigm, in which chow-fed animals are entrained to the appearance of a HFD (offered for a limited 2 h period), acute i.c.v. ghrelin-treated animals consumed more chow, whilst chronic treatment enhanced binge-like behaviour (Bake et al. 2017). However, in the absence of food in a conditioned placed preference test, treatment with ghrelin induced aversion (Lockie et al. 2015). It was subsequently shown that i.c.v. infusion of ghrelin produces conditioned avoidance in both conditioned place preference and avoidance tests and in a conditioned flavour preference/avoidance test (Schéle et al. 2017). It thus appears that central ghrelin results in a non-pleasurable sensation, when behavioural alteration, such as increased feeding, is prohibited.

Mouse preference for sweet food (and place preference) is reduced by genetic or pharmacological blockade of ghrelin signalling (Disse et al. 2010; Egecioglu et al. 2010). Mice adapted to intermittent (3 days per week) or daily access to HFD for 2 h, alongside 24 h ad libitum standard chow, do not differ in 2 h HFD consumption. However, GHSR−/− mice had attenuated HFD consumption regardless of access condition; this was associated with reduced activation of the NAc shell but not core following HFD consumption (King et al. 2016). In prairie voles, the GHS-R1A antagonist JMV2959 was shown to reduce preference for 2% sucrose (without effect at higher sucrose concentrations) (Stevenson et al. 2016).

The ghrelin receptor is also expressed in the LH, and administration of ghrelin to the rat LH increased food intake and motivated behaviour for sucrose in both males and females. In females only, however, ghrelin increased food-seeking behaviour and body weight gain while blockade of LH GHSR reduced food intake, sucrose-seeking behaviour and body weight.
(López-Ferreras et al. 2017). More recently, ghrelin was shown to act in the ventral hippocampus to increase meal size via downstream orexin receptor signalling in the laterodorsal tegmental nucleus (Suarez et al. 2020). In ad libitum-fed rats, intra-amygdala administration of ghrelin produced an orexigenic response and in fasted rats receiving intra-amygdala antagonists of the ghrelin receptor, food intake was reduced (Alvarez-Crespo et al. 2012). Recently, intra-lateral parabrachial nucleus (LPBN) ghrelin was shown to increase intake of standard chow in rats but not lard or sucrose and did not affect the progressive ratio for sucrose or conditioned place preference for chocolate, suggesting that the ghrelin LPBN circuit influences consummatory but not appetite behaviours (Bake et al. 2020). Evidently, ghrelin interacts with multiple reward-related brain regions to influence food intake, but the effects of ghrelin extend beyond the motivation to consume sweet calorific food. In a single bottle test, peripheral ghrelin increased the consumption of saccharin, independently of the availability of food. Under a free choice preference paradigm in which mice could choose between two non-caloric foods, one of which was flavoured with saccharin, increased saccharin consumption was absent in GHSR1a−/− animals (Disse et al. 2010).

In addition to its direct effect on the brain, ghrelin may also act via the vagal afferents. Blockade of vagal afferents attenuated ghrelin’s effect on food intake (Date et al. 2002a). This, however, is controversial, as other studies have reported that vagal afferents are not required for the actions of ghrelin in the rat (Arnold et al. 2006). Ghrelin analogues retain their effect in patients with gastrectomy/vagotomy suggesting that the vagus is not essential for ghrelin’s orexigenic effect (Dornonville de la Cour et al. 2005; Adachi et al. 2010).

In humans, a functional magnetic resonance imaging study in healthy participants demonstrated that fasting sensitized the striatal reward system (as measured by blood oxygen level dependent activity) to the anticipation of food. Furthermore, in the satiated state, circulating ghrelin was associated with increased neural processing during the period in which food was expected. This suggests that ghrelin signalling impacts hedonic food intake (Simon et al. 2017).

In summary, administration of ghrelin or GHSR antagonists i.c.v. or directly into reward-related regions influences food intake/preference and the motivation to consume food rewards in rodent models. There is also evidence that ghrelin and GHSR signalling are involved in binge eating-like behaviour. i.c.v. ghrelin administration results in conditioned avoidance suggesting that central ghrelin induces a non-pleasurable or negative emotional state while circulating ghrelin appears to increase the neural response to food anticipation. Collectively, the highlighted studies suggest ghrelin’s role in hunger and therefore meal initiation may extend to reward-driven behaviour/motivation.

Cholecystokinin. Produced by enteroendocrine I-cells and the CNS, cholecystokinin (CCK) is a gut satiating peptide that is released postprandially in response to ingestion of fat (both saturated and long chain fatty acids), small peptides and amino acids (Lieverse et al. 1994a). Fasting results in a reduction in plasma CCK, whilst peripheral administration before the onset of a meal dose-dependently reduces meal size in rodents and humans; it is therefore considered a short-term satiety signal (Antin et al. 1975; Kissileff et al. 1981; Lieverse et al. 1994b). This anorexigenic effect is mediated by CCK1 receptors on vagal afferent fibres – vagotomy and vagal deafferentation attenuate the effects of peripheral CCK infusion (Smith et al. 1981; Moran et al. 1997). CCK1 receptors are also located in the hypothalamus and hindbrain; microinjection of CCK into the hypothalamus decreases food intake whilst lesions of the AP attenuate the satiating effect of CCK (Edwards et al. 1986; Blevins et al. 2000). Furthermore, intra-cerebral infusion of CCK was shown to decrease food intake (Konkle et al. 2000). This may involve complex cross talk and integration of different neurons, as CCK indirectly (through noradrenergic neurons) increases electrical activity of hindbrain PPG neurons, which project to mesolimbic reward centres (Hisadome et al. 2011; Trapp & Cork, 2015). CCK has also been implicated in thermoregulation, sexual behaviour, anxiety and memory (Shian & Lin, 1985; Dornan et al. 1989; van Megen et al. 1996; Huston et al. 1998).

Peripheral administration of CCK reduces operant responses for Noyes pellets in rats (Hisiao & Deupree, 1983; Babcock et al. 1985). Microinjections of CCK into the NAc attenuated VTA intracranial self-stimulation (ICSS – in which rodents self-administer rewarding electrical stimulation via electrodes implanted in the CNS) suggesting that CCK attenuates reward signalling derived from the VTA (Vaccarino & Koob, 1984). Infusion of proglumide, a CCK receptor antagonist, into the caudal (but not rostral) NAc reduced ICSS (Vaccarino & Vaccarino, 1989). Similarly, ipsilateral electrical stimulation of the medial PFC results in elevated local CCK, in addition to glutamate and dopamine. In rats trained to lever press for stimulation, local CCK production correlated with rewarding efficacy, suggesting that it may modulate reward behaviour (You et al. 1998). CCK administration to the anterior cerebral ventricles of the rat reduces motivation for food, as measured by running speed towards a food-based reward (Zhang et al. 1986). It was previously shown that CCK reduced feeding via aversion and not satiety – an effect which was comparable to the nauseating toxin lithium chloride (Ettenberg & Koob, 1984). CCK was subsequently shown
to block the acquisition of conditioned place preference associated with morphine treatment with high doses of CCK suppressing locomotor activity (Wen et al. 2012).

Pharmacological blockade of CCK2 receptors with the antagonist L-365,260 potentiated the food reward response of animals to NAc amphetamine but produced no effect in control animals suggesting that CCK2 may inhibit potentiated reward-related behaviours (Josselyn & Vaccarino, 1995). This finding was supported by a subsequent study utilising the CCK2 receptor antagonist PD-135158, which also potentiated the amphetamine response (Josselyn et al. 1996b). Interestingly, devazepide, a CCK1 receptor antagonist, blocked the development of conditioned reward. This was not a consequence of taste aversion, nor did it decrease food consumption; rather, it affects incentive learning (Josselyn et al. 1996a). This was supported by a subsequent study in which CCK1 receptor antagonism was shown to attenuate the development of conditioned place preference in response to treatment with morphine, whereas this was not true of CCK2 receptor antagonism (Josselyn & Vaccarino, 1996). Interestingly, neither antagonist changed the effects of morphine on gastro-intestinal motility (Singh et al. 1996).

CCK1 receptor antagonism was also shown to reduce ethanol intake in rats, whilst CCK2 receptor antagonism reduced cocaine consumption (Crespi, 1998). It is also notable that CCK, via its receptor subtypes, also modulates anxiety-related behaviours (reviewed in Bowers et al. 2012).

To summarise, peripheral and central CCK injections attenuate reward-related signalling and motivation for food as measured by operant conditioning and ICSS tests. CCK2 receptor antagonists potentiate food reward responses while CCK1 receptor antagonists attenuate conditioned responses to rewards. Together, this suggests CCK and its receptors play a role in modulating reward-related behaviours.

Glucose-dependent insulino tropic polypeptide. Glucose-dependent insulino tropic polypeptide (GIP), a 42 amino acid peptide hormone, is secreted from enteroendocrine K cells in the duodenum and proximal jejunum in response to nutrients (Buchan et al. 1978). Historically GIP, a known regulator of glucose tolerance, had been thought to play only a minor role in food intake regulation, based on the following observations. Daily peripheral treatment with the GLP-1R agonist exendin-4 (Ex4) and the GIPR agonist N-AcGIP was shown to reduce body weight, a consequence of reduced food intake which was not potentiated by N-AcGIP (Irwin et al. 2009a). Chronic treatment of mice with age-related glucose intolerance with longer-acting forms of GIP, via PEGylation (attachment of polyethylene glycol to increase solubility, decrease immunogenicity and increase stability/reduce proteolysis), was demonstrated to have no effect on food intake and body weight, whilst reducing non-fasting glucose and increasing insulin concentrations (Kerr et al. 2009). Aged GIPR−/− mice were shown to have reduced fat mass, without a reduction in food intake (Yamada et al. 2007). Active immunisation against GIP in leptin-deficient ob/ob mice had previously been shown to increase glycaemic excursion, without altering food intake or body weight (Irwin et al. 2009a). In addition, chronic treatment with enzymatically stable forms of GIP (1–30 and 1–42) had no effect on food intake or body weight in HFD mice, whilst lowering non-fasting glucose levels and increasing insulin levels and improving glycaemic response in an intraperitoneal glucose tolerance test (Gault et al. 2011).

More recently i.c.v. infusion of GLP-1 and GIP reduced food intake and body weight in mice – subeffective doses were used in combination and recapitulated this phenotype. This was associated with increased neuronal activation and POMC expression in the ARC (NamKoong et al. 2017). Peptide-based GIP analogues were also shown to reduce feeding and body weight in diet-induced obese (DIO) mice with weight loss maintained in GLP-1R−/− mice (Mroz et al. 2019). Tirzepatide, a dual GLP-1R and GIPR agonist, was found to reduce food intake and body weight to a greater degree than the GLP-1R-only agonist liraglutide in both humans and mouse models (Coskun et al. 2018; Frias et al. 2018), and another GLP-1/GIP receptor dual agonist reduced food intake and body weight in HFD mice (Wu et al. 2020). A GLP-1/GIP/glucagon receptor triagonist also reduced food intake and body weight in DIO and db/db mice (Cui et al. 2020). The triple agonist approach was previously shown to reduce food intake, body weight and fat mass in HFD mice, improving dyslipidaemia and reversing diet-induced steatohepatitis (the latter to a greater extent in female versus male mice) (Jall et al. 2017). To address the potential mechanism underlying these findings, we mapped central GIPR expression in the CNS using a novel GIPR-Cre mouse, demonstrating GIPR promoter-driven expression in the hypothalamus and hindbrain DVC, well established centres of food intake regulation. Chemogenetic activation of hypothalamic GIPR-expressing cells reduced food intake (Adriaenssens et al. 2019). A recent study further demonstrated the importance of central GIPR for food intake regulation, demonstrating that nestin-Cre-mediated GIPR deletion in the CNS attenuated food intake and body weight reduction in response to a peripherally administered GIPR agonist, implicating neuronal activation in the ARC and the VMH (Zhang et al. 2021).

However, it has been demonstrated that, somewhat counterintuitive to these observations, reducing GIPR signalling can reduce body weight. GIPR−/− mice fed a HFD are protected from obesity and insulin resistance.
even on the hyperphagic leptin-deficient ob/ob background (Miyawaki et al. 2002). Alternatively, a reduction in the number of K cells, and therefore the panel of peptides they produce, via GIP promoter-driven expression of diphtheria toxin A chain, reduced daily food intake and body weight, and increased energy expenditure, in HFD mice – whilst glucose homeostasis was not affected (Althage et al. 2008). Daily treatment of mice with a stable GIPR partial agonist/antagonist, (Pro3)GIP, had no effect on food intake and body weight (glucose tolerance was impaired, showing effectiveness of the drug treatment), and feeding post-18 h fast was unaffected by treatment with this GIPR antagonist (Irwin et al. 2007b). However, other GIPR antagonists do reduce weight in experimental models including non-human primates (reviewed in Holst & Rosenkilde, 2020). Mice treated with a GIPR antagonistic antibody (muGIPR-Ab) demonstrate reduced food intake and body weight gain. These results were replicated in obese non-human primates; the weight loss here was more profound than in mice and in both species the weight loss was potentiated in animals treated with a GLP-1R agonist (Killion et al. 2018). Central administration of a different GIPR blocking antibody in DIO mice was shown to reduce adiposity and body weight, via a reduction in food intake (these effects were not apparent in normal chow-fed, lean mice) (Kaneko et al. 2019) and, in this study, did not notably synergise with concomitant GLP-1R activation. Whilst Kaneko et al. (2019) propose a GIPR-dependent leptin resistance in the ARC to underlie their findings, the mechanism of how GIPR activation or inhibition might result in body weight loss remains controversial. Some studies indicate increased energy expenditure upon GIPR KO or antagonism to be the critical protection from diet-induced obesity (Gault et al. 2007; McClean et al. 2007; Irwin et al. 2007a, 2008), but this effect was not apparent in ob/ob animals (Irwin et al. 2009b). In contrast, in the ovariectomized (OVX) mouse model of obesity, GIPR−/− mice showed significantly reduced cumulative food intake associated with lower hypothalamic mRNA expression of NPY (Isken et al. 2008).

It should be noted that no study has been able to demonstrate increased food intake or even increased body weight gain in response to GIPR agonists. The notion that GIPR activation might promote weight gain is thus based on the reduction of weight gain seen when GIPR signalling is blocked. Recently it has been demonstrated that similar results can be achieved when GLP-1R signalling is blocked with a GLP-1R-blocking antibody (Svendsen et al. 2020). Given the proven anorexic activity of GLP-1RA, no-one would conclude from this finding that GLP-1R signalling is in any way orexigenic or obesogenic. Weak anorexigenic effects of GIPR agonism and stronger effects of GLP-1R/GIPR co-agonists thus remain important new treatment opportunities and the importance of different central GIPR-expressing nuclei is currently a hotspot of research, but no clear link to hedonic feeding regulation has yet emerged. In addition, in contrast to GLP-1, for which there is a well characterised central source, no convincing GIPR-expressing central cell population has so far been identified.

In a recent publication the effects of GIP, GLP-1 and the combined incretins on food intake, appetite and energy expenditure were assessed in overweight/obese men. Whilst GLP-1 infusion lowered energy intake, GIP infusion had no effect on intake, whereas simultaneous GLP-1/GIP infusion did not potentiate the GLP-1 effect (Bergmann et al. 2019). Intravenous (i.v.) GIP infusion in healthy males did not alter gastric emptying, energy intake, energy expenditure, removal of triacylglycerides or free fatty acids and did not affect hunger, satiety, fullness or food consumption versus saline, but did increase insulin (versus saline-treated control individuals) (Asmar et al. 2010). A similar study, but in obese individuals with type 2 diabetes, demonstrated that GIP infusion increased hunger scores, but ad libitum energy intake post infusion was unchanged (Daousi et al. 2009).

In short, GIP analogues reduce food intake and body weight in rodent models and clinical trials both alone and in combination with other gut peptide analogues. Conversely, GIPR antagonists also reduce food intake and body weight, and hence the role of GIP in body weight regulation continues to be debated. Involvement of GIP and GIPR signalling in reward-related feeding is yet to be deciphered.

Glucagon-like peptide-1. GLP-1, derived from preprotglucagon and produced by intestinal L cells in response to food ingestion, has a key role in glucose homeostasis (Eiselle et al. 1992). Its incretin action (to induce glucose-dependent insulin release) has led to the development of GLP-1R agonists, utilised in the clinic to treat type 2 diabetes and obesity. The anorexigenic effect of GLP-1R agonism is well established in animal models and clinical studies in healthy and type 2 diabetic individuals (Finnan et al. 2013; Ten Kulve et al. 2016).

The obesogenic environment is often ignored in animal studies. In one elegant study, the effects of Ex4 on food intake were attenuated in mice fed a cafeteria diet (animals are offered the choice of foodstuffs high in energy/fat/sugar, alongside a standard lab chow and HFD, and choose which to consume) (Sclafani & Springer, 1976; Mella et al. 2017). Previously, the conditioned place preference associated with a palatable food was reduced in rats treated with Ex4, without malaise or locomotor impairment. In satiated rats offered a choice between standard chow and a HFD, Ex4 reduced consumption of the more palatable HFD (Alhadeff et al. 2012). In a conditioned place preference for chocolate, the cafeteria
diet blocked the effect of Ex4 (Mella et al. 2017). This may have long term consequences for the use of GLP-1R agonists in the treatment of obesity. Semaglutide, a GLP-1 analogue, was recently shown to suppress food intake and reduce body weight in DIO mice and rats. Furthermore, semaglutide was shown to reduce energy intake in DIO rats offered standard chow and chocolate in parallel; this decrease was driven by a reduction in chocolate intake (Gabery et al. 2020). Whilst the mechanism for this is unclear, previous data suggest the involvement of dopamine release. Given that semaglutide has been demonstrated to enable drastic weight loss in overweight or obese humans (Wilding et al. 2021), a greater understanding of how this analogue, and GLP-1R signalling more widely, influences food intake and body weight is required. The mesolimbic regions of the brain (such as the VTA, NAc, lateral septum (LS) and PVT) also express GLP-1R and receive projections from PPG neurons in the NTS. Initial experimentation demonstrated that peripheral administration of Ex4 increases c-Fos, a marker of neuronal activation, in the NAc and direct activation of NAc GLP-1R reduces food intake – it was concluded, however, that this was a consequence of aversion or malaise. In addition, the effect was specific to the NAc core; no effect was observed when the NAc shell was targeted (Dossat et al. 2011). Ex4 delivered to the NAc core decreased operant responding for sucrose under an operant conditioning progressive ratio schedule (Dickson et al. 2012). Fast-scan cyclic voltammetry demonstrated that central infusion of Ex4 suppressed dopamine signalling/release in the NAc core. GLP-1-based therapies, therefore, may reduce the reinforcing properties of rewarding pathways if the right region of the CNS is targeted (Fortin & Roitman, 2017). μ-Opioid receptor activation in the NAc increases the consumption of a sweetened fat diet in rats – treatment with Ex4 attenuated this effect, while GLP-1R antagonism with exendin-9 (Ex9) altered μ-opioid receptor agonist-induced binge-like feeding, extending feeding bouts and therefore increasing food consumption (Pierce-Messick & Pratt, 2020). Interestingly, Ex4 decreased food intake when infused into the NAc core and shell in female rats (Abtahi et al. 2018). Similarly, Ex4 administration into the NAc shell blocks alcohol-induced locomotor stimulation and reduces overall alcohol intake (Vallőf et al. 2019a). Furthermore, pre-treatment with Ex4, either by intraperitoneal (i.p.) injection or via intra-VTA infusion, attenuated the increased operant responding for food reward induced by ghrelin (Howell et al. 2019). In addition, mice receiving a GLP-1 analogue demonstrate a reduction in motivation to lever press for a high fat, high sugar reward. This behaviour was further suppressed when mice were treated with an equimolar dose of a GLP-1–dexamethasone conjugate. The effect was associated with transcriptional changes of dopaminergic markers in the NAc, whilst repeated treatment with the conjugate reduced body weight (Décarie-Spain et al. 2019). The LS also contains a high density of GLP-1R; intra-LS administration of GLP-1 reduces food intake in ad libitum-fed mice, while reducing operant responding for sucrose pellets in food restricted mice (Terrill et al. 2019). Similarly, intra-VTA infusion of Ex4 reduces HFD intake in rats by reducing meal size and increasing tyrosine hydroxylase levels in the VTA suggesting a modulation of dopaminergic signalling in this region (Mietlicki-Baase et al. 2013). Intra-VTA infusion of Ex4, in addition to peripheral treatment, also reduces cocaine self-administration in rats (Schmidt et al. 2016; Hernandez et al. 2018). Whilst central infusion of GLP-1 into the BNST reduced chow intake in the dark phase, patch-clamp experiments demonstrated BNST-GLP-1R neurons underwent depolarizing or hyperpolarizing responses following GLP-1 treatment (Williams et al. 2018).

Liraglutide was recently shown to suppress responses to sucrose in trials in which an inhibitory stimulus was also present; this favours the hypothesis that GLP-1 signalling pathways suppress appetitive stimulus by enhancing hippocampus-dependent learned inhibition (Jones et al. 2019). Administration of Ex4 into the lateral ventricle was subsequently shown to suppress the magnitude of cue-evoked dopaminergic activity and sucrose consumption (Konanur et al. 2020). Central (lateral ventricle) injection of Ex4 has been shown to suppress reward behaviour in an operant conditioning progressive ratio task; the effects of Ex4 on food reward, but not intake, were attenuated by pretreatment with an oestrogen receptor antagonist (Richard et al. 2016). Expression of GLP-1R was subsequently shown in the supramammillary nucleus, where infusion of Ex4 reduced ad libitum standard chow, fat and sugar intake in both sexes, and reduced motivated behaviours in male but not female rats, measured via sucrose operant conditioning (López-Ferreras et al. 2019). Previously, a GLP-1–oestrogen conjugate had been shown to reduce food reward, intake and body weight in rats via this nucleus (Vogel et al. 2016). Similarly, motivation for food, as assessed by an operant conditioning progressive ratio schedule for sucrose, was reduced by activation of GLP-1R neurons in the LH, as was food intake and body weight (López-Ferreras et al. 2018, 2019). In addition, agonism of PVT GLP-1R reduced food intake, motivation and food seeking; PVT neurons receive GLP-1 innervation from NTS PPG neurons (Ong et al. 2017).

Treatment of animal models with lithium chloride (LiCl) results in an anorexigenic effect; this effect was attenuated in rats receiving GLP-1R antagonism i.c.v. (Rinaman, 1999). GLP-1, delivered to the lateral ventricle, was subsequently shown to produce a conditioned taste aversion in mice – this effect was absent in GLP-1R−/−
mice. However, GLP-1R antagonism did not block the aversive effects of LiCl in mice (Lachey et al. 2005). The anorexigenic effect of oxytocin was also lost when rats were pretreated with a GLP-1R antagonist suggesting that GLP-1R receptor signalling is an important downstream mediatary of anorexia in rats following oxytocin treatment (Rinaman & Rothe, 2002).

GLP-1 producing neurons project to the LPBN and GLP-1R stimulation of the LPBN reduces food intake (both chow and palatable food) and body weight in rats, associated with increased gene expression of calcitonin gene-related peptide and interleukin-6 (Richard et al. 2014). In addition, electrophysiological studies demonstrated that treatment with Ex4 increases the firing of LPBN neurons (Richard et al. 2014). GLP-1R activation in the LPBN also reduced motivation for food (measured via a progressive ratio schedule) (Alhadeff et al. 2014). Light sheet fluorescence microscopy subsequently demonstrated that liraglutide accessed the hypothalamus and brainstem and activated brain regions intersected by neuronal projections in the LPBN, whilst treatment with semaglutide induced c-Fos in this region (Salinas et al. 2018; Gabery et al. 2020).

Hindbrain infusion, via the fourth ventricle, of Ex4 reduced food intake and body weight, increased protein kinase a (PKA) and mitogen-activated protein kinase (MAPK) activity, and decreased phosphorylation of AMP-activated protein kinase (AMPK), while inhibition of PKA and MAPK (by RfcAMP and U0126) or stimulation of AMPK activity (by AICAR) attenuated the effects of Ex4 (Hayes et al. 2011). Microinjection of Ex4 into the medial NTS reduces intake of a HFD and operant responding for sucrose under a progressive ratio. The conditioned place preference associated with a palatable food is also reduced (Alhadeff et al. 2014). The lateral dorsal tegmental nucleus also expresses GLP-1R; direct activation reduces food intake independent of malaise and nausea (Reiner et al. 2018). Knockdown of GLP-1R in the NTS using a short hairpin RNA increased palatable food intake under fixed and progressive operant conditioning ratios, as well as increasing chow intake (via increased meal size) (Alhadeff et al. 2017). Similarly, knockdown of GLP-1R in the NTS attenuated the anorectic and body weight effect of liraglutide in acute and chronic studies; a chemogenetic strategy targeting a GABAergic population of neurons within the NTS which express GLP-1R replicated the effects (Fortin et al. 2020).

Ex4 infused into the NTS dose-dependently decreases alcohol intake in rats, whilst pharmacological blockade of GLP-1R in the NTS attenuates the alcohol-induced locomotor stimulation effect (Vallöf et al. 2019b). Interestingly, this effect extends to nicotine in mice (Tuesta et al. 2017). However, unlike CCK, Ex4 had no effect on morphine-induced conditioned placed preference suggesting that GLP-1 analogues would not be suitable for the treatment of opioid addiction (Bornebusch et al. 2019).

Higher fasting plasma GLP-1 concentrations are associated with lower carbohydrate and simple sugar intake in humans (with a BMI of 30.3 ± 9.5, without type 2 diabetes) (Basolo et al. 2019). Similarly, higher sugar intake is related to increased striatal response to food cues and decreased GLP-1 release following glucose intake in lean human volunteers (Dorton et al. 2017). Changes in olfactory function have also been noted in obese individuals with type 2 diabetes – these changes are reversed following treatment with GLP-1R agonists (Zhang et al. 2019). This suggests circulating GLP-1 influences food preference in humans, potentially through interacting with neural reward systems as described in animal models.

To summarise, GLP-1R is expressed in multiple reward-related brain regions. GLP-1 and GLP-1 analogues have been shown to reduce food intake, motivation to consume food rewards, and conditioned reward responses when administered peripherally, i.c.v. or via micro-injection into reward-related brain regions. Reduction in food intake and operant responses following Ex4 administration can be blocked by the consumption of a high fat, high sugar cafeteria-style diet. GLP-1 signalling may influence the reward system via changes to the dopaminergic pathway in the mesolimbic system.

Secretin. Secretin (SCT) is a 27 amino acid peptide secreted by the duodenum and the brain (Bayliss & Starling, 1902; Charlton et al. 1981). Its receptor (SCTR) is widely distributed throughout the CNS including in the hippocampus, hypothalamus and medulla (O'Donohue et al. 1981). SCTR−/− mice are protected against DIO and have impaired fatty acid absorption, which might, however, simply reflect defective exocrine pancreas function (Sekar & Chow, 2014). Several studies have implicated SCT in gastric emptying, social behaviour, spatial learning, water homeostasis, motor coordination and food intake (Charlton et al. 1983; Jin et al. 1994; Nishijima et al. 2006; Chu et al. 2011; Jukkola et al. 2011).

In sheep, peripheral treatment with SCT reduced food intake in the fed and fasted state (Anil & Forbes, 1980; Grovum, 1981). The effects of SCT on food intake in rats, however, are inconsistent, with at least one study suggesting this effect involves oxytocin neuron activation (Garlicki et al. 1990; Motojima et al. 2016). Peripheral and central treatment (via i.c.v. infusion) with SCT reduced food intake in fasted mice, an effect dependent on the SCTR (Cheng et al. 2011). Treatment with SCT increased Mc4r, Trh and Pomc gene expression in the hypothalamus and the ability of SCT to reduce food intake was attenuated by pre-treatment with a...
melanocortin-4-receptor antagonist (Cheng et al. 2011). This was not a consequence of aversion or malaise. Interestingly, i.v. infusion of SCT also increased plasma leptin (Sobhani et al. 2000). Fos-immunoreactivity was detected in the NTS, AP and DVC following i.p. infusion of SCT – this effect was not apparent in vagotomised animals or animals treated with capsaicin to cause degeneration of unmyelinated sensory neurons including the nodose ganglion and the vagus nerve (Chu et al. 2013). In addition, peripheral administration of SCT activates vagal afferent and AP neurons, and this activation within the brainstem stimulates POMC neurons in the ARC (Yang et al. 2004; Cheng et al. 2011). Microinjection of SCT into the CeA significantly reduced food intake through cAMP-PKA activation (Pang et al. 2015). More recently, meal-stimulated secretin responses were reported to activate brown adipose tissue and suppress hunger via inhibition of orexigenic neurons and stimulation of anorexigenic signals via POMC neurons (Li et al. 2018). Whether this translates to an effect on food preference however remains to be demonstrated.

Peptide tyrosine tyrosine. Peptide tyrosine tyrosine (PYY) is a 36 amino acid peptide with structural similarity to both NPY and pancreatic polypeptide (Berglund et al. 2003). Released from L cells in the distal ileum and colon, it exhibits a gradient of increased expression along the intestine reaching its highest levels in the colon/rectum (Billing et al. 2019). Following a meal, plasma PYY concentrations rise and reach a peak within 1–2 h post-ingestion, remaining elevated for up to 6 h (Adrian et al. 1985). The composition of a meal influences secretion of PYY, with protein resulting in higher levels than lipids and carbohydrates.

Peripheral administration of PYY3–36 reduces food intake and body weight in experimental animals (Batterham et al. 2003; Challis et al. 2003; Koegler et al. 2005; Abdel-Hamid et al. 2019). Treatment was associated with increased c-Fos expression in the ARC and altered hypothalamic neuropeptide expression (Batterham et al. 2002; Challis et al. 2003). Furthermore, intra-ARC infusion of PYY3–36 reduces food intake. The effects of PYY3–36 on food intake were blocked when animals were pre-treated with a PYY receptor (Y2R) antagonist directed towards the ARC, or in Y2R–/– animals (Batterham et al. 2002; Abbott et al. 2005). Other groups subsequently confirmed that the anorectic effect of PYY was abolished by Y2R antagonism (Scott et al. 2005; Lewis et al. 2020). More recently, PYY was shown to increase food intake, by increasing meal size, via Y1R, when microinjected into the LPBN (Alhadeff et al. 2015). It was subsequently shown, however, that subcutaneous PYY3–36 and Ex4 reduce food intake in a synergistic manner in mice (Kjaergaard et al. 2019). In addition, PYY3–36 has been shown to reduce the motivation to seek high fat food in a rodent model (Ghitza et al. 2007).

The vagal–brainstem pathway may also respond to circulating PYY3–36 as Y2Rs are expressed in vagal afferent neurons – this, however, is controversial. Firstly, peripheral treatment with PYY3–36 increased c-Fos expression within brainstem regions (Halatchev & Cone, 2005; Koda et al. 2005; Blevins et al. 2008). Secondly, vagotomy or transection of hindbrain–hypothalamic pathways in rodents abolished the anorectic effects of peripheral PYY and the neuronal activation seen in the ARC in response to treatment with PYY (Abbott et al. 2005; Koda et al. 2005). However, treatment with capsaicin or vagotomy failed to attenuate the effects of PYY on food intake (Halatchev & Cone, 2005). In the nodose ganglion, fasting (up to 48 h) resulted in a 5-fold decrease in Y2R mRNA (vs ad libitum-fed control rats) (Burdyga et al. 2008).

In both lean and obese humans, i.v. infusion of PYY3–36 reduces food intake, and this anorectic effect is at least in part mediated through Y2 receptors in the ARC, which inhibit NPY/AgRP neurons, resulting in activation of the anorectic POMC neurons (Batterham et al. 2002; Batterham et al. 2003). It was subsequently shown that PYY modulates other neural activity within corticolimbic and homeostatic brain regions. In the fed state, when plasma PYY is elevated, increased neural activity in the caudolateral orbital frontal cortex was observed, whereas in the fasted state, when plasma PYY is low, hypothalamic activation was observed (Batterham et al. 2007). PYY has been shown to be negatively associated with post-prandial activity in the caudate nuclei in non-diabetic humans (Weise et al. 2012). Furthermore, peripherally administered PYY3–36 activates neurons in the AP and NTS and results in conditioned taste aversion (Halatchev & Cone, 2005). The nauseating effect of PYY at higher doses has limited its value as an obesity target to date (Gantz et al. 2007; Sloth et al. 2007; le Roux et al. 2008).

In short, evidence that PYY influences motivation to seek high fat foods in a rodent model and modulates neural activity in reward-related brain regions in humans suggests PYY has some influence on hedonic food intake.

Insulin-like peptide 5. Insulin-like peptide 5 (INSL5), a member of the relaxin peptide family and similar in structure to insulin and insulin-like growth factors, is an endogenous ligand for the G-protein-coupled relaxin/insulin-like family peptide receptor-4 (RXFP4) (Akhter Hossain et al. 2008). It is produced by a subset of L cells in the distal colon, is up-regulated upon caloric restriction and is reduced upon refeeding. It is also an orexigenic signal (Grosse et al. 2014; Billing et al. 2019). Interestingly, RXFP4−/− animals have altered feeding patterns and food preference (Grosse et al. 2014). Subsequently, Insl5 expression was shown to be
higher in germ-free and antibiotic-treated animals, and HFD reduced Insl5 expression in these mice (Lee et al. 2016). INS5−/− mice did not display an evident feeding phenotype (Lee et al. 2016). Small molecule agonism of RXFP3/RXFP4 was shown to increase food intake in rats following central administration (DeChristopher et al. 2019). However, pharmacological administration of INS5 (native and PEGylated forms) failed to affect food intake, body weight or glucose homeostasis in lean and obese mice (Zaykov et al. 2019). We recently observed a possible orexigenic effect of INS5 following stimulation of colonic L-cells in mice which was, however, only apparent when the anorexic effect of co-released PYY was blocked (Lewis et al. 2020). Further work on the role of INS5 and its receptor is therefore required.

Neurotensin. Neurotensin, a 13 amino acid peptide, is expressed in the CNS and GI tract. i.c.v. infusion of neurotensin reduced feeding in fasted and ad libitum-fed rats and the same was found with peripheral treatment (Luttinger et al. 1982; Cooke et al. 2009; Ratner et al. 2016). Chemogenetic activation of neurotensin-expressing neurons in the LH increases locomotor activity and suppresses food intake in ad libitum-fed and fasted mice (Woodworth et al. 2017). In addition to its role in feeding and reward, many studies have implicated neurotensin in a variety of processes including body temperature, analgesia and pain, and psychosis (Torruella-Suárez & McElligott, 2020).

Neurotensin immunoreactivity is found in the VTA, NAc shell, PVN and LPBN (Uhl et al. 1977; Schroeder et al. 2019). Infusion of neurotensin into the VTA results in rats demonstrating conditioned placed preference – a possible consequence of increased dopamine entering the NAc (Glimcher et al. 1984; Sotty et al. 1998; Sotty et al. 2000; Leonetti et al. 2004). A similar result was achieved when neurotensin was infused into the CeA (László et al. 2010). Subsequent studies suggested that neurotensin signalling in the CeA reinforced and promoted learning (László et al. 2012; László et al. 2018).

Neurotensin-Cre mice will nose-poke for optical stimulation of the LH terminals in the VTA (Kempadoo et al. 2013). These neurons contain the long form of the leptin receptor (LepRB) and when stimulated the animals were motivated to consume both food and water (Leinninger et al. 2011; Schifino et al. 2019). LepRB KO specifically in neurotensin-expressing LH neurons alters reward-related feeding; these animals do not demonstrate increased preference for sucrose following treatment with ghrelin.

Substance P. The neurokinin systems play diverse roles in physiological processes ranging from pain and cardiovascular function to behaviour (reviewed in Schank, 2020). Substance P, one of three neurokinin peptides, has been shown to alter the response to alcohol, cocaine and opiate drugs mainly via the neurokinin-1 receptor (NK1R), but i.p. infusion of substance P in rats also resulted in an anorexigenic effect, with increased latency to eat in food-deprived animals (Cador et al. 1986; Hasenöhrl et al. 1994). Peripheral treatment with substance P increased conditioned place preference (Oitzl et al. 1990), an effect that appeared to be brain region specific (reviewed in Lénárd et al. 2018). It was subsequently shown that peripheral treatment with substance P reduced operant responding and i.c.v. infusion of substance P in fasted rats reduced refeeding (Hasenöhrl et al. 1994; Dib, 1999). By contrast, substance P increased food intake in mice, whilst antagonism of the NK1R in DIO and ob/ob animals reduced food intake and body weight (Karagiannides et al. 2008). In humans, treatment of healthy individuals with a NK1R antagonist resulted in a decrease in blood oxygenation level-dependent signals in the NAc during gain anticipation (Saji et al. 2013). The rewarding or aversive effects of substance P are thus brain region specific.

Central versus peripheral mechanisms of activation

Gut peptides, and their receptors, clearly influence neural mechanisms of reward. However, what is less clear is whether gut peptides, with relatively short half-lives, secreted from epithelial enteroeocrine cells, can activate their receptors deep within the brain, shielded by the blood–brain barrier, thus forming a true gut–brain axis. Many gut peptides have direct access to the ARC via the leaky blood–brain barrier in this region or exert their influence via the afferent neuronal pathway or brainstem. For example, CCK was originally identified as a gastrointestinal peptide that controls food intake through binding to receptors on the vagus nerve, activating the NTS, which relays information to the hypothalamus. However, it is also an abundant neuropeptide expressed in the hippocampus, amygdala and hypothalamus (Beinfeld et al. 1981; Williams & Elmquist, 2012). Indeed, a plethora of other gut peptides are also expressed in the CNS – cells expressing GLP-1 (often referred to as GCG+ or PPG neurons) can be found in the brainstem, specifically in the NTS, and the olfactory bulb, confirmed via in situ hybridisation, immunohistochemistry and transgenic mouse models (Jin et al. 1988; Larsen et al. 1997; Reimann et al. 2008). Interestingly, these hindbrain GCG+ neurons lack GLP-1R and therefore cannot be activated by peripheral GLP-1 (Hisadome et al. 2010). However, peripheral GLP-1 can activate the vagal afferents, which in turn activate GCG+ neurons in the NTS (Hisadome et al. 2010). Similarly, PYY has been centrally reported in the hindbrain, with the highest density in the NTS (Glavas
et al. 2008). Neurotensin- and substance P-producing neurons are widely distributed throughout the CNS, whilst secretin has been detected in numerous brain regions (reviewed in St-Gelais et al. 2006; Mashaghi et al. 2016). GIP is reported to be synthesised by a subset of neurons within the brain, limited to the large pyramidal neurons in the cortex and hippocampus (Faivre et al. 2011). GIP has also previously been reported, via in situ hybridisation, in the olfactory bulb (Usdin et al. 1993), but we have so far not been able to detect Cre-reporter activity in central neurons in GIP-Cre mice. Similarly, studies investigating central sources of ghrelin or insulin-like peptide-5 have been inconclusive (recently reviewed in Cabral et al. 2017; Lewis et al. 2020). Hence, with the current evidence it is not possible to determine whether it is peripherally or centrally derived gut peptides that modulate hedonic control of food intake. Nonetheless, the studies examined in this review highlight the actions of gut peptides, their analogues and their receptors in the neural reward system. These actions could be harnessed to improve treatments for food intake and reward-related disorders including obesity.

**Concluding remarks**

At present, bariatric surgery is the only effective treatment for severe obesity, with Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG) being the more commonly used procedures. These operations result in self-reported changes in taste and food preference (reviewed in Nance et al. 2020; Moffett et al. 2021). After RYGB surgery, patients report a shift in food preference away from high-energy foods, correlating with reduced superior parietal lobule and precuneus responses to high-energy food odours and high-energy versus low-energy food pictures, respectively. These changes in neural activity did not correlate with changes in appetite-related hormone concentrations (Zoon et al. 2018). A previous study highlighted that gastric bypass patients have lower hedonic responses to food than individuals who underwent gastric banding. Postprandial plasma gut peptides (the most consistently elevated of which are GLP-1 and PYY), bile acids and symptoms of dumping syndrome are all increased in the RYGB cohort compared to the gastric banding cohort (Pournaras et al. 2012; Dirksen et al. 2013; Scholtz et al. 2014). It is likely that the distal gut’s response to nutrients underlies this altered profile of hormones, whose roles in hunger, satiety, reward and aversion have been highlighted. Recently, it was also reported that individuals receiving bariatric surgery were at increased risk from substance use disorder, further suggesting that the reward system is altered by weight loss surgery (reviewed in Orellana et al. 2019). Gastrointestinal peptides have been also implicated in eating disorders (reviewed in Tong & D’Alessio, 2011), a hallmark of which is dysregulated reward signalling, and liraglutide has recently been shown to reduce global eating disorder psychopathology (Chao et al. 2019). It is therefore essential that we increase our understanding of how gut peptides influence the reward system to prevent unwanted side effects of weight loss treatments and potentially develop alternative therapies for obesity, eating disorders and other reward-related disorders.

We often talk of having a ‘gut feeling’, but how our GI tract regulates our emotional and motivational states, particularly surrounding food intake, is incompletely understood. Gut peptides are well established in the homeostatic control of food intake. Here we have highlighted the emerging role of specific gut peptides in the hedonic control of food intake. Studies in rodent models demonstrating activation of reward-related regions following administration of gut peptides and/or their analogues, alongside changes to intracranial self-stimulation and operant conditioning responses, indicate a role for gut peptides in reward-related signalling and behaviour. This is supported by human studies showing changes to reward-related region activation and food preferences following administration of gut peptide analogues and bariatric surgery. As gut peptide analogues become increasingly utilised in the clinic as therapeutics for type 2 diabetes and obesity, further research into how gut peptides and their analogues influence food intake is paramount.

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Gut peptides and hedonic food intake

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Additional information

Competing interests

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Author contributions

All authors contributed to the drafting of the manuscript. All authors have read and approved the final version of this manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated.
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