The Journal of Physiology

TOPICAL REVIEW

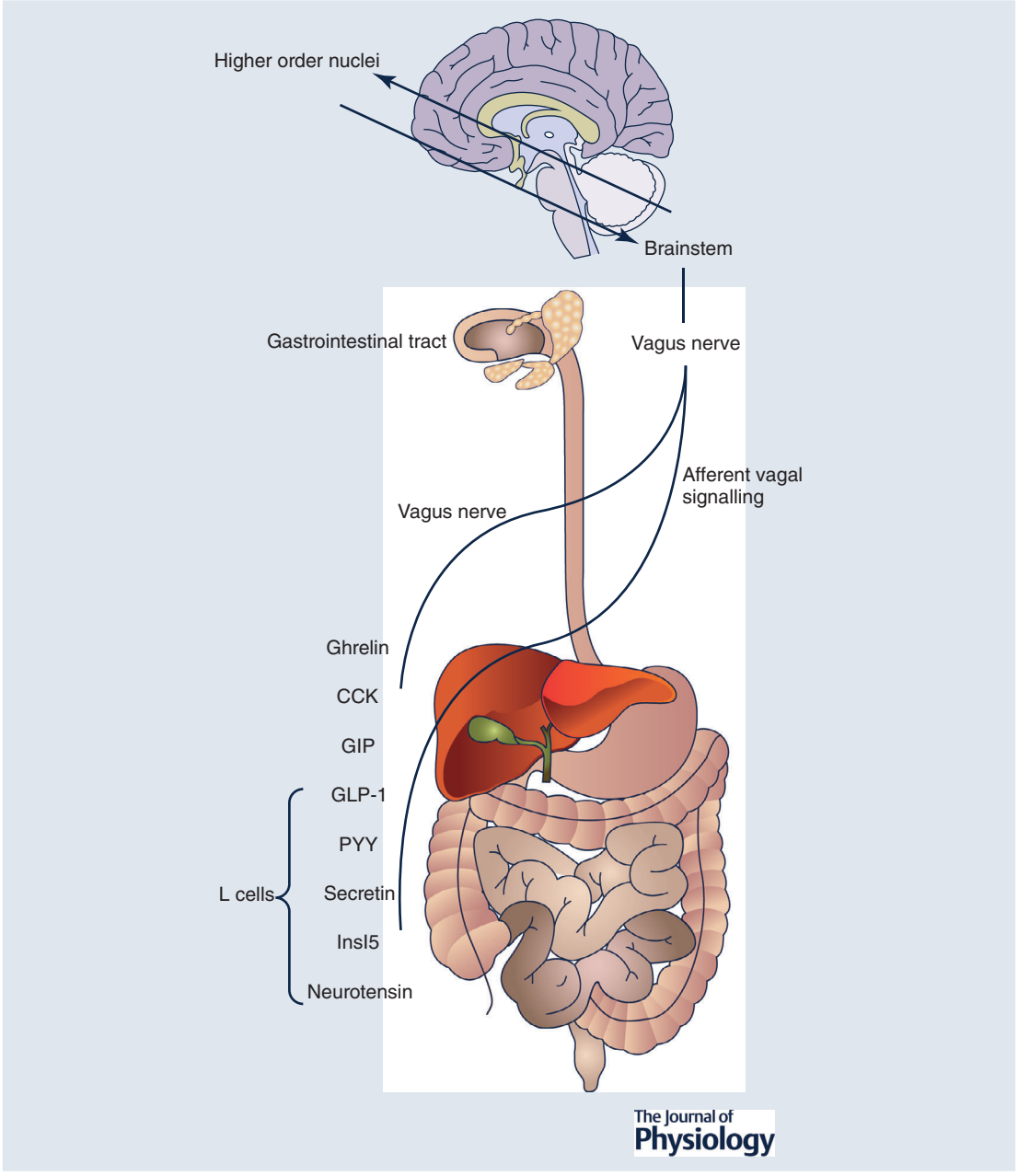
Gut peptide regulation of food intake – evidence for the modulation of hedonic feeding

Orla R. M. Woodward, Fiona M. Gribble, Frank Reimann and Jo E. Lewis

Wellcome Trust – MRC Institute of Metabolic Science Metabolic Research Laboratories, Addenbrooke's Hospital, Hills Road, Cambridge, CB2 0QQ, UK

Edited by: Ian Forsythe & Michel Neunlist

The peer review history is available in the Supporting Information section of this article (https://doi.org/10.1113/JP280581#support-information-section).



DOI: 10.1113/JP280581

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 dorso-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.

(Received 28 February 2021; accepted after revision 17 May 2021; first published online 21 June 2021)
Corresponding author J. E. Lewis: Wellcome Trust – MRC Institute of Metabolic Science Metabolic Research Laboratories, Addenbrooke's Hospital, Hills Road, Cambridge CB2 0QQ, UK. Email: jl2033@medschl.cam.ac.uk

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/m^2) 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

Orla R. M. Woodward is a PhD student at the Wellcome/MRC Institute of Metabolic Science, University of Cambridge. She is supervised by Professors Frank Reimann and Fiona Gribble and her research focuses on gut–brain communication in the control of appetite and feeding behaviour. She has an MRes in the Biology of Ageing and Age-Related Disease from University College London and a BSc in Biological Sciences from Durham University. **Jo E. Lewis** is a postdoctoral research associate (in the Reimann/Gribble group) at the Wellcome/MRC Institute of Metabolic Science, University of Cambridge. He grew up in Wrexham, North Wales, and graduated from the University of Leeds (2004), before obtaining a Masters from the University of Westminster (2008) and a PhD from the University of Nottingham (2015). His research focuses on the gut–brain axis.

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/m^2 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 extends 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 corticolimbic 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 corticolimbic 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, corticolimbic 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

tract) with a known role in the control of food intake and potential role in the regulation of neural systems of reward. Whilst other gut peptides expressed in the enteric nervous system, rather than enteroendocrine cells, have also been implicated in the control of feeding behaviour, including vasoactive intestinal peptide (VIP) implicated in taste perception, pituitary adenylate cyclase-activating polypeptide (PACAP) which reduces feeding behaviour via the VMH, and bombesin-like peptides which suppress food intake when administered peripherally or centrally in rats, these are not the focus of this review (Ladenheim *et al.* 1996; Martin *et al.* 2010; Hurley *et al.* 2016).

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

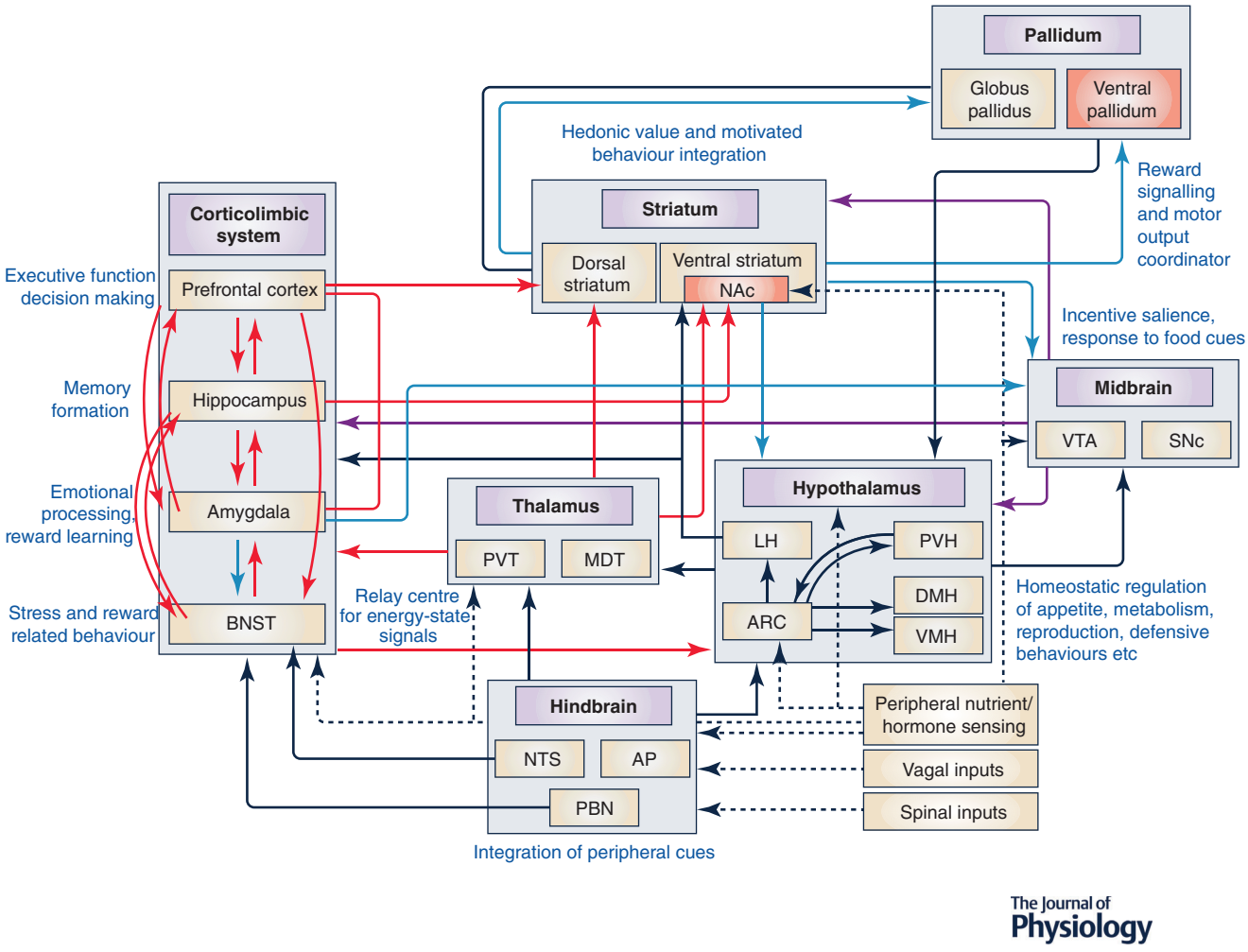


Figure 1. Schematic diagram showing the neural circuitry involved in reward, motivation and food intake
Peripheral signals from vagal and spinal afferents and circumventricular organs are integrated by the hypothalamus and hindbrain. These signals are relayed through thalamic and midbrain regions and integrated with corticolimbic reward signals in the striatum. Striatal projections to the pallidum and hypothalamus enable coordination of reward-seeking and motivated behavioural responses. Pathways with predominantly glutamatergic projections are shown in orange, GABAergic projections are shown in blue and dopaminergic projections are shown in purple. Pathways where projections involve other or unknown neurotransmitters are shown in black. Regions with 'hedonic hotspots', subregions which encode the 'liking' of food, are highlighted in red. Abbreviations: AP, area postrema; ARC, arcuate nucleus; BNST, bed nucleus of the stria terminalis; DMH, dorsomedial hypothalamus; LH, lateral hypothalamus; NTS, nucleus of the solitary tract; PBN, parabrachial nucleus; PVH, paraventricular hypothalamus; PVT, paraventricular thalamic nucleus; VMH, ventromedial hypothalamus; VTA, ventral tegmental area.

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*. 2002*b*; 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*. 2012*a*). 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*. 2012*a*).

In rats offered a choice of palatable foods (sucrose pellets and lard, with standard chow), acute intracerebroventricular (I.C.V.) or intra-VTA ghrelin injections increased chow intake of rats with a high baseline intake of lard – 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 appetitive 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*. 2002*a*). 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*. 1994*a*). 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*. 1994*b*). 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 (Hsiao & 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*. 1996*a*). 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 insulinotropic polypeptide. Glucose-dependent insulinotropic 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*. 2009*a*). 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*. 2009*a*). 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, (Pro^3)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*. 2007*b*). 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*. 2007*a*, 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 anorexic 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 GIP-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 pre-proglucagon and produced by intestinal L cells in response to food ingestion, has a key role in glucose homeostasis (Eissele *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 (Finan *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 (Vallöf *et al.* 2019*a*). 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 behaviour 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 mediatory 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 RpcAMP 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 $\pm$ 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. Reductions 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 supress 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 $PYY_{3–36}$ 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 $PYY_{3–36}$ reduces food intake. The effects of $PYY_{3–36}$ 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 $PYY_{3–36}$ and Ex4 reduce food intake in a synergistic manner in mice (Kjaergaard *et al.* 2019). In addition, $PYY_{3–36}$ 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 $PYY_{3–36}$ as Y2Rs are expressed in vagal afferent neurons – this, however, is controversial. Firstly, peripheral treatment with $PYY_{3–36}$ 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 $PYY_{3–36}$ 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 postprandial activity in the caudate nuclei in non-diabetic humans (Weise *et al.* 2012). Furthermore, peripherally administered $PYY_{3–36}$ 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). INSL5$^{-/-}$ 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 INSL5 (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 INSL5 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 INSL5 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; Schiffino *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 induced 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 enteroendocrine 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 also was 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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Additional information

Competing interests

F.M.G. is a paid consultant for Kallyope, New York. The Gribble-Reimann lab hosts projects that receive funding from AstraZeneca (F.M.G./F.R.). The F.R./F.M.G. laboratory has agreed a collaboration with Eli Lilly & Company. There are no other conflicts of interest to declare.

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

and resolved. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

Funding

O.R.M.W. is a BBSRC-iCase PhD student in collaboration with AstraZeneca. Research in the laboratory of F.M.G. and F.R. is supported by the MRC (MRC_MC_UU_12012/3) and Wellcome Trust (106262/Z/14/Z and 106263/Z/14/Z). J.E.L. acts as guarantor for this manuscript.

Keywords

appeti, CCK, ghrelin, GIP, GLP-1, gut-brain axis, gut peptides, hedonic feeding, Insl5, obesity

Supporting information

Additional supporting information can be found online in the Supporting Information section at the end of the HTML view of the article. Supporting information files available:

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