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GLP-1: Molecular mechanisms and outcomes of a complex signaling system

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ABSTRACT

Meal ingestion provokes the release of hormones and transmitters, which in turn regulate energy homeostasis and feeding behavior. One such hormone, glucagon-like peptide-1 (GLP-1), has received significant attention in the treatment of obesity and diabetes due to its potent incretin effect. In addition to the peripheral actions of GLP-1, this hormone is able to alter behavior through the modulation of multiple neural circuits. Recent work that focused on elucidating the mechanisms and outcomes of GLP-1 neuromodulation led to the discovery of an impressive array of GLP-1 actions. Here, we summarize the many levels at which the GLP-1 signal adapts to different systems, with the goal being to provide a background against which to guide future research.

1. Introduction

Glucagon-like peptide-1 (GLP-1) has long been recognized as a potent stimulator of insulin secretion and key regulator of energy homeostasis. The importance and conservation of its role in physiology is reflected in its almost complete sequence homology across mammalian species (Ørskov, 1992). Over time, the list of physiological functions mediated by GLP-1 has expanded dramatically (Baggio and Drucker, 2007; Holst, 2007; Pabreja et al., 2014; Rowlands et al., 2018). First described as an incretin, GLP-1 protects against hyperglycemia by enhancing insulin secretion and inhibiting glucagon secretion. Within the gut, it also acts to inhibit gastric motility and secretion. More recently, GLP-1 in the brain has become increasingly appreciated to engage a range of neural circuits to regulate appetite and reward related behaviors. This widely expressed receptor system can participate in a diverse assortment of functions partly due to its highly tailorable architecture. From the production of the endogenous ligands, to the coupling of downstream signaling partners and cellular localization, the GLP-1 and GLP-1 receptor (GLP-1r) system exhibits complexity and diversity (Pabreja et al., 2014). This diversity allows for a customizable receptor system specifically attuned to the environment in which it is found. As we continue to uncover the nuances of the GLP-1 signal, it is important to remain aware of the currently known spectrum of its actions. This review will encompass the synthesis, secretion, and metabolism of GLP-1, the structure and expression of the GLP-1r, the intracellular signaling initiated by GLP-1r stimulation, and GLP-1 changes after bariatric surgery. Additionally, we end with a special focus on the role of GLP-1 signaling in feeding and drug reward. Each section will highlight the opportunity for diversity within the GLP-1 and GLP-1r system, from the level of a single amino acid to the impact of the hormone on feeding behavior and reward.

2. Synthesis and secretion of GLP-1

The regulation of GLP-1 synthesis is one mechanism by which the GLP-1 and GLP-1r system can be customized. GLP-1 is produced through the proteolytic cleavage of proglucagon, a protein expressed in the enteroendocrine cells, α cells of the pancreas, as well as in the

Abbreviations: AMPK, AMP-activated protein kinase; CCK, cholecystokinin; CGRP, Calcitonin gene-related peptide; DPP IV, dipeptidyl-peptidase IV; EPAC, exchange protein directly activated by cAMP; ERK1/2, extracellular signal-regulated kinases; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, Glucagon-like peptide-1; GLP-1r, Glucagon-like peptide-1 receptor; GLP-1 EECs, enteroendocrine GLP-1 producing cells; GPCRs, G protein-coupled receptors; IP_3, inositol triphosphate; MAPK, mitogen-activated protein kinase; mTOR, mechanistic target of rapamycin; NTS, nucleus of the solitary tract; PBN, parabrachial nucleus; PI3K, phosphatidylinositol 3-kinase; PKC, protein kinase C; PLC, phospholipase C; POMC, proopiomelanocortin; SGLT, sodium coupled glucose transporters; VGCCs, voltage gated calcium channels

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nucleus of the solitary tract (NTS) in the brainstem. The amino acid sequence of this 18 kDa protein was first deduced from the translation of the nucleotide sequence of the glucagon gene (Bell et al., 1983a; Heinrich et al., 1984). The protein contains three separate hormonal sequences separated by two intervening peptides (IP), IP-1 and IP-2 (Bell et al., 1983b). Proteolytic processing of proglucagon is performed by a number of prohormone convertase enzymes. Expression of prohormone convertase occurs in a tissue specific manner. Consequently, the products produced by cleavage of proglucagon are also tissue-specific (Ørskov et al., 1987).

In the pancreas, proglucagon undergoes posttranslational processing by prohormone convertase 2 (Smeekens et al., 1991) to produce glucagon, GRPP, and the major proglucagon fragment (MPGF) (Holst et al., 1994). This MPGF contains both glucagon-like peptide (GLP)-1 and GLP-2, as well as the IP-2 sequence. A small amount (10–20%) of the MPGF is cleaved to produce GLP-1 (Holst et al., 1994). Pancreatic synthesis and secretion of GLP-1 can be stimulated by elevated glucose, activation of the bile acid receptor TGR5, and β cell destruction (Whalley et al., 2011). Organ specific genetic manipulation of GLP-1 synthesis has revealed that pancreatic GLP-1 production may be solely responsible for the effect of GLP-1 on glucose homeostasis (Chambers et al., 2017). This finding highlights the ability of specific populations of GLP-1 producing cells to alter distinct aspects of physiology.

The main sources of GLP-1 in the gastrointestinal tract are the enteroendocrine GLP-1 producing cells (GLP-1 EECs) found in the small intestine and colon. GLP-1 EEC density varies along a proximal to distal axis, with a sparse number of cells localized in the duodenum, increasing number in the jejunum, and the greatest numbers in the ileum and colon (Baggio and Drucker, 2007). In GLP-1 EECs, proglucagon is cleaved by prohormone convertase 1/3 to produce glicentin, GLP-1 and GLP-2, liberating the IP-2 peptide. Glicentin can be further processed to produce GRPP and oxyntomodulin (Dhanvantari et al., 1996). Oxyntomodulin contains the glucagon peptide sequence in addition to the IP-1 sequence and acts as an agonist at both GLP-1r and the glucagon receptor (Jorgensen et al., 2007). The brain also synthesizes GLP-1, utilizing a strategy similar to that of the GLP-1 EECs. Prohormone convertase 1/3 is the main species expressed (Seidah et al., 1991), and it acts to produce GLP-1 in the NTS (Jin et al., 1988; Larsen et al., 1997; Rinaman, 1999a).

GLP-1 can be secreted in four different forms, produced by differential post-translational modification. These forms include GLP-1 (1–37), GLP-1 (1–36)NH_2, GLP-1 (7–37), and GLP-1 (7–36)NH_2. The truncated versions listed are produced through action of prohormone convertase 1/3 (Dhanvantari et al., 1996). Terminal amination is then mediated by α-monooxygenase (Wettergren et al., 1998). Despite the variety of possible species, the vast majority (80%) of GLP-1 that reaches circulation in humans is the GLP-1 (7–36)NH_2 variety (Ørskov et al., 1994). The complex process leading to the production of these multiple species of GLP-1 affords multiple levels of control over what is ultimately secreted by the cell. Importantly, these different forms of GLP-1 have been shown to activate signaling pathways to different degrees (Furness et al., 2018). The ultimate form of GLP-1 secreted by the cell then has the potential to be directed to a specific signaling outcome, and this bias can be controlled by expression of enzymes controlling the post-translational modifications.

GLP-1 secretion from GLP-1 EECs is triggered the by carbohydrates (Baggio and Drucker, 2007), proteins (Belza et al., 2013), and fats (Hirasawa et al., 2005) present in a meal, an area that has been reviewed in great detail (Gribble and Reimann, 2017). Glucose induced GLP-1 secretion is mediated primarily by glucose uptake into GLP-1 EECs by the sodium coupled glucose transporters (SGLT), as shown by pharmacological and genetic interference of SGLT function or expression (Gorboulev et al., 2012; Parker et al., 2012). Co-transport of Na^+ results in membrane depolarization, triggering opening of voltage-gated Ca^{2+} channels and exocytosis of GLP-1 vesicles (Reimann et al., 2008). Amino acids can influence GLP-1 secretion via a similar electrogenic mechanism mediated by Na^+ cotransport (Reimann et al., 2004). Oligopeptides can act at G protein-coupled receptors (GPCRs), including CASR (Diakogiannaki et al., 2013) and GPR142 (Lin et al., 2016). Fatty acids are also detected by GPCRs, with long chain fatty acids mainly signaling through GPR40 and GPR120 (Gribble et al., 2016). Mono-oleoylglycerols signal through GPR119, a receptor that appears to be critical for GLP-1 secretion based on rodent knockout studies (Moss et al., 2016). However, human trials of a GPR119 agonist failed to significantly increase GLP-1 levels (Nunez et al., 2014), complicating the interpretation of previous results from model systems. In addition to direct sensing of fats, bile acids secreted upon fat ingestion are able to signal at GLP-1 EECs through the GPCR TGR5 and the nuclear receptor FXR (Albaugh et al., 2019). These above mechanisms are critical for GLP-1 secretion, and nutrients must pass through the gut to trigger GLP-1 secretion. This is best shown in studies where intravenous glucose administration produces no significant change in GLP-1 levels (Herrmann et al., 1995). However, early phase GLP-1 secretion that occurs before nutrients reach the distal intestine and the GLP-1 EECs relies on other mechanisms, likely mediated by vagus nerve transmission (Rocca and Brubaker, 1999). Enhancing the secretion of GLP-1 is a goal of diabetes and obesity pharmacological interventions, and thus, significant effort has been expended towards identifying the molecular mechanisms that trigger GLP-1 secretion The magnitude of GLP-1 secretion is strongly correlated to the rate of gastric emptying, which may explain some of the secretion-promoting effects of bariatric surgeries that reduce stomach volume and increase gastric pressure (Belza et al., 2013). Future work in this area could focus on specific signaling pathways that promote GLP-1 and other hormone secretion, promoting or augmenting natural satiety processes during a meal.

Central GLP-1 release is mediated by firing of preproglucagon expressing neurons in the NTS. These neurons show activation following gastric distension or systemic administration of lipopolysaccharide, lithium chloride, and cholecystokinin (CCK) (Rinaman, 1999a; Vrang et al., 2003). They also respond to local application of CCK and leptin (Hisadome et al., 2011, 2010). In addition to responding to systemic signals, preproglucagon neurons are also synaptically connected to inputs releasing fast neurotransmitters as well as others releasing neuromodulators. NTS preproglucagon neurons have been shown to express functional post-synaptic glutamate receptors (Hisadome et al., 2011). Additionally, they have been shown to be inhibited by exogenously applied 5-HT (Holt et al., 2017), and excited by epinephrine and norepinephrine (Hisadome et al., 2011), all of which likely endogenously originate from local modulatory inputs. An in depth analysis of the synaptic connectivity of the NTS preproglucagon neuron population has yet to be undertaken.

Peripheral GLP-1 secretion has the ability to trigger further GLP-1 secretion in the brain. GLP-1 released in the intestine is able to act through GLP-1 receptors expressed on the vagus nerve, leading to vagal excitation (Bucinskaite et al., 2009; Kakei et al., 2002). Vagal excitation then stimulates NTS preproglucagon neurons, resulting in GLP-1 release in the brain (Williams, 2009). In this model, peripheral GLP-1 secretion has a direct impact on central GLP-1 secretion, despite the rapid elimination of the circulating peptide. This connection has been shown to be functionally important for GLP-1 mediated anorexia through vagal deafferentation studies (Williams, 2009; Yeğen et al., 1997). Further, this route may play a significant role in GLP-1 enhancement of insulin response, as denervated mice show no response to low doses (0.1 nmol/kg) of GLP-1 (Ahrén, 2004). Sensory denervated mice retain enhanced insulin response to glucose following high doses of GLP-1, and this has been interpreted as a preference for GLP-1 to signal via circuit mechanisms at physiological levels, but an ability to signal in an endocrine manner at higher doses (Ahrén, 2004).

Together, these results highlight clear differences in the stimuli that trigger GLP-1 release from the GLP-1 EECs and the preproglucagon expressing NTS neurons. While GLP-1 EECs primarily respond to nutrient signals, GLP-1 releasing neurons of the NTS are stimulated by

hormonal signals and vagal firing. The combination of excitatory, inhibitory, and neuromodulatory influences on NTS GLP-1 neurons allows integration of different information prior to the propagation of the GLP-1 signal to other central nodes. While the majority of these signals are stimulated by nutrient signaling within the gut, the same nutrient signals that influence GLP-1 secretion from GLP-1 EECs, central GLP-1 signaling is gated behind the integration of these signals and thus is insulated from directly responding to nutrient availability in the gut. This allows for greater control over the central GLP-1 response, and may allow for longer term control over energy homeostasis by considering long term energy stores in addition to acute nutrient availability. It would be interesting to see if signal integration at the level of the NTS was influenced by long term metabolic manipulations, and how that signal integration altered central GLP-1 signaling. The dynamic responses of NTS GLP-1 releasing neurons also remains to be examined. By utilizing calcium reporter molecules driven by genetic identifiers, future researchers could characterize the responses of these neurons to food cues, nutrients, gastric distension, and other stimuli to build an understanding of how these neurons decide to release GLP-1. An interesting direction would be to examine whether that decision is subject to learning, similar to what has been found in other central integrators of energy state (Beutler et al., 2017; Su et al., 2017).

3. Metabolism of GLP-1 and the therapeutic actions of long-lasting agonists

GLP-1 has an extremely short half-life once released in the plasma, ranging from 2 to 11 min (Deacon et al., 1995; Ørskov et al., 1994, 1993; Wettergren et al., 1998). The enzyme responsible for the majority of GLP-1 metabolism is dipeptidyl-peptidase IV (DPP IV) (Hopsu-Havu and Glenner, 1966), a serine aminopeptidase that can exist in both a membrane bound as well as soluble form (Engel et al., 2003). It inactivates GLP-1 by cleaving a X-Pro or a X-Ala dipeptide, producing mainly GLP-1 (9–36) NH_2(Kieffer et al., 1995). DPP IV is expressed in numerous organs, including the kidney (Kettmann et al., 1992), liver (Hanski et al., 1988), pancreas (Heymann et al., 1985), blood vessels (Lojda, 1979), gut (Mulvihill et al., 2017), and brain (Bernstein et al., 1987). In the periphery, the main functional burden of GLP-1 metabolism rests on the liver and endothelial populations of DPP IV (Mulvihill et al., 2017). In a recent study using a conditional DPP IV knockout mouse, it was shown that although enteric DPP IV contributes significantly to reducing GLP-1 in the intestine, knockout of enteric DPP IV did not significantly disrupt incretin hormone levels or glucose tolerance (Mulvihill et al., 2017). These results place increased importance on the endothelial population of DPP IV. Although present in neurons during development (Bernstein et al., 1987), in the mature brain the enzyme is found on the ependymal cells of the blood-brain barrier (Bernstein et al., 1987), and low concentrations of the soluble form of the enzyme can be found in the cerebrospinal fluid (Kato et al., 1979). GLP-1 readily crosses the blood-brain barrier by simple diffusion, although presumably the amount of peripheral endogenous GLP-1 that reaches the central nervous system is small based on its short half-life (Kastin et al., 2002). Indeed, one study showed that only 20% of GLP-1 released from GLP-1 EECs was able to pass through the liver and reach the pancreas through circulation (Hjøllund et al., 2011). These results underscore the emphasis on the vagal route by which peripheral GLP-1 spurs central GLP-1 release. DPP IV inhibition has been explored as a potential therapeutic route for type 2 diabetes with the goal of increasing circulating GLP-1 levels by reducing metabolism (Deacon and Lebovitz, 2016). There are now several DPP IV inhibitors on the market, including sitagliptin (Herman et al., 2006), and alogliptin (DeFronzo et al., 2008).

In order to improve the clinical efficacy of GLP-1 agonism for type II diabetes and obesity, long-lasting analogues for GLP-1 have been developed which delay metabolism by DPP IV and increase their half-life in the blood. One GLP-1 analogue, Exendin-4, was discovered in the venom of the Gila monster (*Heloderma suspectum*), a lizard native to the southwestern United States and Mexico (Eng et al., 1992). Exendin-4 is a 39 amino acid peptide with 53% sequence homology to GLP-1 (Eng et al., 1992). The synthetic version of Exendin-4 is FDA approved and marketed as Exenatide. This analogue is metabolized much slower than endogenous GLP-1, resulting in a half-life of 3–4 h (Pinkney et al., 2010). The increased half-life is due mainly to the substitution of a glycine for an alanine residue in the 8th position, making the peptide a poor substrate for DPP IV(Pinkney et al., 2010). Unlike Exenatide, the GLP-1 agonist Liraglutide shares 97% homology with endogenous GLP-1 (Pinkney et al., 2010). This analogue features a arginine to lysine substitution at position 34, as well as the addition of a fatty acid moiety bonded to lysine 26 (Pinkney et al., 2010). This fatty acid moiety facilitates binding to albumin, further increasing the half-life of the drug in circulation to 11–13 h (Chia and Egan, 2008). Development of these analogues allowed GLP-1 agonism to become a widespread treatment strategy for type II diabetes and obesity, as well as expanding the potential for studies of the GLP-1 system in basic science. Notably, Exendin-4 has been shown to attenuate both the psychomotor stimulant action of amphetamine (Erreger et al., 2012) as well as the rewarding and addictive properties of cocaine (Graham et al., 2013; Reddy et al., 2016; Sørensen et al., 2015), topics covered later in this review.

Further progress has been made by identifying GLP-1 agonists that additionally target receptors for either the glucose-dependent insulinotropic polypeptide (GIP) receptor, the glucagon receptor, or both (Brandt et al., 2018). Polyagonists engage complementary signaling systems to enhance outcomes beyond additive effects while reducing adverse effects (Müller et al., 2018). This synergy has been shown with other gut hormones at the behavioral (Roth et al., 2007; Talsania et al., 2005) and neural level (Su et al., 2017). Unimolecular polyagonists represent a significant advancement over simple co-administration of multiple peptides by normalizing the absorption, distribution, and metabolism of the therapeutic. Since the first production in 2009 (Day et al., 2009), substantial progress has been made in producing these polyagonists, utilizing previous successful strategies including lipidation and building off the exendin backbone (Evers et al., 2017; Finan et al., 2013). Notably, a dual GIP/GLP-1 receptor agonist has been shown in clinical trials to improve glucose control and reduce body weight in patients with type 2 diabetes (Frias et al., 2017).

These results show that combining the GLP-1 signal with other hormonal pathways produces a synergistic, or greater than additive, response. EECs expressing GLP-1 are known to produce other hormones (Egerod et al., 2012) and in some cases these products can even be found stored in the same vesicles (Billing et al., 2018; Fothergill et al., 2017). Similar to the GIP/GLP-1r polyagonists, co-administration of GLP-1 and neurotensin has been shown to produce a synergistic effect (Grunddal et al., 2016). This raises questions about whether there are mechanisms regulating co-secretion, and if that regulation can be manipulated for therapeutic value.

4. GLP-1r structural characteristics and expression

The GLP-1r was first discovered in 1987 through radioligand binding assays with GLP-1 in rat pancreatic islet cell cultures (Drucker et al., 1987). Soon after, it was localized to a wide variety of tissues, including the brain (Shimizu et al., 1987). Expression cloning from cDNA libraries allowed for the identification of the gene responsible for the production of the receptor (Dillon et al., 1993; Graziano et al., 1993; Thorens, 1992; Thorens et al., 1993; van Eyll et al., 1994). Many early studies of the receptor focused on the rat GLP-1r, which exhibits 90% sequence homology with the human form (Dillon et al., 1993), highlighting the conservation of this important physiological signaling system.

Based on its structure and similarity to the secretin receptor, GLP-1r belongs to the Class B family of GPCRs. This family is defined by its peptide ligands as well as its extensive extracellular N-terminal ligand

binding domain (Lagerström and Schiöth, 2008). GLP-1r and other Class B GPCRs exhibit a characteristic tertiary structure, despite relatively low sequence homology across the class (40–60%) (Lagerström and Schiöth, 2008). The Class B GPCR common structure consists of a lengthy N-terminal extracellular binding domain, followed by seven transmembrane domains interspersed by intra and extra-cellular loops (Hollenstein et al., 2013; Liang et al., 2017; Neumann et al., 2008; ter Haar et al., 2010). Recent cryo-EM structures of GLP-1r show this characteristic structure with GLP-1 or modified exendin-4 bound between the N-terminal binding domain and the transmembrane domains (Liang et al., 2017; Zhang et al., 2017). Upon binding, the ligand extends into the transmembrane core of the receptor, allowing a plethora of interactions with almost every transmembrane helix (Liang et al., 2017; Zhang et al., 2017). While the interactions made with the receptor are largely similar between GLP-1 and modified exendin peptide, there are some subtle differences in the positioning of transmembrane residues (Liang et al., 2017). On the intracellular side, the C terminus is critical for the desensitization and internalization of the receptor due to three phosphorylation sites which regulate these processes (Vázquez et al., 2005; Widmann et al., 1997, 1996a, 1996b).

Polar residues within the transmembrane region, in addition to extracellular residues, have been shown to be important for producing differential signaling by different ligands, including the endogenously produced varieties of GLP-1 as well as agonists like exendin-4 (Furness et al., 2018; Wootten et al., 2016, 2013). In pharmacological studies, alanine scanning mutagenesis shows that residues in the transmembrane region and extracellular loops are critical for the differential signaling response produced by different ligands (Furness et al., 2018; Wootten et al., 2016, 2013). These pharmacological data align with the differences in transmembrane residue orientation found between GLP-1r bound to GLP-1 or a modified exendin peptide (Liang et al., 2017). Thus the GLP-1 receptor is capable of diverse outcomes even when signaling though a common g protein. This occurs despite a relatively conserved intracellular face forming interactions with the g protein, even when compared to class A receptors (Zhang et al., 2017). These results point to an exquisitely tuned receptor able to differentiate between subtle differences in ligand structure to produce varied intracellular responses. The most well-known example of this in GLP-1r signaling was the failure of Taspoglutide in clinical trials. Taspoglutide failed due to the unwanted side-effects of severe nausea and vomiting, known consequences of intense GLP-1r stimulation, which occurred despite the agonist having a 93% sequence homology to endogenous GLP-1 (Rosenstock et al., 2013). Thus, even small deviations in ligand structure can significantly alter physiological outcome.

GLP-1r is expressed in a wide variety of tissues, including the pancreas, lung, heart, kidneys, stomach, intestine, pituitary, vagus nerve, and multiple regions of the central nervous system (Baggio and Drucker, 2007). The highest densities of GLP-1r in the brain are found in the nucleus of the solitary tract, area postrema, interpeduncular nucleus, posterodorsal and ventral tegmental nucleus, hypothalamic nuclei, thalamic nuclei, nucleus accumbens, and lateral septum (Göke et al., 1995; Merchenthaler et al., 1999; Van Dijk et al., 1996). There are some discrepancies among studies examining GLP-1r expression by radioactive binding or mRNA expression in brain, likely as a result of presynaptic receptor populations. However, there may be alternative splicing of the receptor, differences in translation, or another receptor entirely producing this effect. Having such wide distribution of GLP-1r allows a ligand to exert a host of different effects on whole body physiology depending on where the receptor is found, as has been reviewed (Holst, 2007). This is especially important to consider when using a long lasting therapeutic agonist which will likely act at many different receptor populations, effectively resulting in an endocrinization of a signal which is normally restricted by specific spatial release at distinct sites and powerful deactivation constraints.

5. GLP-1r intracellular signaling

GLP-1 acts in the pancreas to decrease blood glucose concentrations. It achieves this by increasing the synthesis and release of insulin, in addition to increasing neogenesis, proliferation, and by decreasing apoptosis of β cells. GLP-1-induced insulin release from pancreatic β cells is the most well studied intracellular signaling mechanism by GLP-1r.

In this system, GLP-1r acts through $G\alpha_s$ to stimulate adenylate cyclase and increase cyclic AMP (cAMP) levels (Drucker et al., 1987). This increase in cAMP has been shown to result in both protein kinase A (PKA)-dependent intracellular signaling, as well as exchange protein directly activated by cAMP (EPAC) dependent processes. The activation of these pathways allows GLP-1 to initiate a wide variety of mechanisms within the cell to ultimately trigger insulin release and genetic alterations (Baggio and Drucker, 2007; Cho et al., 2014; Holst, 2007; MacDonald et al., 2002; Seino and Shibasaki, 2005). GLP-1 has been shown to act through PKA and EPAC (cAMP dependent mechanisms) to inhibit ATP-regulated potassium channels (Kang et al., 2006; Light et al., 2002; Nakazaki et al., 2002; Shiota et al., 2002), increase activity of L-type voltage gated calcium channels (VGCCs) (Britsch et al., 1995) (Yada et al., 1993), and trigger opening of non-specific cation channels (Fig. 1) (Holz et al., 1995) (Leech and Habener, 1997). Together, these actions lead to increased calcium influx, thereby enhancing calcium-induced insulin secretion. Notably, inhibition of ATP-regulated potassium channels leads to increased glucose induced membrane depolarization, enhancing the sensitivity of that cell to glucose (Holz IV IV

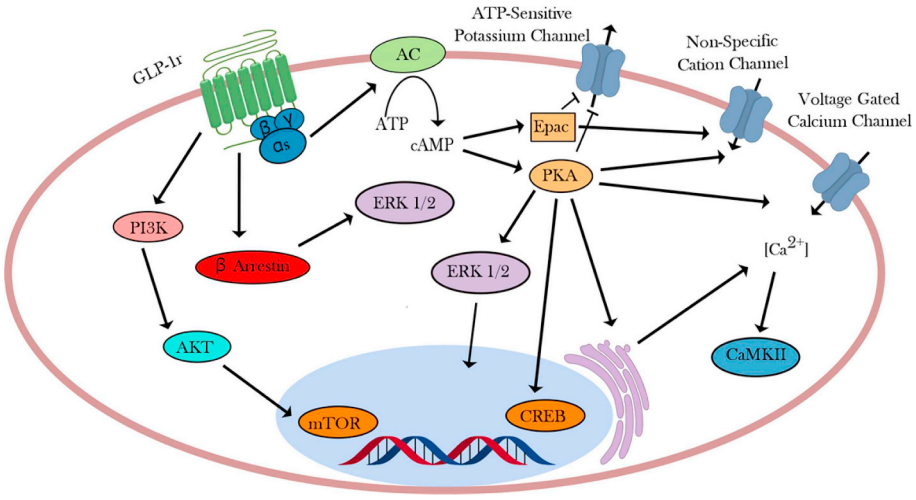

Fig. 1. GLP-1r mediated intracellular signaling via $G\alpha_s$. Although GLP-1r is known to associate with multiple different G proteins, $G\alpha_s$ is the most well studied coupling. Here, the diversity of downstream signaling is shown through the differential actions of ERK 1/2 depending on its activation. Activation by PKA results in transient translocation to the nucleus, while activation by β arrestin results in the targeting of cytoplasmic partners.

et al., 1993). There is limited evidence indicating that similar mechanisms may occur in hippocampal and hypothalamic GLP-1r expressing neurons (Beak et al., 1998; Gilman et al., 2003; Hayes et al., 2011).

Other effects of GLP-1 in β cells may or may not result from $G\alpha_s$ signaling. GLP-1r has been shown to associate in cultured cells with not only $G\alpha_s$, but also $G\alpha_q$, $G\alpha_i$, and $G\alpha_o$ (Montrose-Rafizadeh et al., 1999). There is also evidence supporting GLP-1 initiating a phospholipase C (PLC)-mediated mobilization of intracellular calcium, likely through $G\alpha_q$ (Gromada et al., 1995; Holz et al., 1999; Thompson and Kanamarlapudi, 2015). Additionally, limited evidence shows that GLP-1r signaling can initiate activation of CaMKII via calcium influx through L-type VGCCs, opening up further downstream pathways (Gomez et al., 2002). Further actions may be mediated through transactivation of other receptors. For example, GLP-1 acts to promote DNA synthesis and further inhibit potassium channels through transactivation of the epidermal growth factor receptor, leading to activation of phosphatidylinositol 3-kinase (PI3K) (Buteau et al., 2001). PI3K activation also leads to inhibition of apoptosis-related transcription factors. These actions also may result through $G\beta\gamma$ signaling. Coupling of GLP-1r to different G proteins opens up a wide variety of signaling pathways activated by the same ligand, underscoring the potential for diversity within the GLP-1r system.

The GLP-1r and other GPCRs inactivate following stimulation. GLP-1r signaling in β cells results in β-arrestin recruitment and signaling via extracellular signal-regulated kinases (ERK1/2) (Jorgensen et al., 2005; Quoyer et al., 2010; Sonoda et al., 2008). In pancreatic cells, GLP-1r internalizes following stimulation with GLP-1 or various agonists, whereby the receptor is ultimately recycled to the cell surface (Roed et al., 2014). The mechanism leading to this internalization is unclear. There is evidence in cultured cells for both a clathrin-dependent as well as a caveolin-dependent mechanism (Syme et al., 2006; Widmann et al., 1995). Moreover, additional evidence in HEK cells points to a $G\alpha_q$ dependent mechanism triggering activation of protein kinase C (PKC) and ERK 1/2, shown using specific chemical inhibitors of $G\alpha_q$ (Thompson and Kanamarlapudi, 2015). Under this mechanism, activation of $G\alpha_q$ triggers a PLC mediated increase in inositol triphosphate (IP_3), raising intracellular calcium through mobilization of endoplasmic reticulum calcium stores. A rise in calcium concentrations activates PKC, which phosphorylates ERK 1/2, which in turn phosphorylates the C-terminus of GLP-1r. This C-terminal phosphorylation then leads to internalization via an unknown mechanism. It is possible that no one mechanism holds true across all contexts in which GLP-1r is expressed.

Although the observation that GLP-1 activates signaling in the brain has been known for over three decades (Hoosein and Gurd, 1984), much less is known about GLP-1r initiated intracellular signaling in the central nervous system. In the hindbrain, GLP-1r acts through $G\alpha_s$ and PKA to enhance calcium influx through VGCCs, and stimulate mitogen-activated protein kinase (MAPK) and AMP-activated protein kinase (AMPK) (Hayes et al., 2011). In the hypothalamus and hippocampus, GLP-1 acts to increase cAMP levels and activate L type VGCCs, indicating $G\alpha_s$ mediated signaling (Beak et al., 1998; Gilman et al., 2003; Hayes et al., 2011). In cultured neurons, GLP-1 activates PI3K, AKT, and mechanistic target of rapamycin (mTOR) to protect against apoptosis (Kimura et al., 2009). In the paraventricular nucleus of the hypothalamus, GLP-1 has been shown to enhance glutamatergic transmission via PKA mediated phosphorylation of the AMPA receptor GluR1 subunit (Liu et al., 2017). More work is needed to elucidate the intracellular actions enacted by GLP-1r in the CNS; it is likely there will be subtle differences between pathways activated depending on the brain region and cellular context.

Investigation of ligand bias in GLP-1r signaling has focused on the three main signaling pathways initiated by $G\alpha_s$: cAMP production, ERK 1/2 activation, and increases in intracellular calcium (Furness et al., 2018; Wootten et al., 2016, 2013). As previously mentioned, these differences in signaling arise due to structural differences in the receptor conformations produced by binding of various ligands (Furness et al., 2018). This signaling bias has been meticulously studied mainly in conditions designed to mimic pancreatic GLP-1r signaling. However, it would be interesting to see if similar bias occurs at central GLP-1r populations and whether this alters the synaptic and behavioral outcomes of GLP-1r agonism.

The result of GLP-1r activation can differ depending on spatial and temporal factors. Compartmentalization can lead to a restriction of the action of downstream signaling partners (Calebiro and Maiellaro, 2014). This formation of microdomains has been shown to impact GLP-1r signaling. For example, PKA-induced activation of ERK 1/2 has been shown to be transient and result in its translocation to the nucleus (Khoo et al., 2003; Quoyer et al., 2010). In contrast, GLP-1r β-arrestin-induced ERK 1/2 activation does not result in translocation, and instead, preferentially targets cytoplasmic targets (Quoyer et al., 2010). The targeting of signaling partners to GLP-1rs is likely mediated by in some areas by A-kinase anchoring protein (AKAP) scaffolding proteins, which have been shown to target PKA to GLP-1r (Lester et al., 1997). Temporally, the action of GLP-1r is controlled through the timing of cAMP oscillations in β-cells, leading to only sustained elevations of cAMP triggering a nuclear translocation of activated PKA (Dyachok et al., 2006). Greater spatial and temporal resolution will likely provide a more complete picture of the factors influencing the environment specific outcomes of GLP-1r signaling.

6. Bariatric surgery, reduced food intake and the GLP-1-bile acid axis

The prevalence of obesity in the United States continues to increase. Bariatric procedures such as Roux-en Y gastric bypass (RYGB) and vertical sleeve gastrectomy (VSG) are the most effective and durable treatments for obesity and coincident type 2 diabetes (T2D) (Vetter et al., 2009). These procedures rapidly normalize glucose metabolism and enhance insulin secretion both before (Isbell et al., 2010) and after significant weight loss (Salehi et al., 2011). Such discoveries have prompted intensive efforts into identifying the mechanisms by which GLP-1 and other proglucagon peptides contribute to metabolic improvements after these surgeries.

Enhanced incretin responsiveness is a major proposed mechanism by which bariatric procedures improve oral glucose tolerance. Our group (Hansen et al., 2011; Isbell et al., 2010) and others (Laferrère et al., 2007; le Roux et al., 2007; Morínigo et al., 2006) have described a large increase in postprandial GLP-1 immediately after RYGB that is sustained (Mousumi et al., 2010; Vidal et al., 2009). At one month, postoperative elevations in GLP-1 are concurrent with enhanced insulin responses to enteral glucose and other incretin effects (Laferrère et al., 2007). Hansen et al. investigated nutrient bypass of the foregut for its contributions to enhanced glucose tolerance, insulin sensitivity and incretin responses in humans after a mixed meal was delivered orally before RYGB (gastric), and both orally (jejunal) and by gastrostomy tube (gastric) postoperatively (Hansen et al., 2011). They observed GLP-1 (active form) responses were absent preoperatively and restored postoperatively by both jejunal and gastric feeding routes. Such findings are consistent with more responsive GLP-1 EECs, located primarily in the distal ileum and proximal colon, to the rapid delivery of nutrients to the distal small intestine with both administration routes. We assessed GLP-1 responses upon enteral glucose via nasogastric or nasojejunal tubes in non-surgical glucose-tolerant obese subjects (Breitman et al., 2013). In this crossover study, glucose excursions obtained with nasogastric and nasojejunal delivery were replicated using isoglycemic glucose infusions, enabling determination of the GI tract to postprandial glucose disposal. Such determinations were made by comparing the amount of intravenous glucose required to match plasma glucose curves obtained following delivery of the same glucose load via nasogastric and nasojejunal delivery. Comparison of glucose excursion curves upon nasogastric versus nasojejunal glucose delivery revealed there was a

more rapid and six-fold greater GLP-1 response via nasojejunal delivery. Additionally, there was a twofold increase in the contribution of the GI tract to glucose disposal after nasojejunal compared to nasogastric delivery. These findings suggest that foregut bypass may alter GLP-1 responses by enhanced nutrient delivery to the hindgut.

We have also investigated bile acids for their role in regulating metabolic improvements, GLP-1 secretion, and weight loss after bariatric procedures. We (Albaugh et al., 2015), and others (Kohli et al., 2013; Patti et al., 2009; Pournaras et al., 2012; Steinert et al., 2013) have observed increases in serum bile acids after bariatric procedures. More specifically, we examined total and species-specific BA changes in Class III obese (BMI ≥ 40 kg/m2), pre-operatively and followed longitudinally at 1, 6, 12 and 24 months after RYGB. One month after surgery, bile acid levels increased nearly 3-fold relative to pre-operative levels, declined slightly at 6 months, then progressively increased up to 2-years after surgery. The bile acid increases we detected were concordant with improvements in both hepatic and muscle insulin sensitivity as we previously reported (Fabbrini et al., 2010; Tamboli et al., 2014). We hypothesized that the altered enterohepatic circulation of bile acids after RYGB mediates the metabolic improvements that underlie the resolution of T2D after the procedure. We utilized a novel surgical procedure in diet-induced obese (DIO) (Flynn et al., 2015) and lean (Albaugh et al., 2019) mice wherein bile is diverted from the gallbladder (GB) to the duodenum (GB-D, a sham procedure), the jejunum (GB-J), or ileum (GB-IL). This biliary diversion (BD) procedure permitted examination of altered bile flow, similar to that observed after RYGB, independent of alterations in gastrointestinal tract anatomy. Remarkably, the GB-IL procedure, but not GB-D or GB-J, recapitulated many of the beneficial metabolic outcomes observed after RYBG. In obese mice fed a high fat (60%) diet after GB-IL, dramatic reductions in food intake, body weight, hepatic steatosis and adiposity were concurrent with increases in serum bile acids, significantly improved oral glucose tolerance and changes in the gut microbiome. DIO GB-IL mice additionally exhibited significant fat malabsorption confounding the establishment of a direct cause and effect relationship between bile acids and improved glucose metabolism. To mitigate these confounding variables, we implemented GB-IL and sham (GB-D) surgeries in normal, low-fat (4.5%) chow-fed mice and again assessed their effects on nutrient metabolism and physiology. Remarkably, neither GB-IL of GB-D had effects on food intake, body weight or body composition. However, GB-IL mice maintained on a low-fat chow diet displayed significant elevations in serum bile acids as well as dramatic improvements in oral glucose tolerance. These improvements were not attributable to detectable differences in hepatic glycogen content, insulin sensitivity or intestinal glucose uptake, but were associated with enhanced insulin secretion. To investigate the potential contribution of GLP-1 to this phenomenon, we utilized a lymphatic fistula procedure and measured incretin concentrations in intestinal lymph. GLP-1 levels in the fasted state were significantly higher than controls. Postprandial GLP-1 excursions after a mixed meal, however, were similar. These observations contrasted with those of lymphatic GIP, which were similar to controls in both the fasted and fed states. Importantly, pretreatment of GB-IL mice with exendin 9 (Ex-9; 50 μg intraperitoneally), a GLP-1r antagonist, or cholestyramine (500 mg/kg p. o., daily for 3 days), a bile acid resin, mitigated improvements in fasting glycemia after GB-IL. Improvements in oral glucose tolerance after GB-IL were also assessed in GLP-1r knockout mice maintained on a low-fat, normal chow diet. Body weight and adiposity after GB-IL in Glp-1r null mice were unaffected by GB-IL surgery and were similar to controls, suggesting the importance of the Glp-1r in mediating the responses of the GB-IL procedure.

Finally, recent findings additionally suggest that the GLP1r also modulates systemic metabolism by limiting the bioavailability of intestinal GLP-1 (He et al., 2019). Deletion of integrin $\beta7^{+}$ ($It\beta7^{-/-}$) renders mice deficient of natural gut intraepithelial T lymphocytes (IELs) resident throughout the enterocyte layer of the small intestine. These mice exhibit metabolic hyperactivity when fed a high-fat and high sugar diet and are additionally resistant to obesity, hypercholesterolaemia, hypertension, diabetes, atherosclerosis and were protected from cardiovascular disease. These mice, on a pro-atherosclerotic $Ldlr^{-/-}$ background (chimeras) exhibited high basal GLP-1 tone with high gut *gcg* mRNA levels contrasting the relative GLP1r deficiency observed in $It\beta7^{-/-}$ mice containing fewer and mostly GLP1rl^{ow} T cells. in other words, loss of the GLP1r in natural IELs associated with increased plasma GLP-1. Chimeras lacking GLP1R ($Glp1r^{-/-}$ $\beta7^{-/-}$ $Ldlr^{-/-}$) exhibited elevated GLP-1 tone were protected from glucose intolerance, hypercholesterolaemia and cardiovascular disease. These results indicate that $\beta7^{+}$ IELS as critical gatekeepers of dietary metabolism in a GLP-1R manner.

7. GLP-1 in feeding and reward

GLP-1 is able to influence energy homeostasis through a multiplicity of actions. Although it is best known for its incretin effect, GLP-1 also exerts a potent effect on feeding behavior to control nutrient intake. Early studies utilized intracerebroventricular injections to show that exogenous modulation of GLP-1 action could dose dependently increase (through antagonism) (Meeran et al., 1999) or decrease (through agonism) (Donahey et al., 1998; Tang-Christensen et al., 1996; Turton et al., 1996) food intake in rodents. Intravenous infusions of synthetic GLP-1 also reduced food intake and subjective reporting of hunger in human participants (Gutzwiller et al., 1999). While the anorectic effect of GLP-1 was clear, it was more difficult to localize the effect to a specific circuit within the brain. Due to the wide distribution of GLP-1r, different groups attributed the anorectic effect to interactions with homeostatic (Goldstone et al., 1997; Gunn et al., 1996; Meeran et al., 1999; Turton et al., 1996) or aversion circuitry (Rinaman, 1999b; Seeley et al., 2000; Thiele et al., 1997). By directing GLP-1 infusions to specific brain regions, it was shown that specific populations of GLP-1r expressing cells mediated the visceral illness response associated with conditioned aversion, and that the anorectic effect could be separated from the aversion phenotype (Kinzig et al., 2002). Following these findings, there has been considerable focus on GLP-1's role in brainstem and hypothalamic nuclei in the regulation of homeostatic feeding.

7.1. Hindbrain

In the hindbrain, the role of GLP-1 in feeding has been studied in the parabrachial nucleus (PBN). The PBN receives monosynaptic connections from GLP-1 producing neurons in the NTS (Alhadeff et al., 2014), and applying exendin-4 to this region results in a suppression in chow and palatable food intake (Alhadeff et al., 2014; Richard et al., 2014). Exendin-4 also elevates the firing rate of neurons within the PBN, and enhances cFos expression, consistent with a stimulatory effect on neuronal activity (Richard et al., 2014). Further, lesion of the PBN disrupts the ability of exendin-4 to alter feeding behavior (Swick et al., 2015). Calcitonin gene-related peptide (CGRP) expressing cells within the PBN are likely the cell type mediating the effect of GLP-1r signaling within the PBN, as shown by localizing Fos immunoreactivity to CGRP cells and by silencing these neurons during exendin-4 administration (Campos et al., 2016). The PBN is thought to regulate satiety processes within the feeding network (Sternson and Eiselt, 2017), and an increase in activity following intra-PBN exendin-4 administration is consistent with this role. Further work in this area could integrate these GLP-1 responsive PBN neurons into currently known feeding circuits and behavioral circuits (Alhadeff et al., 2018), as started by work integrating the role of the arcuate nucleus input to the PBN(Campos et al., 2016). GLP-1 is also capable of acting within the NTS at local receptors (Card et al., 2018; Richard et al., 2015). Knockdown studies of GLP-1r within the NTS has shown that endogenous GLP-1 signaling in this region suppresses chow intake and meal size as well as self-administration of palatable food on both a fixed and progressive ratio schedule (Alhadeff

et al., 2017). Interestingly, GLP-1 within the NTS has been shown to be taken up by astrocytes and influence calcium dynamics of these astrocytes, indicating they may play a role in the function of GLP-1 within this nucleus (Reiner et al., 2016).

7.2. Hypothalamus

GLP-1 is able to act within several hypothalamic nuclei to alter feeding behavior. In the arcuate nucleus, studies of GLP-1 have yielded conflicting results. One group using intra arcuate nucleus microinjections of GLP-1 itself found no effect on 2 h cumulative food intake (Beiroa et al., 2014), while another found a reduction of 24 h food intake applying liraglutide (Sandoval et al., 2008). It is clear that GLP-1 is taken up by proopiomelanocortin (POMC) cells within the arcuate nucleus, and these neurons are depolarized by application of GLP-1 (Secher et al., 2014). This same study found that intra-arcuate nucleus application of the GLP-1 antagonist exendin-9 attenuated liraglutide-induced weight loss, examined at 14 days following chronic administration (Secher et al., 2014). Further work has found that GLP-1 also acts at kisspeptin expressing neurons (Heppner et al., 2017), indicating that GLP-1 in the arcuate nucleus may be participating in nodes connected to the hypothalamic-pituitary-gonadal axis. Importantly, the arcuate nucleus receives GLP-1 positive terminals (Heppner et al., 2017), but is also able to take up peripherally administered GLP-1r agonists (Secher et al., 2014). While it is clear that GLP-1 is able to alter neuronal function within the arcuate nucleus, the specific circuits and behavioral phenotypes modulated by this signal are still being elucidated.

In the paraventricular nucleus of the hypothalamus (PVN), both GLP-1 and exendin-4 reduce food intake (Burmeister et al., 2017; Sandoval et al., 2008). Glp-1r neurons in the PVN show markers of activity following refeeding, and inactivation of these neurons results in increased food intake and increased breakpoint on a progressive ratio task (Li et al., 2018). Expectedly, inducible silencing of GLP-1r expressing neurons in the PVN does not fully ablate the anorectic effect of peripherally administered liraglutide, likely due to redundancy in the ability of GLP-1 to alter feeding behavior (Li et al., 2018). A study investigating the molecular mechanisms of GLP-1 acting within the PVN found that using a genetic strategy to block AMPA receptor trafficking following exendin-4 administration to the PVN resulted in a blunted reduction in food intake (Liu et al., 2017). Thus post synaptic modulation of excitatory transmission appears to be a key player in the effect of GLP-1r on food intake within the PVN. However, the circuits in which these GLP-1r expressing neurons are participating also remain unknown. Future work could investigate the role of these hypothalamic GLP-1r expressing neurons in homeostatic feeding following weight loss, or whether GLP-1 in this region alters feeding to different degrees for different nutrients.

7.3. Mesolimbic dopamine system

Nodes of the mesolimbic reward circuitry are also impacted by local GLP-1r signaling. Intra VTA injections of exendin-4 result in a reduction in palatable food intake (Alhadeff et al., 2012; Mietlicki-Baase et al., 2013), as well as a reduction in the willingness to work for a palatable food reward on a progressive ratio schedule (Dickson et al., 2012). Based on functional studies of excitatory transmission, the GLP-1r receptor population mediating the effect of exendin-4 in the VTA is thought to be presynaptic (Mietlicki-Baase et al., 2013). Circuit analysis revealed the medial NAc shell VTA population to be modulated by exendin-4 (Wang et al., 2015). Intra NAc exendin-4 injections have shown that GLP-1r signaling in the NAc core, but not NAc shell, result in a reduction in food intake (Dossat et al., 2011). A more detailed analysis of licking microstructure found that the effect of GLP-1r in the NAc primarily effects the size of a “meal”, as defined by lick bursts (Dossat et al., 2013). Interestingly, this effect was specific to sucrose solution and did not occur with a saccharine solution, indicating a nutrient dependent effect. Similar to the VTA, analysis of excitatory transmission shows that GLP-1r stimulation primarily changes presynaptic measures of release probability, again indicating a presynaptic GLP-1r localization (Mietlicki-Baase et al., 2014). However, the specific input at which the GLP-1r dependent effect is produced remains unknown.

The GLP-1r exhibits a wide central distribution, with some populations outside of brain regions classically associated with modulation of feeding behavior. There is some evidence for that GLP-1 can act within the hippocampus to alter feeding behavior (Hsu et al., 2015). A more recent line of work has shown that GLP-1r agonism in the lateral septum is able to alter feeding behavior (Terrill et al., 2018, 2016).

7.4. Psychostimulants

Studies on the role of GLP-1 in regulating food intake led to the discovery that GLP-1 signaling also regulates reward and motivation associated with drugs of abuse (Mietlicki-Baase et al., 2013). This led to the discovery that administration of GLP-1 blunted the action of psychostimulants (Erreger et al., 2012; Graham et al., 2013). Notably, GLP-1r activation in the VTA and NAc has been linked to a reduction in cocaine seeking behavior (Hernandez et al., 2018, 2017). GLP-1 agonism has been shown to reduce locomotor activity stimulated by amphetamine (Erreger et al., 2012), a process that is known to depend on dopamine signaling in the NAc(Heusner et al., 2003). More recent work has shown that GLP-1 is able to dampen phasic dopamine transmission in the NAc core (Fortin and Roitman, 2017). This suppression of dopamine signaling may explain the GLP-1 induced alterations in psychostimulant reward-related behaviors, including conditioned place preference (Graham et al., 2013) (Reddy et al., 2016) and self-administration (Sørensen et al., 2015). Notably, in self-administration studies, researchers were able to determine that GLP-1 agonism had decreased the efficacy of cocaine as a reinforcer rather than simply reduced cocaine potency (Sørensen et al., 2015). However, it is likely that other brain regions also contribute to the ability of GLP-1 to dampen drug reward. A GLP-1r population in the lateral septum has been shown to be critical for the influence of GLP-1 agonism over cocaine conditioned place preference (Harasta et al., 2015; Reddy et al., 2016). This GLP-1r population occupies the dorsal portion of the lateral septum, a region which has been shown to constitute an important relay mediating the incorporation of contextual information from the hippocampus into reward processing in the VTA(Luo et al., 2011). Further studies have shown that GLP-1 agonism in the lateral septum is able to alter cocaine's action and dopamine homeostasis through the modulation of endocannabinoid signaling and the function of the dopamine transporter (Reddy et al., 2016). Thus, the modulation of the dopamine transporter by GLP-1r signaling likely plays an important role in the impact of GLP-1 agonism on psychostimulant induced behaviors in the lateral septum. The antagonistic relationship between GLP-1 and cocaine is well supported by preclinical work, as shown above. However, a study finding reduced serum GLP-1 levels in human participants following intravenous cocaine administration shows that this relationship may be bidirectional (Bouhlal et al., 2017).

7.5. Alcohol and nicotine

Subsequent work has expanded the effect of GLP-1 to impact alcohol intake and reward (Egecioglu et al., 2013b; Shirazi et al., 2013). GLP-1 agonism is able to dampen alcohol self-administration as well as alcohol conditioned place preference, indicating that these effects may also be mediated by the same circuitry controlling response to psychostimulants (Shirazi et al., 2013). In humans, a genetic variant of the GLP-1r has been found to be associated with alcohol use disorder, enhancing the validity of the preclinical results in this area (Suchankova et al., 2015). In contrast to these preclinical data, there have been reports that

bariatric surgeries in humans, that elevate gut hormones like GLP-1, may result in an increased propensity to abuse alcohol in a small proportion of the population (Ertelt et al., 2008). Follow up studies in animals have produced mixed results (Davis et al., 2012; Hajnal et al., 2012). A more detailed and controlled analysis of the clinical population is necessary to determine whether this represents a real consequence of bariatric surgery. Correlation to pre and post-operative variables would allow a better idea of what could be contributing to the phenomena. A more detailed discussion of the role of GLP-1 in preclinical studies of alcohol related behaviors can be found elsewhere (Jerlhag, 2018). GLP-1 has also been shown to influence nicotine intake (Egecioglu et al., 2013a; Tuesta et al., 2017). The influence of GLP-1 agonism on nicotine is likely mediated by classical reward circuitry in addition to aversion circuits.

Due to the widespread expression of GLP-1r, it is important to consider the context in which the peptide is signaling when understanding its effect. For example, GLP-1r populations in the VTA and nucleus accumbens likely allow GLP-1 to modulate salience and rewarding efficacy of drug rewards (Schmidt et al., 2016; Sørensen et al., 2015). On the other hand, the GLP-1r population in the lateral septum likely mediates associations of context and reward, measured through place preference and reinstatement paradigms (Luo et al., 2011; Reddy et al., 2016; Sartor and Aston-Jones, 2012). Thus, GLP-1 is able to alter distinct properties of the rewarding signal depending on the circuit context. Furthermore, the mechanism by which GLP-1 acts to alter the behavior of cells within the circuit can differ. While it has been shown that GLP-1 can act to blunt dopamine transmission in both the nucleus accumbens (Fortin and Roitman, 2017) and the lateral septum (Reddy et al., 2016), this has been shown to occur via a transporter-independent and a transporter-dependent manner, respectively. This may arise from differences in intracellular signaling initiated by the receptor, directed by receptor localization and grouping with intracellular signaling partners (Calebiro and Maiellaro, 2014; Lester et al., 1997; Quoyer et al., 2010). Future work is needed to identify the intracellular events that lead to these different signaling outcomes, and greater anatomical resolution will illuminate the precise localization of the receptor populations mediating these outcomes.

8. Concluding remarks

The GLP-1 signal represents a propagating message which spreads throughout multiple tissues to modulate an astonishingly wide variety of processes. The broad reach of this signal and its evolutionary conservation underscore its critical role in normal physiological functioning. Thus, it should come as no surprise that GLP-1 is able to potently regulate systems ranging from glucose homeostasis to motivated behavior. It should be equally recognizable that this multiplicity of actions requires immense diversity of the GLP-1 signal. This diversity has been found to be expressed at many levels, including synthesis, receptor function, and downstream signaling partners. There is little doubt that there are additional complexities of the GLP-1 system that will be found to differentiate populations. Future work will rely on relatively recent technologies which allow for the conditional expression of genes and the delicate pharmacological manipulation of intracellular signaling, as has been used to produce the most recent results presented here. With these tools and the knowledge accrued from the previous three decades of GLP-1 research, we will hopefully see novel clinical applications of the already FDA approved GLP-1 receptor agonists.

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