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STATE-OF-THE-ART REVIEW

Glucagon-like peptide-1 drives energy metabolism on the synaptic highway

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Glucagon-like peptide-1 (GLP-1), a gut–brain hormone, coordinates energy balance in both peripheral organs and the central nervous system (CNS). In the pancreas, GLP-1 facilitates insulin exocytosis or suppresses glucagon exocytosis via multiple pathways such as regulating K_{ATP}/Kv channels, N-type Ca^{2+} channels, and the readily releasable pool. In the CNS, GLP-1 signaling regulates neuronal excitability in various brain regions, including neurons in the hippocampus, hypothalamus, and mesolimbic systems. GLP-1 modulation on synaptic transmission includes both pre- and postsynaptic pathways that are either excitatory or inhibitory. Synaptic transmission conveys information flow in the brain and governs brain-mediated behaviors. The study of GLP-1 control of energy metabolism at a synaptic level may shed light on the role of GLP-1 function in the brain. Various challenges remain including defining the mechanism of GLP-1 release in the brain.

Introduction

The high prevalence of obesity results in a range of negative health and socioeconomic consequences for modern society. Recently, analogs of glucagon-like peptide-1 (GLP-1) are being used clinically as therapies to combat obesity [1].

GLP-1, an incretin hormone derived from post-translational processing of preproglucagon (PPG), is mainly produced in the L-cells of the intestine and a subpopulation of neurons in the caudal brain stem [2]. The GLP-1 receptor (GLP-1R) is a G protein-coupled receptor (GPCR) that is expressed abundantly in the periphery as well as in the central nervous system (CNS). GLP-1 has been reported to directly affect the liver [3], although the classical GLP1R is not expressed in hepatocytes of mice [4] or primates [5]. The hepatic effects might therefore involve a yet unidentified alternative receptor. Even intracellular signal induced by the classical GLP-1R, however, can recruit various G proteins, including $G\alpha_s$, $G\alpha_{1/2}$, $G\alpha_q$, as well as $G\alpha_{i/o}$ [6,7]. When the GLP-1R is coupled to G proteins, its

Abbreviations
AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; ARC, arcuate nucleus; CNS, central nervous system; CNQX, 6-cyano-7-nitroquinoxaline-2,3-dione; DA, dopamine; DG, dentate gyrus; DMV, dorsal motor nucleus of the vagus; Epac, exchange protein directly activated by cAMP; EPSCs, excitatory postsynaptic currents; EPSPs, excitatory postsynaptic potentials; Exn4, exendin-4; Exn9, exendin (9-39); GABA, γ-aminobutyric acid; GLP-1, glucagon-like peptide-1; GLP-1R, glucagon-like peptide-1 receptor; GluRs, glutamate receptors; IPSCs, inhibitory postsynaptic currents; Kv, voltage-gated K^+ channel; K_{ATP}, ATP-dependent K^+ channel; LHA, lateral hypothalamus area; LPS, lipopolysaccharide; LTP, long-term potentiation; MSN, medium spiny neuron; NAc, nucleus accumbens; NMDA, *N*-methyl-D-aspartate; NTS, nucleus of solitary tract; PKA, protein kinase A; PPG, preproglucagon; PPR, paired pulse ratio; PVN, paraventricular nucleus of hypothalamus; SNAREs, soluble NSF attachment proteins; TTX, tetrodotoxin; T2DM, Type II diabetes mellitus; VMH, ventromedial hypothalamus; VTA, ventral tegmental area.

activation leads to the stimulation of adenylate cyclases, increases in cAMP levels, and activation of the cAMP-dependent PKA/Epac2 pathway [6,8–10], followed by Ca^{2+} release and inhibition of other ion channels, i.e., voltage-dependent potassium channels (Kv) and ATP-sensitive potassium channels (K_{ATP}) [11,12]. This pathway is crucial for both insulin and glucagon release in the pancreas, as well as neuronal excitability in the CNS [13,14]. The presynaptic PKA/Epac2-mediated increase of intracellular [Ca^{2+}] triggers neurotransmitter release [15], and postsynaptic PKA activity may increase the phosphorylation of postsynaptic receptor and thus regulate receptor membrane trafficking (Fig. 1) [16]. Besides coupling with $G\alpha_s$, GLP-1 can initiate signal transduction via the activation of phospholipases in skeletal muscle [17], and stimulate inositol phosphate production in the liver and adipose tissue [18], although it remains unknown whether a yet unidentified alternative GLP-1R may mediate these effects. The physiological consequences of $G_{o/i}$-coupled GLP-1R are less known [7]. However, recent studies reported that GLP-1R activation suppressed glutamatergic receptor-mediated synaptic responses [19], as well as a small population of paraventricular nucleus of hypothalamus (PVN) neurons [20], which may indicate a $G_{o/i}$-mediated effect by the GLP-1R.

In general, it is well documented that GLP-1R activation reduces feeding behavior and that GLP-1 regulates neuronal activity on the synaptic level. To document whether synaptic transmission and plasticity play an important role during GLP-1 regulation on behaviors like food intake, we summarized the synaptic effects of GLP-1 in the CNS in this review.

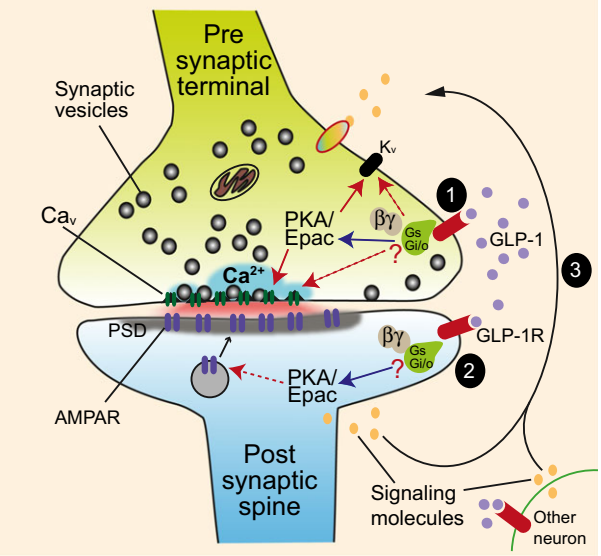

Fig. 1. The schematic 'putative' simplified pathways for GLP-1 regulation on presynaptic and postsynaptic components of the nervous system. GLP-1 binds to GLP-1R and activates the PKA or Epac pathway, followed by an increase in intracellular [Ca^{2+}] in presynaptic nerve terminals, which triggers neurotransmitter release (1). In the postsynaptic compartment, PKA or Epac activation potentially phosphorylates GluRs and then stimulates their membrane trafficking (2). Alternatively, the modulation on synaptic vesicle exocytosis from the presynaptic terminal can arise from a postulated signaling molecule (indicated by the yellow dots) from the postsynaptic neurons or indirectly from another neuron (3).

GLP-1 regulates hippocampal neuronal function

While the hippocampus is classically considered as a key limbic structure that is important for learning and memory, it has been shown that hippocampal GLP-1, leptin, and ghrelin signaling regulates food intake behavior [21–23]. The activation of GLP-1R has profound effects on hippocampal neurons, in regions such as CA1, CA3, and the dentate gyrus (DG).

In the hippocampal CA1 region, GLP-1R activation increases the spontaneous firing activity of neurons. This facilitatory effect can be blocked by the glutamate inhibitor, 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX), suggesting that GLP-1 signaling increases excitatory synaptic transmission in the hippocampus [24]. Similarly, GLP-1 protects against the Aβ1-40-induced decrease in frequency of the miniature excitatory postsynaptic currents (mEPSCs) in hippocampal neurons [25]. While no evidence has shown that PPG neurons of the nucleus of solitary tract (NTS) project to the hippocampus, abundant GLP-1 receptors are found in the caudal area of CA1 and CA3, as well as the DG [26–28], suggesting that GLP-1 may be derived from volume transmission or peripheral circulation [21]. Interestingly, GLP-1 enhances long-term potentiation (LTP) of synaptic transmission in CA1, while GLP-1R knockout mice displayed severe impairment in this synaptic plasticity [29–35]. Consistently, GLP-1 activation can restore lipopolysaccharide (LPS)-induced impairment of LTP in CA1 [36]. We believe that GLP-1 regulates CA1 neuronal function through a postsynaptic mechanism because CA1 LTP originates from a postsynaptic mechanism [37,38].

The CA3 pyramidal neurons are also regulated by GLP-1 signaling. GLP-1R activation by GLP-1 or its analog exendin-4 (Exn4) increases both the frequency and amplitude of spontaneous inhibitory postsynaptic currents (IPSCs); however, the effects are blocked by

tetrodotoxin (TTX), suggesting the requirement of action potentials [39]. The most plausible explanation is that GLP-1R activation increases the action potential firing in the presynaptic inhibitory neurons to increase the inhibitory tone on postsynaptic CA3 neurons. On the other hand, the tonic stimulation of $GABA_A$ receptors by ambient and/or synaptic GABA is facilitated by GLP-1R activation, even in the presence of TTX [39], suggesting an involvement of postsynaptic GLP-1R. Thus, GLP-1 enhances $GABA_A$ signaling in CA3 by both pre- and postsynaptic mechanisms.

In the DG of the hippocampus, pretreatment of animals with a GLP-1R antagonist (Exn9) increases the input–output relation and decreases the paired pulse ratio (PPR) of field excitatory postsynaptic potentials (EPSPs), suggesting that endogenous GLP-1R blockade facilitates excitatory synaptic transmission [40]. This is different from the aforementioned facilitation of synaptic releases, indicating that, depending on the neuronal subtype, GLP-1 may use different G protein signaling (G_s or $G_{i/o}$) cascades to achieve its function [6,7]. Nevertheless, it has also been reported that application of a GLP-1 agonist results in a biphasic response beginning with increased and followed by decreased single unit activity in the hippocampal CA1 region [24].

GLP-1 signaling in the hypothalamus

The hypothalamic nuclei play crucial roles in energy homeostasis, e.g., lesions of the PVN or ventromedial hypothalamus (VMH) induce overeating, while damaging the ventrolateral hypothalamus leads to the cessation of feeding behavior [41–43]. GLP-1R is widely expressed in the hypothalamic region paraventricular nucleus (PVN), arcuate nucleus (ARC), as well as the dorsal medium hypothalamus (DMH) and lateral hypothalamic area (LHA) [26]. Interestingly, NTS GLP-1 neurons only project to the PVN and DMH in hypothalamus, but not in the ARC [44], suggesting that the PVN and DMH receives synaptic regulation by GLP-1 released from the NTS, while ARC neurons are regulated by volume GLP-1 input, either from NTS or from circulating levels of GLP-1.

GLP-1 receptor activation in hypocretin/orexin LHA neurons causes an increase in the firing frequency of action potentials, but has no effect on melanocortin-concentrating hormone (MCH)-expressing neurons [20]. This increase in neuronal excitability in orexin neurons is likely dependent on both the facilitation of excitatory synaptic transmission and direct postsynaptic depolarization of the cell membrane [20]. What is interesting is that the depolarization of the orexin neuronal membrane is dependent on extracellular sodium, but not potassium. Considering that G proteins activate voltage-gated potassium channels (GIRK) directly, but not sodium channels, the membrane potential modulation by GLP-1 may be determined by the particular second messenger cascade activated by the GLP-1 receptor. In addition to direct regulation by GLP-1R on orexin neurons, the facilitation of excitatory synaptic transmission by GLP-1 may also be mediated by the afferent nerve terminal, as only the frequency but not the amplitude of mEPSCs in the presence of TTX is increased [20]. Thus, inhibitory synaptic inputs to LHA orexin neurons are also positively regulated by GLP-1R activation via presynaptic regulation [20]. These inputs to LHA, which can be regulated by GLP-1, may come from PVN or ARC, as both nuclei have abundant GLP-1 receptor expression.

GLP-1R action differs in the VMH, where aspartic acid, but not glutamate release seems to be facilitated and suggests that *N*-methyl-D-aspartate (NMDA) receptor activation is involved in the GLP-1 regulation of energy metabolism [45]. Interestingly, glutamine is increased due to treatment with GLP-1 [45]. Considering that most of the glutamine is released by astrocytes, GLP-1 may modulate astrocyte activity through the glutamine receptor in the VMH. Interestingly, GLP-1 has been found to inhibit LPS-induced production of IL-1β by cultured rat astrocytes [46], and a more recent paper suggested that GLP-1 signaling in astrocytes might contribute to food intake suppression [47].

In the PVN, GLP-1R activation results in diverse responses with the majority (~ 57%) of the cells showing facilitation of action potential firing, while ~ 28% show no responses and ~ 14% show decreased neuronal firing [20]. However, all the tested PVN neurons show a depolarization following GLP-1 application in a recent study [26]. Considering the diversity of cell subtypes in the PVN, and the possible cell type-specific expression of G_s- or $G_{i/o}$-coupled GLP-1Rs, it is not surprising that the regulation of GLP-1 signaling in the PVN is heterogeneous.

Taken together, it is most likely that presynaptic regulation is one major pathway by which GLP-1 regulates hypothalamic neuronal activity. Recent study suggests that synaptotagmin-7 (Syt7) can be phosphorylated by GLP-1 [48] and Syt7 is ubiquitously expressed in the CNS including hypothalamus [49]. Considering that Syt7 has been shown to be important for slow asynchronous synaptic vesicle exocytosis [50] and regulation of readily reliable pool (RRP) [51], it is of interest to

study whether GLP-1/Syt7 signaling cascade is involved in the presynaptic function of GLP-1 in the hypothalamic neurons to control feeding behavior.

The mesolimbic system plays a key role in mediating GLP-1 regulation of food intake

Both homeostatic (hunger-driven) signals and hedonic (reward-related) signals contribute to the control of feeding behavior. The mesolimbic dopamine (DA) system is a common neural integrator involved in the control of hedonic food intake [52,53]. GLP-1 receptors are broadly expressed in reward neural centers, such as the nucleus accumbens (NAc) and the ventral tegmental area (VTA) [28], and the activation of GLP-1R in both the NAc and VTA causes reduction in food intake [54,55]. Unlike the hippocampus, both the NAc and VTA receive projections from NTS GLP-1 neurons [44]. Blockade of the GLP-1R increases highly palatable high-fat food intake, which indicates these connections are physiologically relevant for the control of food intake [56].

GLP-1 facilitates excitatory synaptic inputs to medium spiny neurons (MSNs) in the NAc core of rats [55], likely via increase of presynaptic release probability (increased mEPSC frequency, no change in mEPSC amplitudes, and a reduction in PPR) [55]. However, GLP-1 application within the NAc core seems to have no effects on DA release, suggesting no presynaptic regulation on DAergic nerve terminals [55]. It is interesting that GLP-1 seems to cause hyperpolarization in MSN cells and suppresses the input–output necessary for generation of action potentials when injecting currents [55]. These data show that within the NAc, the role of GLP-1 in regulating MSN functions is multifaceted.

In the rat VTA, application of the GLP-1 analog, Exn4, facilitated excitatory synaptic inputs to putative VTA DA neurons, likely via a presynaptic mechanism, i.e., it increased the frequency of sEPSCs and decreased the PPR [54]. However, our recent data suggest that GLP-1 regulation of VTA neurons might be cell type-specific. GLP-1 activation suppresses excitatory synaptic strength without any perturbation in the synaptic strength of non-DA neurons that are projecting to the NAc [19]. Taken together, the two lines of evidence support a complex '*Yin-Yang*' regulation of GLP-1 in the VTA, which is dependent on cell type and pre-/postsynaptic regulation. Nevertheless, VTA DA neurons projecting to the NAc or prefrontal cortical brain regions have differential responses toward reward and avoidance [57,58], suggesting that cells in the VTA are functionally heterogeneous.

Functions of GLP-1 in caudal hindbrain neurons and the dorsal vagal complex

GLP-1-producing PPG neurons in the brain are mainly localized to the NTS [44]. The NTS receives direct vagus inputs and appears to play an important role in food intake motivation. Intra-NTS activation of the GLP-1R reduces intake of palatable high-fat food, operant responding for sucrose under a progressive ratio schedule of reinforcement, and the conditional place preference for a palatable food [59]. The detailed synaptic mechanisms mediating these responses remain to be elucidated [60]. Interestingly, using a transgenic PPG-GFP mouse model, it has been shown that GLP-1-producing PPG neurons are rapidly and directly depolarized by leptin, but are unaffected by GLP-1 itself [61]. This is not surprising because no GLP-1 receptor was found in NTS PPG neurons, while leptin receptor depletion in GLP-1-expressing neurons induces hyperphagia [60,62,63]. Thus, GLP-1 signaling within the NTS is possibly mediated by non-PPG neurons located in the NTS.

The dorsal motor nucleus of the vagus (DMV) in the brain stem provides the preganglionic motor fibers that project to the visceral organs [64], innervates the intrapancreatic ganglia, and modulates pancreatic secretory functions, including insulin secretion and glucose homeostasis [65,66]. Half of the pancreas-projecting neurons in the DMV respond only to GLP-1 [67], indicating that its regulation of this system is mediated via a very specific population of neurons in the DMV. Both postsynaptic and presynaptic mechanisms are suggested to be involved in GLP-1 regulation of DMV neurons. Activation of the GLP-1R depolarizes a subpopulation of DMV neurons through inhibiting K^+ currents, which is not affected by TTX, suggesting a postsynaptic inhibition of K^+-conductance, similar as reported previously [20]. Meanwhile, TTX application suppressed the GLP-1-induced depolarization in some DMV neurons, which suggests an involvement of presynaptic function (likely via regulating $GABA_A$ receptor-mediated current responses) [67]. Taken together, GLP-1 treatment activates DMV preautonomic neurons, which project to the pancreas and results in insulin exocytosis and/or inhibition of glucagon release. How GLP-1 exactly regulates DMV neurons, particularly their synaptic transmission, is currently unclear.

As a gut–brain hormone, GLP-1 coordinates energy metabolism via actions in both the peripheral and CNSs. Vagal afferent neurons serve as a neural conduit between the gut and brain. The potent satiety

effect of peripherally administered GLP-1 can be greatly reduced by vagotomy or chemically induced deafferentation [68–70]. Moreover, GLP-1 has been shown to directly excite hepatic vagal afferents [71], and vagotomy impaired the effect of GLP-1 regulation on blood glucose [72].

GLP-1 is capable of increasing excitability in a subpopulation of nodose ganglion cells. Like in islet β-cells (described in detail below), nodose ganglion neurons express Kv channels, which mediate the repolarization of membrane potential. GLP-1 inhibits the Kv current, resulting in membrane depolarization and increase in intracellular [Ca^{2+}] [73]. On the other hand, knockdown of the GLP-1 receptor in vagal afferent neurons in the nodose ganglion blunted insulin release after a meal [74]. Thus, it is clear that the GLP-1 signaling in nodose ganglion cells controls insulin release. However, it is still unknown whether this pathway is cAMP/PKA-dependent.

Lessons from pancreatic effects of GLP1

GLP-1 signaling is well studied in the pancreatic system. Given the similarity of synaptic vesicle exocytosis and the exocytotic pathways in the pancreatic cells, results from studies on pancreatic system provide a critical perspective for GLP-1R action in other tissues.

GLP-1 augments insulin release in pancreatic β-cells

Insulin is secreted in response to glucose by regulated exocytosis of insulin-containing secretory granules. GLP-1 is believed to augment glucose-stimulated insulin secretion. There is an excellent review on how GLP-1 regulates insulin release from β-cells [for review see 75]. There are many ion channels related to the exocytosis of insulin, such as K_{ATP}, Kv, voltage-dependent Ca^{2+} channels (VDCC), and nonselective cation channels [12,76], which may be modulated by GLP-1 at different levels.

In general, GLP-1 regulates insulin exocytosis in β-cells in the following ways:

1 *K_{ATP} channels:* GLP-1 inhibits β-cell K_{ATP} channels, which leads to membrane depolarization and insulin release [77–79]. Interestingly, the inhibition of GLP-1 on K_{ATP} is mediated by the cAMP/PKA pathway [80], indicating that it may be influenced by glucose level. The catalytic subunit of PKA (cPKA) inhibits K_{ATP} current in an ADP-dependent manner. ADP is converted to ATP in the presence of high glucose levels. cPKA reduces K_{ATP} function under low levels of ADP, which consequently induces exocytosis of insulin.
2 *Kv channels*: Knocking out Kv channels enhances glucose-stimulated insulin secretion [81]. GLP-1 and its agonist Exn4 antagonized β-cell repolarization by reducing Kv currents [12]. Further studies indicate both cAMP/PKA and PI_3 kinase/PKCζ signaling via transactivation of the epidermal growth factor (EGF) receptor are required for antagonism of Kv currents on β-cells. Like K_{ATP} channels, the inhibition of GLP-1 on Kv channel-induced insulin secretion is also glucose-dependent [11].
3 *Ca^{2+}-signaling:* L-type Ca^{2+} channels mediate Ca^{2+} influx and induce insulin secretion [82,83]. GLP-1 can directly facilitate Ca^{2+} entry through them via the PKA pathway [84]. Again, like the GLP-1 effects on β-cell K_{ATP} and Kv channels, the stimulation of Ca^{2+} channels is cAMP-dependent. Besides Ca^{2+} channels, GLP-1 is thought to enhance a nonspecific cation channel carrying predominantly Na^{+} currents [85,86], as well as cause a Ca^{2+} wave via IP_3, which can activate Ca^{2+}-dependent Cl^{-} outflux [87]. Thus, it contributes to the insulin release from β-cells and may also contribute to synaptic vesicle release in the CNS.
4 *Synaptotagmin:* Insulin granule exocytosis is mediated by a multiprotein complex composed of SNARE proteins (SNAP-25, Syntaxin, and synaptobrevin2) and Munc18-1 by a process that shares similarities with synaptic vesicle exocytosis in neurons [88]. In addition to SNARE proteins, synaptotagmin, as a Ca^{2+} sensor in the membrane of the presynaptic axon terminal plays an important role in the regulation of hormone secretion and neuropeptide release [50,89,90]. Synaptotagmin 7 is a major Ca^{2+} sensor for insulin exocytosis [91–93]. Interestingly, a very elegant recent work suggested that GLP-1R activation phosphorylates Syt7 to facilitate insulin secretion [48]. This study may shed light on the therapeutic agents for the treatment of diabetes by improving insulin secretion. Moreover, as Syt7 functions as a slow Ca^{2+} sensor at CNS synapses [50], further study is needed to elucidate whether Syt7 is a target for GLP-1 signaling-mediated synaptic releases.
5 *Regulation of Readily releasable pool (RRP):* The insulin granule vesicles in the RRP of β-cells are primed vesicles that are immediately ready to be released upon triggering. Vesicles in the RRP are usually predocked at the plasma membrane in a complex with SNAREs and Ca^{2+} sensors that allow for a rapid Ca^{2+}-dependent fusion [94]. Both PKA

and exchange protein directly activated by cAMP (Epac) pathways have been shown to be involved in modulating the insulin granule RRP sizes [95,96], thus it is conceivable that GLP-1 signaling affects RRP and increases the apparent vesicle release probability upon Ca^{2+} influxes.

GLP-1 inhibits glucagon secretion in pancreatic α-cells

It is well known that GLP-1 inhibits glucagon secretion [97]. GLP-1 receptors are expressed on α-cells although the distribution is much lower than β-cells [98]. The α-cell is electrically activated during hypoglycemia. Ca^{2+} enters via N-type Ca^{2+} channels, which are open during the firing of action potentials. The entry of Ca^{2+} triggers exocytosis of glucagon-containing secretory vesicles [98,99]. When GLP-1 binds to GLP-1 receptor on α-cells, G_s associated activation induces a small increase in intracellular cAMP concentration, which in turn activates the PKA pathway, but not the low-affinity cAMP sensor Epac pathway. PKA-dependent inhibition of N-type Ca^{2+} channels may lead to the strong suppression of glucagon exocytosis [98]. It is of interest to note that N-type Ca^{2+} channels are a major player at nerve terminals in the CNS as well, thus it is conceivable that at specific synapses in the CNS, GLP-1 activation suppresses presynaptic releases of neurotransmitter.

In addition to the direct effect of GLP-1 on α-cells, a recent article reported that GLP-1Rs also express in somatostatin δ-cells [4]. As we know, somatostatin has strong inhibition effects on glucagon release [100]. Thus, it is possible that GLP-1 may inhibit α-cell glucagon release indirectly (similar to what we proposed in Fig. 1 in the nervous system) via stimulating δ-cells somatostatin secretion.

Taken together, three important channels can be modulated by GLP-1R signaling that are relevant to insulin/glucagon release: Kv, K_{ATP}, and N-type Ca^{2+} channels. Additional mechanism for GLP-1 function also includes the regulation of RRPs [95,96]. Like neurotransmitter release, Ca^{2+} sensors, especially the synaptotagmins, are crucial for insulin/glucagon exocytosis. For example, Syt7 is proposed to be a principal Ca^{2+} sensor for Ca^{2+}-triggering of glucagon exocytosis from pancreatic α-cells [101]. It is of interest to investigate whether GLP-1 inhibits glucagon release via SNARE proteins and/or synaptotagmins modulation in the future [15].

Summary

GLP-1, a potent gut–brain peptide, regulates metabolism by suppressing food intake, facilitating insulin release, inhibiting glucagon release, as well as slowing gastrointestinal mobility. How GLP-1 regulates neuronal activity is not clear. As synaptic transmission is responsible for brain-mediated behavior, including feeding behavior, understanding the effects of GLP-1 at the synaptic level is crucial. In this review, we focused on how GLP-1 signaling affects synaptic response, as well as Ca^{2+}-triggered insulin release in the pancreas. Briefly, in the pancreas, GLP-1 inhibits Kv/K_{ATP} and Ca^{2+} channels in β and α cells, respectively, resulting in stimulation of insulin release and suppression of glucagon release. GLP-1 has also been shown to increase RRP via both PKA and Epac pathways [95] in β-cells. Moreover, the phosphorylation of Syt7 by GLP-1 was showing to augment insulin secretion for β-cells [48]. In the CNS, GLP-1 excites neurons in the hippocampus CA1, DG, NAc, and most regions of the hypothalamus, likely by regulating both presynaptic releases, as well as postsynaptic cellular signaling. Hippocampus CA3, VTA DA neurons can be suppressed by GLP-1. Most likely, the vagal complex, which connects to the pancreas and brain stem, is strengthened by GLP-1 (Table 1).

Table 1. Region-specific effects of GLP-1 signaling in CNS.

Brain region	Effects
Hippocampus	
CA1	Increase glutamate release [24]
	Strengthen LTP [29]
CA3	Increase GABA release [39]
DG	Facilitate excitatory synaptic release [40]
Hypothalamus	
LHA	Facilitate presynaptic excitatory synaptic release [20]
	Depolarize postsynaptic membrane potential [20]
PVN	Depolarize PVN neurons, increase most of PVN neurons firing [20,26]
VMH	Facilitate aspartic and glutamine release [45]
Mesolimbic system	
NAc	Increase of presynaptic release probability [55]
VTA	Facilitated excitatory synaptic inputs [54]
	Decreased excitatory synaptic strengths in VTA-to-NAc-projecting neurons [19]
Dorsal vagal complex	
DMV	Depolarize pancreas-projecting neurons [67]
Nodose ganglion	Inhibit Kv channel [73]

The molecular mechanism mediating the impact of GLP-1 on neuronal function is far from clear because of: (a) the various neuronal subtypes, as well as complex neuronal connections in the brain. (b) GLP-1R couples to diverse subtypes of G proteins including G_s or $G_{i/o}$, which adds another dimension of complexity in mediating cellular functions. (c) GLP-1 regulates neuronal function via both presynaptic (regulating synaptic vesicle release) as well postsynaptic (regulating postsynaptic receptor trafficking) mechanisms. It is of interest to note that Syt7 has multifaceted functions in synaptic transmission: function both as a Ca^{2+} sensor [50] and a regulator for RRP [51]. However, whether GLP-1/Syt7 signaling is involved in synaptic transmission in the CNS remains to be elucidated.

The majority of the published data have relied on the effect of pharmacological application of the GLP-1 analog (Exn4). Therefore, a pressing question is to understand how endogenous GLP-1 functions at the cellular and synaptic levels, and how they may regulate food intake, as well as how they communicate with peripheral organs to achieve regulation in metabolism. Further understanding is essential to our understanding of fundamental biology, i.e., how neuromodulator works in the brain, and is also important to developing effective therapies in combating eating disorders and obesity.

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Authors contributions

JL and ZP wrote the manuscript.

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