CANDIDATE
REVIEWS

Glucagon-like Peptide-1 is Much More Than an Incretin

Erin E. Watt

Abstract

This review will discuss glucagon-like peptide-1 (GLP-1) in both the periphery and the brain; GLP-1 analogues as treatments for type-2 diabetes mellitus (T2DM) and obesity; and examine the recent findings about GLP-1 signaling and striatal dopamine (DA) homeostasis. The published literature was reviewed, with an emphasis on recent publications investigating GLP-1's actions beyond its typical incretin role, such as novel signaling pathways in the brain. In patients with T2DM, GLP-1 levels are reduced, but GLP-1 receptor (GLP-1R) signaling remains intact. Therefore, GLP-1R agonists are ideal therapies for T2DM. Furthermore, GLP-1R signaling reduces appetite, decreases fat mass, promotes cardiovascular protection, and can modulate striatal DA homeostasis, making GLP-1R agonists an ideal therapy for obesity. GLP-1R agonists can cross the blood-brain barrier, while GLP-1R's in the brain contribute to the reduction in appetite and decrease in fat mass shown in GLP-1R agonist studies. Recent studies show that GLP-1R signaling may also regulate striatal DA homeostasis, which is known to be dysfunctional in obesity, further implicating GLP-1R agonists as powerful obesogenic therapies.

Keywords

Glucagon-like peptide-1
Incretin
Obesity
Type-2 diabetes mellitus
Dopamine
Reward

Introduction

The identification of glucagon-like peptide-1 (GLP-1) as a potent incretin (an insulinotropic gut hormone), along with the development of non-hydrolysable forms of this incretin, has revolutionized the treatment of diabetes mellitus type-2 (T2DM). The physiological effects of GLP-1 have been extensively studied in the periphery due to its important clinical application in the treatment of T2DM. Clinical studies have revealed that, in addition to its ability to enhance glucose-stimulated insulin secretion, GLP-1 analogues are able to curb appetite (hypophagia)[1] and have a protective effect on cardiovascular function[2]. GLP-1's hypophagic properties have led many researchers to explore its actions in appetite-regulating regions of the brain. Evidence indicates that GLP-1 acts directly in the brain to control appetite and energy balance[3]; this evidence, in addition to data suggesting cardiovascular protection (a known comorbidity with obesity[2]), has led investigators to view GLP-1 as a potential therapeutic for obesity.

Obesity is a medical condition in which there is a positive energy balance (calories taken in are greater than calories expended). Brain regions, such as the hypothalamus, tightly regulate this important homeostatic process. However, reward pathways can override the hypothalamic signals, leading to compulsive overeating, obesity, and T2DM[5]. In obesity, there are deficits in reward pathways, such as dysregulated striatal dopamine (DA) signaling. These deficits are similar to what is seen in other substance use disorders[6]. Recent evidence shows that GLP-1 can regulate striatal DA through a novel, transynaptic signaling mechanism, involving nitric oxide (NO)[4], potentially making it an even more powerful therapy for obesity. This review will discuss what is known about GLP-1 in both the periphery and the brain; GLP-1 as a treatment for T2DM and obesity; and examine the recent findings about GLP-1 signaling and striatal DA homeostasis.

1. GLP-1 in the Periphery

1.1 Source

GLP-1 (7-36-NH_2 or 7-37) is a peptide derived from the 180-amino acid prohormone preproglucagon (PPG) encoded in the proglucagon gene[7]. This prohormone contains the sequences of several small peptide hormones, such as GLP-1, glucagon-like peptide-2, and glucagon. Prohormone convertases (PCs) that process PPG are localized to specific tissues, allowing for targeted production of PPG products. For example, glucagon is produced in the pancreas by PC2, while GLP-1 (1-37) is produced in the gut by PC1/3[8, 9]. In the gut, after PPG has been cleaved to create GLP-1 (1-

36-NH_2 or 1-37), it undergoes further processing by the removal of six amino acids from the amino terminus, generating the mature GLP-1 (7-36-NH_2 or 7-37)[10]. This mature form (most commonly 7-36-NH_2) can activate the GLP-1 receptors (GLP-1R) located in GLP-1's target tissues.

1.2 Secretion, Action & Metabolism

GLP-1 is an incretin, a substance secreted from the gut to enhance oral glucose-stimulated insulin release (**Figure 1**). After a meal, GLP-1 is secreted from the small intestine. The specific gastrointestinal cells that process and secrete mature GLP-1 are L-cells found in the distal ileum and colon[11, 12]. Upon ingestion of a meal, L-cells release GLP-1 in two phases: an early phase (10-15 minutes post prandial[a]) and a later phase (30-60 minutes post prandial)[13]. The early phase is stimulated by gastrin-releasing peptide, acetylcholine, gastric inhibitory peptide (the other known incretin) and the vagus nerve[14-16], whereas the later phase is induced by direct nutrient sensing on the apical surface of the L-cells[17]. GLP-1 has a half-life of only 2 minutes; once secreted, it is inactivated by the serine exopeptidase, dipeptidyl peptidase-4 (DPP-4), which hydrolyses peptides at serines with prolines or alanines in the penultimate positions[18]. GLP-1's quick biphasic response to a meal and rapid clearance by DPP-4 allows GLP-1 to enhance glucose-dependent insulin release at exactly the right time for the appropriate amount of time[11, 12]. Other than the enhancement of glucose-dependent insulin secretion, GLP-1 also decreases glucagon secretion[19]; increases insulin sensitivity in both α-cells and β-cells[20]; increases β-cell mass and insulin gene expression[21]; inhibits stomach acid production; slows gastric emptying[22]; and indirectly increases insulin sensitivity in muscle, liver and adipose tissue[23]. All of the effects mediated by GLP-1 are critical for the body to properly metabolize a meal. Each direct action of GLP-1 described above occurs when GLP-1 binds to its receptor, GLP-1R, which will be discussed in more detail below.

1.3 Receptors

The GLP-1R is a seven transmembrane, heterotrimeric, G-protein coupled receptor (GPCR)[24]. In order for this receptor it to be fully functional, it must be glycosylated[25]. The GLP-1 binding domain is the N-terminal region of the GLP-1R. The third intracellular loop of this GPCR is critical for G-protein coupling. The GLP-1R can couple with many G-proteins including $G\alpha_s$, $G\alpha_q$, $G\alpha_i$, and $G\alpha_o$[26]. This GPCR has been most extensively studied in the context of enhancing glucose-dependent insulin secretion post prandial in the pancreatic β-cell. In these cells it is known to be $G\alpha_S$-coupled. Upon activation of GLP-1R in the pancreas, $G\alpha_S$ dissociates from GLP-1R and stimulates membrane-anchored adenylate cyclase (AC). AC catalyzes the conversion of adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cAMP). As this reaction continues, high levels of cAMP accumulate and can activate protein kinase A (PKA), among other intracellular messengers, having the combined effect of increasing intracellular calcium (Ca^{2+}) levels and depolarizing the membrane. Activating PKA, increasing intracellular Ca^{2+} concentrations, and depolarizing the membrane all lead to enhancement of glucose-dependent insulin secretion[11, 17, 27]. In pancreatic islet cell lines, the GLP-1R localizes to lipid rafts[b]; the subcellular localization, trafficking, and signaling is dependent on its interaction with caveolin-1[c]. In these same cell lines, there is evidence of rapid desensitization and internalization of the GLP-1R, which is dependent on phosphorylation of certain residues on this GPCR. However, some *in vivo* studies of chronic GLP-1R stimulation show no such sensitization[28].

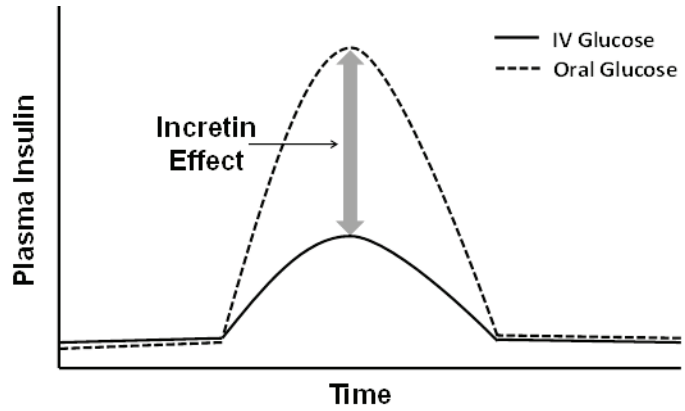

Figure 1: The incretin effect accounts for 50-70% of insulin secretion after oral glucose ingestion. GLP-1 is an incretin.

Structurally identical GLP-1R's are expressed in many areas of the body other than the pancreas, including the heart, stomach, and numerous brain regions[29]. In clinical trials, GLP-1 analogues have been shown to exert a protective effect on cardiovascular function, prompting researchers to explore GLP-1R activity in vasculature endothelial cells. It was found that GLP-1R signaling increased phosphorylation (thereby increasing activity) of endothelial

a. After a meal

b. Glycolipoprotein microdomains responsible for centralizing signaling molecules needed for specific signaling pathways and trafficking of membrane receptors and transporters

c. Integral membrane protein that mediates receptor-independent endocytosis

nitric oxide synthase (eNOS), and decreased inflammation through inhibiting expression of genes encoding inflammatory molecules[2]. The specific cellular mechanisms as to how GLP-1R modulates phosphorylation of eNOS and inflammatory gene expression are still unknown and are under further investigation. Activation of the GLP-1R in the brain will be discussed in more detail below.

2. GLP-1 Analogues as T2DM Drugs

2.1 GLP-1R Agonist

GLP-1 plays an important role in maintaining proper glucose homeostasis in the body[29]. In patients with T2DM, GLP-1 secretion is reduced while GLP-1R signaling remains intact[30], making the GLP-1R a logical pharmaceutical target for the treatment of T2DM. The administration of the native form of GLP-1 must be given continually by intravenous therapy (IV) in order to be effective because of DPP-4-mediated rapid enzymatic degradation of GLP-1, making it an infeasible solution[23]. Fortunately, non-hydrolysable analogues of GLP-1 have since been created. There are currently two GLP-1R agonists available for the treatment of T2DM: exenatide (Byetta, Eli Lilly) and liraglutide (Victoza, Novo Nordisk). Both are synthetic analogues of the GLP-1 peptide that act as agonists at the GLP-1R and have been modified to be resistant to enzymatic cleavage by DPP-4[30]. Exenatide is a mimetic of a naturally occurring peptide hormone found in the saliva of Hela monsters. It has 53% sequence identity to native GLP-1 but lacks the DPP-4 cleavage site[31]. As a therapeutic, it must be given twice daily; when given along with other oral anti-diabetic drugs (such as metformin), exenatide is efficient at maintaining glycemic control in patients with T2DM[1]. Furthermore, it has been reported that exenatide promotes β-cell proliferation[32] and protects β-cells from apoptosis[33]. In clinical trials, it has been reported that exenatide reduces food intake and promotes weight loss[1]. Meanwhile, liraglutide has 97% sequence homology with native GLP-1[34]. What makes this peptide resistant to enzymatic degradation is the addition of a C16 fatty acid side chain that can reversibly bind albumin, prolonging its activity to over 24 hours. Much like exenatide, liraglutide (given along with metformin) is effective in maintaining glycemic control and aiding in weight loss[35]. These GLP-1R agonists have recently been shown to have protective cardiovascular action[2]. Since there is a high comorbidity of obesity and cardiovascular disease, this further supports that GLP-1R agonists are appropriate for treating obesity as well as T2DM.

2.2 DPP-4 Inhibitors

Another class of GLP-1 drugs used to treat T2DM is the DPP-4 inhibitors. DPP-4, as described above, is a serine protease that is responsible for the degradation of GLP-1. DPP-4 inhibitors increase endogenous levels of native GLP-1 by inhibiting the enzyme responsible for its degradation. There are four approved DPP-4 inhibitors on the market: sitagliptin, vildagliptin, saxagliptin, and alogliptin. All of these drugs are small molecules and can be taken orally. They also have good efficacy and have been proven to be very safe with few side effects, but are not as popular as GLP-1R agonists[36].

3. GLP-1 in the Brain

3.1 Source

PPG is expressed in two brain regions, the nucleus of the solitary tract (NTS) and the olfactory bulb. PPG expression in the olfactory bulb is contained in interneurons, signifying that the only known GLP-1 projections in the brain originate from the NTS[37]. mRNA expression of PC1/3 coincide with regions of the NTS that have been shown to express both PPG and GLP-1, indicating that PPG is similarly processed in the NTS as to what has been shown in the periphery[28, 38, 39]. Through retrograde tracing, immunoreactive staining of PPG, and GLP-1 specific antibodies, investigators have determined that NTS neurons containing GLP-1 most densely project to the hypothalamus[40]. The specific regions of the hypothalamus receiving these projections are important for food intake and the regulation of energy balance[41]. No other known GLP-1 projections have been discovered at this time.

3.2 Receptors

Although GLP-1 projections mainly target the hypothalamus, the GLP-1R is found throughout the brain and is structurally identical to GLP-1R's in the periphery. GLP-1R agonists easily cross the blood brain barrier[42]. Therefore, the study of GLP-1R signaling in other brain regions is critical. There have been extensive studies exploring which brain regions express the GLP-1R. One of the most comprehensive studies was done using *in situ* hybridization to show that GLP-1R-expressing cells are found in the olfactory bulb, cortex, striatum, amygdala, hippocampus, bed nucleus of the stria terminalas, hypothalamus, thalamus, medulla and many other specific nuclei[37]. As previously mentioned, GLP-1R is structurally identical throughout, but the G-protein coupling and subsequent signaling of GLP-1R in

each region has not yet been elucidated.

3.3 Studies of GLP-1 and the Brain

Some of the earliest studies of GLP-1 in the brain showed that intracerebro-ventricular (ICV) injection of GLP-1 could reduce food intake[3] and body weight in rats. This effect was specific to GLP-1R signaling because GLP-1R antagonists could block these effects[43]. This indicates that at least some of the anorexic effects of GLP-1R agonists given peripherally could be due to actions on GLP-1R's in the brain. More recently, investigators have shown that knocking down PPG in the NTS or blockade of GLP-1R's with an antagonist in the hypothalamus of rats leads to hyperphagia and fat accumulation[44]. This is the best recent evidence that GLP-1R signaling in the brain, specifically in the hypothalamus, is critical for maintaining energy balance.

Some investigators have found common pathologies between Alzheimer's disease (AD) and T2DM, prompting researchers to explore GLP-1R signaling in the hippocampus and in mouse models of AD. In hippocampal neuron cultures, it was discovered that GLP-1R activation is neuroprotective against glutamatergic excitotoxicity[45]. In mouse models of AD, GLP-1R signaling was able to prevent the formation of β-amyloid plaques[46]. These studies, among others, show that GLP-1R signaling is much more complex than previously thought.

The important role of DA signaling in obesity has become increasingly apparent. GLP-1R's are expressed in the striatum, an important brain region for reward[37]. Dr. Aurelio Galli and colleagues at Vanderbilt University have recently discovered that GLP-1 can regulate trafficking of the DA transporter (DAT) in the striatum. DAT is an important component of the machinery used to maintain proper DA homeostasis and clearly instrumental in reward pathways, as many drugs of abuse target DAT. The molecular mechanism by which GLP-1R signaling can modulate DAT is entirely novel from what is currently known about GLP-1R signaling and is the first account of GLP-1R signaling in the striatum. The pathway these investigators propose entails the employment of the diffusible transynaptic messenger, nitric oxide (NO), to regulate surface levels of DAT protein. They have shown that the GLP-1R is not on DA terminals in the striatum, but rather on a subpopulation of neuronal NO synthase (nNOS, the enzyme that produces NO in neurons)-producing interneurons. In acute rat striatal slices, they demonstrate that GLP-1 acts by reducing the activity of nNOS via phosphorylating nNOS at serine 847 (an inhibitory site on nNOS), thereby increasing surface levels of DAT on nearby DA terminals[4] (Figure 2).

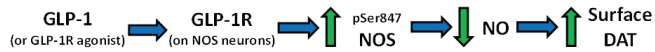

Figure 2: Schematic of proposed GLP-1R signaling in the striatum by Erreger et. al, 2011

The regulation of monoamine transporters by NO[47] and GLP-1R coupling to NO[2] is not completely novel, yet these experiments illustrate that GLP-1R signaling has even more versatility than previously imagined. The implications of GLP-1R signaling regulating DA homeostasis in the striatum, independent of known mechanisms for regulating DAT, are that GLP-1 may play a role in regulating the reward component of food intake (striatal DA), not just the homeostatic (hypothalamus) or peripheral (pancreas) roles it is already known to have. If this is the case, GLP-1 may be a potential therapy for other substance use disorders in which dysregulated striatal DA is also present.

Summary & Future Directions

GLP-1 was first discovered as an incretin but has since proven to have other vital roles. GLP-1R agonist and therapies that increase endogenous levels of GLP-1 (DPP-4 inhibitors) are powerful pharmaceutical agents used to treat T2DM. GLP-1R signaling has been studied in several regions of the periphery and brain. While the amino acid structure of the GLP-1R is identical in all regions of the body, its signaling is versatile. Studies to further elucidate the molecular mechanisms behind GLP-1R coupling to NO in the cardio-vasculature and striatum will be essential in maximizing the use of the powerful GLP-1R agonists.

In the United States today, about one third of the population is obese[48], and over 1.5 million new cases of T2DM are diagnosed per year[49]. The leading cause of T2DM is obesity, a disease of positive energy balance that is most commonly the outcome of compulsive overeating and lack of physical activity. Homeostatic pathways in brain regions, such as the hypothalamus, have been extensively studied in hopes of finding therapeutics for obesity[5]. Thus far, this has not been a successful route for the treatment of obesity. More recently, it has been demonstrated that reward pathways, specifically striatal DA, are altered in obese subjects and that therapies that target striatal DA would be beneficial in the treatment of obesity[6]. GLP-1 treats dysglycemia; regulates food intake; protects against cardiovascular disease in T2DM and obesity; and now potentially rescues dysregulated DA signaling seen in obesity (Figure 3).

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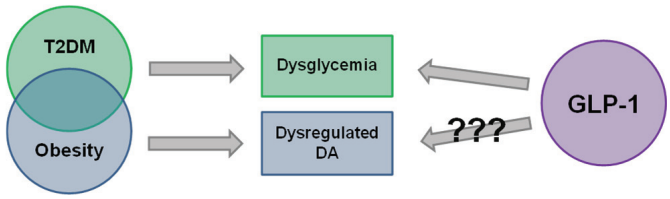

Figure 3: Obesity and T2DM are comorbid disorders. In T2DM there is dysglycemia, and in obesity there is dysregulated DA homeostasis. GLP-1 agonists are used to treat dysglycemia in T2DM, and new evidence suggests that GLP-1 analogues can treat dysfunction in DA signaling in the striatum[4].

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