Glucagon-like peptide 1 and appetite

Megan J. Dailey[1] and **Timothy H. Moran**[1]

[1]Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, 21205

Abstract

Glucagon-like peptide 1 (GLP-1) and GLP-1 analogs have received much recent attention due to the success of GLP-1 mimetics in treating type II diabetes mellitus (T2DM), but these compounds may also have the potential to treat obesity. The satiety effect of GLP-1 may involve both meal entero-enteric reflexes and across meal central signaling mechanisms to mediate changes in appetite and promote satiety. Here, we review the data supporting the role of both peripheral and central GLP-1signaling in the control of gastrointestinal motility and food intake. Understanding the mechanisms underlying the appetite suppressive effects of GLP-1 may help in developing targeted treatments for obesity.

Keywords

GLP-1; appetite; gastrointestinal motility; food intake

Introduction

Glucagon-like peptide-1 (GLP-1) has been the focus of much research because of the success of GLP-1 mimetics in treating T2DM, acting as incretins (see glossary) in the pancreas. It is becoming clear that GLP-1 may also have potential for the treatment of obesity. GLP-1 or its synthetic analogues, exendin 4 (Ex 4) and liraglutide, are potent inhibitors of food intake in both animal models and human subjects. Thus, understanding the mechanisms underlying the appetite suppressive effects of GLP-1 may help in developing targeted treatments for obesity.

GLP-1 biology and physiological properties

GLP-1 is derived from the proglucagon gene, which in the gastrointestinal tract and brain is post-translationally modified and cleaved into the biologically active forms, GLP-1 (7-36) amide and GLP-1 (7-37) [1]. The major circulating bioactive species in humans is the truncated form GLP-1 (7-36) amide [2]. The hormone has been identified as playing a prominent role in glucose homeostasis, gastrointestinal motility, appetite and additional roles beyond ingestive behaviors [3–5].

[1]Corresponding Author: Megan Dailey, mdailey5@jhmi.edi Phone: 410-955-2996 Fax: 410-502-3769.

GLP-1 is secreted from mucosal endocrine L cells of the intestine in response to intraluminal nutrients, but non-nutrient driven increases in GLP-1 also have been reported such as cephalic[6] and meal anticipatory increases [7]. With regards to nutrients, there are two peaks in GLP-1 secretion that are seen in response to a meal in humans [8]. The first peak appears within 15 min after meal initiation before nutrients may even access the L-cells lower in the intestine. This rapid rise in GLP-1 levels appears to involve a neuroendocrine loop where nutrients in the stomach or proximal intestine stimulate the release of hormones, such as gastric inhibitory peptide [9] and gastrin-releasing peptide [10], that act through vagal pathways to stimulate L cells to secrete GLP-1 [11] (Figure 1E). The enteric nervous system may contribute to this early GLP-1 rise after a meal [11] (Figure 1B). The second peak occurs later, is larger, and is thought to derive from direct nutrient contact with intestinal L cells. Thus, nutrients within the gastrointestinal tract have the ability to stimulate GLP-1 directly and indirectly through hormonal and neural mechanisms.

GLP-1 is also expressed by neurons within the nucleus of the solitary tract of the brainstem (NTS) and is released from terminals across a variety of brain areas including hypothalamic nuclei and hippocampal and cortical sites [12]. Central GLP-1 appears to be an important link in the downstream mediation of anorexia produced by a number of factors. Stimulation of the endogenous caudal brainstem GLP-1 activity has been implicated in the mediation of the anorexic effect of lipopolysaccharide (LPS; [13, 14]), lithium chloride (LiCl; [14, 15]), cholecystokinin (CCK; [14]) leptin [16] and oxytocin [17]. Many of these factors administered to rodents at doses that decrease food intake, increase c-fos expression in GLP-1 neurons [14] and the anorexic effects are attenuated or eliminated with central injection of a GLP-1 receptor (GLP-1R) antagonist [13, 15, 17]. The central GLP-1 pathway involved in reducing appetite may involve some of the same neural circuits known to be involved in ingestive behaviors because GLP-1 fibers are found within these brain sites [12] and GLP-1 actively binds to receptors in these same areas [18, 19]. However, there does appear to be a mismatch between the density of GLP-1 nerve fibers and GLP-1 receptors. There are few GLP-1 nerve fibers present in some brain nuclei where GLP-1 binding is high [12], a finding that suggests a role for peripheral GLP-1 in the central GLP-1 receptor activation.

Glucagon-like peptide 1 receptor

The actions of GLP-1 are mediated by the activation of a glucagon-like peptide 1 receptor (GLP-1R). GLP-1R is a G-protein coupled receptor that is expressed throughout the periphery (*ie*. enteric nerves, vagal nerves, pancreas, stomach, small and large intestine and adipose tissue [20–22]) and brain (*ie*. caudal brainstem, hypothalamic, hippocampal, cortical nuclei [12, 23]). It is still not completely clear if peripheral GLP-1 acts locally to alter gastrointestinal motility and appetite, or if GLP-1 can directly activate brain GLP-1R to modulate these functions/behaviors. Endogenous GLP-1 released from the L cells diffuses into the lamina propria and enters the lymph or capillaries [24] (Figure 1A). Once GLP-1 enters the capillaries, it is rapidly degraded by dipeptidyl peptidase IV (DPP-IV), an enzyme expressed on the capillary walls [25] and throughout the body [26, 27]. It has been estimated that only 25% of the absorbed GLP-1 reaches the liver through the hepatic portal vein[26]. It is possible, though, that GLP-1 could act on GLP-1R on vagal afferents in the lamina propria or enteric nerves in the intestinal wall, before entering the capillaries [22, 28] (Figure 1B,C and D). It also may be possible that greater and longer increases in GLP-1 could saturate the available DPP-IV and allow for more GLP-1 to enter into general circulation. This idea is supported by an accumulation of evidence showing that mRNA expression or blood levels of DPP-IV are altered under a variety of conditions and, thus, could be a mechanism by which greater GLP-1R stimulation could occur throughout the body [29–31]. If GLP-1 survives degradation from DPP-IV, it is possible that it could activate central GLP-1R, because circulating GLP-1 appears to pass the blood brain barrier by simple diffusion to

circumventricular organs [32] and elsewhere [33]. As mentioned above, peripheral GLP-1 activation of central receptors appears likely because there are few GLP-1 nerve fibers present in feeding related brain nuclei such as the arcuate nucleus[12], where GLP-1 binding is high [18, 19]. It has also been suggested that there are regional differences in DDP-IV present in rat cerebral capillaries that could account for a more precise control of brain access of peripherally derived GLP-1 [33].

GLP-1 and gastrointestinal motor functions

One mechanism by which GLP-1 can alter appetite is through changes in gastrointestinal function. GLP-1 decreases gastric emptying and intestinal motility [34, 35] and contributes to the ileal break [36], an inhibitory feedback mechanism that functions to optimize nutrient digestion and absorption. GLP-1 appears to affect gastrointestinal motor functions through both peripheral and central nervous system mechanisms. Vagal-mediated pathways have been shown to participate in the attenuation of gastric motility and emptying induced by GLP-1 in non-human animal models [37, 38] and in intestinal motility in humans [34]. Interactions with brain GLP-1R may also contribute to these changes because intracerebroventricular (icv) injection of GLP-1 inhibits gastric emptying through non-cholinergic and non-adrenergic pathways in rats [37]. A third, more direct route of GLP-1 mediated changes in motor function can occur through GLP-1R activation in enteric neurons in the gastrointestinal wall. GLP-1R immunoreactivity is present on myenteric neurons and a few submucosal neurons of the duodenum and proximal colon in mice [28]. In mouse intestinal explants, the hormone was found to inhibit intestinal motility through direct interaction and activation of GLP-1R, in enteric neurons [28]. More specifically, GLP-1 appears to inhibit evoked activity (provided by electrical field stimulation on parallel sides of intestinal segments from mice) in the circular muscle of the intestine by modulating parasympathetic cholinergic input presynaptically [28]. GLP-1 administered intra-arterially in an *ex vivo* canine prep also inhibits evoked activity of the circular muscle and this response is blocked by a GLP-1 receptor antagonist, exendin-9 (Ex 9) [39]. Conversely, GLP-1 does not affect spontaneous circular muscle activity or evoked or spontaneous activity in the longitudinal muscle[28, 40]. Taken together, these results suggest that GLP-1 may modulate neural input to the circular, but not the longitudinal, muscle layer and are consistent with the notion that the circular muscle layer contraction is dominant in peristalisis. These results also show that GLP-1 may only inhibit evoked, but not spontaneous, neural action on motility. This finding may provide insight into the mechanisms underlying the ability of GLP-1to inhibit gastrointestinal function only in normal, but not vagotomized patients [41]. Much of the neural stimulation of the gut wall is provided by the parasympathetic fibers of the vagus nerve and severing this connection would block electrical stimulation of the circular muscle of the intestine. Since the role of GLP-1 appears to be to modulate cholinergic stimulation of the circular muscle, an attenuated response to GLP-1 in vagotomized human patients would be expected.

In contrast to the inhibitory effect of GLP-1 in the stomach and small intestine, GLP-1 increases colonic transit and this effect may be mediated through a central mode of action [42, 43]. Indeed, icv, but not intraperitoneal (ip), injections of GLP-1 dose-dependently accelerate colonic transit [44]. The central GLP-1 effect on colonic transit was attenuated by methods that blocked the parasympathetic nervous system, such as vagotomy, use of the competitive antagonist for the muscarinic acetylcholine receptor atropine, or the ganglionic blocker hexamethonium, but not the sympathetic nervous system (*ie.* guanethidine) [44]. Cholinergic stimulation enhances colonic motor activity and transit in humans [45], thus, GLP-1 may act within the dorsal motor nucleus of the vagus to mediate changes in the parasympathetic innervation to alter motor contractions in the colon.

GLP-1 and satiety

Peripheral action of GLP-1 in reducing food intake

GLP-1 decreases food intake after peripheral (ip) [46], intravenous [47] [48, 49] and central administration (icv) [50, 51], but the relative roles of peripheral and central GLP-1R in the actions of endogenous intestinal GLP-1 remain to be clarified. The story is complicated by the fact that many of the studies investigating the action of GLP-1 use ip or iv administration of the GLP-1 synthetic analogues Ex 4 or liraglutide, which escape the degradation of DPP-IV and are able to cross the blood brain barrier [47, 52]. Thus, the effectiveness of these GLP-1R agonists may depend in part on an enhanced ability to access additional GLP-1R, compared with endogenously released or exogenously administered GLP-1. There is some evidence, though, to support a peripheral action of GLP-1 in reducing food intake. For example, central administration of the GLP-1R antagonist Ex 9 is not able to block the decreases in food intake produced after peripheral administration of GLP-1, but is able to block decreases in food intake after central injection of GLP-1 [53]. Ex 9 administered peripherally is also able to block decreases in food intake after a nutrient preload and a peripheral GLP-1 injection [53]. These data suggest that the satiety actions of intestinally derived GLP-1 are through peripheral receptors.

It is not clear where in the periphery GLP-1 may be acting to decrease appetite. The rapid degradation of GLP-1 that occurs soon after release into the capillaries of the intestinal wall, supports the notion that GLP-1 may act locally on enteric or vagal neurons. The results from studies using varying routes of administration of GLP-1 do not clearly support this idea, though. The decreases in food intake after ip GLP-1 in rats [54] and Ex-4 in mice [55] are attenuated by complete sub-diaphragmatic vagotomy or by capsaicin administration (a procedure that lesions sensory nerves), respectively. When GLP-1 is infused in rats at the onset of the first spontaneous dark-phase meal (a model that may mimic the initial meal-induced secretion of GLP-1 from the intestine), decreases in food intake occurred after hepatic portal vein (HPV), vena cava (vc) and ip infusions of GLP-1 [56]. Sub-diaphragmatic vagal deafferentation attenuates the decrease in food intake after ip GLP-1 infusion, but not after HPV GLP-1 infusions [56]. Moreover, the effect of iv infusion of GLP-1 to reduce sucrose intake was not abolished by capsaicin treatment or vagotomy [57]. Thus, the satiating effect of ip, but not HPV or iv GLP-1, requires vagal afferent signaling. The different findings with different routes of administration suggest that in each case GLP-1 could be binding to different GLP-1R populations, even though each is producing a decrease in food intake after administration. It is possible that only ip, and not HPV, vc or iv, infusion of GLP-1 may be able to access the GLP-1R on enteric or vagal nerves of intestinal origin that are normally and immediately accessible to endogenous GLP-1 released from intestinal L cells. HPV, vc and iv infusions of GLP-1 could mimic endogenous circulating GLP-1 if enough GLP-1 is able to escape degradation from DPP-IV in the capillaries of the intestine and enter the HPV and systemic circulation, at each step encountering more DPP-IV. Thus, just where in the periphery GLP-1 acts to inhibit feeding behavior remains unresolved. A study that investigates whether local administration of Ex 9 in the intestinal wall increases food intake would prove useful in defining the role of local GLP-1R.

Central action of GLP-1 in reducing food intake

Central mechanisms are certainly important in the mediation of the satiety actions of both peripheral and central GLP-1. Even if peripheral GLP-1 acts locally on enteric or vagal neurons, the downstream neural or hormonal responses must activate many brain circuits to affect food intake. For example, lesions of the projections from the brainstem to the hypothalamus reduce the appetite suppression mediated by peripheral GLP-1 in rats [54]. Even though peripheral and central GLP-1 utilizes brain mechanisms to inhibit feeding, some

differing neural substrates appear to be involved. Both peripheral and central injections of GLP-1 induce cfos in the paraventricular nucleus of hypothalamus (PVN), but only central and not peripheral GLP-1 injection induces cfos in the Arc [58], suggesting differential mechanisms underlying the ability of central versus peripheral GLP-1 in decreasing appetite.

Central injections of GLP-1 inhibit food intake [50, 51] and this central effect does not require the presence of food in the stomach or an inhibition of gastric emptying [59]. The caudal brainstem appears to be sufficient in mediating GLP-1-induced decreases in food intake. Ip or 4th ventricular Ex-4 are still able to decrease intake in chronic supracollicular decrebrate rats [60]. Only a 4th ventricular injection of Ex-9, not a forebrain injection with aquaduct occlusion, blocked the decreases in food intake induced by LPS administration [13]. Moreover, 4th ventricular injection of Ex-9 prior to 4th ventricular leptin administration attenuates the inhibitory effect of leptin. Co-administration of Ex-4 and leptin into the 4th ventricle suppresses food intake in an additive manner [16]. Within the brainstem, leptin receptors are exclusively expressed within the medial NTS and the medial NTS has been suggested as the main site of action for GLP-1 [16, 61]. This would mean that the central endogenous GLP-1 produced exclusively in the NTS, might act on GLP-1R within the same nuclei. Such a local feedback loop may play defined roles in satiety, but this is only part of an integrated process that also involves forebrain processing.

Endogenous brainstem GLP-1 and feeding control

A role of endogenous brainstem GLP-1 in overall feeding control is supported by data showing that knockdown of the proglucagon gene in the NTS using RNA interference, results in hyperphagia and weight gain [62]. NTS GLP-1 neurons project widely throughout the brain and, thus, this food intake and body weight response could be mediated by multiple neural circuits. Sandoval et al. [63] have demonstrated that GLP-1 administration into the Arc affected glucose metabolism and insulin release, while PVN GLP-1 reduced food intake. Many others, though, have provided evidence that the Arc does play a role in GLP-1 mediated anorexic effects. This discrepancy may result from differences in the methods for manipulating GLP-1 signaling in the Arc, and if it was targeting both orexigenic and anorexigenic neurons or differentiating between the two.

Arc orexigenic and anorexigenic neurons are known to respond to many ingestive signals, including GLP-1. Receptors for GLP-1 are present on the orexigenic neuropeptide Y/agouti-related peptide (NPY/AgRP) neurons, and the anorexigenic proopiomelanocortin (POMC) neurons, and icv injections of GLP-1 induces cfos immunoreactivity within the Arc [64]. Seo et al., [65] found that icv injection of GLP-1 at doses that decrease fasting induced feeding, attenuates fasting induced increases in NPY and AgRP mRNA levels, and decreases in POMC and CART mRNA levels. In the Arc, fasting induced increases in AMP-activated kinase $\alpha 2$ (AMPK$\alpha 2$) mRNA levels and phoshorylation of AMPKα and acetyl-CoA carboxylase (ACC) are also attenuated by icv GLP-1 [65]. These data suggest that NTS-GLP-1 projections to the Arc could mediate satiety by affecting both orexigenic and anorexigenic signaling. Further data, though, have suggested that GLP-1 actions are mediated through the anorexigenic component and not the orexigenic one. Icv injections of GLP-1 in fasted or ad libitum fed rats did not alter Arc NPY expression levels [50]. Ex-4 administration also failed to alter hypothalamic NPY gene expression [66]. In addition, responses to central GLP-1 remain after NPY/AgRP neurons are destroyed by lesions induced by saporin, a ribosomal inactivating toxin conjugated to NPY (NPY-SAP) [67]. Although GLP-1 may not directly decrease Arc NPY mRNA levels to induce satiety, GLP-1R signaling may still affect NPY signaling. If GLP-1R is blocked by icv administration of Ex-9, prior to icv injection of NPY, there is a significant increase in food intake beyond that with NPY alone [50]. Along these lines, the contribution of POMC neurons in producing anorexia under a variety of stimuli has been well documented and involves POMC projections to other brain sites expressing

melanocortin receptors. POMC neurons project to the NTS [68] where GLP-1 producing cells are located and may be a component of a forebrain- brainstem circuit in which a variety of signals interact with GLP-1 signaling. Arc POMC cells also project to melanocortin receptor expressing cells within the PVN [68], suggesting a circuit where GLP-1 may indirectly affect PVN mediated decreases in food intake.

There are direct, reciprocal neural connections between the PVN and NTS which allow for an additional integration of anorexic signals with GLP-1 signaling [68]. GLP-1 producing neurons of the NTS have strong projections to GLP-1R expressing cell bodies in the PVN [14] and central GLP-1 activates oxytocin (OT) and corticotrophin releasing hormone (CRH) neurons within the PVN [64]. OT neurons express GLP-1R and the anorexigenic effect of OT is eliminated in rats injected in the 3rd ventricle with GLP-1R antagonist, but an OT antagonist does not block the anorexigenic effect of GLP-1 [17]. This suggests that NTS GLP-1 producing cells may act through OT GLP-1R positive cells to alter OT cell signaling or OT release. GLP-1 also activates the HPA axis through CRH neurons [69] and GLP-1 positive nerve terminals densely innervate CRH neurons [70]. Thus, GLP-1 mediated decreases in food intake may be at least partially mediated by activation of the stress axis. CRH neuronal activity is essential for LPS induced decreases in food intake and may utilize this additional hypothalamic-brainstem circuit to activate NTS GLP-1 neurons [71]. Thus, the satiety effects of GLP-1 may be mediated by both hypothalamic Arc and PVH connections to brainstem.

GLP-1 neurons in the NTS also project directly to the ventral tegmental area (VTA) [72] and nucleus accumbens [37] core and shell [72, 73], nuclei involved with food reward that have also been demonstrated to express GLP-1R. GLP-1 or Ex-4 injected into the VTA and NAc core, decrease food intake of rats on chow, high-fat diet, or sucrose solution [72, 73]. Dissimilar effects of GLP-1 are found in the NAc core versus the shell. Ex-4 injected into the NAc shell was also able to decrease high-fat food intake, but Ex-4 and GLP-1 had no effect on intake of chow or sucrose solution [72, 73] at this site. In each case where there was a decrease in food intake with agonist administration, a GLP-1 antagonist was able to induce an increase in chow, high-fat diet, or sucrose solution intake. These data suggest a role for endogenous GLP-1R in the VTA and NAc in mediating satiety and that this effect may be due to modifying reward signaling.

GLP-1 and conditioned taste aversion

A concern about the specificity of the feeding inhibitory actions of GLP-1 has arisen due to the idea that the decreases in food intake after treatment with GLP-1 or a synthetic analogue are attributable to visceral illness or feelings of nausea [74]. GLP-1 is able to induce a conditioned taste aversion (CTA) under a variety of conditions, but the satiety and CTA effects appear to be nuclei specific [74]. Lateral and fourth ventricle injections of GLP-1 in rats decreased food intake similarly, but only lateral ventricle GLP-1 injections produced CTA [75]. Furthermore, direct injections of GLP-1 into the PVN decreases food intake without a CTA [76]. In contrast, the typical CTA response after LiCl administration is attenuated by bilateral injections of a GLP-1R antagonist into the central nucleus of the amygdala [29 75]. These data suggest that the illness response to GLP-1 may be dependent on discrete receptors outside of the brainstem or PVN.

GLP-1 and control of meal size

A final issue is whether endogenously released GLP-1 works as a within-meal or across-meal stimulus for reducing food intake. The decreases in food intake that are typically elicited by GLP-1 (or Ex-4) are attributed to decreases in meal size, not meal number [48, 53, 56, 77]. Ruttimann [56] and others have shown that GLP-1 works within a meal if

administered during a first meal, and decreases meal size of that first meal without affecting intermeal interval or total food intake. In line with these results, Ex-4 decreased meal size across a 6h daily feeding period in non-human primates [77]. Chelikani et al [48] reported that 3 h intrajugular infusions of GLP-1 reduced meal frequency in addition to meal size, but the reduction in meal size came before meal frequency. However, they further demonstrated that feeding remained reduced following the termination of the GLP-1 infusion, suggesting lasting effects on subsequent meals. Thus, examinations of the role for endogenous GLP-1 in the controls of meal size have produced mixed results. This may have to do with the timing of antagonist administration relative to the initiation of food intake.

The release and effects of GLP-1 may involve within meal enteroenteric reflexes and across meal central signaling to mediate changes in appetite. The timing and levels of GLP-1 may signal the type of nutrients, amount of food and/or timing of ingestion and the body may receive this information based on which central or peripheral receptors are activated. Additional knowledge on the modes and mechanisms of action of GLP-1 induced reductions in food intake may contribute to the development of obesity treatments targeting GLP-1 signaling.

Concluding Remarks

We have concentrated on reviewing the actions of endogenous GLP-1 on appetite in an attempt to understand its normal physiological role. Certainly the GLP-1 analogues that escape degradation by DPP-IV are effective at decreasing appetite, but the high incidence of side-effects reported in patients taking these analogs raises concerns about their utility for treating obesity. The GLP-1 analogues appear to activate additional mechanisms that are not utilized by endogenous GLP-1. GLP-1 and the synthetic analogues share a similar mode and binding affinity to the human GLP-1R, thus, it seems likely that the side effects are caused by greater GLP-1R stimulation from the long-lasting GLP-1 analogues [78]. Understanding which GLP-1R populations are stimulated under endogenous GLP-1-induced decreases in appetite may help in designing effective obesity drugs without the negative side effects.

Acknowledgments

Glossary

Colonic transit	the time it takes a substance to enter the colon and move completely through the colon to be excreted.
Dipeptidyl peptidase IV (DPP-IV)	an enzyme that degrades incretins such as GLP-1 and thus plays a major role in glucose metabolism. A new class of oral hypoglycemics called dipeptidyl peptidase-4 inhibitors work by inhibiting the action of this enzyme, thereby prolonging incretin effect in vivo.
Exenatide	a GLP-1 like agonist used for the treatment of T2DM. It belongs to the group of incretin mimetics. Exenatide enhances glucose-dependent insulin secretion by pancreatic beta- cells, suppresses glucagon secretion, and slows gastric emptying.
Exendin-4 (Ex-4)	a hormone found in the saliva of the venomous lizard Gila monster. Ex-4, similar to GLP-1, regulates glucose metabolism and insulin secretion.

Evoked activity	brain activity that is the result of a task, sensory input or motor output. It is the opposite of spontaneous brain activity that takes place in the absence of any explicit task.
Glucagon-like peptide-1 (GLP-1)	a gut hormone secreted from intestinal L cell. It is derived from selective cleavage of the proglucagon gene. The biologically active forms of GLP-1 are GLP-1-(7-37) and GLP-1-(7-36)amide.
Glucagon-like peptide 1 receptor (GLP1R)	G-protein-coupled receptor that binds specifically GLP1. GLP1R is expressed in pancreatic beta cells and in the brain where it is involved in the control of appetite. Activated GLP1R stimulates adenylyl cyclase resulting in increased insulin synthesis and release. Therefore, GLP1R has been suggested as a potential target for the treatment of diabetes.
Ileal brake	the primary inhibitory feedback mechanism to control transit of a meal through the gastrointestinal tract. It helps optimize nutrient digestion and absorption.
Incretins	a group of gastrointestinal hormones. They increase insulin release from pancreatic beta cells after eating, even before blood glucose levels rise. They also inhibit glucagon release from pancreatic alpha cells. Incretins slow the rate of absorption of nutrients into the blood stream by reducing gastric emptying and may directly reduce food intake.
Liraglutide	a long-acting GLP-1 like agonist and anti-diabetic medication.
Peristalsis	is a radially symmetrical contraction and relaxation of muscles, which propagates in a wave down the muscular tube, in an anterograde fashion. In humans, peristalsis is found in the contraction of smooth muscles to propel contents through the digestive tract.
Secretagogue	a substance that causes another substance to be secreted.

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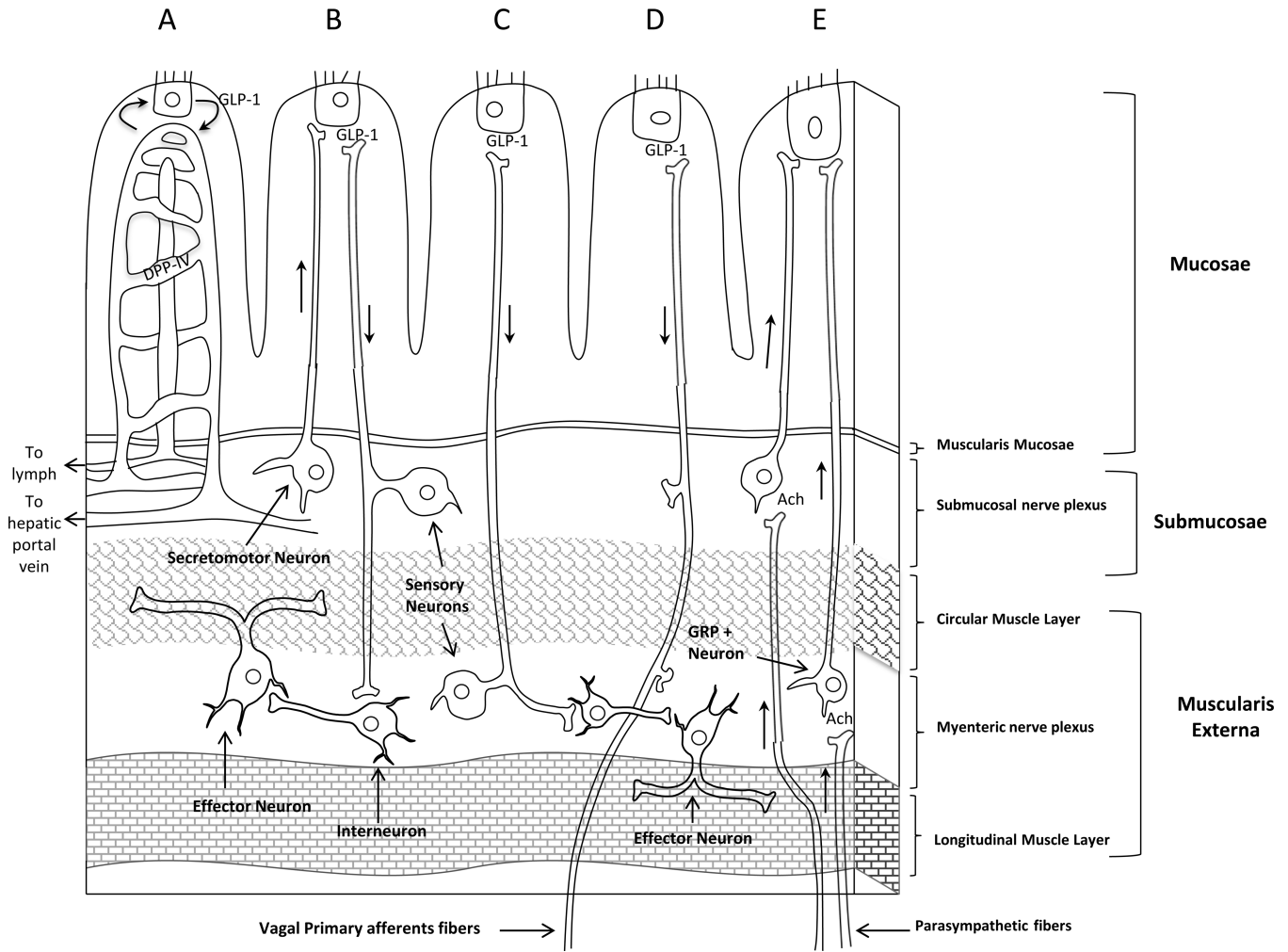
Figure 1. GLP-1 action in the gut

(**A**) GLP-1 released from the L cells diffuses into the lamina propria and enters the lymph or capillaries. DPP-IV is expressed in the capillaries and can immediately begin to degrade GLP-1 before it even reaches the hepatic portal vein. GLP-1 released from the L cell can mediate changes in the submucosal (**B**) and myenteric nerves (**C**). (**D**) GLP-1 can have a direct effect on vagal primary afferents. (**E**) Luminal nutrients in the proximal GI tract may stimulate distal GLP-1 secretion through an enteroendocrine loop that involves vagal and enteric neural connections. Hormones released from the stomach or proximal intestine stimulate vagal pathways that synapse on GRP neurons in the myenteric plexus to cause downstream stimulation of GLP-1 fom the L cell in the mucosal epithelium.

Ach: acetylcholine, GRP: gastrin-releasing peptide, DPP-IV: dipeptidyl peptidase-4, GLP-1: Glucagon-like peptide-1.