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Neuronal and intracellular signaling pathways mediating GLP-1 energy balance and glycemic effects

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Abstract

The glucagon-like peptide-1 (GLP-1) system is physiologically involved in the control of energy balance and blood glucose homeostasis. Thus, GLP-1-based pharmaceuticals are emerging as a potent treatment for not only type II diabetes mellitus (T2DM), but potentially for obesity as well. Despite the plethora of investigations over the last two decades examining the physiological, endocrine, and behavioral responses mediated by the GLP-1 receptor (GLP-1R), the field is only recently embracing the perspective that GLP-1-mediated control of food intake and glycemia involves action on GLP-1R that are distributed throughout the periphery (e.g. pancreatic β -cells, vagus nerve), as well as action on many GLP-1R-expressing nuclei within the central nervous system (CNS). This review highlights peripheral, as well as central GLP-1R populations that mediate GLP-1's food intake inhibitory and glycemic effects. In addition, focus is devoted to recent studies that examine the GLP-1R-mediated intracellular signaling pathways that are required for GLP-1's glycemic and feeding responses.

Keywords

leptin; GLP-1; NTS; hypothalamus; pancreas; insulin; PKA; AMPK; MAPK; ERK; CREB; food intake; obesity

Introduction

The glucagon-like peptide-1 (GLP-1) receptor (GLP-1R) is a 7-transmembrane G protein-coupled receptor (part of the secretin-receptor family) [1] that was first identified and cloned in pancreatic islets nearly two decades ago [2]. From this initial discovery, the expression of GLP-1R has now been identified in many tissues in addition to β -cells and includes abundant expression in the brain, heart, kidney, vagus nerve, and GI tract [3]. Among an array of physiological and behavioral functions mediated by the GLP-1R, a case could be made that food intake inhibition and GLP-1's incretin response (food ingestion-induced increase in insulin secretion) are among the most critical. This review highlights specific cellular signaling pathways downstream of GLP-1R activation that are involved in GLP-1's glycemic and energy balance effects. Focus is given to comparing GLP-1R-mediated signaling in peripheral tissues (e.g. β -cells) to signaling responses in the central nervous

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system (CNS). Behavioral, endocrine, and autonomic responses to GLP-1R activation are also discussed in context to food intake and glycemic regulation by the peripheral and central GLP-1 systems.

GLP-1R populations mediating glycemic and food intake responses

Vagal-dependent mediation of GLP-1's effects

The incretin response refers to an increase in the amount of insulin secreted from pancreatic β -cells following oral vs. intravenous glucose administration. This response is largely due to the release of insulinotropic gut peptides [e.g. GLP-1 and gastric inhibitory polypeptide (GIP)] from enteroendocrine cells within the intestine following nutrient entry into the GI tract (see [3, 4] for review). While it is clear that GLP-1's impact on glucose tolerance requires GLP-1R activation, the mechanisms and relevant GLP-1R populations mediating this effect are still being heavily explored. Relevant to glycemic control, GLP-1Rs are expressed peripherally on: 1) vagal afferent fibers of gastrointestinal and hepatoportal origin, 2) on pancreatic β -cells, and 3) within CNS neurons [see [3, 4] for review]. Under normal physiological conditions, the amount of endogenous post-prandial GLP-1 released from intestinal L-cells in humans is correlated with the size of the meal (both nutrient density and total volume), although the vast majority of endogenous GLP-1 is rapidly degraded by the DPP-IV enzyme, resulting in extremely minimal circulating levels of GLP-1 [3]. Therefore, GLP-1 paracrine-like signaling (i.e. GLP-1 secreted from L-cells, acting on adjacent GLP-1R expressed on the peripheral terminals of vagal afferent fibers innervating the intestine) is likely an essential process in the mediation of endogenous GLP-1 effects [3–5]. The activation of GLP-1R expressed on the terminals of vagal afferent fibers innervating the intestine promotes for insulin secretion and subsequent glycemic control, putatively via a vago-vagal reflex [6] that stimulates the β -cells to secrete insulin (see [4] for review). Until recently, however, previous research overlooked the paracrine site-of-action for endogenous peripheral GLP-1 and instead suggested that GLP-1Rs within the hepatoportal region are the primary population responsible for endogenous GLP-1's glycemic effects [7–10]. Using selective surgical procedures, recent data challenge this perspective and show a unique contribution of GLP-1R expressed on vagal afferent fibers that do not include those of the common hepatic branch (CHB) of the vagus (the principal hepatoportal innervating branch of the vagus [11]) in mediating glycemic responses from physiological levels of GLP-1 [5]. These responses likely involve vagal afferent mediation by the celiac and/or gastric branches of the vagus that innervate the gastrointestinal (GI) tract. In addition, the CHB of the vagus was also found to not be required to mediate the intake suppressive effects of pharmacological levels of GLP-1 [5]. A conservative interpretation of these findings together with a previous report examining GLP-1 signaling in the hepatoportal bed [7], would be to conclude that while GLP-1R expressed within the hepatoportal region *can* mediate GLP-1-induced incretin signaling, CHB GLP-1R are *not* required for endogenous GLP-1-mediated glycemic control or pharmacological GLP-1-mediated food intake control. Thus, support is gained for a paracrine-mode of action for endogenous GLP-1 signaling, and leaves open an endocrine-mode of signaling for pharmacological levels of GLP-1 or GLP-1R agonists.

Following exogenous pharmacological administration of either DPP-IV inhibitors (e.g. sitagliptin) or long-acting GLP-1R agonists (e.g. exendin-4 or liraglutide), the mediating GLP-1R populations are likely more extensive for both glycemic and food intake control compared to that of endogenous peripheral GLP-1, as the available pool of circulating GLP-1-ligands would be enhanced in quantity and in duration of action. Indeed, a recent report demonstrated that food intake suppression by IP administration of exendin-4 and liraglutide is mediated by both a vagal afferent-dependent, as well as a vagal afferent-independent pathway that likely involves blood-brain barrier (BBB) penetrance and

subsequent direct CNS GLP-1R activation [12]. While there have been no similar experiments to date that have tested whether the incretin/glycemic response for peripherally administered long-acting GLP-1R agonists also involves direct CNS GLP-1R activation, there is strong evidence to suggest that the CNS GLP-1 system does play an endogenous role in glycemic regulation.

CNS GLP-1R signaling in glycemic and food intake control

In addition to the incretin response produced by peripheral GLP-1, the CNS GLP-1 system is also a critical regulator of blood glucose utilization [3, 8, 13, 14]. Acute intracerebroventricular (ICV) administration of the GLP-1R antagonist, exendin-(9–39), attenuates the utilization of glucose and increase in glycogen synthesis in skeletal muscles [3], indicating an endogenous role for the CNS GLP-1 system in glycemic control. While the CNS GLP-1R-mediated glycemic effects in the skeletal muscle appear to occur independently from insulin receptor activation [3], CNS GLP-1R activation does result in a significant increase in insulin secretion [8]. Thus, in the absence of central GLP-1 signaling, insulin secretion and glucose tolerance should theoretically be compromised. Indeed, glucose intolerance has been reported in rats with chronic ICV administration of exendin-(9–39) or with virally-mediated RNA interference and knockdown of the CNS GLP-1-producing neurons in the nucleus tractus solitarius (NTS) of the hindbrain [14].

The CNS nuclei mediating GLP-1's glycemic effects are likely distributed throughout the brain, with evidence supporting roles for both hypothalamic and brainstem (e.g. dorsal motor nucleus of the vagus; DMV) GLP-1R activation. Within the hypothalamus, activation of GLP-1R in the arcuate nucleus (ARH) decreases hepatic glucose production and increases β -cell insulin secretion, however, no discernable effects on food intake are reported [15]. Conversely, the same report shows a dissociable effect for GLP-1R expressed within the paraventricular nucleus of the hypothalamus (PVH), activation of which significantly reduces food intake but does not alter glucose homeostasis [15]. The CNS GLP-1 glycemic effects are not limited to just the ARH, as GLP-1R activation in the ventral medial hypothalamic nucleus (VMH) also plays an important role in glycemic control [16].

To date, the endocrine and/or neuronal mechanism(s) by which ARH and VMH GLP-1R activation increases insulin secretion have not been identified. Given that CNS GLP-1 signaling is able to modulate the hypothalamo-pituitary-adrenocortical (HPA) axis [17], it is possible that part of these effects could be due to alterations in corticosterone levels. Equally likely, a parasympathetic- or sympathetic nervous system (SNS)-mediated pathway from the hypothalamus to the skeletal muscle and pancreas could play a role in the CNS GLP-1 mediated glycemic effects. Similar pathways of hypothalamic and brainstem glucose sensing modulating pancreatic insulin secretion and peripheral glucose utilization have been reviewed (see [18–20] for review). Finally, given that GLP-1R are expressed on ARH proopiomelanocortin (POMC) neurons [15], and that hypothalamic POMC neurons project directly to the hindbrain (i.e. NTS and DMV) [21], a third possible mechanism by which forebrain GLP-1 signaling may regulate glycemic control would be through a polysynaptic parasympathetic-mediated pathway that involves DMV-vagal efferent signaling. While each of these hypotheses requires direct assessment, evidence exists that GLP-1 signaling in the DMV excites pancreatic-projecting vagal motor neurons [22, 23]. Whether this vagal efferent excitation is responsible for insulin secretion, however, has not been investigated.

That the peripheral and central GLP-1 systems play a physiologically relevant role in food intake and glycemic control is well established. However, remaining largely unexplored is the neuroanatomical, cellular, behavioral, and physiological mechanisms by which these effects occur. Likewise, the field at large has only recently begun to embrace the perspective that FDA-approved long-acting GLP-1R agonists for the treatment of type II diabetes

mellitus (T2DM), are producing their effects through action not only within the periphery, but also through direct action in the brain (see [12] for example). What is undisputed, however, is that with administration of DPP-IV inhibitors or long-acting GLP-1R agonists, GLP-1R expressed on pancreatic β -cells are certainly being directly activated, putatively resulting in increased insulin secretion. The GLP-1R-mediated intracellular signaling responses in β -cells have served as a reference for investigations examining GLP-1-mediated effects in other tissue (e.g. neurons, heart, kidney). Below, a subset of the GLP-1 intracellular signaling pathways is highlighted with special emphasis devoted to CNS GLP-1 and energy balance control.

GLP-1R-mediated intracellular signaling

GLP-1 intracellular signaling in pancreatic β -cells

In pancreatic β -cells, GLP-1R activation leads to stimulation of adenylate cyclase, elevated cAMP, and subsequent activation of protein kinase A (PKA) [24, 25]. The increase in adenylate cyclase and cAMP following β -cell GLP-1R activation is required for insulin secretion, whereas the PKA signaling is an important component for insulin secretion, but one that is not required (see [26] for review). The GLP-1-induced increase in cAMP potentiates glucose-stimulated insulin secretion by increasing the immediate fusion of insulin granules in the β -cell to the plasma membrane and subsequently stimulates insulin exocytosis. This process is mediated by both a PKA-dependent, but also a PKA-independent pathway that involves Epac (exchange protein activated by cAMP) [26, 27].

CNS GLP-1R-mediated intracellular signaling

Given that PKA signaling is well documented as a critical upstream component for many intracellular cytoplasmic signals, gene transcription, and protein-synthesis responses that are implicated in energy balance regulation, a logical question was whether GLP-1R activation in the CNS would also result in a significant increase in PKA activity and whether this signaling pathway is required for GLP-1R-mediate suppression of intake. While endogenous GLP-1R signaling in forebrain nuclei is required for the normal control of food intake (e.g. ventral tegmental area, and nucleus accumbens) [28, 29], neural processing in the isolated caudal brainstem is sufficient to mediate the intake inhibitory effects of both peripheral, as well as hindbrain delivery of a selective GLP-1R agonist, exendin-4 [30]. Moreover, medial NTS GLP-1R are also physiologically required for the normal control of food intake [31]. Thus, using a combination of *in vivo* and *in vitro* techniques with the GLP-1R agonist exendin-4, the intracellular signaling pathways mediating the intake suppressive effects of NTS-GLP-1R activation were examined and found to occur through a coordinated intracellular signaling cascade that is downstream of cAMP/PKA activity [32]. Specifically, hindbrain GLP-1R activation suppress food intake via PKA-mediated suppression of adenosine monophosphate protein kinase (AMPK) activity and simultaneous activation of p44/42 mitogen-activated protein kinase [p44/42 MAPK; a.k.a. ERK-1/2]/mitogen-activated protein kinase kinase (MEK) signaling. Each or all of these intracellular responses may promote Ca^{2+} -dependent depolarization of the GLP-1R expressing neuron, and in addition, likely lead to long-term cAMP response element-binding protein (CREB)-mediated transcriptional effects (see [4] for review).

It is interesting to note that NTS GLP-1R activation rapidly increases PKA activity, with a peak in activity occurring 10min following hindbrain administration of exendin-4, and a return to baseline (vehicle) levels seen at 30min-post administration [32]. Yet, behavioral analyses show that the suppression of intake of standard rodent chow following hindbrain (4th ICV) exendin-4 delivery is not observed until 3h post-administration, an effect that is dependent upon an increase in PKA and MAPK activity, as well as a decrease in AMPK

activity [32]. This discrepancy in the time-course effects for the intracellular signaling cascades from tissue lysates and the behavioral feeding response are reported previously for other anorectic ligands acting within the brain [33–35]. These findings suggest that although PKA-, MAPK-, and AMPK-signaling are required to mediate the suppression of intake by NTS GLP-1R activation, other downstream signaling cascades and recruitment of additional CNS nuclei are *also required* to mediate the intake-suppressive effects following hindbrain GLP-1R activation.

Converging intracellular signaling pathways as a mechanistic mediator for interactions between diverse energy balance signals

Evaluation of the behavioral, neuronal, and cellular mechanisms by which the CNS GLP-1 system controls for food intake and energy balance will provide necessary information needed to determine the most effective energy balance-relevant systems that may be targeted in combination with GLP-1R ligands for the treatment of obesity. This need is underscored by current leading theories which attest that combination therapies may offer a better treatment option for obesity and associated comorbidities than mono-drug therapies or lifestyle modifications alone [36–39]. Thus, identification of the neuronal phenotype of GLP-1R-expressing neurons in energy balance-relevant nuclei, the other neurotransmitter receptor classes that are expressed in combination with GLP-1R on these neurons, as well as the intracellular signaling pathways that mediate energy balance responses of these GLP-1R-expressing neurons are all important pieces of information needed to effectively combine GLP-1-based pharmacotherapies with other drug treatments.

It is reasonable to assume that many of the GLP-1R-mediated intracellular signaling pathways are similar throughout the brain, as *ex vivo* intracellular signaling responses following NTS GLP-1R activation (e.g. PKA mediated-increase in p44/42 MAPK and – decrease in AMPK phosphorylation) were also found to occur *in vitro* in hypothalamic GT1-7 cells by GLP-1R activation [32]. By contrast, given the very wide distributed expression of GLP-1R throughout the brain [40, 41], what is likely to be different across the CNS is the phenotype of neurons that express the GLP-1R. Specifically, the neurotransmitter/neuropeptides produced by these GLP-1R-expressing neurons, as well as the other receptors [e.g. NMDA, leptin receptor (LepR), serotonin (5-HT)] that are co-expressed along with the GLP-1R may be very diverse throughout the brain. Therefore, in order to understand the mechanisms by which GLP-1R activation suppresses food intake and body weight, it is imperative to investigate whether the GLP-1R-activated intracellular signaling pathways influence the neuronal responsivity to other signals that also convey information regarding energy availability. Converging intracellular signaling responses from two separately activated receptors is one mechanism that may account for synergy or additivity between two separate, yet cooperative systems involved in energy balance regulation (see [32, 42–45] for example). Further, neuronal receptor activation can produce long-term changes in gene transcription and protein synthesis, which may potentiate the intake inhibitory effects of other anorectic systems that also act upon the same neurons. While these ideas are certainly intriguing, there has been virtually no proof of concept for either of these possibilities in regard to the GLP-1-mediated control of energy balance. It is possible that these proposed intracellular signaling mechanisms could account for the cooperative interaction between GLP-1 and other anorectic signals (e.g. leptin, amylin, peptide-YY) [46–51].

Conclusions

The intake inhibitory and glycemic effects mediated by the GLP-1R involve a complex, coordinated, and very distributed system. Beyond simple action on pancreatic β -cells, GLP-1 control of glycemia involves mediation by GLP-1R expressed on peripheral vagal

afferent fibers, as well as CNS nuclei. Similarly, GLP-1R-mediated suppression of food intake also involves a vagal-dependent, as well as direct CNS action. Thus, future research aimed at treating both obesity and T2DM would be greatly advanced by embracing the notion that pharmacological levels of GLP-1 and GLP-1R agonists are gaining access to the CNS to produce their intake inhibitory and glycemic effects. Given recent findings analyzing the intracellular signaling and neuronal mechanisms by which CNS GLP-1R signaling controls for energy balance, we are in a position to determine what other pharmacological treatments can be combined with GLP-1R agonists to yield the most effective food intake inhibitory and incretin effects.

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References

1. Mayo KE, Miller LJ, Bataille D, Dalle S, Goke B, Thorens B, et al. International Union of Pharmacology. XXXV. The glucagon receptor family. *Pharmacological reviews*. 2003; 55:167–94. [PubMed: 12615957]
2. Thorens B. Expression cloning of the pancreatic beta cell receptor for the gluco-incretin hormone glucagon-like peptide 1. *Proc Natl Acad Sci U S A*. 1992; 89:8641–5. [PubMed: 1326760]
3. Holst JJ. The physiology of glucagon-like peptide 1. *Physiol Rev*. 2007; 87:1409–39. [PubMed: 17928588]
4. Hayes MR, De Jonghe BC, Kanoski SE. Role of the glucagon-like-peptide-1 receptor in the control of energy balance. *Physiol Behav*. 2010; 100:503–10. [PubMed: 20226203]
5. Hayes MR, Kanoski SE, De Jonghe BC, Leichner TM, Alhadeff AL, Fortin SM, et al. The common hepatic branch of the vagus is not required to mediate the glycemic and food intake suppressive effects of glucagon-like-peptide-1. *Am J Physiol Regul Integr Comp Physiol*. 2011
6. Rinaman L, Card JP, Schwaber JS, Miselis RR. Ultrastructural demonstration of a gastric monosynaptic vagal circuit in the nucleus of the solitary tract in rat. *J Neurosci*. 1989; 9:1985–96. [PubMed: 2723763]
7. Vahl TP, Tauchi M, Durler TS, Elfers EE, Fernandes TM, Bitner RD, et al. Glucagon-like peptide-1 (GLP-1) receptors expressed on nerve terminals in the portal vein mediate the effects of endogenous GLP-1 on glucose tolerance in rats. *Endocrinology*. 2007; 148:4965–73. [PubMed: 17584962]
8. Knauf C, Cani PD, Perrin C, Iglesias MA, Maury JF, Bernard E, et al. Brain glucagon-like peptide-1 increases insulin secretion and muscle insulin resistance to favor hepatic glycogen storage. *J Clin Invest*. 2005; 115:3554–63. [PubMed: 16322793]
9. Nishizawa M, Nakabayashi H, Kawai K, Ito T, Kawakami S, Nakagawa A, et al. The hepatic vagal reception of intraportal GLP-1 is via receptor different from the pancreatic GLP-1 receptor. *J Auton Nerv Syst*. 2000; 80:14–21. [PubMed: 10742535]
10. Nishizawa M, Nakabayashi H, Uchida K, Nakagawa A, Nijima A. The hepatic vagal nerve is receptive to incretin hormone glucagon-like peptide-1, but not to glucose-dependent insulinotropic polypeptide, in the portal vein. *J Auton Nerv Syst*. 1996; 61:149–54. [PubMed: 8946334]
11. Wang FB, Powley TL. Vagal innervation of intestines: afferent pathways mapped with new en bloc horseradish peroxidase adaptation. *Cell Tissue Res*. 2007; 329:221–30. [PubMed: 17453246]
12. Kanoski SE, Fortin SM, Arnold M, Grill HJ, Hayes MR. Peripheral and Central GLP-1 Receptor Populations Mediate the Anorectic Effects of Peripherally Administered GLP-1 Receptor Agonists, Liraglutide and Exendin-4. *Endocrinology*. 2011; 152:3103–12. [PubMed: 21693680]
13. Knauf C. Brain glucagon-like peptide-1 increases insulin secretion and muscle insulin resistance to favor hepatic glycogen storage. *J Clin Invest*. 2005; 115:3554–63. [PubMed: 16322793]

14. Barrera JG, Jones KR, Herman JP, D'Alessio DA, Woods SC, Seeley RJ. Hyperphagia and increased fat accumulation in two models of chronic CNS glucagon-like peptide-1 loss of function. *J Neurosci.* 2011; 31:3904–13. [PubMed: 21389245]
15. Sandoval DA, Bagnol D, Woods SC, D'Alessio DA, Seeley RJ. Arcuate GLP-1 receptors regulate glucose homeostasis but not food intake. *Diabetes.* 2008
16. Baggio LL, Drucker DJ. Biology of incretins: GLP-1 and GIP. *Gastroenterology.* 2007; 132:2131–57. [PubMed: 17498508]
17. Merchenthaler I, Lane M, Shughrue P. Distribution of pre-pro-glucagon and glucagon-like peptide-1 receptor messenger RNAs in the rat central nervous system. *J Comp Neurol.* 1999; 403:261–80. [PubMed: 9886047]
18. Thorens B. Brain glucose sensing and neural regulation of insulin and glucagon secretion. *Diabetes Obes Metab.* 2011; 13 (Suppl 1):82–8. [PubMed: 21824260]
19. Thorens B. Sensing of glucose in the brain. *Handbook of experimental pharmacology.* 2012; 209:277–94. [PubMed: 22249819]
20. Watts AG, Donovan CM. Sweet talk in the brain: glucosensing, neural networks, and hypoglycemic counterregulation. *Front Neuroendocrinol.* 2010; 31:32–43. [PubMed: 19836412]
21. Parker HE, Reimann F, Gribble FM. Molecular mechanisms underlying nutrient-stimulated incretin secretion. *Expert Rev Mol Med.* 2010; 12:e1. [PubMed: 20047700]
22. Wan S, Browning KN, Travagli RA. Glucagon-like peptide-1 modulates synaptic transmission to identified pancreas-projecting vagal motoneurons. *Peptides.* 2007; 28:2184–91. [PubMed: 17889966]
23. Wan S, Coleman FH, Travagli RA. Glucagon-like peptide-1 excites pancreas-projecting preganglionic vagal motoneurons. *Am J Physiol Gastrointest Liver Physiol.* 2007; 292:G1474–82. [PubMed: 17322063]
24. Gomez E, Pritchard C, Herbert TP. cAMP-dependent protein kinase and Ca²⁺ influx through L-type voltage-gated calcium channels mediate Raf-independent activation of extracellular regulated kinase in response to glucagon-like peptide-1 in pancreatic beta-cells. *J Biol Chem.* 2002; 277:48146–51. [PubMed: 12364324]
25. Perfetti R, Merkel P. Glucagon-like peptide-1: a major regulator of pancreatic beta-cell function. *Eur J Endocrinol.* 2000; 143:717–25. [PubMed: 11124853]
26. Seino S, Takahashi H, Fujimoto W, Shibasaki T. Roles of cAMP signalling in insulin granule exocytosis. *Diabetes Obes Metab.* 2009; 11 (Suppl 4):180–8. [PubMed: 19817800]
27. Kashima Y, Miki T, Shibasaki T, Ozaki N, Miyazaki M, Yano H, et al. Critical role of cAMP-GEFII–Rim2 complex in incretin-potentiated insulin secretion. *J Biol Chem.* 2001; 276:46046–53. [PubMed: 11598134]
28. Alhadeff AL, Rupprecht LE, Hayes MR. GLP-1 neurons in the nucleus of the solitary tract project directly to the ventral tegmental area and nucleus accumbens to control for food intake. *Endocrinology.* 2011 In Press.
29. Dossat AM, Lilly N, Kay K, Williams DL. Glucagon-like Peptide 1 receptors in nucleus accumbens affect food intake. *J Neurosci.* 2011; 31:14453–7. [PubMed: 21994361]
30. Hayes MR, Skibicka KP, Grill HJ. Caudal brainstem processing is sufficient for behavioral, sympathetic, and parasympathetic responses driven by peripheral and hindbrain glucagon-like-peptide-1 receptor stimulation. *Endocrinology.* 2008; 149:4059–68. [PubMed: 18420740]
31. Hayes MR, Bradley L, Grill HJ. Endogenous hindbrain glucagon-like peptide-1 receptor activation contributes to the control of food intake by mediating gastric satiation signaling. *Endocrinology.* 2009; 150:2654–9. [PubMed: 19264875]
32. Hayes MR, Leichner TM, Zhao S, Lee GS, Chowansky A, Zimmer D, et al. Intracellular signals mediating the food intake-suppressive effects of hindbrain glucagon-like peptide-1 receptor activation. *Cell Metab.* 2011; 13:320–30. [PubMed: 21356521]
33. Sutton GM, Duos B, Patterson LM, Berthoud HR. Melanocortinergic modulation of cholecystokinin-induced suppression of feeding through extracellular signal-regulated kinase signaling in rat solitary nucleus. *Endocrinology.* 2005; 146:3739–47. [PubMed: 15961554]

34. Morton GJ, Blevins JE, Kim F, Matsen M, Figlewicz DP. The action of leptin in the ventral tegmental area to decrease food intake is dependent on Jak-2 signaling. *Am J Physiol Endocrinol Metab.* 2009; 297:E202–10. [PubMed: 19435852]
35. Niswender KD, Morton GJ, Stearns WH, Rhodes CJ, Myers MG Jr, Schwartz MW. Intracellular signalling. Key enzyme in leptin-induced anorexia. *Nature.* 2001; 413:794–5. [PubMed: 11677594]
36. Vetter ML, Faulconbridge LF, Webb VL, Wadden TA. Behavioral and pharmacologic therapies for obesity. *Nat Rev Endocrinol.* 2010; 6:578–88. [PubMed: 20680034]
37. Greenway FL, Whitehouse MJ, Guttadauria M, Anderson JW, Atkinson RL, Fujioka K, et al. Rational design of a combination medication for the treatment of obesity. *Obesity (Silver Spring).* 2009; 17:30–9. [PubMed: 18997675]
38. Day JW, Ottaway N, Patterson JT, Gelfanov V, Smiley D, Gidda J, et al. A new glucagon and GLP-1 co-agonist eliminates obesity in rodents. *Nat Chem Biol.* 2009; 5:749–57. [PubMed: 19597507]
39. Zinman B, Gerich J, Buse JB, Lewin A, Schwartz S, Raskin P, et al. Efficacy and safety of the human glucagon-like peptide-1 analog liraglutide in combination with metformin and thiazolidinedione in patients with type 2 diabetes (LEAD-4 Met+TZD). *Diabetes Care.* 2009; 32:1224–30. [PubMed: 19289857]
40. Merchenthaler I, Lane M, Shughrue P. Distribution of pre-pro-glucagon and glucagon-like peptide-1 receptor messenger RNAs in the rat central nervous system. *J Comp Neurol.* 1999; 403:261–80. [PubMed: 9886047]
41. Rinaman L. Ascending projections from the caudal visceral nucleus of the solitary tract to brain regions involved in food intake and energy expenditure. *Brain Res.* 2010; 1350:18–34. [PubMed: 20353764]
42. Berthoud HR, Sutton GM, Townsend RL, Patterson LM, Zheng H. Brainstem mechanisms integrating gut-derived satiety signals and descending forebrain information in the control of meal size. *Physiol Behav.* 2006; 89:517–24. [PubMed: 16996546]
43. Myers MG, Cowley MA, Munzberg H. Mechanisms of leptin action and leptin resistance. *Annu Rev Physiol.* 2008; 70:537–56. [PubMed: 17937601]
44. Daniels D, Patten CS, Roth JD, Yee DK, Fluharty SJ. Melanocortin receptor signaling through mitogen-activated protein kinase in vitro and in rat hypothalamus. *Brain Res.* 2003; 986:1–11. [PubMed: 12965224]
45. Daniels D, Yee DK, Faulconbridge LF, Fluharty SJ. Divergent behavioral roles of angiotensin receptor intracellular signaling cascades. *Endocrinology.* 2005; 146:5552–60. [PubMed: 16123155]
46. Nowak A, Bojanowska E. Effects of peripheral or central GLP-1 receptor blockade on leptin-induced suppression of appetite. *J Physiol Pharmacol.* 2008; 59:501–10. [PubMed: 18953093]
47. Williams DL, Baskin DG, Schwartz MW. Leptin regulation of the anorexic response to glucagon-like peptide-1 receptor stimulation. *Diabetes.* 2006; 55:3387–93. [PubMed: 17130484]
48. Tang-Christensen M. Central administration of GLP-1-(7–36) amide inhibits food and water intake in rats. *Am J Physiol.* 1996; 271:R848–R56. [PubMed: 8897973]
49. Bello NT, Kemm MH, Ofeldt EM, Moran TH. Dose combinations of exendin-4 and salmon calcitonin produce additive and synergistic reductions in food intake in nonhuman primates. *Am J Physiol Regul Integr Comp Physiol.* 2010; 299:R945–52. [PubMed: 20554932]
50. Neary NM, Small CJ, Druce MR, Park AJ, Ellis SM, Semjonous NM, et al. Peptide YY3–36 and glucagon-like peptide-17–36 inhibit food intake additively. *Endocrinology.* 2005; 146:5120–7. [PubMed: 16150917]
51. Talsania T, Anini Y, Siu S, Drucker DJ, Brubaker PL. Peripheral exendin-4 and peptide YY(3–36) synergistically reduce food intake through different mechanisms in mice. *Endocrinology.* 2005; 146:3748–56. [PubMed: 15932924]

Highlights

- GLP-1R mediation of blood glucose involves action in the periphery and CNS
- Vagal and CNS GLP-1R control for food intake
- CNS GLP-1R activation suppresses food intake via a cAMP/PKA-dependent pathway
- Common intracellular signaling pathways can represent a mechanism for additivity/synergy between two separate anorectic signals