Published in final edited form as:

Mol Cell Endocrinol. 2015 December 15; 418 Pt 1: 27–32. doi:10.1016/j.mce.2015.02.017.

Brain GLP-1 and Insulin Sensitivity

Darleen Sandoval^a and Stephanie R. Sisley^b

^aDepartment of Surgery, University of Michigan, Ann Arbor, MI

^bDepartment of Pediatrics, Division of Nutrition, Baylor College of Medicine, Houston, TX

Abstract

Type 2 diabetes is often treated with a class of drugs referred to as glucagon-like peptide-1 (GLP-1) analogs. GLP-1 is a peptide secreted by the gut that acts through only one known receptor, the GLP-1 receptor. The primary function of GLP-1 is thought to be lowering of postprandial glucose levels. Indeed, medications utilizing this system, including the long-acting GLP-1 analogs liraglutide and exenatide, are beneficial in reducing both blood sugars and body weight. GLP-1 analogs were long presumed to affect glucose control through their ability to increase insulin levels through peripheral action on beta cells. However, multiple lines of data point to the ability of GLP-1 to act within the brain to alter glucose regulation. In this review we will discuss the evidence for a central GLP-1 system and the effects of GLP-1 in the brain on regulating multiple facets of glucose homeostasis including glucose tolerance, insulin production, insulin sensitivity, hepatic glucose production, muscle glucose uptake, and connections of the central GLP-1 system to the gut. Although the evidence indicates that GLP-1 receptors in the brain are not necessary for physiologic control of glucose regulation, we discuss the research showing a strong effect of acute manipulation of the central GLP-1 system on glucose control and how it is relevant to type 2 diabetic patients.

Keywords

GLP-1; glucagon-like peptide-1; GLP-1R; receptor; glucose; brain; insulin sensitivity; glucose tolerance; muscle; liver

1. Introduction*

The rising incidence of type 2 diabetes and the side effects of available therapies have led to searches for new more effective drug targets. One of these targeted systems that has met with good success is the glucagon-like peptide-1 (GLP-1) system. Decades ago, researchers

Corresponding Author: Stephanie Sisley 1100 Bates Ave Houston, TX, USA 77459 713-798-0391 713-798-7057 (fax) sisley@bcm.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

* Abbreviations: ARC – arcuate nucleus; AP – area postrema; CRH – corticotropin-releasing hormone; GLP-1 – Glucagon-like peptide-1; GLP-1R – GLP-1 receptor; GTT – glucose tolerance test; NS – nucleus of the solitary tract; PVN – paraventricular nucleus; VMH – ventromedial hypothalamus

observed that orally given glucose resulted in a smaller glucose excursion than intravenously administered glucose and the lower glucose excursion was associated with a greater rise in insulin. This difference was referred to as the incretin effect and the physiology suggested that it was due to a nutrient-induced intestinal secretion that then acted on the pancreas to stimulate insulin secretion. GLP-1 was discovered as an incretin in humans in 1987¹. GLP-1 is made in the L-cells of the intestine and has only one known receptor, the GLP-1 receptor (GLP-1R)². Not surprisingly, GLP-1Rs are located on the insulin producing cells of the pancreas³ and long-acting analogs to activate GLP-1Rs have been effective as antidiabetic therapies⁴. However, GLP-1 also is produced within the brain and its receptors are in key regions associated with both food intake and glucose control (discussed below). Thus, much research has sought to answer if brain GLP-1 signaling is necessary for the effects of GLP-1 on glucose tolerance. This review will focus on the glucose homeostatic effects of GLP-1 in the brain, both pharmacological and physiological.

2. Glucose control by the brain

Glucose is a tightly regulated nutrient in the body and is affected by nutrient ingestion, tissue uptake, new synthesis by the liver, and release of stored glucose (in the form of glycogen). Glucose levels are remarkably stable throughout the day despite changes in feeding or activity status. The stability of glucose levels, also referred to as glucose homeostasis, is a result of several physiological processes. For many years after the discovery of insulin, glucose homeostasis was thought to be regulated only by peripheral processes. Insulin, produced by the beta cells of the pancreas, has well known actions within fat and skeletal muscle cells to stimulate glucose uptake and within the liver to suppress glucose output. However, within the brain, distinct regions have also proven to be important in regulation of glucose homeostasis⁵, specifically the arcuate nucleus of the hypothalamus (ARC), the ventromedial hypothalamus (VMH), the nucleus of the solitary tract (NTS) as well as cell bodies for the vagus nerve. Several hormones and cellular signaling systems including insulin, leptin, the melanocortin system, K-ATP channels, and mTOR have all been shown to have effects on glucose homeostasis through brain mechanisms⁶.

3. Characteristics of GLP-1 Action in the Brain

GLP-1 is made in the periphery but the extent to which peripherally secreted GLP-1 reaches CNS-located GLP-1Rs is debated. GLP-1 is rapidly degraded in the circulation by proteases rendering a half-life of only a couple of minutes². Despite this, radiolabeled GLP-1 and GLP1R agonists can cross the blood-brain-barrier after peripheral administration⁷⁸. GLP-1 is also synthesized by the hindbrain in a discrete set of neurons within the nucleus of the solitary tract (NTS) in rats⁹ and similarly in non-human primates¹⁰. These neurons have wide projections to hypothalamic, thalamic and cortical areas^{11,12}. Overall, there is evidence for high conservation of GLP-1 positive cells in the CNS across multiple species¹³. However, little is known about the neurophysiology of these neurons and whether it is peripheral or central secretion of GLP-1 that activates CNS GLP-1 receptors. Thus, critical questions remain unanswered regarding the source of GLP-1 that activates CNS GLP-1 receptors.

Much of what is known about the activation of CNS GLP-1 receptors is via exogenous administration of GLP-1 or its antagonist directly into the CNS. When administered centrally, GLP-1 induced c-fos expression, a marker of neuronal activation, in specific brain areas including distinct regions of the paraventricular nucleus (PVN), supraoptic nuclei, ARC, NTS, and area postrema (AP)¹⁴. GLP-1R agonists, albumin-exendin-4 conjugate, and peripheral exendin-4 increased c-fos in the AP, NTS, and PVN as well¹⁵. Within the PVN, central GLP-1 administration has been shown to cause c-fos expression in corticotropin-releasing hormone (CRH) neurons¹⁶. Thus, GLP-1 or its analogs can directly activate regions of the brain shown to be important for glucose control.

GLP-1R mRNA was found in the human brain¹⁷ and autoradiography showed that it bound to multiple sites in both rat and mice brains, including the thalamus, hypothalamus, AP, amygdala, hippocampus, and NTS^{11,18}. GLP-1R mRNA was found in micropunches of the rat NTS, AP, ARC, VMH, PVN and lateral hypothalamus, with highest expression in ARC and AP¹⁹. More recent genetic tools have demonstrated that fluorescent reporter strains showed abundance of GLP-1R expressing cells in mouse AP, ARC, PVN, and VMH³. Much is to be learned regarding the phenotype of these neurons but it has been demonstrated that GLP-1R nerve fibers have been shown to synapse on rat CRH neurons¹⁶ which has implications for glucose control under stressful stimuli. In addition, the ARC is an extremely important loci for CNS regulation of glucose homeostasis and GLP-1R mRNA co-localizes with ARC POMC but not AgRP cells in rats²⁰. Thus, it is clear that the ability of GLP-1 to signal through its receptor is present in multiple areas of the brain.

4. Measuring Glucose Homeostasis

Since glucose homeostasis is affected by several processes, including glucose uptake (insulin and non-insulin mediated), glucose production (mainly by the liver), and insulin secretion, we will briefly review the techniques to assess these different processes.

Glucose tolerance

A glucose tolerance test (GTT) measures the body's ability to clear glucose from the blood. GTT's are performed by rapidly administering a bolus of glucose and performing serial glucose measurements. Glucose can be administered orally (OGTT), intraperitoneally (IpGTT), or intravenously (IVGTT). Oral administration of glucose will evoke the gut to respond and secrete hormones to aid in the clearance of glucose (e.g. incretin effect). Intraperitoneal glucose administration bypasses the intestine and instead gets rapidly absorbed from the peritoneal cavity into the portal vein. The overall result from a GTT describes how quickly the body can respond and clear glucose from its system but not the underlying processes responsible. Although pairing a GTT with a measurement of insulin can be informative, the differing glucose excursions between groups and the difficulty in timing the measurements with the glucose dose only provide for a gross comparison of glucose and insulin responses to a given glucose load. To study insulin secretion, one strategy is to use an IVGTT. With this technique, a small amount of glucose is infused intravenously which then directly stimulates pre-formed β -cell vesicles containing insulin^{20–23}. This is often referred to as the “first phase” insulin response. In addition, the

presence of an indwelling catheter for blood sampling allows for rapid and multiple blood draws giving a better sense of timing of the insulin response to glucose.

Hyperinsulinemic-euglycemic clamps

The gold standard to assess insulin sensitivity is the hyperinsulinemic-euglycemic clamp. In this technique, a constant intravenous infusion of insulin is given to the animal. The glucose is monitored closely and held steady, or “clamped”, at a set concentration through the use of a variable glucose infusion. Animals with higher insulin sensitivity will require higher glucose infusions to keep their plasma glucose levels steady. The bonus of this technique is that when coupled with radioisotopes, one can discriminate whether it is the liver or peripheral tissues that are more insulin sensitive. Using a different radioisotope, tissue specific glucose uptake can be measured. This allows the determination of whether glucose is increased across the board, or whether specific tissues are more sensitive than others. This technique is most useful when the insulin infusion rate is high which drives greater glucose clearance. During a clamp, the dose of insulin can be manipulated depending on the goal in mind. Supraphysiologic insulin administration is most useful in determining the maximal glucose clearance but will maximally suppress hepatic glucose production limiting the understanding of changes in hepatic insulin sensitivity. A basal clamp is also used which employs the use of somatostatin to cease any endogenous insulin production. This technique is effective at determining the impact of experimental manipulations on hepatic rather than skeletal muscle insulin sensitivity. Thus, the experimental design of “glucose clamp” experiments can vary widely and it is important to consider the implications of a particular design on experimental outcome.

Hyperglycemic clamps

Another glucose clamping technique often used to examine insulin secretion is to artificially raise and then maintain glucose levels at a supraphysiological state for a period of time, usually 1h. The benefit of a hyperglycemic clamp is that it can measure the response of an intervention on the release of insulin by the pancreatic β -cells. Sometimes, a hyperglycemic clamp is combined with hyperinsulinemia in order to maximize glucose clearance in a state of nutrient excess.

5. GLP-1 and Peripheral Glucose Regulation

In addition to its effects on insulin secretion, GLP-1 has been reported to influence glucose levels independent of insulin secretion by decreasing gastric emptying rate, decreasing glucagon secretion, and decreasing liver glucose production^{2,24}. These multi-factorial effects are supported by the fact that GLP-1R agonists, albumin-exendin-4 conjugate and exendin-4, both decreased glucose excursions in oral and intraperitoneal GTTs and significantly increased the insulin:glucose ratio in both chow and high-fat fed mice¹⁵. Additionally, whole-body GLP-1R null mice have impaired oral and intraperitoneal glucose tolerance tests and early work attributed this to their decreased insulin secretion¹⁸. Although GLP-1 was previously thought to increase muscle glucose uptake²⁵, in hyperinsulinemic-euglycemic clamps GLP-1R null mice have a global increase in insulin sensitivity, driven by increased muscle glucose uptake, but at the same time reduced hepatic insulin sensitivity²⁶.

This would suggest that GLP-1 actually decreases muscle insulin sensitivity but increases hepatic insulin sensitivity. A different group found that chronic blockade of endogenous GLP-1 action with intraperitoneal administration of a GLP-1R antagonist, exendin(9-39), lead to an overall improvement in glucose tolerance in diabetic, high-fat fed mice²⁷. The high fat diet used in that study (72% fat, <1% carbohydrate) was likely ketogenic and under these conditions, it is possible that the liver effects of GLP-1 antagonism are obscured while the muscle effects predominate. Regardless, these differences indicate there may be differential effects of GLP-1R action with regard to nutrient availability. Altogether these data demonstrate that GLP-1 has multiple effects on regulating glucose homeostasis and that divergent effects on insulin sensitivity suggest that the GLP-1R is necessary for normal glucose turnover. However, the brain is also known to affect muscle glucose uptake and liver glucose output and thus may also be involved in the effects observed in these “peripheral” studies.

6. GLP-1 and Central Regulation of Glucose

6.1 Glucose tolerance and insulin production

The effects of GLP-1 in the brain with regard to glucose changes have been controversial. Larsen et al. showed that central GLP-1 decreased peripheral glucose levels transiently but Perez-Tilve et al. demonstrated hyperglycemia after central exendin-4^{14,28}. The latter study is likely an isolated and species-specific effect, as the hyperglycemia associated with peripheral administration of exendin-4 in rats is attenuated with chronic treatments and has not been shown in other species or with GLP-1 treatment. Thus, there may be a difference in the action of exendin-4 and GLP-1 within the CNS. Interestingly, though, both papers showed the ability of GLP-1R agonism to increase corticosterone levels, a stress hormone elevated in episodes of hypoglycemia which aids in returning glucose levels back to normal. Thus, GLP-1 action in the brain causing both increased insulin and corticosterone would likely have no observed effect on glucose tolerance. On the other hand, if one of these responses is preferentially activated, hypo- or hyperglycemia could result. Since corticosterone levels are often not measured during glucose testing, these divergent effects are likely to be missed.

50% of pancreas-projecting dorsal motor nucleus of the vagus nerves are depolarized by GLP-1 or exendin-4²⁹, thus, connections exist for central GLP-1 to directly stimulate insulin production. During an IVGTT, central GLP-1 increases insulin levels transiently²⁰. Others have shown that central GLP-1 can improve glucose levels through increased insulin levels during an OGTT in high-fat fed mice³⁰. However, a recent publication did not find any effect of central administration of the long-acting GLP-1R agonist, liraglutide, on glucose or insulin levels during an OGTT in high-fat fed rats³¹. Thus, there may be differences in the pharmacologic action of native GLP-1 vs. liraglutide or there may be species-specific variations. Acutely, central GLP-1R blockade impairs glucose tolerance in lean animals²⁰ but likely has no effect on glucose tolerance in high fat-fed animals³². In a hyperglycemic clamp, a paradigm where there is maximal β -cell stimulation, central exendin-4 also increased insulin levels when given centrally²⁷.

Perhaps most telling however, is recent data showing no differences in glucose tolerance in chow or high-fat diet fed animals with neuronal-specific deletion of the GLP-1R in the nervous system compared to wild type mice³³. Additionally, although liraglutide did not reduce body weight, it did retain its full ability to lower glucose excursions despite loss of central GLP-1R³³. Whether the loss of neuronal GLP-1R during development is compensated for by peripheral GLP-1R remains unknown, and overall insulin sensitivity or insulin secretion were not tested in those animals. However, recent data demonstrate that pancreatic GLP-1R are necessary for a GLP-1R antagonist to impair glucose tolerance after both peripheral and central administration^{34,35}. Overall, these data suggest that neuronal GLP-1R are not, as a whole, necessary for regulation of glucose homeostasis, yet acute pharmacological activation or blockade of CNS GLP-1R signaling does impact regulation of glucose tolerance and the mechanisms for these effects will be discussed in the next sections.

6.2 Insulin Sensitivity

Multiple groups have now shown that under hyperinsulinemic-euglycemic clamp parameters with central GLP-1^{20,30} or central exendin-4 treatment³⁶, there were no effects on overall insulin sensitivity based on the exogenous glucose infusion rate needed to maintain euglycemia. Similarly, acute central GLP-1R antagonism had no effect on global insulin sensitivity in animals fed a 44% or 60% high-fat diet during a hyperinsulinemic-euglycemic clamp^{30,37}. In a hyperinsulinemic-hyperglycemic state, central exendin-4 decreased, while exendin-9 increased, insulin sensitivity^{27,36,38}. However, these latter studies used diabetic mice on an unbalanced diet (72% fat, <1% carbohydrates). As previously discussed, peripheral GLP-1 action is thought to increase liver insulin sensitivity while decreasing muscle insulin sensitivity. Thus, underlying divergent changes in glucose flux may equate to a net zero change in global insulin sensitivity (to be discussed more below). Given previously published data that low-carbohydrate diets increase insulin resistance³⁹, it is possible that the muscle effects of central GLP-1 action predominate in an artificial nutrient state, which isn't observed in chow-fed or hyperinsulinemic-euglycemic testing conditions. Despite a lack of central GLP-1 agonism/antagonism to alter insulin sensitivity in hyperinsulinemic-euglycemic clamps, central GLP-1R antagonism attenuated the improvement in insulin sensitivity caused by peripheral GLP-1 infusion³⁷. Thus, some of the actions of peripheral GLP-1 on insulin sensitivity may occur through central signaling despite a lack of improvement with direct central pharmacologic activation.

6.3 Hepatic glucose production

Acute administration of brain GLP-1 decreased hepatic glucose production during hyperinsulinemic-euglycemic clamp conditions when given both in the lateral ventricle³⁰ and directly into the arcuate, but not the paraventricular nucleus²⁰. However, this effect is impaired when animals are on a high fat diet^{30,37}. Chronic GLP-1R antagonism in animals receiving a high-fat, low carbohydrate diet decreased hepatic glycogen synthesis in a hyperinsulinemic-hyperglycemic clamp, which would suggest increased hepatic insulin resistance⁴⁰. These same authors saw no effect on hepatic glycogen synthesis after activation of central GLP-1R with exendin-4. Thus, GLP-1R activation in the brain seems to improve hepatic insulin sensitivity but these effects are diminished when on a high-fat diet

or in hyperglycemic conditions. Combined, these data suggest that dysfunction of the central GLP-1R system may be integral in the impairment in hepatic insulin sensitivity with high fat feeding or diabetes.

6.4 Effects on muscle glucose uptake

While acute central GLP-1 may improve hepatic insulin sensitivity, it seems to do the opposite to peripheral insulin action. Central GLP-1 has been shown to both have either no effect³⁰ or to decrease glucose clearance²⁰. The differences in results may be secondary to the different lengths of fasting (5 hours vs. overnight respectively) or the species used (mice vs. rat respectively). In animals fed a high-fat, ketogenic diet (72% fat, <1% carbohydrate), GLP-1R activation decreased glucose utilization in one of three tested muscles but GLP-1R antagonism increased glucose utilization in 2 of 3 muscles and increased muscle glycogen content²⁷.

Chronic GLP-1R blockade was also shown to increase muscle glycogen in chow-fed mice in hyperglycemic-hyperinsulinemic clamps independent of the muscle insulin receptor⁴¹.

Denervation of limbs negated effects of GLP-1R antagonism on muscle glycogen storage²⁷, implying a direct effect of central GLP-1R action on peripheral muscles. This may be secondary to a change in arterial blood flow as central exendin-4 decreased femoral arterial blood flow in hyperinsulinemic-hyperglycemic conditions³⁸. The preponderance of evidence shows that despite the testing conditions, central GLP-1R activation decreases muscle glucose uptake while GLP-1R blockade increases muscle glucose uptake. This is in striking contrast to the above sections where the diet and testing conditions play a large role in the effects of central GLP-1R action. Additionally, the effects of brain GLP-1R action seem to be a direct result of brain to muscle connections and not secondary to altered insulin action. The overall impact of this may be to slow glucose turnover and retain or preferentially restore hepatic glycogen under postprandial conditions.

6.5 Brain to Gut Connections

If CNS GLP-1Rs have a physiological role in regulating glucose homeostasis, the conundrum is that plasma GLP-1 is cleared within minutes likely limiting CNS access. An alternative explanation is that peripherally secreted GLP-1 activates GLP-1R located in the innervation of both the intestine and portal vein. This would account for the rapid effect of this incretin in regulating glucose homeostasis in the face of rapid cleavage by proteases. Indeed, GLP-1 activates vagal afferent neurons⁴² and administration of a GLP-1R antagonist directly into the portal vein impairs glucose tolerance⁴³. These data suggest the potential for a gut-brain-pancreas or gut-brain-liver axis in regulating postprandial glucose homeostasis. In support of this, blockade of brain GLP-1R diminished changes in glucose turnover in response to intragastric glucose administration⁴¹. Selective ablation of the common hepatic branch of the vagus did not alter the ability of peripheral GLP-1R antagonism to increase blood glucose levels during an oral GTT⁴⁴. However, peripheral GLP-1R antagonism had no effect on glucose tolerance in animals with deafferentation higher up on the vagus (subdiaphragmatic)⁴⁴. The significance of this, though, is unknown since there was no difference in glucose excursions with exendin-9 treatment in control vs. subdiaphragmatic

vagal deafferentation and there appeared to be an intermediate effect of the surgery by itself. Thus, it is possible that the study was underpowered to detect a significant difference in the surgery treated groups. The hindbrain contains the cell bodies synthesizing GLP-1R on vagal nerve afferents. Blockade of GLP-1 synthesis or GLP-1R activation in the hindbrain was associated with impaired glucose tolerance, but this was likely secondary to the accompanying increased weight gain³². No changes were found in glucose tolerance in mice lacking the ability to produce GLP-1R on vagal nerve afferents, which should affect innervation to both the portal vein and intestine³³. Thus, again it seems that acute manipulation of neuronal GLP-1R (in this case the vagus and above directly in the CNS) regulates glucose homeostasis but these receptors are not necessary for normal glucose tolerance. It could be by measuring only glucose tolerance, subtle differences in the system were missed (i.e. differences in insulin secretion or organ-specific glucose turnover vs. the impact of GLP-1 on the stress response). What is important from these data is that liraglutide improved glucose tolerance regardless of CNS or vagal GLP-1R populations³³, providing a key to the necessary GLP-1R populations for clinical efficacy.

6.6 Central GLP-1 and stress

GLP-1 has been implicated in an animal's response to stress, both via autonomic and the hypothalamo-pituitary-adrenocortical (HPA) axis¹³. Given the importance of both of these systems in raising glucose levels, and the presence of GLP-1 reactive fibers and receptors in key areas of stress regulation in the brain¹³, it is possible that central GLP-1 signaling may affect glucose levels indirectly through actions in these systems. As previously mentioned (see section 6.1), central exendin-4 has been shown to cause hyperglycemia and an increase in corticosterone levels²⁸. However, in this study, the hyperglycemia was likely the result of increased metanephrines and not corticosterone (as the hyperglycemia was abrogated in exendin-4 treated animals without adrenal medullas but the corticosterone response was still present). Mice have also been shown to have increased corticosterone levels after intraperitoneal exendin-4 and humans have increased cortisol levels after intravenous GLP-1⁴⁵. However, in humans, changes in cortisol levels after intravenous infusion of GLP-1 do not cause hyperglycemia, and in fact occur simultaneously with decreased glucose levels in healthy subjects and no changes to glucose levels in type 2 diabetics⁴⁵. Additionally, changes in pulse rate and blood pressure parameters, controlled by the autonomic system, have shown increases after acute peripheral agonism of the GLP-1 system⁴⁶, but no effects with long-term treatment in humans⁴⁷. GLP-1R null mice have normal circulating levels of stress hormones and an increase in their corticosterone response to stress⁴⁸. Together, these studies do not implicate a significant role of central GLP-1 signaling as a stress hormone in the control of whole-body glucose. However, it is possible that direct manipulation of the central GLP-1 system may evoke these responses, leading to changes in glucose, especially in rats.

7. Conclusions and Clinical Implications

GLP-1 has clear beneficial effects on glucose tolerance and insulin secretion when given peripherally. Additionally, there is a large body of literature showing that acute manipulation of central GLP-1 signaling also regulates glucose homeostasis in lean and

obese animals. However, there is a consistent discrepancy of the effects of central GLP-1 action in diabetic animals on a high-fat, ketogenic diet or in hyperglycemic testing conditions. This may indicate that GLP-1 signaling in the brain with regard to glucose homeostasis is affected by the nutritional status of the animal, which has previously been shown to be true with the effects of GLP-1 on food intake^{49–51}. This may have important clinical implications since GLP-1R agonists are used in diabetic patients who are generally overweight or obese. Given recent evidence regarding the lack of glucose phenotypes in animals without central or vagal nerve GLP-1 receptors³³, it is unlikely that central GLP-1 signaling is required for the beneficial glucose-lowering effects of current GLP-1R agonists. Thus, the genetic models reveal that GLP-1Rs are important peripherally for normal glucose homeostasis but not centrally. The acute manipulation data further demonstrate that a central GLP-1R system exists and can be manipulated to affect glucose control but that the testing conditions are important in the overall effects of central GLP-1R activation. From a clinical standpoint, however, central GLP-1R signaling is necessary for the full anorectic actions of peripheral GLP-1R agonists on weight loss³³. Thus, as an antidiabetic therapy, the central actions of GLP-1R signaling should not be ignored given its potent weight-lowering effects, which is the first-line treatment in type 2 diabetes.

References

1. Kreymann B, Williams G, Ghatti MA, Bloom SR. Glucagon-like peptide-1 7-36: a physiological incretin in man. *Lancet*. 1987; 2:1300–1304. [PubMed: 2890903]
2. Baggio LL, Drucker DJ. Biology of incretins: GLP-1 and GIP. *Gastroenterology*. 2007; 132:2131–57. [PubMed: 17498508]
3. Richards P, et al. Identification and characterization of GLP-1 receptor-expressing cells using a new transgenic mouse model. *Diabetes*. 2014; 63:1224–33. [PubMed: 24296712]
4. Buse JB, et al. Exenatide once weekly versus liraglutide once daily in patients with type 2 diabetes (DURATION-6): a randomised, open-label study. *Lancet*. 2013; 381:117–24. [PubMed: 23141817]
5. Sisley S, Sandoval D. Hypothalamic control of energy and glucose metabolism. *Rev. Endocr. Metab. Disord.* 2011; 12:219–33. [PubMed: 21695389]
6. Grayson BE, Seeley RJ, Sandoval DA. Wired on sugar: the role of the CNS in the regulation of glucose homeostasis. *Nat. Rev. Neurosci.* 2013; 14:24–37. [PubMed: 23232606]
7. Hassan M, et al. In vivo dynamic distribution of 131I-glucagon-like peptide-1 (7-36) amide in the rat studied by gamma camera. *Nucl. Med. Biol.* 1999; 26:413–20. [PubMed: 10382845]
8. Hunter K, Hölscher C. Drugs developed to treat diabetes, liraglutide and lixisenatide, cross the blood brain barrier and enhance neurogenesis. *BMC Neurosci.* 2012; 1333
9. Larsen PJ, Tang-Christensen M, Holst JJ, Orskov C. Distribution of glucagon-like peptide-1 and other preproglucagon-derived peptides in the rat hypothalamus and brainstem. *Neuroscience*. 1997; 77:257–70. [PubMed: 9044391]
10. Vrang N, Larsen PJ. Preproglucagon derived peptides GLP-1, GLP-2 and oxyntomodulin in the CNS: role of peripherally secreted and centrally produced peptides. *Prog. Neurobiol.* 2010; 92:442–62. [PubMed: 20638440]
11. Göke R, Larsen PJ, Mikkelsen JD, Sheikh SP. Distribution of GLP-1 binding sites in the rat brain: evidence that exendin-4 is a ligand of brain GLP-1 binding sites. *Eur. J. Neurosci.* 1995; 7:2294–300. [PubMed: 8563978]
12. Llewellyn-Smith IJ, Reimann F, Gribble FM, Trapp S. Preproglucagon neurons project widely to autonomic control areas in the mouse brain. *Neuroscience*. 2011; 180:111–21. [PubMed: 21329743]
13. Ghosal S, Myers B, Herman JP. Role of central glucagon-like peptide-1 in stress regulation. *Physiol. Behav.* 2013; 122:201–7. [PubMed: 23623992]

14. Larsen PJ, Tang-Christensen M, Jessop DS. Central administration of glucagon-like peptide-1 activates hypothalamic neuroendocrine neurons in the rat. *Endocrinology*. 1997; 138:4445–55. [PubMed: 9322962]
15. Baggio LL, Huang Q, Cao X, Drucker DJ. An albumin-exendin-4 conjugate engages central and peripheral circuits regulating murine energy and glucose homeostasis. *Gastroenterology*. 2008; 134:1137–47. [PubMed: 18313669]
16. Sarkar S, Fekete C, Légrádi G, Lechan RM. Glucagon like peptide-1 (7-36) amide (GLP-1) nerve terminals densely innervate corticotropin-releasing hormone neurons in the hypothalamic paraventricular nucleus. *Brain Res*. 2003; 985:163–8. [PubMed: 12967720]
17. Wei Y, Mojsov S. Tissue-specific expression of the human receptor for glucagon-like peptide-I: brain, heart and pancreatic forms have the same deduced amino acid sequences. *FEBS Lett*. 1995; 358:219–24. [PubMed: 7843404]
18. Scrocchi LA, et al. Glucose intolerance but normal satiety in mice with a null mutation in the glucagon-like peptide 1 receptor gene. *Nat. Med*. 1996; 2:1254–8. [PubMed: 8898756]
19. Li B, Xi X, Roane DS, Ryan DH, Martin RJ. Distribution of glucokinase, glucose transporter GLUT2, sulfonylurea receptor-1, glucagon-like peptide-1 receptor and neuropeptide Y messenger RNAs in rat brain by quantitative real time RT-PCR. *Brain Res. Mol. Brain Res*. 2003; 113:139–42. [PubMed: 12750016]
20. Sandoval DA, Bagnol D, Woods SC, D'Alessio DA, Seeley RJ. Arcuate glucagon-like peptide 1 receptors regulate glucose homeostasis but not food intake. *Diabetes*. 2008; 57:2046–54. [PubMed: 18487451]
21. Cobelli C, et al. Assessment of beta-cell function in humans, simultaneously with insulin sensitivity and hepatic extraction, from intravenous and oral glucose tests. *Am. J. Physiol. Endocrinol. Metab*. 2007; 293:E1–E15. [PubMed: 17341552]
22. Best JD, et al. Role of glucose effectiveness in the determination of glucose tolerance. *Diabetes Care*. 1996; 19:1018–30. [PubMed: 8875104]
23. Chan HM, Jain R, Åhrén B, Pacini G, D'Argenio DZ. Effects of increasing doses of glucagon-like peptide-1 on insulin-releasing phases during intravenous glucose administration in mice. *Am. J. Physiol. Regul. Integr. Comp. Physiol*. 2011; 300:R1126–33. [PubMed: 21307364]
24. Campbell JE, Drucker DJ. Pharmacology, physiology, and mechanisms of incretin hormone action. *Cell Metab*. 2013; 17:819–37. [PubMed: 23684623]
25. Villanueva-Peñacarrillo ML, Alcántara AI, Clemente F, Delgado E, Valverde I. Potent glycogenic effect of GLP-1(7-36)amide in rat skeletal muscle. *Diabetologia*. 1994; 37:1163–6. [PubMed: 7867889]
26. Ayala JE, et al. The glucagon-like peptide-1 receptor regulates endogenous glucose production and muscle glucose uptake independent of its incretin action. *Endocrinology*. 2009; 150:1155–64. [PubMed: 19008308]
27. Knauf C, 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]
28. Pérez-Tilve D, et al. Exendin-4 increases blood glucose levels acutely in rats by activation of the sympathetic nervous system. *Am. J. Physiol. Endocrinol. Metab*. 2010; 298:E1088–96. [PubMed: 20197503]
29. 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]
30. Burmeister MA, et al. Acute activation of central GLP-1 receptors enhances hepatic insulin action and insulin secretion in high-fat-fed, insulin resistant mice. *Am. J. Physiol. Endocrinol. Metab*. 2012; 302:E334–43. [PubMed: 22094469]
31. Sisley S, Smith K, Sandoval DA, Seeley RJ. Differences in acute anorectic effects of long-acting GLP-1 receptor agonists in rats. *Peptides*. 2014; 58:1–6. [PubMed: 24879927]
32. Barrera JG, et al. 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]

33. Sisley S, et al. Neuronal GLP1R mediates liraglutide's anorectic but not glucose-lowering effect. *J. Clin. Invest.* 2014 doi:10.1172/JCI72434.
34. Smith EP, et al. The role of β cell glucagon-like peptide-1 signaling in glucose regulation and response to diabetes drugs. *Cell Metab.* 2014; 19:1050–7. [PubMed: 24836562]
35. Lamont BJ, et al. Pancreatic GLP-1 receptor activation is sufficient for incretin control of glucose metabolism in mice. *J. Clin. Invest.* 2012; 122:388–402. [PubMed: 22182839]
36. Cabou C, et al. Brain glucagon-like peptide-1 regulates arterial blood flow, heart rate, and insulin sensitivity. *Diabetes.* 2008; 57:2577–87. [PubMed: 18633100]
37. Parlevliet ET, de Leeuw van Weenen JE, Romijn JA, Pijl H. GLP-1 treatment reduces endogenous insulin resistance via activation of central GLP-1 receptors in mice fed a high-fat diet. *Am J Physiol Endocrinol Metab.* 2010; 299:E318–24. [PubMed: 20530733]
38. Cabou C, Vachoux C, Campistron G, Drucker DJ, Burcelin R. Brain GLP-1 signaling regulates femoral artery blood flow and insulin sensitivity through hypothalamic PKC- δ . *Diabetes.* 2011; 60:2245–56. [PubMed: 21810595]
39. Bielohuby M, et al. Impaired glucose tolerance in rats fed low-carbohydrate, high-fat diets. *Am. J. Physiol. Endocrinol. Metab.* 2013; 305:E1059–70. [PubMed: 23982154]
40. Knauf C, et al. Brain glucagon-like peptide 1 signaling controls the onset of high-fat diet-induced insulin resistance and reduces energy expenditure. *Endocrinology.* 2008; 149:4768–77. [PubMed: 18556349]
41. Knauf C, et al. Role of central nervous system glucagon-like Peptide-1 receptors in enteric glucose sensing. *Diabetes.* 2008; 57:2603–2612. [PubMed: 18519802]
42. Nakabayashi H, Nishizawa M, Nakagawa A, Takeda R, Nijima A. Vagal hepatopancreatic reflex effect evoked by intraportal appearance of tGLP-1. *Am. J. Physiol.* 1996; 271:E808–13. [PubMed: 8944665]
43. Vahl TP, 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]
44. Hayes MR, 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; 301:R1479–85. [PubMed: 21849636]
45. Gil-Lozano M, et al. GLP-1(7-36)-amide and Exendin-4 stimulate the HPA axis in rodents and humans. *Endocrinology.* 2010; 151:2629–40. [PubMed: 20363879]
46. Gustavson SM, et al. Effects of a long-acting GLP-1 mimetic (PF-04603629) on pulse rate and diastolic blood pressure in patients with type 2 diabetes mellitus. *Diabetes. Obes. Metab.* 2011; 13:1056–8. [PubMed: 21812891]
47. Mendis B, Simpson E, MacDonald I, Mansell P. Investigation of the haemodynamic effects of exenatide in healthy male subjects. *Br. J. Clin. Pharmacol.* 2012; 74:437–44. [PubMed: 22320349]
48. MacLusky NJ, et al. Neuroendocrine function and response to stress in mice with complete disruption of glucagon-like peptide-1 receptor signaling. *Endocrinology.* 2000; 141:752–62. [PubMed: 10650957]
49. Hayes MR, 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]
50. Sandoval D, et al. The Anorectic Effect of GLP-1 in Rats Is Nutrient Dependent. *PLoS One.* 2012; 7:e51870. [PubMed: 23284795]
51. 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]

Highlights

- Glucagon-like peptide-1 (GLP-1) can be produced by the brain and has receptors in key brain areas for glucose control
- Central manipulations of the GLP-1 system can alter glucose homeostasis
- Brain GLP-1 receptors do not seem to be integral to normal glucose homeostasis or in the glucose-lowering effects of long-acting GLP-1 analogs