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CNS GLP-1 Regulation of Peripheral Glucose Homeostasis

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Abstract

Current models hold that peripheral and CNS GLP-1 signaling operate as distinct systems whereby CNS GLP-1 regulates food intake and circulating GLP-1 regulates glucose homeostasis. There is accumulating evidence that the arcuate nucleus, an area of the CNS that regulates energy homeostasis, responds to hormones and nutrients to regulate glucose homeostasis as well. Recent data suggest that GLP-1 may be another signal acting on the arcuate to regulate glucose homeostasis challenging the conventional model of GLP-1 physiology. This review discusses the peripheral and central GLP-1 systems and presents a model whereby these systems are integrated in regulation of glucose homeostasis.

Introduction

In response to a meal, a complex network of physiological responses, including neural and endocrine signals, regulate the digestion, absorption, and storage of ingested nutrients. Many of these signals are generated in response to the physiochemical properties of ingested food passing through the gut. The importance of these signals was first hypothesized by McIntyre et al. (1) in 1964 after observing that the glucose clearance and insulin levels were much greater following oral vs. intravenous administration of the same dose of glucose in human subjects. The authors hypothesized that this incretin effect (greater secretion of insulin in response to oral vs. intravenous glucose) was due to the secretion of hormones from the gut stimulated by a glucose load. The first incretin found was glucose-dependent insulintropic polypeptide (GIP), and a decade later, glucagon-like peptide-1 (GLP-1) was discovered (2). Both hormones are released from the gut, GIP from the duodenal K cells, and GLP-1 from the L-cells. Although both hormones stimulate insulin secretion, beta cell sensitivity to GIP but not GLP-1 is reduced over time. This has proven to be advantageous clinically as two recently approved treatments for type 2 diabetes mellitus activate GLP-1 signaling to improve glucose homeostasis.

GLP-1 is also made in a discrete population of neurons in the hindbrain (3;4). The physiological function of CNS GLP-1 receptor (GLP-1r) has been linked to the control of food intake, endocrine and behavioral responses to stress, and visceral illness (5–7). The function of the central and peripheral GLP-1 signaling systems are generally held to be separate; ie. peripheral GLP-1 regulates glucose homeostasis while central GLP-1 regulates food intake. This review challenges this dogma by providing recent evidence linking the CNS GLP-1 system to glucose homeostasis as well and proposes a model that integrates the role of CNS and peripheral GLP-1 systems in regulation of glucose homeostasis.

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MODEL FOR INTEGRATION OF PERIPHERAL AND CNS GLP-1 SYSTEMS IN REGULATION OF GLUCOSE HOMEOSTASIS

The importance of GLP-1 in regulation of glucose homeostasis is illustrated by the widespread clinical use of drugs that activate the GLP-1 system to treat type 2 diabetes mellitus. The generally accepted model for GLP-1 regulation of glucose homeostasis is that following the ingestion nutrients, GLP-1 is secreted from the intestine and acts directly on the β -cells to stimulate insulin secretion which in turn modulates glucose homeostasis. Recent data demonstrate increases in vagal afferent activity that seems to stem from the hepatoportal region (8) (9), linking peripheral GLP-1 to the CNS. In the last five years, data have accumulated linking the same CNS circuits that regulate energy homeostasis, to regulation of glucose homeostasis (10–13). Our recent data suggest that the CNS also responds to GLP-1 to modulate glucose fluxes and the coordinated effects of the CNS GLP-1 system are to improve overall glucose homeostasis. We suggest that the peripheral and central GLP-1 systems are integrated in order to limit postprandial glycemic excursions. A hypothesis regarding the integration of these two systems is illustrated in Figure 1.

THE ROLE OF PERIPHERAL GLP-1 IN GLUCOSE HOMEOSTASIS

GLP-1 is cleaved from preproglucagon in mucosal endocrine cells (L-cells) located predominantly in the distal intestinal tract (14;15). To date, only one GLP-1r has been described and thus far, there are no other naturally occurring mammalian ligands for the GLP-1r. Following the ingestion of glucose, fat, or mixed nutrient meals, GLP-1 increases several fold within 20–30 minutes and remains elevated for up to 4 hours (16). As stated above, GLP-1 augments nutrient-induced insulin release (2;17), but also inhibits gastric emptying (18) and reduces glucagon secretion (19). The increase in insulin and reduction in glucagon restrains hepatic glucose production, favors peripheral glucose uptake and together with the restraint on gastric emptying effectively limits postprandial glycemic excursions. In addition, GLP-1 has been found to have islet-independent effects to reduce hepatic glucose production (20–23). In fact, across many studies, when GLP-1 signaling was blocked or reduced, abnormally high blood glucose levels are seen following enteral or parenteral glucose administration (24–27). Thus, the actions of circulating GLP-1 are a set of coordinated processes that promote glucose tolerance.

THE CNS GLP-1 SYSTEM

In addition to being secreted from the intestine, GLP-1 is also a neurotransmitter synthesized in a discrete population of neurons found in the nucleus of the solitary tract (NTS) within the hindbrain (3;14;28). These GLP-1 cells have rich axonal innervation to the hypothalamus and the central nucleus of the amygdala (28;29). After third ventricular administration of GLP-1, c-fos like immunoreactivity, a marker for neuronal activation, is increased in the paraventricular (PVN) and arcuate nucleus (ARC) of the hypothalamus as well as areas of the forebrain (central amygdala) and hindbrain (NTS, area postrema, lateral parabrachial nucleus). GLP-1r mRNA has widespread distribution in the brain, including but not limited to, the hippocampus, hypothalamus (ARC and PVN in particular), and hindbrain regions (30).

CNS GLP-1 action has been implicated in the regulation of a variety of physiological functions including food and water intake, visceral illness, energy expenditure, core body temperature, HPA axis function, GI function, and autonomic nervous system responses (6;31–37). While the regulation of these physiological functions has been assumed to be due to the action of GLP-1 released from neurons in the NTS, this has not been conclusively established. Regulation of hindbrain GLP-1 release has been inferred with regional administration of GLP-1r antagonists or by using c-fos histochemistry (38).

The anorexic effect of CNS GLP-1 is perhaps one of the more widely studied CNS effect (39;31;34;40). It has also been established that specifically the PVN and hindbrain are two important CNS areas responsible for the GLP-1-induced anorexia (6;41;42). Peripheral administration of GLP-1 can also activate hypothalamic neurons and reduce food intake (43–45) and in humans decrease meal size (46–49).

Although it is reasonable to hypothesize that GLP-1 regulates food intake by either direct or indirect action on pro-opiomelanocortin (POMC), and/or neuropeptide Y (NPY)/agouti-related peptide (AgRP) responsive neurons, the data do not support this hypothesis. These neurons integrate information from afferent neuronal activity as well as circulating hormones and nutrients to regulate energy homeostasis. While some data indicate an interaction between NPY and GLP-1 to regulate food intake (50–52), others show no interaction between AgRP (53) or POMC neurons (54) and GLP-1 in regulation of food intake (55). Further, we were unable to inhibit food intake with GLP-1 administration directly into the ARC at a dose that did inhibit food intake when given into the PVN (56). Although we have found a subset of GLP-1r that co-localize to POMC but not NPY neurons (55) and *in vitro* GLP-1 directly stimulates POMC neuronal activity (57), the function of these receptors remain unknown. As discussed below, it may be that these receptors play a role in regulating glucose homeostasis.

CENTRAL REGULATION OF PERIPHERAL GLUCOSE METABOLISM

There is accumulating evidence that in addition to regulation of energy homeostasis, the CNS, specifically the ARC, also regulates normal glucose homeostasis. Glucose homeostasis is maintained via glucose output by the liver and glucose uptake by the tissues. Central administration of anorectic peptides (leptin, insulin, α -melanocortin stimulating hormone) and nutrients (glucose, lactate, long chain fatty acids) have all been found to alter glucose production by the liver while glucose uptake by peripheral tissues remain unchanged (13;58–61). Insulin infused directly into the ARC inhibited hepatic glucose production (11), an effect that was also found to be dependent on insulin receptors located in the ARC (62). In addition, ICV leptin-induced changes in hepatic glucose flux is at least partially dependent on POMC neurons as the same type and dose of melanocortin receptor antagonist that prevents leptin induced anorexia (54) prevented leptin-induced increases in gluconeogenesis but not leptin-induced decreases in glycogenolysis. However, when insulin was infused peripherally, to levels mimicking postprandial increases, a central infusion of a melanocortin receptor antagonist did not prevent inhibition of hepatic glucose production as was shown with ICV administration of a K_{ATP} channel blocker (62). These data indicate that peripheral insulin can activate hypothalamic regulation of hepatic glucose production and this effect is dependent on K_{ATP} channels, but not the melanocortin system. Taken together these data illustrate the sensitivity of the CNS to changes in hormonal status and the importance of the CNS in regulating glucose homeostasis.

Effects of CNS GLP-1 on Glucose Metabolism

Given that GLP-1r are located in the ARC but do not regulate food intake (56), one possibility is that those receptors regulate glucose homeostasis instead. For example, CNS infusion of GLP-1 causes a transient reduction in blood glucose levels (63), and this effect was ameliorated by chemical lesions of the ARC (64). Knauf and colleagues have also reported that CNS GLP-1 signaling is involved in the regulation of insulin secretion and partitioning of glucose disposal (65). These effects were reversed by central administration of a GLP-1r antagonist, and were mediated in part by neural innervation of muscle. We have similar findings with ICV GLP-1 to increase insulin secretion during an intravenous glucose tolerance test (56). However, we have also found that blocking endogenous CNS GLP-1r impairs glucose tolerance and GLP-1 administration directly into the ARC inhibits glucose production and glucose uptake in a

K_{ATP} channel dependent manner (56). Given the neuronal interactions described above and the fact that GLP-1r and GLP-1 immunoreactivity are both found in high concentrations in the ARC, it seems likely that central GLP-1r signaling in the ARC plays an important role in regulating peripheral glucose levels.

MECHANISMS OF CNS GLP-1 SIGNALING

While the data indicate the CNS GLP-1 plays a role in regulating glucose homeostasis, it remains unknown how this system is activated. Potential sources of peripheral GLP-1 that can activate CNS GLP-1r are via circulating blood after secretion from the GI tract, or via neural feedback to the hindbrain. Alternatively, it may be the case that other factors (e.g. cholecystokinin) released during meal absorption initiate central GLP-1 action (66). There are several pieces of data illustrating that circulating GLP-1 may activate the CNS. For example, GLP-1 and exendin-4 have been reported to cross the blood brain barrier (67) and when radiolabeled GLP-1 is administered intravenously, it binds specifically to cells in the area postrema and subfornical organ (68), a finding consistent with a hormonal connection from the gut to the brain. The medial portions of the NTS are accessible to circulating factors through fenestrated capillaries (69), and it has also been demonstrated that GLP-1r are present on neural cells in circumventricular organs that are accessible to circulating GLP-1 (70). Further, peripherally administered GLP-1r agonists have been shown to activate NTS GLP-1 neurons (71) although it is not clear if this is through direct stimulation or through intermediate steps. Peripheral GLP-1r agonists do seem to act primarily at the area postrema (AP) with little neural activation in other circumventricular sites (72). The pattern of neural activation induced by intravenous and intracerebroventricular exendin-4 differs suggesting distinct CNS signaling systems for peripheral and central GLP-1 (71). Taken together these data do suggest that circulating GLP-1r agonists can act on the CNS to initiate physiological responses.

However, another mechanism whereby peripheral GLP-1, like CCK (73), could signal to the brain is through visceral afferent neural pathways. Exendin-4 and a GLP-1-albumin conjugate, too large to cross the blood brain barrier, have similar potency in suppressing food intake and activating hindbrain and hypothalamic neurons (72;74) potentially through afferent feedback. In fact, infusion of GLP-1 into the portal vein increases the firing rate of hepatic vagal nerves (75), and capsaicin treatment blocks the anorectic effect of exendin-4, implicating sensory afferent neural activity in its mechanism of action (76). Further supporting this are data illustrating that suppression of food intake by peripherally administered GLP-1 is ablated with subdiaphragmatic vagotomy (45) and peripheral GLP-1-induced inhibition of gastric emptying is also dependent on vagal activity (77;78). Although these data are highly suggestive that peripheral GLP-1 activates CNS GLP-1 through afferent pathways as well, it remains unknown whether GLP-1 regulates glucose homeostasis via afferent feedback to the CNS.

THE NERVOUS SYSTEM AND PERIPHERAL GLP-1

Peripheral administration of GLP-1 and its agonists are very effective in reducing blood glucose levels in humans with type 2 diabetes (79). Understanding the integration of specific functions of the peripheral and CNS GLP-1 systems will aid in our continued understanding of dysfunction in glucose homeostasis. Although at present there are many more questions than answers, that data is intriguing enough to generate an integrated model for peripheral and central GLP-1-induced regulation of glucose homeostasis.

Following glucose ingestion approximately 30% of absorbed glucose is distributed to the liver, 30% is distributed to the skeletal muscle and adipose tissue, and the remainder is distributed to non-insulin dependent tissues, including the CNS (80). This process is regulated by peripheral hormone secretion, CNS signals, and by circulating glucose levels per se. Glucose sensing in the hepatportal system seems to be of importance in determining glucose

distribution. Data suggest that enterally absorbed glucose disproportionately increases hepatic glucose uptake compared to intravenous glucose (81), an effect that is mimicked by infusion of glucose directly into the hepatic portal vein in conscious dogs (82). Portal glucose infusion also stimulates insulin secretion (83) and suppresses skeletal muscle glucose uptake (84), potentially due to alterations in sympathetic nervous system activity (85). These data illustrate the importance to the hepatportal region in regulating glucose homeostasis.

While the hepatportal region has been demonstrated to be an important region for glucose sensing, it may also be an important area for integration of central and peripheral GLP-1 action. GLP-1 stimulates hepatic vagal afferent nerves (75) and intraportal GLP-1 increased action potentials and calcium influx in neurons of the nodose ganglion (9). Hepatic expression of GLP-1r is low (86;87) if any (88;89) but GLP-1r are expressed on nodose ganglion nerves (90;91) and GLP-1r protein is located on nerve terminals within the portal vein region (91). Blocking endogenous GLP-1 signaling in this region leads to impaired oral glucose tolerance (91) and when GLP-1 is released into the hepatic portal circulation it has a direct effect on liver glucose flux, despite the lack of hepatic GLP-1r (21–23;92). Intraportal GLP-1 stimulates insulin secretion, an effect that is dependent on afferent nerve activity (93). The GLP-1r also seems to be necessary for the functioning of a hepatportal glucose sensor, since this response is absent in mice with targeted deletion of the GLP-1r gene (94) and various other studies have shown a link between portal GLP-1 and regulation of glucose homeostasis (95–98). We believe these data together suggest an interaction and potential integration site between the peripheral and CNS GLP-1 systems.

A DETAILED MODEL FOR INTEGRATION OF PERIPHERAL AND CNS GLP-1 SYSTEMS IN REGULATION OF GLUCOSE HOMEOSTASIS

Putting all of these data together, we see that regulation of glucose homeostasis should be added to the many distinct functions of CNS GLP-1 (regulation of stress responses, visceral illness, and food intake). It is important to note that this is in addition to the beneficial effects of peripheral GLP-1 on glucose homeostasis (Fig. 1). Specifically, we hypothesize that after a meal peripheral GLP-1 is secreted from the L-cells within the small intestine. GLP-1 acts directly on the β -cells to stimulate insulin secretion but also activates vagal afferent nerves within the hepatportal region. This afferent feedback stimulates the CNS GLP-1 system within the hindbrain. Neural projections from the hindbrain to the ARC activate GLP-1r, located on either POMC or as of yet unidentified neurons. Activation of these neurons leads to efferent output to peripheral organs to modulate glucose flux. Although it remains to be tested, others have shown that nutrient stimulation of the ARC leads to vagal efferent output in regulation of hepatic glucose production (11) and CNS administration of exendin-4 leads to sympathetic efferent output that in turn regulates skeletal muscle glucose uptake (65). The end results is that the pancreas is stimulated to secrete insulin and glucose production by the liver and glucose uptake by the periphery is inhibited in a K_{ATP} channel dependent manner (56). The overall effect of this concerted effort between the peripheral and central GLP-1 systems is to limit postprandial glycemic excursions.

In conclusion, while numerous studies have shown that peripherally derived GLP-1 regulates glucose homeostasis, the role of CNS GLP-1 in regulation of glucose homeostasis is just beginning to be realized. Although there are hints throughout the literature that peripheral GLP-1 activates CNS GLP-1, more data are needed understanding this interesting possibility. As stated above, activating the GLP-1 system has proven to be therapeutically advantageous for type 2 diabetes mellitus patients. The degree to which these changes in glucose homeostasis are modulated via the peripheral vs. the CNS remains to be elucidated but may also be important for understanding the etiology of type 2 diabetes.

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Figure 1.

Model for integration of peripheral and CNS GLP-1 systems in regulation of glucose homeostasis. a) After a meal, peripheral GLP-1 is secreted from the L-cells within the small intestine. b) GLP-1 binds to GLP-1r within the hepatportal region. c&d) This activates vagal afferent feedback to the nodose ganglia. e and f) this afferent feedback stimulates the GLP-1 neurons within the nucleus of the solitary tract (NTS) which projects to the arcuate nucleus of the hypothalamus. g) this leads to increased efferent activity to the pancreas, liver, and skeletal muscle and consequently an increase insulin secretion, and decrease glucose production and uptake, respectively. The overall effect of the peripheral and CNS GLP-1 system is to limit postprandial glycemic excursions.