Glucagon-Like Peptide-1 and Energy Homeostasis[1–3]

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Abstract

A growing body of evidence demonstrates the role of gut-derived hormones in the control of energy homeostasis. Among those intestinal signals, physiological and therapeutic interest has been drawn to glucagon-like peptide-1 (GLP-1). The main reasons are that this hormone *1*) is secreted by epithelial intestinal L-cells in response to glucose and lipids, *2*) enhances glucose-stimulated insulin secretion, *3*) improves blood glucose profiles of type 2 diabetic patients by means of several actions on pancreatic hormone secretions, *4*) reduces body weight and food intake, and *5*) slows gastric emptying. Furthermore, recent evidence has suggested that the nervous system is a key player accounting for the beneficial role of GLP-1 on the control of energy homeostasis. Hence, the role of GLP-1 on the gut-to-brain axis is reviewed.   J. Nutr. 137: 2534S–2538S, 2007.

Introduction

The regulation of energy homeostasis requires that nutrients have to be specifically detected by specialized cells of the enteric area when absorbed by the digestive tract. The first site of energy sensing is the intestinal epithelium, where numerous endocrine cells are located. The secretion of hormones such as ghrelin, cholecystokinin, incretins [glucose-dependent insulinotropic polypeptide (GIP),[6] glucagon-like peptide-1 (GLP-1)], gastrin, or neuropeptide YY is regulated, at least in part, by nutrients. These hormones are among the first messengers signaling the new metabolic status to the body. These gut hormones control the fate of nutrients, i.e., storage or oxidation, by directly triggering metabolic functions. Importantly, 2 different routes for the regulation of energy metabolism by the intestinal hormones can be suggested. The first corresponds to the direct binding of the hormone to its specific receptor at the level of the target tissue that is involved in the physiological function that will be in charge of the specific nutrient use. The second corresponds to a nervous relay that will be triggered by gut hormones and will signal the brain about the income or output of nutrients.

The enteric nervous system is a well-described structure playing a crucial role in the gut-to-brain axis. It is also involved in the wide distribution of hormonal and nutrient signals toward peripheral tissues. Another identified site of energy detection in the enteric location is the hepatoportal vein. Numerous data have shown that the hepatoportal vein contains a glucose sensor that is an important structure where a positive gradient of glucose between the portal and the arterial blood regulates energy homeostasis controlling hepatic glucose storage, production, utilization, and pancreatic hormone secretion (1–3). Furthermore, with the advent of transgenic and knockout mice, we can generate the first molecular evidence showing the role of the glucose transporter isoform GLUT2 and of the GLP-1 receptor on the control of glucose utilization (4,5). Within the gut-to-brain axis, it is now established that glucose-sensitive systems are regulated by intestinal hormones and generate a signal to the brain (6,7). Furthermore, our recent data showed that impaired incretin secretion would affect glucose sensing (8). Therefore, one could speculate that an altered secretion of intestinal hormones would impair *1*) the specific detection of nutrients by enteric glucose sensors; *2*) the generation of the gut-to-brain glucose signal; *3*) the distribution of the brain signal toward peripheral effectors for the control of glucose metabolism. The critical role of GLP-1 in nutrient sensing and signaling is the focus of this article.

The generation of the GLP-1 signal: the incretin concept
From the observation that food intake, or enteral glucose administration, leads to a greater insulin release when compared with similar amount of glucose infused intravenously, the so-called incretin concept emerged (9–11). Among gut peptides

the proglucagon-derived sequence called GLP-1 and GIP were identified. Both peptides are synthesized as precursors and formed on maturation in the L and K cells, respectively. The L cells are the second most abundant population of endocrine cells in the human intestine, exceeded only by the population of enterochromaffin cells. A high abundance of L cells is present in the distal jejunum and ileum and along the colon (12–15). The oral intake of glucose stimulates GLP-1 release, whereas its systemic administration does not, indicating that the glucose-sensing machinery is distributed on the luminal side of the intestine (16). The presence of fat in the duodenum increases circulating GLP-1 to the same extent as is observed after direct administration of fat into the ileum. It is noteworthy that, although the L cells are distally distributed from the glucose or lipid absorption site, i.e., the duodenum, the hormone is rapidly secreted (within minutes) into the hepatoportal blood. These observations suggest the existence of a proximal-to-distal signaling pathway regulating the secretory response of the L cells to ingested nutrients (17). This could contribute to the significant increase in circulating GLP-1 levels within 5–10 min after ingestion of a meal, before any contact of nutrients with the L cells (16,18,19). In addition to nutrients, neuronal mechanisms explain the rapid postprandial onset of secretion (**Fig. 1**). In vivo and in vitro studies demonstrate that cholinergic agonists

stimulate GLP-1 release and suggest that M1 and M2 muscarinic receptors are involved in this process (20,21). All these studies suggest that acetycholine could be a neurotransmitter in a neural stimulatory pathway for GLP-1 secretion (Fig. 1). However, all of the factors and their integrated roles in the control of GLP-1 secretion are mostly unknown.

A tremendous amount of data converged to support the conclusion that the release of GIP and GLP-1 increases glucose-stimulated insulin secretion. This mechanism requires at least that the peptides reach the targeted cell, i.e., the pancreatic β-cell, bind to their receptors, and initiate a cascade of event leading to the secretion of insulin. This cascade is linked to GαS-coupled protein receptors, adenylate cyclase, and protein kinase A, leading to the increase of intracellular cAMP. GLP-1 is believed to enhance insulin secretion also through mechanisms involving the regulation of ion channels (including ATP-sensitive K^+ channels, voltage-dependent Ca^{2+} channels, voltage-dependent K^+ channels, and nonselective cation channels) and by the regulation of intracellular energy homeostasis and exocytosis (22). Consequently, granule trafficking and insulin secretion are enhanced. Furthermore, in addition to these acute mechanisms, GLP-1 is known to reduce β-cell apoptosis and to enhance proliferation and differentiation of putative ductal epithelial stem cells into mature β-cells (23). This mechanism would involve the PI3 kinase, *Src* oncogene, FoxO-1, and epithelial growth factor signaling (24–27). Altogether, the remarkable characteristic of incretins is their glucose dependence property.

The gut hormones increase insulin secretion in response to a glucose- or lipid-primed β-cell. The mechanisms related to the properties of incretins are not fully understood but are clearly linked to the increased intracellular cAMP concentration. Recently, the incretin concept has been reevaluated with regard to the direct role of GLP-1 on β-cells for the stimulation of insulin secretion. Arguments evoked in the next paragraph led to the suggestion that the local, almost paracrine, secretion of GLP-1 plays a key role in the regulation of oral-glucose-enhanced insulin secretion.

The intestinal hormonal signal: the purpose of a short life

A majority of gut hormones are secreted within minutes after nutrient ingestion, and their concentrations rise transiently in the circulation with concentrations higher in the hepatoportal blood than the arterial blood. This blood profile is particularly adapted to GLP-1, GIP, neuropeptide YY, and a few others. The characteristic short half-life (<2 min) of GLP-1 is mainly a result of the action of the dipeptidyl peptidase IV (DPP-IV), which removes the first 2 amino acids of the NH_2-terminal end. The presence of an alanine residue in position 2 is an obligatory feature for this enzyme, which generates mostly inactive peptides or slight antagonists of the corresponding receptors. In consequence, only 10–15% of the total GLP-1 secreted reaches the systemic circulation in the active form. Once released, before it enters the capillaries and comes into contact with DPP-IV, GLP-1 may interact with its receptor present on afferent sensory nerve fibers from the nodose ganglion (Fig. 1) (28). These neural cells present in the intestinal mucosa could be targeted by the paracrine release of GLP-1 (Fig. 1).

Pharmacological strategies aim at inhibiting DPP-IV to increase the endogenous active GLP-1 concentration. This potent strategy increases by 4- to 6-fold the concentration of biologically active GLP-1 on a continuous infusion of GLP-1. It is noteworthy that DPP-IV circulates in the blood and can continuously degrade GLP-1 (29). Similarly, it is suggested that the hepatoportal
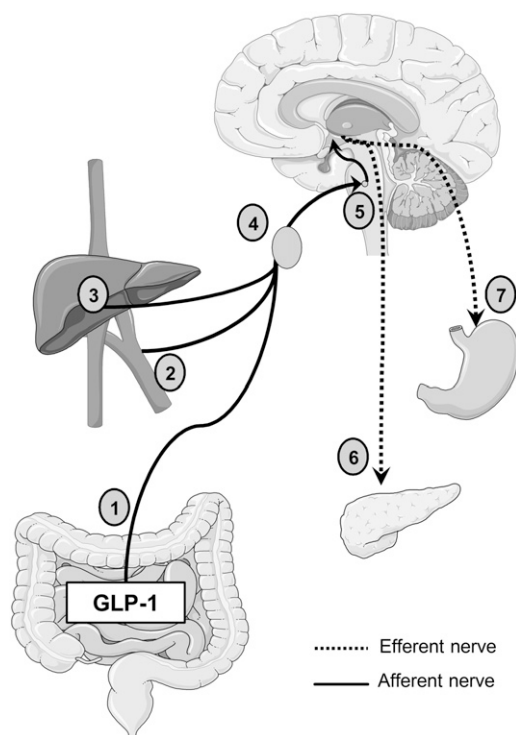

FIGURE 1 Schematic diagram of the neuronal pathway for the actions of GLP-1. GLP-1 secretion is stimulated by nutrients in the L-cell. GLP-1 released diffuses across the basal lamina into the lamina propria. On its way to the capillary, it may bind to and activate sensory afferent neurons (*1*). The same neuronal pathway may be activated by sensory neurons in the hepatoportal region (*2*) or in the hepatic tissue (*3*). The signal arrives in the nodose ganglion (*4*), which may, in turn, activate neurons of the solitary tract nucleus (*5*). The afferent signal coming from the fibers from the solitary tract neurons generates reflexes in the hypothalamus, and efferent nervous signals send stimulatory (*6*) or inhibitory (*7*) impulses to the pancreas and the gastrointestinal tract, leading to insulin secretion or delaying gastric emptying, respectively (31).

concentration of the biologically active form of GLP-1 is increased by the pharmacological treatment. Importantly, some of the GLP-1 effects could not be mimicked by DPP-IV inhibitors, i.e., gastric emptying, suggesting that some GLP-1 releasing sites or targeted cells are protected from the action of DPP-IV inhibitors (30,31). Along the same line of evidence suggesting that GLP-1 targets are close to the release site of the hormone, we and others previously showed that the hepatoportal glucose sensor requires a fully activated GLP-1 receptor (5,32–34). Mice with an antagonist of the GLP-1 receptor (Exendin 9) infused directly into the hepatoportal vein and GLP-1 receptor knockout mice were no longer sensitive to the portal glucose infusion. The latter triggered muscle glucose utilization leading to increased glucose clearance (5). Furthermore, the acute injection of GLP-1 into the portal vein increased plasma insulin secretion, which was prevented when the vagus nerve was cut or an antagonist of the parasympathetic nervous system was injected. (34).

The incretin effect: a brain relayed signal
In the light of the previous arguments suggesting that the target of GLP-1, for the enhanced glucose-stimulated insulin secretion, would be at the vicinity of its release site, we suggested that brain GLP-1 could be an important relay. In the brain, only a limited number of cells contain GLP-1, and these are mainly located in the nucleus of the solitary tract and the area postrema (35). In addition, GLP-1 receptors are located in nuclei of the hypothalamus where axons originating from the brainstem project (36). Therefore, it is suggested that signals triggering GLP-1 expressing neurons in the brainstem would signal neurons in the hypothalamus for the generation of a complex response (Fig. 1). This new signal would set the concentration of glucose and the fate of nutrients. The origin of the afferent signal most likely originates from the gut because the gut-to-brain axis is an important regulator of energy homeostasis. The cerebral GLP-1 activation leads to the secretion of catecholamines, providing inputs to sympathetic preganglionic neurons. Therefore, GLP-1 is linked to the regulation of the autonomic nervous system (Fig. 1). This link explains the observation that intracerebroventricular administration of a GLP-1 receptor agonist increases blood pressure and heart rate (37,38). Furthermore, as a neuropeptide, brain GLP-1 regulates several neuroendocrine and autonomic nervous system-dependent responses such as food and water intake. To delineate whether brain GLP-1 could be a relay to the gut-to-brain glucose dependent signal, we recently infused mice with intragastric glucose and studied insulin secretion. By means of a hyperglycemic glucose clamp, blood glucose concentration was maintained at 10 or 20 mmol for 3 h. Plasma insulin concentration assessed every hour was 4–6 times higher than when glucose was infused into the systemic blood directly. Importantly, this incretin effect was totally blunted by the simultaneous infusion of the antagonist of the GLP-1 receptor exendin 9 into the brain. These data strongly demonstrated that brain GLP-1 signaling was a crucial mechanism for the incretin effect (6). Interestingly, the increased insulin secretion in response to the gastric glucose infusion was associated with reduced peripheral glucose utilization; i.e., brain GLP-1 signaling induced insulin resistance. The rate of glucose utilization by the muscles was reduced when GLP-1 was infused into the brain. Importantly, this effect disappeared when the nerves efferent to the hindlimb muscles were cut, showing the importance of the peripheral nervous system in the relay of the brain GLP-1-dependent information (6). Conversely, when exendin 9 was infused in the brain, muscle glucose utilization was increased, suggesting that insulin sensitivity was improved. Surprisingly, exendin 9 was still able to increase insulin-stimulated

muscle glucose utilization even in the absence of the muscle insulin receptor (MIRKO mice). This last set of data suggested that the brain GLP-1-dependent signal required the peripheral nervous system to trigger a nonmuscle insulin receptor-dependent mechanism (6). This could be considered as an important mechanism to alleviate insulin resistance in type 2 diabetes.

Intestinal glucose sensing and afferent nerve stimulation: possible involvement of G-protein-coupled receptor for glucose
Before stimulating afferent nerves, dietary monosaccharides are transported across the brush border membrane of enterocytes by the Na^+/glucose cotransporter, SGLT1. Evidence demonstrates that luminal glucose enhances the number of functional SGLT1 in the intestinal brush border membrane, independently of glucose metabolic activation (39). Recently, Dyer et al. demonstrated that luminal glucose may be sensed by a glucose-sensitive system distinct from SGLT1 and residing on the external face of the luminal membrane (40). This glucose sensor initiates a signaling pathway involving a Toll-Like receptor for sweet taste, G-protein-coupled (41), and linked to a cAMP-PKA pathway, which resulted in enhancement of SGLT1 expression.

The GLP-1 dependent gut-to-brain axis during diabetes
Original observations showing the role of GLP-1 on glucose-stimulated insulin secretion have led numerous authors to demonstrate the potency of this hormone on the control of blood glucose profiles (42). The new meaning of this strategy was based on the strict glucose dependence of the mechanism because most if not all GLP-1-dependent actions disappeared in euglycemic conditions. This last feature suggested that iatrogenic hypoglycemia would be avoided as well as all correlated secondary effects. Although a few mild secondary effects, mostly related to gastric emptying and nausea, were noticed during long-term treatment with GLP-1 and related molecules, pharmacological strategies based on GLP-1 secretion or replacement are devoted to a promising future and a significant improvement of diabetes treatment. It is also noticed that a reduced body weight gain or an increased weight lost was observed during GLP-1 receptor agonist treatments, further adding to the benefit of GLP-1-related therapeutic strategies (43,44). In addition to the important feature of the glucose dependence of the GLP-1 action is that type 2 diabetic patients are still sensitive to GLP-1-induced insulin secretion. On the other hand, this effect is not observed with GIP, which diminishes interest in this molecule for a treatment. However, strategies aiming at avoiding the lack of GLP-1 secretion observed during diabetes or further increasing circulating levels of GLP-1 by the mean of a GLP-1 replacement therapy cannot increase the hormone concentration in the portal vein. Based on the above argument, it makes strategic sense to restore GLP-1 secretion and consequently its local action (31). This represents a clear advantage of DPP-IV inhibitors compared with GLP-1-related molecules. However, the treatment only mildly increases the portal concentration of GLP-1 and cannot fully increase the systemic concentration of the hormone. Therefore, one could argue with the credit given to such therapy for the direct effect of the endogenously secreted GLP-1 at the surface of the β-cells to enhance glucose-stimulated insulin secretion. Because the DPP-IV inhibitor treatment is indeed efficient, one can strongly suggest that the mild augmentation of GLP-1 secretion at the vicinity of its putative targets, i.e., the intestinal mucosa or the hepatoportal vein, represents a major regulator of GLP-1 functions.

We and others have previously shown that nondigestible carbohydrates (i.e., inulin-type fructans, resistant starch) could

be potent modulators of endogenous GLP-1 production (45–51). We specifically reported that oligofructose feeding almost doubled portal plasma GLP-1 content, a phenomenon correlated with a higher colonic GLP-1 and proglucagon mRNA content, in mice and rats. These observations are extensively reported by Delzenne et al. (this Supplement), thus suggesting that non-digestible carbohydrate such as fermentable dietary fibers could constitute a useful way to physiologically promote endogenous GLP-1 production and physiological effects related to this gut hormone.

Throughout evolution Nature has allowed the emergence of very short-half-life peptides secreted by the gut in response to nutrient intake. Hence, targets of these peptides would be expected to be found close to their release site and connected with a signaling system allowing the wide distribution in the body of the nutrient signal. Therefore, we strongly suggest that the gut-to-brain axis is a main target of the gut-released GLP-1. Enhancing gut glucose sensitivity, GLP-1 secretion, and signaling should lead to a cascade of events taking into account most if not all GLP-1 related functions. The physiological relay of GLP-1 receptors located in the brain or the β-cells will be a similar target to a gut-born GLP-1-dependent signal.

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