Nutrient Control of Energy Homeostasis via Gut-Brain Neural Circuits

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Abstract
Intestinal gluconeogenesis is a recently described function in intestinal glucose metabolism. In particular, the intestine contributes around 20–25% of total endogenous glucose production during fasting. Intestinal gluconeogenesis appears to regulate energy homeostasis via a neurally mediated mechanism linking the enterohepatic portal system with the brain. The periportal neural system is able to sense glucose produced by intestinal gluconeogenesis in the portal vein walls, which sends a signal to the brain to modulate energy and glucose homeostasis. Dietary proteins mobilize intestinal gluconeogenesis as a mandatory link between the sensing of these proteins in the portal vein and their well-known effect of satiety. Comparably, dietary soluble fibers exert their antiobesity and antidiabetic effects via the induction of intestinal gluconeogenesis. Finally, intestinal gluconeogenesis might be involved in the rapid metabolic improvements in energy homeostasis induced by gastric bypass surgeries of obesity.

Introduction

The worldwide increase in obesity and associated pathologies urges researchers to seek a better understanding of the mechanisms of control relating to food intake and energy homeostasis. The sensations of hunger and fullness are key determinants in the control of food intake. In normal-weight individuals, there is a balance between the sensation of hunger preceding a meal and the sensation of fullness after nutrient absorption. This balance is deregulated in obesity, resulting in the sensation of fullness being inappropriately delayed or blunted [1]. The mechanisms underlying the shift from sensation of hunger to sensation of fullness after meals include the modulation of gastric distension, changes in gut motility and the secretion of gastrointestinal hormones such as ghrelin, cholecystokinin, peptide YY3–36 and glucagon-like peptide 1 [2]. It is generally considered that these effects occur only after changes in circulating gastrointestinal hormone, the levels of which are detected by the hypothalamus [3–6]. However, the gastrointestinal neural system plays a key role in the hunger-curbing effect of gastric distension. The latter is sensed by baroreceptors present in the nerves of the stomach walls and is transmitted to the brain by the ventral vagus nerve [2]. There is also ev-
Glucose is a major macronutrient, can regulate hunger and food intake via activation of peripheral nerves [7].

Gluconeogenesis Is a New Intestinal Metabolic Function

It is well documented that the gut can participate in the regulation of glucose homeostasis via its capacity to uptake and metabolize glucose [7]. In the 1970s, using a new model of isolated perfused intestine in the rat, Windmueller and Spaeth [8,9] showed that the small intestine (SI) is able to utilize glutamine with the same efficiency as glucose. Glutamine was previously considered only as a major energy substrate for the SI, but it is now shown that the glucose-6-phosphatase (Glc6Pase) gene is expressed in the rat and human SI, i.e. the gene conferring gluconeogenesis function to the liver and kidney [10]. This report documented a key connection between glutamine and glucose intestinal metabolisms. Basically, it showed that, like the liver and kidney, the SI is able to contribute to endogenous glucose production via gluconeogenesis. In particular, this change takes place during fasting or under insulin deficiency conditions, such as streptozotocin-induced diabetes [11], and glutamine is the major precursor of glucose formed in the SI during fasting [11]. Interestingly, both Glc6Pase and phosphoenolpyruvate carboxykinase-cytoplasmic forms (PEPCK-C) are controlled by insulin at the level of gene expression both in the SI [10–13] and the liver [14–16]. Biochemical mechanisms of regulation of Glc6Pase activity also exist and are dependent either on insulin signaling [17,18] or on nutrients [19–22]. Intestinal glucose production is rapidly inhibited by insulin [11]. Therefore, short-term regulations of Glc6Pase activity may take place in the SI. This is an issue that requires experimental consideration. It is interesting to mention that the expression of gluconeogenesis enzymes in the SI has been confirmed in several species, including trout [23], rat [24] and human [25]. It has also been suggested that intestinal glucose production may take place during the anhepatic phase of liver transplantation in humans [26].

Sensing of Glucose in the Portal Vein Regulates Food Intake

It has long been hypothesized that glucose might regulate hunger in the course of meal digestion. In line with this rationale, seminal studies reported that glucose infusions into the portal vein at a rate equivalent to, or slightly higher than endogenous glucose production, decrease food intake in previously fasting rats [27,28]. Portal glucose infusions initiated various physiological and behavioral responses, including acquisition of food preference [29], activation of vagal nerves [30], and activation of neurons in the nucleus of the solitary tract [31] and in the hypothalamus [32,33]. However, glucose infusions at much lower rates are sufficient to initiate both the activation of hypothalamic nuclei and a limitation of food intake in rats [34,35]. Since intestinal gluconeogenesis releases glucose in the portal vein, this led to the hypothesis that intestinal gluconeogenesis could regulate food intake via portal glucose sensing. Recently, the molecular mechanism was described for the portal sensing of glucose. A body of evidence allowed us to suggest that the sodium-glucose co-transporter 3 (SGLT3) could be responsible for portal glucose sensing-initiated events, rather than the glucose transporter Glut2, as generally hypothesized [35] (fig. 1).

Induction of Intestinal Gluconeogenesis and Protein-Induced Satiety

It has long been known that dietary proteins exert potential satiety effects, but the underlying mechanisms were not understood. In fact, it has been shown that protein-enriched diets (PEDs) initiate their satiety effects indirectly via intestinal gluconeogenesis and portal glucose sensing. PEDs induce the expression in the gut of genes regulating gluconeogenesis. This results in release of glucose into the portal vein in the postabsorptive period that amounts to 20–25% of endogenous glucose production [34]. This is sufficient to activate the portal glucose sensor and to curb hunger and food intake. The portal ascending nerves are essential in this phenomenon. This effect of PEDs is lost in mice deficient for intestinal Glc6Pase, which demonstrates the causal relationship between intestinal gluconeogenesis and the satiety effect deriving from food protein [36]. The mechanism by which PEDs were able to induce intestinal gluconeogenesis gene expression has been recently elucidated. In the brain, μ-opioid receptors (MORs) can interfere with the control of food intake via their role in the ‘reward’ system [37]. Previous studies showed that various proteolytic moieties released from ingested protein exhibit μ-opioid activity in vitro [38–41]. Also, peptides derived from the digestion of protein could be delivered into the portal blood after crossing the enterocyte mucosa [42]. This has raised the attractive hypothesis that MOR present in the portal vein
**Fig. 1.** Mechanisms underlying the regulation of intestinal gluco- neogenesis (IGN) and its central and metabolic effects. **a** The ingestion of dietary protein (1) is followed by the appearance in the portal vein of peptides that antagonize MOR present in the portal vein nerves (2), which sends a signal to the brain. In response, IGN is activated (3). **b** Following the ingestion of dietary soluble fiber (1), SCFAs are produced from microbiotal fermentation in the distal gut. Propionate released in the portal vein activates FFAR3 present in the portal nerves (2), which sends a signal to the brain. IGN is activated in response to this signal (3). **c** After gastric bypass surgery, nutrients released directly in the distal gut activate IGN by a mechanism dependent on the integrity of the portal vein nerve that remains to be identified. **d** On activation of gluconeogenesis (3), glucose released into the portal vein binds to and activates SGLT3 (4), signaling to the brain regions controlling energy homeostasis, including the hypothalamus. The metabolic benefits are multiple: inhibition of hepatic glucose production, decreased hunger, decreased adipose storage, increased insulin sensitivity (particularly at the level of hepatic glucose production).
nerves might be involved in the control of food intake by protein via intestinal gluconeogenesis. Comparing the effect of MOR agonists, MOR antagonists or various peptides, we showed that peptides behave as MOR antagonists to induce intestinal gluconeogenesis and that this MOR-dependent induction of intestinal gluconeogenesis genes (resulting from an effenter nervous signal from the brain) might account for the decreased hunger promoted by PEDs [43] (fig. 1). In addition, MOR-knockout mice are insensitive to PED and mice with intestinal Glc6Pase deletion do not decrease food intake in response to portal infusions of MOR antagonists or peptides [43].

**Antiobesity and Antidiabetic Effects of Dietary Fiber and Intestinal Gluconeogenesis**

Dietary fiber is a key component of healthy food, encompassing fruit and vegetables. Unlike insoluble fiber (as cellulose), soluble fiber (as fructo-oligosaccharides) is fermented by microbiota in the distal gut to produce short-chain fatty acids (SCFAs): acetate, propionate and butyrate, which are used in metabolism by the host. Fiber-enriched diets are known to improve insulin sensitivity and glucose tolerance in lean and obese diabetic subjects [44]. However, as for PED, the mechanisms underlying the metabolic benefits associated with soluble fiber remained elusive. These benefits were thought to be mediated by SCFAs through regulation of whole-body energy homeostasis. Because propionate is a possible substrate of gluconeogenesis, we raised the possibility that intestinal gluconeogenesis and portal glucose sensing contribute to the metabolic benefits of soluble fiber [45].

We have shown that propionate is a precursor of glucose in the intestine [45]. There is also a strong induction of the regulatory gluconeogenesis genes Glc6Pase and PEPCK-C in the jejunum of rats fed a diet enriched in either fructo-oligosaccharides, propionate or butyrate. Interestingly, the induction of gluconeogenesis gene expression takes place in the colon, where microbiota reside. At a mechanistic level, butyrate stimulates the expression of gluconeogenesis genes directly in the enterocyte mucosa via an intracellular cAMP increase, the latter being a key factor influencing intestinal gluconeogenesis gene expression [46]. In contrast, propionate acts via a portal-hypothalamic neural circuit initiated by the activation of the free fatty acid receptor FFAR3 to increase intestinal gluconeogenesis gene expression [45] (fig. 1).

As expected feeding of soluble fiber or SCFAs is related to several metabolic benefits for rats. These include a moderation of body weight gain and a decrease of fat depots deriving from increased energy expenditure, and a better insulin tolerance and glucose tolerance resulting in a lowering by 10–15% of fasting plasma glucose. In agreement with a causal role of intestinal gluconeogenesis and portal glucose sensing in these metabolic improvements, the benefits are strictly dependent on the integrity of the periportal nervous system in rats and are absent in mice with a deletion of intestinal Glc6Pase [45].

**Intestinal Gluconeogenesis in Gastric Bypass**

Unlike gastric banding, gastric bypass surgery produces dramatic benefits on body weight and glucose homeostasis in morbidly obese diabetic patients [47]. It is generally believed that enhanced secretion of glucagon-like peptide 1 in response to a meal could account for the benefits of gastric bypass [47]. However, using a model of gastroenteroanastomosis (promoting metabolic benefits comparable to those of gastric bypass in mice), we observed that a marked induction of intestinal gluconeogenesis relayed by portal glucose sensing occurred in obese mice with diabetes after gastric bypass, and not after gastric banding [48] (fig. 1). No metabolic benefits of bypass occurred after inactivation of periportal nerves, suggesting a key role of portal glucose sensing [48]. Interestingly, the question of intestinal gluconeogenesis has been raised recently in relation to gastric bypass surgery in humans [49]. It is strongly suggested that, intestinal glucose release may take place during the postabsorptive period after gastric bypass surgery in obese humans [49, 50]. It must also be noted that data from our study in mice [48] have recently been supported by a similar study of bypass surgery in the Goto-Kakisaki diabetic rat [51]. Finally, it must be emphasized that intestinal gluconeogenesis curbing hunger sensation and improving insulin sensitivity, and glucagon-like peptide 1 secretion improving insulin secretion, may act in synergy to promote the whole beneficial effect of gastric bypass surgeries on glucose and energy homeostasis [52].

**Conclusions**

The gut has long been known as a high glucose consumer. Recently, the role of intestinal gluconeogenesis in the control of energy homeostasis through portal glucose sensing and a communication with the brain was described. Dietary proteins mobilize intestinal glucone-
genesis as a mandatory link between their detection in the portal vein (depending on peptide sensing by MOR) and their effect of satiety. In the same manner, dietary soluble fibers exert their antiobesity and antidiabetes effects via the induction of intestinal gluconeogenesis. FFAR3 is a key neural receptor involved in the specific action of propionate to activate a gut-brain reflex arc triggering the induction of the gut gluconeogenesis genes. Relating to the mechanism of glucose sensing from intestinal ‘gluconeogenic’ origin, the role of the glucose receptor SGLT3 in the periportal nerves has been strongly inferred. Finally, intestinal gluconeogenesis might also be involved in the rapid metabolic improvements induced by gastric bypass surgeries of obesity. Thus, the knowledge of intestinal gluconeogenesis and its dialog with the brain might pave the way to future approaches of prevention and/or treatment of metabolic diseases.

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Disclosure Statement

The author declares no conflict of interest in relation with this article.

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