The gut-brain axis: a major glucoregulatory player

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Abstract

Glucose homeostasis corresponds to the overall physiological, cellular, and molecular mechanisms which tightly maintain the glycaemia between ~4.5 and ~6 mM. The resulting blood glucose concentration is the consequence of a balance between the mechanisms that ensure the entry and the output of glucose in the blood. A dynamic balance needs hence to be perfectly achieved in order to maintain a physiological glycaemic concentration. Specialized cells from the intestine continuously detect changes in glucose concentration and send signals to peripheral tissues and the brain through the vagus nerve. The molecular mechanisms involved in glucose detection have not been perfectly defined but could resemble those from the insulin-secreting beta cells. The brain then integrates the enteric and circulating endocrine signals to generate a new signal towards peripheral tissues such as the pancreas, liver, muscles, and blood vessels. This metabolic reflex is called anticipatory since it allows the peripheral tissues to prepare for the adequate handling of nutrients. Diabetes is associated with an impaired anticipatory reflex, which hampers the proper detection of nutrients and leads to hyperglycaemic episodes. Recently, GLP-1-based therapies have demonstrated the improvement of glucose detection and their efficacy on glycaemic control. Although not yet fully demonstrated, GLP-1-based therapies regulate glucose sensors, which leads to the glycaemic improvement. Certainly other molecular targets could be identified to further generate new therapeutic strategies.

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Keywords: Diabetes; Incretins; Autonomic nervous system; Review

Résumé

L’interrelation intestin-cerveau, un axe régulateur métabolique majeur


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1. Introduction

During a meal, nutrients once absorbed are rapidly detected by specialized cells from the intestinal tract. Glucose is detected by glucostats, which send a neural signal towards the brain. Numerous signals are sent at once, all components of the new nutritional status [1-4]. The brain has to integrate these enteric signals and those coming from the circulating blood. Indeed, peripheral glands secrete hormones such as leptin, glucagon, insulin, and ghrelin, and changes in their concentrations are detected by the hypothalamus, mostly by the arcuate nucleus. Altogether, the brain generates new signals towards the peripheral tissues and controls hepatic glucose metabolism (storage and production), endocrine pancreatic secretions (insulin, glucagon) and intestinal hormone secretion such as incretins, in addition to food intake and arterial blood flow, to cite some of the triggered functions. This concept is called the anticipatory metabolic reflex, since it prepares the peripheral tissues to handle nutrients (Fig. 1).

During fasting, it is mainly the liver that accounts for all the glucose produced. Therefore, the glucose gradient is generated by the liver and is inverted when compared to the absorptive state. The brain and the enteric nervous system detect this negative hepatic portal glucose gradient and send signals to the peripheral tissues, thus leading to increased glycaemia or food intake [5].

In type 2 diabetes, this gut-to-brain-to-peripheral tissue metabolic axis is impaired [6]. Hence, nutritional signals are no longer properly detected. This concept could serve as the basis for new therapeutic strategies, which would aim at enhancing enteric glucose detection and the generation of a metabolic signal issued from the brain towards peripheral tissues. The advantage of such a strategy would be to regulate glucose metabolism from a very upstream target. Hence, all downstream tissues would be coordinately regulated. This could therefore reduce the number of adverse events such as hypoglycaemia. Glucagon-like peptide-one (GLP-1) based therapy contributes to the activation of the gut-brain axis. I will focus the topic of this review on the role of this hormone since most of the literature refers to it.

2. Intestinal glucose detection and enteric nervous system

Specialized cells from the intestine are able to detect the entry of glucose into the mesenteric blood. The precise location of these cells is not exactly known but could be related to the presence of glial-like structures or neurons surrounding the hepatic portal vein [7,8]. This enteric glucose sensing system regulates numerous functions. Hepatic glucose production has been mostly described [9-12]. A gut signal of neural origin increases a cholinergic dependent system, which leads to the activation of hepatic glucose storage [13,14]. Similarly, hepatic glucose production can be blocked by the glucose activation of the vagus nerve [15,16]. We previously described...
the enteric glucose sensor system as also being linked to the control of peripheral glucose utilization [4]. Muscle glucose utilization was increased in the absence of a rise in insulin secretion. The mechanisms involved the triggering of nerves surrounding the femoral artery, since their corresponding destruction prevented muscle glucose utilization. The molecular mechanisms associated with this effect were dependent on the presence of GLUT4, and of AMP-activated kinase but not insulin receptors [17]. Hence, in states of insulin resistance, this mechanism could be recruited to enhance muscle glucose utilization and better control glycaemia.

The molecular mechanisms responsible for glucose detection are poorly understood since we cannot visualize or directly address the molecular component of the system. First, glucose is detected by enterocytes and transported into these cells by glucose transporters, the SGLT1 [18] which increases the ATP/ADP ratio as observed in beta cells [19,20]. Consequently, an electrochemical gradient is generated which induces a signal for the secretion of GLP-1 into the enterocyte glucose. A role of the glucose transporter GLUT2 and the glucokinase could be also supposed but no direct demonstrations have been made. Glucose is then released into the mesenteric blood and reaches the portal vein. Other receptors seem to be involved in the firing of the vagus nerve activity. More recently, the role of carbohydrate receptors has been proposed. These are the sweet taste receptors of the T1R family expressed in the intestinal tract and enteroendocrine cells. The luminal sugar is sensed by a glucose sensor residing on the luminal membrane of the gut epithelium and linked to a G-protein-coupled receptor, cAMP/PKA (protein kinase A) pathway, resulting ultimately in modulation of intestinal monosaccharide absorption. In the small intestine and the enteroendocrine cell line, STC-1, expression has been reported, of members of the T1R sweet taste receptors and the alpha-subunit of the G-protein gustducin. In the small intestine, there is a highly coordinated expression of sweet taste receptors and gustducin, a G-protein implicated in intracellular taste signal transduction, throughout the gut. The potential involvement of these receptors in sugar sensing in the intestine has been suggested. The enteric nervous system is connected to the enteric glucostat. This neural system, also called the first brain, is composed of 200 million neurons within two plexi: the myenteric and the submucosal plexi [21]. These cellular structures secrete neuropeptides, which target smooth muscle cells, thus regulating gastric emptying, intestinal contraction, and most likely enteroendocrine cells. The neural fibres afferent to the brain are primary sensory fibres, which are connected with both plexi and make the link between the enteric brain and the central brain. Some of these fibres have prolonged dendrites within the lamina propria of the intestinal epithelium, ensuring therefore total intestinal innervation. One could easily imagine that these nerve endings are directly releasing neuromediators to enteroendocrine cells for controlling the production of the corresponding hormone, such as the incretins. Similarly, these terminal ends could sense nutrients such as glucose and lipids. The electrocapillarv

administration of glucose onto the vagus nerve immediately triggers its firing rate activity [22-24]. Glial-like cells have been described within the enteric nervous system. These cells are supposed to feed the neurons and produce numerous signalling molecules like neuromediators, cytokines and, metabolites, which inform the neurons of the ambient environment [25]. The hypothesis is that such cells are connected to glucose sensors and send the neural signal towards the brain stem. Therefore, the gut would be the first brain to sense glucose and to signal towards peripheral tissues that the nutrients had been absorbed. This hypothesis was demonstrated in mice and dogs when small amounts of glucose were infused into the portal vein to directly activate the sensor [4,26,27]. Muscle glucose utilization and liver production were regulated by the glucose signal to prepare these cells to handle the large amount of glucose that would be coming from the gut. This metabolic reflex was described as anticipatory.

3. GLP-1 and the gut-brain axis

More recently, the role of GLP-1 has been proposed as a major regulator of the gut-brain axis [27-30]. GLP-1 is a hormone secreted by the gut in response to a meal. It binds to its G-protein coupled receptor and increases cAMP production. It has been mostly described at the surface of the insulin secreting beta cells [31] and facilitates glucose-induced insulin secretion [32]. This is defined as the incretin concept [33,34]. GLP-1 is now the basis of numerous therapeutic strategies. However, this peptide has a major drawback. Following the incretin concept, the enzyme dipeptidylpeptidase (DPP-4), which prototypically inactivates the incretins, was discovered [35,36]. Cleavage of the N-terminus of GLP-1 by DPP-4 converts the active GLP-1-[7-37] and [7-36] – amide to the inactive GLP-1-[9-37] and [9-36] – amide, respectively. Therefore, other strategies based on the inhibition of the DPP4 are now widely used for the treatment of type 2 diabetes. Importantly, although the two strategies both consist of enhancing circulating GLP-1 concentration by means of GLP-1 analogues that cannot be degraded by the DPP4 or by using DPP4 inhibitors, both contribute to glycaemic control in different manners. The difference consists in the fact that GLP-1 analogues are provided subcutaneously and reach the systemic circulation. Therefore, the enteric to arterial gradient is not respected. One could suggest that the gut-brain axis is hence not activated. In addition, this strategy leads to a large increase in circulating GLP-1 concentration, which could reach the brain and regulate food intake as described below. Conversely, DPP4 inhibitors increase the portal vein GLP-1 concentration and activate the vagus nerve. Therefore, the gut-brain axis would be restored in type 2 diabetic patients. However, the amount of GLP-1 protected by the inhibitor strongly depends on the secretion of the peptide. Interestingly, this could be partially overcome by treating the patient with metformin [37].

This first set of analysis strongly suggests that GLP-1 analogues and DPP4 inhibitors control glycaemia by two
different mechanisms. The arguments are that the circulating concentration of GLP-1 (within the pM range) is too low to match the Km of the GLP-1 receptor, which is in the nM range. Second, the DPP4 makes sure that less that 10% of the secreted GLP-1 reaches the beta cells in an active form (GLP-1 7-36) and not in its degradation product form of GLP-1 9-36. Conversely, arguments are strongly in favour of an indirect route for the activation of insulin secretion. First, GLP-1 strongly activates the vagus nerve [38-43]. This effect leads to the control of vascular blood flow, gastric emptying, food intake and numerous other physiological functions. We initially showed that the enteric GLP-1-dependent glucose sensor system tightly regulated muscle glucose utilization [6] through a mechanism targeting vascular blood flow [44,45]. Importantly, in high-fat diet-fed diabetic mice, insulin-induced vasodilatation was blunted, testifying to a state of insulin resistance and vasoconstriction. This could be alleviated when brain GLP-1 signalling is impaired [44]. Hence, the brain to periphery axis is a strong regulator of vascular and metabolic functions.

4. Putative therapeutic outcome

From a therapeutic point of view, the enteric glucose sensor concept could certainly be considered a pharmacological target in order to control the main features of metabolic diseases, since it is involved in hepatic glucose production, peripheral glucose utilization, insulin secretion, glucagon production and GLP-1 secretion. Furthermore, the glucose sensing system seems to also be involved in the regulation of vascular and cardiac functions. As a proof of concept, numerous therapeutic strategies have emerged from the GLP-1 based concept. However, glucose sensors are not directly targeted but should be in charge of controlling many physiological functions. One advantage in targeting the enteric glucose sensing system rather than the brain glucose sensor is that the brain is downstream from the gut and therefore receives most of the nutritional information from the gut. This upstream position of the gut would allow a therapeutic strategy to efficiently regulate in a coordinated manner most of the downstream features that become dysregulated during metabolic diseases. One drawback of this concept is that the autonomic nervous system is often impaired during diabetes, which probably prevents the nutritional signals from being sent to peripheral tissues. This suggests that targeting the wires that connect tissues to each other should be done first or simultaneously. Certainly this new era of investigation should be detailed and further understood in order to accurately define a pharmacological strategy.

5. Conflict of interest

None related to the content of this article.

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