Review

Hypothalamic integration of portal glucose signals and control of food intake and insulin sensitivity

F. Delaere\textsuperscript{a,b,c,d}, C. Magnan\textsuperscript{e}, G. Mithieux\textsuperscript{a,*\textsuperscript{,b,c}}

\textsuperscript{a} Inserm U855, Institut national de la santé et de la recherche médicale, faculté de médecine Laennec, rue Guillaume-Paradin, 69372 Lyon cedex 08, France
\textsuperscript{b} Université de Lyon, 69008 Lyon, France
\textsuperscript{c} Université Lyon-I, 69622 Villeurbanne, France
\textsuperscript{d} AgroParisTech ENGREF, 75732 Paris, France
\textsuperscript{e} Centre national de la recherche scientifique (EAC4413), université Paris-Diderot, 75013 Paris, France

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Abstract

Glycolysis is an essential metabolic function that lies at the core of any cellular life. Glucose homoeostasis is, thus, a crucial physiological function of living organisms. A system of plasma glucose-sensing in the portal vein plays a key role in this homoeostasis. Connected to the hypothalamus via the peripheral nervous system, the system allows the body to adapt its response to any variation of portal glycaemia. The hypothalamus controls food intake (exogenous glucose supply) and hepatic glycogenolysis (endogenous glucose supply). Intestinal gluconeogenesis, via the release of glucose into the portal vein, plays a key role in the control of hunger and satiety, and of endogenous glucose production through the modulation of liver insulin sensitivity. The induction of intestinal gluconeogenesis provides a physiological explanation for the satiety effects induced by protein-enriched diets. In particular, the influence of protein-enriched diets on the hypothalamus is comparable to the activation observed after glucose infusion into the portal vein. The induction of intestinal gluconeogenesis also offers an explanation for the early improvement in glycaemia control observed in obese diabetic patients treated by gastric-bypass surgery. In addition to intestinal gluconeogenesis, a number of gastrointestinal hormones involved in the control of food intake exert their effects, at least in part, via the peripheral afferent nervous system. These data emphasize the importance of the gut–brain axis in the understanding and treatment of obesity and type 2 diabetes.

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Keywords: Portal glucose signal; Intestinal gluconeogenesis; Hypothalamus; Energy homoeostasis; Insulin sensitivity; Review

Résumé

Intégration hypothalamique du signal glucose portal et contrôle de la prise alimentaire et de la sensibilité à l’insuline.

La glycolyse anaérobie est une fonction essentielle à la base de toute vie cellulaire. L’homéostasie glycémique est donc une fonction physiologique cruciale des êtres vivants. Un système de détection du glucose plasmatique dans la veine porte joue un rôle clé dans cette homéostasie. Connecté à l’hypothalamus par le biais du système nerveux gastro-intestinal, il permet au corps d’adopter la réponse appropriée à toute variation (en plus ou en moins) de la glycéémie portale. L’hypothalamus contrôle aussi bien la prise alimentaire (apport de glucose exogène), que la glycogénolyse hépatique (apport de glucose endogène). La néoglucogenèse intestinale, en libérant du glucose dans le sang portal, joue ainsi un rôle clé de contrôle des sensations de faim et de satiété, et de la production endogène de glucose à travers la modulation de la sensibilité hépatique à l’insuline. Son induction par les régimes riches en protéines a permis d’apporter une explication physiologique à leurs effets de satiété. Les cibles hypothalamiques activées par les régimes hyperprotéiques sont ainsi très comparables à celles activées par la perfusion de glucose directement dans le sang portal. L’induction de la néoglucogenèse intestinale a également permis d’apporter une explication à l’amélioration très rapide du contrôle glycémique observée chez les obèses diabétiques traités par chirurgie gastro-intestinale de type « by-pass ». En plus de la néoglucogenèse intestinale, de nombreuses hormones gastro-intestinales impliquées dans le contrôle de la prise alimentaire exercent au moins en partie leurs effets via le système nerveux périphérique afférent. Ces données mettent en exergue l’intérêt de l’axe intestin-cerveau dans le domaine de l’obésité et du diabète de type 2.

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* Corresponding author. Tel.: +33 4 78 77 87 88; fax: +33 4 78 77 87 62.
E-mail address: gilles.mithieux@inserm.fr (G. Mithieux).

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1. Why is the sensing of plasma glucose an essential physiological function?

Maintaining plasma glucose concentrations at around 1 g/L (glucose homoeostasis) is an essential bodily function, as it is widely believed that glucose is a ‘major energy source’ for living cells. Glycolytic function (and, consequently, its substrate glucose) is essential for the life of every cell in the body. Glycolysis is indeed the ‘biological skeleton’ to which are ultimately connected all specialized biochemical pathways. However, the notion that glucose is a major energy source is potentially confusing. The brain, kidneys and gut are often cited as being among the most glucose-utilizing organs. However, although the bulk of glucose taken up by the brain is oxidized and, therefore, used for energy purposes, the brain can derive up to two-thirds of its energy from ketone bodies. This is especially true under conditions where glucose may be lacking, such as in postabsorptive and fasting states [1]. Similarly, the energy supply of the kidneys may also be largely accounted for by ketone bodies. As regards the gut, while it is established that this organ may account for up to 20 to 25% of the glucose turnover in the entire body, less than 10% of the glucose taken up by the gut is recovered as respiratory CO₂ [2]. Again, ketone bodies represent about half of the CO₂ produced from energy fuels in the intestine [2].

This means that glucose metabolism in the gut is essentially anaerobic (glycolytic). Another key feature is its coupling with the metabolism of another crucial intestinal substrate—glutamine, which is also partially oxidized—via a common enzyme: glutamate-pyruvate transaminase (GPT) [3,4]. Basically, the primary usefulness of the incomplete gut and glutamine glucose metabolism is to save the 3-carbon skeleton essential for gut functions such as the synthesis of citrulline and proline (and other amino acids), and preservation of the gluconeogenic potential of the body via the release of lactate and alanine (the major gluconeogenic precursors in the liver) [3,4]. Thus, as the major glucose-requiring organs can easily derive their energy from alternative sources (such as ketone bodies), it is probable that the glucose requirement of biological tissues is the consequence of ‘qualitative’ reasons (to enable, for example, specific metabolic pathways) rather than ‘quantitative’ purposes (such as for energy supply). This probably explains why the regular supply of glucose to living cells is so important, and also why the sensing of plasma glucose concentrations is so essential for the whole of the body.

2. Portal glucose-sensing and central control of food intake

For the above-mentioned reasons, it is essential that the body senses plasma glucose ceaselessly, so as to be able to rapidly and adequately respond when supplies are insufficient. Because food intake is an immediate way to restore plasma glucose in response to a fall in glucose concentration, it makes sense that glucose itself should be a key determinant of the sensation of hunger. In fact, a drop in plasma glucose concentration of no more than 5% is able to trigger an eating response in rats [5]. As it receives blood from the whole of the gut, the portal vein appears to be a key site in the initial sensing of plasma glucose concentrations, before the ultimate integration of glycaemia information by the central nervous system. Indeed, the portal vein has been demonstrated to be the critical locus for the detection of slowly induced hypoglycaemia [6,7]. Several studies have also established that infusions of glucose into the portal vein can induce a wide array of physiological and behavioural effects, including: a decrease in spontaneous food intake [8–11]; acquisition of food preferences [8]; rapid-phase secretion of insulin [12] and induction of glucose uptake [13,14]; and inhibition of the hypoglycaemia-induced sympathoadrenal response [15,16].

These effects depend on the integrity of portal innervation [7,17], as detection of glucose decreases the electrical activity of the hepatoportal vagal and spinal afferents [18]. A few studies have also demonstrated that the portal glucose signal influences the impulse activity of central neurons in areas involved in the control of food intake and metabolism—namely, the nucleus of the solitary tract [19] and the lateral hypothalamus [20,21].

The usual variations in portal glucose concentration are seen in the fasted-to-fed transition. Therefore, it has been generally hypothesized that activation of the portal glucose signal most likely plays a key role in the decrease of hunger that takes place under postprandial conditions—in other words, the satiation phenomena. In line with this argument, the research cited above was performed under conditions of high rates of portal glucose, matching those occurring during postprandial periods—in other words, comparable to (or even greater than) the total endogenous glucose production (EGP) of the animal studied. However, various other studies have shown that portal delivery of glucose does not determine termination of an ongoing meal [22,23] but, instead, determines the size of the next meal [23]. This strongly suggests that the portal glucose signal is related to satiety phenomena, but not satiation phenomena. It also raises the following intriguing question: what is the source of the portal glucose involved in the physiological satiety phenomenon, which occurs separately from the absorption of dietary glucose? The attempt to answer this question has led to an appealing hypothesis that suggests activation of intestinal gluconeogenesis during the postabsorptive period under certain nutritional conditions. Consistent with this theory, glucose-6-phosphatase (Glc6Pase), the key enzyme of EGP, is known to be regulated by nutrients and hormones at the level of gene expression and enzymatic activity in the liver, kidneys and small intestine [24–31].

3. Role of intestinal gluconeogenesis in the central control of glucose and energy homoeostasis

3.1. Intestinal gluconeogenesis and regulation of satiety

Endogenous glucose production is a critical function that allows the body to maintain plasma glucose concentrations at around 1 g/L in the absence of glucose supplied by food, as is the case between meals and during the night. Only three organs can perform this function, as they are the only organs known to express Glc6Pase (see Mithieux et al. [32] for a review of the subject). All three organs express all the enzymes mandatory for glucose synthesis [26,33,34], and all are able to release glucose...
when needed, such as during fasting [28,32,34,35]. The hypothesis that protein-enriched food might be able to induce intestinal gluconeogenesis is derived from three sets of information:

- rats fed a protein-enriched, carbohydrate-free diet adapt rapidly by inducing phosphoenolpyruvate carboxykinase (PEPCK) and G6Pase (in this case, in the liver) [36], and such induction is even more rapid than adaptation to fasting [36];
- milk-feeding (a specific type of food that is almost devoid of glucose, but rich in lipid and protein) strongly activates gluconeogenesis in the liver and intestine during the neonatal period [37–40];
- protein-feeding reduces hunger and subsequent food intake in animals and humans by inducing satiety, and not satiation, phenomena [41–43].

In support of this hypothesis, high protein-feeding strongly induces expression of the three regulatory enzymes of gluconeogenesis in the small intestine (SI): GclcPase; PEPCK-c; and glutaminase [17]. Indeed, glutamine is an important intestinal gluconeogenic substrate [4,32]. Also, as the SI is a major glucose-utilizing organ (see above), the putative gut glucose release cannot be reliably estimated through the use of only arteriovenous glucose-balance determinations. However, using these measurements in combination with tracer-based studies, it was possible to establish that the gut releases glucose in the postabsorptive state in protein-fed rats [17]. However, even if this approach is somewhat inaccurate (see the discussion by Pillot et al. [44] for a comprehensive analysis of its strengths and weaknesses), the rate of glucose release by the gut can be estimated to provide about 15 to 20% of EGP in protein-fed rats. Interestingly, this is sufficient to account for the reduction in food intake observed in protein-fed rats, where an equivalent infusion of glucose into the portal vein of the control (chow-fed) rats (not exhibiting substantial intestinal glucose release) also decreased food intake and by a comparable value [17]. It is, however, noteworthy that the glucose derived by intestinal gluconeogenesis did not increase EGP in protein-fed rats. Also, the liver adapts by decreasing its own glucose production by increasing glycogen storage [44].

The crucial role of intestinal gluconeogenesis in the control of food intake by dietary protein was firmly established with the use of transgenic mice in which Glc6Pase expression was specifically and conditionally abolished in the intestine. These animals did not decrease their food intake, as was observed in wild-type animals habituated to a protein-enriched diet (Penhoat et al., manuscript in preparation). The same insensitivity to the satiety effect of dietary proteins and portal glucose was observed in animals whose portal vein afferents were chemically or surgically destroyed [17].

Taken altogether, these studies demonstrate that portal sensing of intestinal gluconeogenesis is a key mechanism in the satiety effect induced by dietary protein.

To objectify the central impact of protein-enriched diets and portal glucose infusions on the main hypothalamic areas involved in the control of food intake, two complementary approaches have been used. First, an immunohistochemical study of the expression of transcription factor c-Fos (as a marker of neuronal activation) in the hypothalamus found that the arcuate nucleus, the dorsomedial, ventromedial and paraventricular nuclei, and the lateral area of the hypothalamus are all similarly activated during the postabsorptive period both in high-protein-fed rats and in chow-fed rats receiving infusions of glucose in the portal vein (Fig. 1). However, no such activation is seen in either situation if portal afferents are destroyed [17]. On the other hand, it is noteworthy that central infusions of lipids via the carotid artery, which promote a metabolic state associated with an increase in food consumption, decrease c-Fos expression in most of the above-mentioned hypothalamic nuclei [45]. Second, a transcriptomic approach using whole-genome rat microarray (34,000 genes, CodeLink™, GE Healthcare) was able to obtain a comparative global view of the genomic response in the hypothalamus to protein-feeding and portal glucose-sensing compared with a high-fat/high-sucrose diet. The hypothalamic transcriptomic profiles (compared with the control hyperglucidic Chow diet) were then used in a hierarchical clustering of the individual animals according to degree of similarity. This analysis strongly suggested that both portal infusion of glucose and a high-protein diet promote similar alterations in global gene expression in the hypothalamus compared with a high-fat/high-sucrose diet (Fig. 2). Nevertheless, further studies are needed...
to identify the specific genes and/or pathways underlying the similarity.

3.2. Intestinal gluconeogenesis and regulation of insulin sensitivity

It is well known that the hypothalamus, via modulation of sympathetic–parasympathetic balance, takes part in the control of whole-body glucose metabolism. Several studies have demonstrated that the hypothalamus influences insulin secretion [46], glucose utilization by skeletal muscle [13], and liver glucose storage and production [47,48]. In particular, the neural afferents connecting the hypothalamus to the liver tightly control EGP via regulation of hepatic glycogen storage [47,48], and expression of the regulatory gluconeogenic enzymes Glc6Pase and PEPCK-c [49]. More specifically, neurons in the ventromedial hypothalamus control the stimulation of liver glycogenolysis through activation of the sympathetic nervous system. In contrast, neurons in the lateral hypothalamus stimulate liver glycogenogenesis via activation of the parasympathetic nervous system. Additional circuits from both nuclei via the paraventricular nucleus are also involved in the control of hepatic glycogen storage via modulation of the sympathetic–parasympathetic balance (Uyama et al. [47]). Studies using portal infusions of glucose suggest that such peripheral detection triggers a neural circuit leading to glucose utilization in the periphery [13,14] and liver [14,50]. It was, therefore, tempting to postulate that intestinal gluconeogenesis and portal glucose-sensing might influence liver glycogen storage. Moreover, because impaired control of liver glycogenolysis by insulin is a hallmark of EGP deregulation in type 2 diabetics [51], intestinal gluconeogenesis might also play a role in the control of hepatic insulin sensitivity. In support of this rationale, rats fed a protein-enriched diet were found to exhibit increased suppression of EGP by insulin associated with increased stimulation of liver glycogen storage [44]. Interestingly, studies in diabetic patients have reported marked amelioration of glucose control in obese type 2 diabetic patients who followed, for only 5 weeks, a diet containing twice as much protein as did the control regimen [52–54]. Confirmation that intestinal gluconeogenesis may play a critical role in the control of hepatic insulin sensitivity has come from a study of surgery to treat obesity. Two techniques are most often used, with different physiological consequences. Gastric bands (GB) only reduce stomach volume (aiming to decrease meal size), whereas an increasingly used technique—the so-called ‘gastric bypass’ (GBP)—also excludes the proximal gut from direct contact with food nutrients. Both GB and GBP patients lose weight over time. However, only the GBP patients exhibit metabolic improvement (as reflected by fasting glucose, glycosylated haemoglobin and glucose tolerance) very early on, before any weight loss has occurred [55,56].

To understand the specificity of the bypass technique, two models of GB and GBP mice were developed, and their glucose metabolism studied. Surgery was performed on obese insulin-resistant mice fed a high-fat/high-sucrose diet for 12 weeks. Two weeks after surgery, the GBP mice recovered quasi-normal insulin sensitivity, while the GB and sham-operated mice continued to exhibit marked insulin resistance, as revealed by glucose and insulin tolerance tests [57]. Hyperinsulinaemic–euglycaemic clamp experiments further demonstrated that the improvement in insulin sensitivity occurs in the liver (EGP), corresponding to decreased activity of hepatic Glc6Pase. As previously shown by the satiety effect of dietary protein on food intake, the improvement in insulin sensitivity initiated by GBP was strongly blunted in the mice in which portal vein afferents had been destroyed [57].

4. Nutrient gut–brain axis in glucose and energy homeostasis

It is now becoming increasingly clear that the gut–brain axis is a key factor in both the control of hunger and satiety, and regulation of whole-body glucose metabolism. In addition to the effects of intestinal gluconeogenesis, which can be initiated in the postabsorptive state following protein-enriched meals, a recent study has suggested that prandial lipid metabolism in the upper intestine inhibits food intake and glucose homeostasis through an intestine–brain–liver neural pathway [58]. This means that processed nutrients can induce either satiation or satiety via the extensive innervation of the gut. Furthermore, the numerous hormones involved in the control of hunger sensations promote their effects at least in part via the gastrointestinal nervous system. The hunger-modulating effects initiated by the release of meal-dependent gut–hormones—including cholecystokinin [59], glucagon-like peptide-1 [60], peptide YY3-36 [60,61] and ghrelin [62]—and, more surprisingly, by the adipose-tissue hormone leptin [63] are all strongly attenuated by disrupting the connection between the gastrointestinal and central nervous systems.
The gut is lined by a vast and complex neural network, which interacts with numerous enteroendocrine cells bearing multiple receptors for nutrients and hormones, and much remains to be deciphered to clarify the interoceptive mechanisms and their specificity, as well as the potentially physiological roles of gut–brain communication. Elucidation of the whole picture is likely to provide novel paradigms that will no doubt pave the way for new approaches of prevention and/or treatment of obesity and type 2 diabetes.

Conflicts of interests

The authors report no conflicts of interest.

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