Brain, liver, intestine: a triumvirate to coordinate insulin sensitivity of endogenous glucose production

G. Mithieux

Institut National de la Santé et de la Recherche Médicale, U855, Lyon, F-69372, France
Université de Lyon, Lyon, F-69008, France
Université Lyon I, Villeurbanne, F-69622, France

Abstract

The brain, especially the hypothalamus, can modulate hepatic glucose fluxes. The sympathetic system promotes glycogen breakdown. The parasympathetic system stimulates glycogen deposition. Central insulin signalling or hypothalamic long-chain fatty acid oxidation can both control insulin’s suppression of endogenous glucose production. Intestinal gluconeogenesis initiates a portal glucose signal, transmitted to the brain via the gastrointestinal nervous system. This signal may modulate the sensation of hunger and satiety and insulin sensitivity of hepatic glucose fluxes as well, via the modulation of hypothalamic activity.

Keywords: Liver; Intestine; Brain; Gluconeogenesis; Insulin sensitivity; Portal glucose signal; Gut-brain axis; Review

Résumé

Cerveau, foie, intestin : un triumvirat pour coordonner la sensibilité à l’insuline de la production endogène de glucose

Le cerveau, en particulier l’hypothalamus, peut moduler les flux hépatiques de glucose. Le système sympathique promeut la dégradation du glycogène. Le système parasympathique stimule le stockage du glycogène. La signalisation centrale de l’insuline ou l’oxydation hypothalamique des acides gras à longue chaine sont deux mécanismes capables de contrôler la suppression par l’insuline de la production endogène de glucose. La néoglucogenèse intestinale initie un signal glucose portal, transmis au cerveau par le système nerveux gastro-intestinal. A travers la modulation de l’activité hypothalamique, ce signal peut moduler aussi bien les sensations de faim et de satiété que la sensibilité à l’insuline des flux hépatiques de glucose.

Mots clés : Foie ; Intestin ; Cerveau ; Néoglucogenèse ; Sensibilité à l’insuline ; Signal glucose portal ; Axe intestin-cerveau ; Revue générale

1. Introduction

Endogenous glucose production (EGP) is a crucial function, which allows the body to maintain plasma glucose concentration around 1g/L in absence of glucose supplied by food, i.e. between the periods of assimilation of meals and during the night. Three organs only can perform this function, because they are the only organs known to express glucose-6-phosphatase (Glc6Pase), the key enzyme of EGP (see [1] for a review). All three organs express all the enzymes mandatory for glucose synthesis [2-4], and all are able to release glucose when needed, e.g. during fasting [5-7]. In line with this key role in fasting glucose homeostasis, Glc6Pase together with phosphoenolpyruvate carboxykinase (PEPCK), the other key regulatory enzyme of EGP, are regulated by nutrients and hormones (notably insulin) at the level of gene expression and enzymatic activity in the liver, kidney and small intestine [2-5, 8-12].

Among the three organs capable of performing EGP, the liver is most often regarded as the major contributor. This is essentially due to its specific capacity of glycogen storage, a store of glucose that it can mobilize via the activation of glycogenolysis. This allows it to rapidly and finely tune blood glucose concentration at the beginning of post-absorptive and fasting periods. The other two organs (kidney and intestine) do not exhibit this capacity, and it is generally observed that they increase their participation in EGP as fasting is lasting [1,6,8,13,14]. For this reason, a vast majority of previous studies about the regulation of EGP have focused on hepatic glucose fluxes.
2. Central control of endogenous glucose production

In addition to the control by insulin, it is well known that the hypothalamus, via the modulation of the sympathetic-parasympathetic balance, takes part in the control of whole body glucose metabolism, notably at a liver level. Several studies demonstrated that the hypothalamus influences insulin secretion [15], glucose utilization in the skeletal muscle [16] and liver glucose storage and production [17,18]. Particularly, the nervous efferents connecting the hypothalamus to the liver tightly control EGP via the regulation of hepatic glycogen storage [17,18]. More specifically, neurons in the ventromedial hypothalamus control the stimulation of liver glycogenolysis, through the activation of the sympathetic system. Conversely, neurons in the lateral hypothalamus stimulate liver glycogenogenesis, via the activation of the parasympathetic system. Additional circuits from the paraventricular nucleus to the liver have also been involved in the control of hepatic glycogen storage, via a modulation of the sympathetic-parasympathetic balance. In addition, the paraventricular nucleus has been suggested to also serve as a relay for signals from both the ventromedial and the lateral hypothalamus to the liver (for a review, see [17]).

More recently, the role of the hypothalamus in the control of glucose production by the liver has been specified, either in rats or in mice bearing targeted gene mutations affecting insulin receptor expression and signalling. A key role for insulin signalling within the hypothalamus has been suggested. Notably, insulin’s suppression of EGP is decreased in rats with decreased insulin signalling in the hypothalamus [19,20]. Moreover, insulin receptor-KO mice with partial restoration of insulin receptor in the brain, liver and pancreatic β-cells are rescued from neonatal death and diabetes ketoacidosis. However, despite a full restoration of insulin signalling in the liver, they still exhibit defects in the control of HGP by insulin, due to persisting partial deficiency of insulin signalling in the arcuate and paraventricular hypothalamic nuclei [21]. At an intracellular mechanistic level, a central sensing of long chain fatty acil-CoAs, through their oxidation, and a relay via the activation state of hypothalamic ATP-dependent potassium channels, has been suggested to be involved in the suppression of glucose production by insulin [22-24]. Moreover, the descending nerve fibres of the hepatic branch of the vagus have been shown to convey a causal efferent signal to the liver [23,24]. In addition, the efferent signal is also able to regulate both hepatic Glc6Pase and PEPCK gene expression [24].

3. Gut-brain axis control of hepatic glucose production and insulin sensitivity

Numerous studies have established that the detection of portal glucose appearance within the walls of the portal vein, a phenomenon referred to as “portal glucose signal”, is able to initiate several neural-mediated mechanisms influencing either the sensation of hunger and satiety or glucose homeostasis. Among them: i) a decrease in spontaneous food intake [25-28]; ii) a rapid-phase secretion of insulin [29]; iii) the induction of glucose uptake in the liver and peripheral tissues [16,30]; and iv) the inhibition of hypoglycaemia-induced sympathoadrenal response [31-34]. These effects depend on the integrity of portal innervation as the detection of glucose decreases the electrical activity of hepatoporal vagal and spinal afferents [35]. Few studies also demonstrated that this portal glucose signal influences the impulse activity of central neurons, in areas involved in the control of food intake and of glucose metabolism, the nucleus of the solitary tract [36] and the lateral hypothalamus [37, 38].

It was, therefore, tempting to speculate that intestinal gluconeogenesis, via the release of glucose into the portal vein and activation of the portal glucose signal, could modulate in the same time food intake and glucose homeostasis. This hypothesis was first tested in the context of protein-enriched regimen, known to induce satiety in animals and humans [39-41], and to rapidly improve glucose control in obese diabetic patients [42-44]. In agreement with the hypothesis, high protein-feeding induces a strong induction of the expression of the regulatory enzymes of gluconeogenesis in the small intestine (SI): Glc6Pase, PEPCK-c and glutaminase [45] (glutamine is indeed an important intestinal gluconeogenic substrate (1)). Using arterio-venous glucose balance determinations in combination with tracer-based studies, it was possible to establish that the gut actually releases glucose in the post-absorptive situation in protein-fed rats [45]. Even if this approach is somewhat inaccurate (see the discussion of ref [46] for a comprehensive analysis of its strengths and weaknesses), the rate of glucose release by the gut could be estimated to provide about 15-20% of EGP in protein-fed rats. Interestingly, this appeared sufficient to account for the decrease in food intake observed in protein-fed rats, since an equivalent infusion of glucose into the portal vein of control chow-fed rats (not exhibiting substantial intestinal glucose release) actually decreased their food intake by a comparable value [45]. An immunohistochemical study of the expression of the transcription factor c-fos (as a marker of activation of neurons) in the hypothalamus showed that the arcuate nucleus, the dorsomedial, ventromedial and paraventricular nuclei and the lateral area are similarly activated during the post-absorptive period both in high-protein fed animals, and in chow-fed rats receiving infusions of glucose in the portal vein. It is noteworthy to point out that the appearance of glucose from intestinal gluconeogenesis does not increase EGP in protein-fed rats. The liver, indeed, adapts by decreasing its proper glucose production, through the enhancement of glycogen storage [46], in agreement with previous studies [30]. In association with this increased liver glycogen deposition, rats fed upon a protein-enriched diet exhibited an increased suppression of EGP by insulin during hyperinsulinemic euglycemic clamps [46].

A further strong argument, that intestinal gluconeogenesis can have a crucial role in the control of food intake and
hepatic insulin sensitivity, has come from a study pertaining to the surgery of obesity. Two types of techniques are mostly used, with different physiological consequences. Gastric banding (GB) only consists in the reduction of the stomach volume (aiming to decrease meal size), and an increasingly used technique, the so-called “gastric bypass” (GBP), additionally excludes the proximal gut from direct contact with nutrients. Both GB and GBP patients loose weight with time. However, only GBP patients, and not GB patients, exhibit very early metabolic improvements (e.g. decreased hunger and improvements in fasting glucose, glycosylated haemoglobin or glucose tolerance), before any weight loss has occurred [47,48]. To understand this specificity of the bypass technique, two models of GB and GBP mice were developed and their glucose metabolism studied [49]. The surgery was performed in obese insulin-resistant mice fed on a high fat-high sucrose diet for 12 weeks. Two weeks after surgery, GBP mice dramatically reduce food intake and recover a quasi-normal insulin sensitivity, while GB and sham-operated mice still exhibit marked insulin resistance, as revealed from glucose and insulin tolerance tests [49]. Hyperinsulinemic euglycemic clamp experiments have demonstrated that the improvement of insulin sensitivity takes place in the liver (EGP). This corresponds notably to a decreased activity of hepatic Glc6Pase, very similar to what was observed upon activation of a brain-liver circuit in a previous study [24]. It was further observed that a marked induction of the expression of both Glc6Pase and PECK-C enzymes occurs in the distal jejunum and ileum in EGA mice. Both enzymes are poorly expressed in these portions of the SI in the normal situation. This translated in glucose release into the portal blood during the post-absorptive period, as was observed in protein fed rats. On the contrary, the expression of gluconeogenic enzymes remained low in the same parts of the SI in GB mice. As previously shown for the satiety effect of dietary protein on food intake [45], the improvement in insulin sensitivity initiated by GBP is strongly blunted in mice in which the portal vein afferents have been destroyed [49].

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6. Conflict of interest

None related to the content of this article.

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