Cell Metabolism
Perspective

Gut-Brain Glucose Signaling in Energy Homeostasis

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Intestinal gluconeogenesis is a recently identified function influencing energy homeostasis. Intestinal gluconeogenesis induced by specific nutrients releases glucose, which is sensed by the nervous system surrounding the portal vein. This initiates a signal positively influencing parameters involved in glucose control and energy management controlled by the brain. This knowledge has extended our vision of the gut-brain axis, classically ascribed to gastrointestinal hormones. Our work raises several questions relating to the conditions under which intestinal gluconeogenesis proceeds and may provide its metabolic benefits. It also leads to questions on the advantage conferred by its conservation through a process of natural selection.

Introduction

The capacity of the liver to produce "sweet matter" was first reported by Claude Bernard in his doctoral thesis in the mid-nineteenth century (Bernard, 1853). It took almost one century before Coris suggested in 1938 that hexose-phosphatase was involved in the process, which led Fantl and Rome in Australia and the de Duve team in Belgium to identify an enzymatic activity, named "glucose-6 phosphatase," specifically involved in glucose release by the liver (Cori and Cori, 1946). High glucose-6 phosphatase (G6Pase) activity was then rapidly revealed in the kidney, which led to the discovery of the kidney's gluconeogenic capacity in the sixties (Krebs, 1963). Compared with the two other organs, the intestine expresses weaker specific G6Pase activity. This explains why it was not until the identification of the gene encoding the catalytic subunit of G6Pase in the nineties (Lei et al., 1993), along with the presence of its mRNA and its modulation by fasting and diabetes, that it became possible to firmly assert that G6Pase is actually expressed in the intestine (Chatelain et al., 1998; Rajas et al., 1999). The demonstration of the gluconeogenic capacity of the intestine followed (Croset et al., 2001; Rajas et al., 2000). The first suggestion of the regulatory role of intestinal gluconeogenesis (IGN) as a brain signal of importance in energy homeostasis was published some years later (Mithieux et al., 2005), thus quite recently regarding the knowledge accumulated in the past in the field of glucose control and energy balance. During the last 10 years, the various nutritional situations in which IGN is induced and the various impacts it may have on energy homeostasis have been documented. Nowadays, numerous questions are being asked about the moment and the conditions under which IGN is effective and provides its metabolic benefits, how it fits in the puzzle of previous knowledge on glucose control, and finally, to what extent it actually changes our understanding of energy homeostasis. Another question is that of the advantage gained by its conservation through a process of natural selection. The purpose of this paper is to attempt to answer these various questions and to discuss the perspectives opened from this new knowledge.

Why Is Blood Glucose Control a Physiological Function of Absolute Necessity?

Maintaining plasma glucose concentration at around 0.9–1 g/L is a critical requirement for the body. Most mammals including humans are incapable of tolerating hypoglycemic episodes for more than only a few minutes. Essential organs such as those most metabolically active (e.g., the kidneys and intestine), and above all the brain, would suffer from potentially irreversible damage. The reason generally put forward is that glucose is the major energy source for every living cell. However, the dogma that glucose equals "energy source" is potentially confusing. It can be assumed, indeed, that the glycolytic function and consequently its substrate (glucose) are essential for the life of all cells, since glycolysis is the biochemical "skeleton" on which all other specialized biochemical pathways ultimately depend. However, oxidizing glucose up to respiratory CO_2 to fully utilize its energy content is far from being a necessity. The brain for instance can derive up to 3/4 of its energy from ketone bodies. This is especially true under conditions where glucose supply from food may be lacking, such as in the post-absorptive and fasting states (Owen et al., 1967). Similarly, ketone bodies represent a major energy supply for the kidneys, intestine, and heart (Windmueller and Spaeth, 1978). This allows the body to preserve glucose to essential functions in addition to glycolysis, e.g., the pentose shunt, another critical non-oxidative glucose metabolic pathway that provides the carbon skeletons needed for the synthesis of nucleotides and chromosomal duplication. Permanent cell renewal in certain organs, indeed, is critical even during starvation. The intestine is a good example since the longevity of intestine mucosa cells is about 3 days. Moreover, saving glucose is a hallmark of metabolism in any organ during fasting. Accordingly, bodily metabolism adapts during fasting in order to dramatically decrease global glucose turnover (Croset et al., 2001; Pillot et al., 2009). (It should be pointed out that this makes sense from the energetic viewpoint. The energy requirement to build a glucose molecule from two pyruvate molecules in mammals [4 ATP + 2 GTP + 2NADH+H^+] is considerably less than the energy required to build glucose from 6 CO_2 molecules,

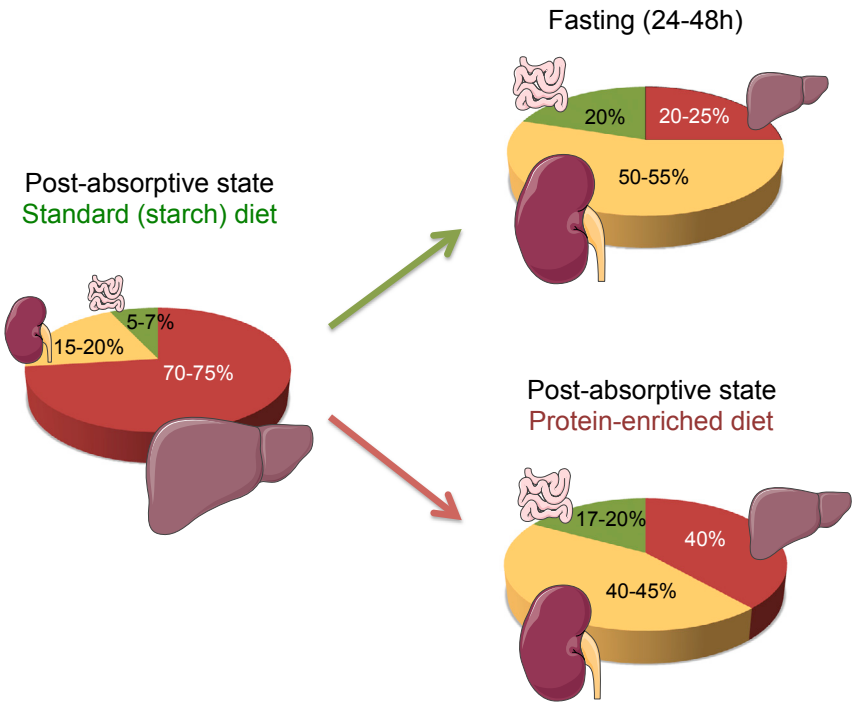

Figure 1. Repartition of Glucose Production among Gluconeogenic Organs in Various Nutritional Situations

When animals are fed a standard starch-based diet, glucose production from the kidney represents about 15%–20% of EGP at the fed to fasted transition (beginning of the post-absorptive period; i.e., 6 hr after food removal) in rats. Kidney glucose production increases to about 50% at 24 hr of fasting (Pillot et al., 2009). Comparable results were obtained in humans in post-absorptive state (Gerich et al., 2001) and long fasting (Owen et al., 1969). Glucose production from the intestine accounts for about 5%–7% of EGP at the fed to fasted transition and increases to about 20%–25% from 24 hr of fasting in the rat (Croset et al., 2001; Mithieux et al., 2006b). For more details on the effect of fasting on gluconeogenesis gene expression in the kidney and in the intestine, please refer to our previous papers and reviews (Mithieux, 1997; Mithieux et al., 2004a, 2004b; Rajas et al., 2000). Comparable augmentations of the contributions of the intestine and the kidney take place upon feeding a protein-enriched diet, a situation in which the intestine accounts for about 20% of EGP and the kidney 45% at the beginning of the post-absorptive period (Pillot et al., 2009). It must be mentioned that a comparable contribution of the intestine to about 20% of EGP was measured upon feeding a fiber-enriched diet (De Vadder et al., 2014). Kidney glucose production was not determined in this situation. Illustration was done with the help of Servier Medical Art.

a process that only plants are able to perform since they are able to derive energy from photosynthesis in the Calvin cycle [18 ATP + 12 $NADPH+H^+$].)

Regarding the gut, whereas it is established that this organ may account for up to 20%–25% of body glucose utilization, gut glucose oxidation is virtually undetectable in the fasting state (Windmueller and Spaeth, 1978). A specific gut feature is the coupling of glycolysis with the metabolism of glutamine (also incompletely oxidized, which has led to the concept of "glutaminolysis," by analogy with "glycolysis") by a common enzyme, namely glutamate-pyruvate transaminase, also called alanine transaminase (Hartmann and Plauth, 1989; Mithieux, 2001). This two-substrate enzyme converts glutamate and pyruvate into alpha-ketoglutarate and alanine, respectively. Interestingly, the main utility of incomplete gut glutamine and glucose oxidation is to save the carbon skeletons for essential body functions, such as the synthesis of citrulline for ureogenesis and of amino acids for proteosynthesis, allowing the body to preserve protein stores (Mithieux, 2001). Another obvious interest is the preservation of the gluconeogenic potential of the whole body: (1) through the release in blood of lactate and alanine, which are the major gluconeogenic precursors in the liver, and (2) through the incorporation of 3 carbons from glutamine in intestinal gluconeogenesis (via alpha-ketoglutarate incorporated in the Krebs cycle), something that also occurs for renal gluconeogenesis (Hartmann and Plauth, 1989; Mithieux, 2001).

In the eventuality of fasting, the release of glucose from liver glycogen stores (for several hours; estimated to about 10–12 hr in rodents and 20 hr in humans) and then gluconeogenesis, which occurs in the liver, kidney, and intestine, relay food to maintain blood glucose levels (Croset et al., 2001; Mithieux, 2001; Pillot et al., 2009). From the energetic viewpoint, the increasing importance of gluconeogenesis from the kidney and intestine is noteworthy, as fasting continues (Croset et al., 2001; Owen et al., 1969; Pillot et al., 2009) (Figure 1). This presents two major advantages. Indeed, hepatic gluconeogenesis from lactate and alanine (the 2 major substrates) is an endergonic process that consumes energy. On the contrary, renal and intestinal gluconeogenesis is performed from glutamine as the main substrate. This reaction is exergonic and produces 4 ATP per mole of synthetized glucose (Mithieux et al., 2004a). Therefore, this switch allows the body to first maintain plasma glucose constant and simultaneously preserve the energetic status of the body for anabolic purposes.

Hence, the absolute glucose requirement of biological tissues in any situation is driven by the need to sustain glycolysis and associated non-oxidative metabolic pathways, in view to satisfying specific purposes, rather than by the need to provide energy, a nonspecific purpose that can be fulfilled efficiently by other means. Interestingly, comparable functioning was proposed for the higher brain functions. Indeed, the activation of specific brain areas in response to various stimuli has been associated with increased glucose uptake, but not increased glucose oxidation (Dienel, 2012). Altogether, this likely explains why the presence of sufficient glucose in the blood and continuous glucose supply to the cells is so crucial at any given time. Above all, this highlights the importance of blood glucose sensing for the brain to secure survival.

Glucose Sensing: Primacy of the Portal Vein or the Brain?

Since food is an obvious source of glucose, food intake is a rapid means of providing glucose in blood. It therefore seems logical that there is a close relationship between glucose in blood and

hunger. (This may also be related to the innate preference for sweet taste observed in mammals [Ventura and Mennella, 2011] and to the increased liking for food associated with sugar supplementation [Nasser, 2001].) For instance, a drop in systemic blood glucose by only 5% in the rat is sufficient to determine its decision to eat (Louis-Sylvestre and Le Magnen, 1980). Hunger is determined at the level of the brain. However, the question of whether the brain itself or a peripheral site is responsible for sensing blood glucose has long been a topic of debate. It was Russek who first proposed in 1963 (Russek, 1963) that glucose sensors in the hepatic-portal area are involved in the limitation of food intake in response to increased glucose. This was abundantly documented during the next decades, especially regarding the effect of intraportal infusions of glucose on food intake (Langhans et al., 2001; Niijima, 1982; Tordoff and Friedman, 1986; Tordoff et al., 1989), and with the identification of nerve connections between the portal vein and the brain stem and the hypothalamic areas controlling food intake (Adachi et al., 1984; Niijima, 1983; Schmitt, 1973; Shimizu et al., 1983).

Glucose Sensing: Primacy of the Portal Vein

Given the major problem raised in the treatment of diabetes, the question of the primacy of the possible sites of glucose sensing during insulin-induced hypoglycemia has received much attention. In the case of deep prolonged hypoglycemia, brain-triggered activation of the secretion of counter-regulatory hormones (e.g., epinephrine, norepinephrine, and pancreatic glucagon) occurs to rapidly restore blood glucose from endogenous sources, e.g., liver glycogen stores. This paradigm was utilized to question the primacy of portal glucose sensors and central glucose sensors under various hypoglycemic conditions. Compelling evidence has suggested that portal glucose sensors are much more sensitive than brain sensors in counteracting the slow-onset hypoglycemia. For example, during whole-body hypoglycemia, maintaining normoglycemia only in the portal vein markedly suppresses the counter-regulatory response (Donovan et al., 1991a, 1994; Hevener et al., 1997). However, in the same situation, normalizing glycemia in the brain via glucose infusion in the carotid arteries or in the vertebral arteries fails to combat counter-regulation (Cane et al., 1988; Donovan et al., 1991b; Frizzell et al., 1993). Conversely, establishing hypoglycemia in the portal vein only in a situation of whole body normoglycemia is sufficient to trigger the counter-regulatory response (Lamarche et al., 1996).

It is notable that, in situations of rapid-onset hypoglycemia, the brain is able to trigger a counter-regulatory response in animals with periportal sensory denervation, in which periportal glucose sensing is absent. However, the response is weaker than in control animals (Saberi et al., 2008). This type of response could perhaps take place in the case of catastrophic drops in blood glucose, following insulin injection in the treatment of diabetes or in patients with glycogen storage disease type 1 (the human deficiency in G6Pase) for example, in pathophysiological situations (Mutel et al., 2011; Rajas et al., 2013). However, one may legitimately ask whether this could match possible physiological variations of plasma glucose, such as during the fed-fasted and fasted-fed transitions that occur in nature, which are always gradual and take time to establish. Hence, it may assumed that this brain counter-regulatory response to rapid onset hypoglycemia could depend on a cellular stress mechanism deriving from insufficient glucose supply (see paragraph 1), instead of a true "glucose sensing" mechanism. It should be mentioned that glucose sensing has been thought to take place in the nervous carotid body. However, the conditions under which this might function are not yet fully understood, and this topic remains controversial (Donovan and Watts, 2014).

It is important to emphasize that the portal vein is certainly the most suitable place in the body for sensing blood glucose. Due to the high glucose consumption of the intestine (see above), the portal glucose concentration drops below the systemic glucose concentration when glucose of dietary origin begins to lack during the post-absorptive period (Croset et al., 2001). Conversely, the portal glucose concentration increases more than systemic blood glucose during the fasted to fed transition (Strubbe and Steffens, 1977), since a substantial part of the glucose arriving in the portal vein will be extracted by the liver for glycogen storage. Hence, the portal vein is exposed to larger ranges of concentration than the rest of the body. This is an advantage for sensing variations in glucose accurately. The primacy of the portal vein regarding glucose sensing has justified interest in the neural mechanisms underlying portal glucose sensing.

Does the Same System Sense Increased and Decreased Portal Glucose?

A major question is that of whether the same neural system senses decreases and increases in portal glucose. Contrary to the generally accepted dogma that the vagal system is preponderant in conveying gastrointestinal sensory signals to the brain, disrupting the vagal nerves by surgery has no effect on the counter-regulatory response to hypoglycemia (Fujita and Donovan, 2005) or on the suppression of food intake in response to portal glucose infusion (Delaere et al., 2012). Conversely, denervation of the portal vein by capsaicin, which acts via the vanilloid receptor type 1 (a receptor principally expressed in splanchnic spinal nerves; Ward et al., 2003), or dissecting the celiac-superior mesenteric ganglion connected to the spinal cord (Barja and Mathison, 1984) both blunt counter-regulation to hypoglycemia and the satiety effect of portal glucose (Fujita and Donovan, 2005; Mithieux et al., 2005). Moreover, the portal infusion of glucose modulates the electrical activity of portal sensory nerves (Niijima, 1983) and of lateral hypothalamic neurons (Schmitt, 1973; Shimizu et al., 1983) and the expression of C-FOS (a marker of neural activation) in the main regions of the hypothalamus controlling energy homeostasis (Mithieux et al., 2005). In line with the spinal transmission of these effects, they were blunted by severing the splanchnic (but not the vagal) nerves (Schmitt, 1973), and by capsaicin (Mithieux et al., 2005). Finally, the infusion of portal glucose activates the expression of C-FOS in the parabrachial nucleus (PBN), which receives the afferents from the spinal cord, and not in the nucleus of the solitary tract or the area postrema, which receive the afferents from the vagal nerves (Berthoud, 2004; Delaere et al., 2013). Together, these data strongly suggest that portal glucose signaling is conveyed to the central nervous system by the spinal route and not by the vagal route. Interestingly, neurons expressing the neuropeptide calcitonin-gene related product (CGRP) are found in the splanchnic (and not vagal) nerves and in the PBN (Barja and Mathison, 1984). Moreover, CGRP-expressing neurons in the PBN were recently identified as a master switch in a powerful circuitry

controlling food intake (Carter et al., 2013). Thus, the hypothesis that CGRP-expressing neurons might be involved in conveying the hunger-curbing effect of the portal glucose signal via periportal splanchnic nerves and the PBN deserves further consideration.

It is noteworthy that the sodium-coupled glucose co-transporter 3 (SGLT3), a glucose receptor previously identified in the gastrointestinal nervous system (Diez-Sampedro et al., 2003), and not the facilitative glucose transporter GLUT2 or sweet taste receptors, namely TAS1R1 and TAS1R2, may account for portal glucose sensing (Delaere et al., 2012; Soták et al., 2017). This makes physiological sense since the affinity of SGLT3 for glucose (Km around 6 mM) makes it ideally suited for the neural sensing of decreases and increases in plasma glucose within the physiological range (O'Malley et al., 2006). On the contrary, the low affinity of GLUT 2 (Km around 15–20 mM; Efrat et al., 1994) and of sweet taste receptors (Km around 70–80 mM; Li et al., 2002) should make them suitable for sensing increases in blood glucose above basal glycemia, but not decreases in blood glucose below basal glycemia (O'Malley et al., 2006). It remains to be confirmed that portal glucose signaling is absent in mice with SGLT3 deficiency.

Intestinal Gluconeogenesis Modulates Energy Homeostasis via Portal Glucose Sensing: How and When?

Intestinal Gluconeogenesis Promotes Brain-Dependent Metabolic Benefits

In addition to the decrease in spontaneous food intake (Delaere et al., 2012; Langhans et al., 2001; Mithieux et al., 2005; Russek, 1963; Tordoff and Friedman, 1986; Tordoff et al., 1989), the infusion of glucose into the portal vein can induce a wide array of beneficial effects related to the brain's control of energy homeostasis, including, for example, the acquisition of a food preference (Tordoff and Friedman, 1986), the rapid-phase secretion of insulin (Fukaya et al., 2007), and the switch from non-hepatic to hepatic glucose utilization (Cardin et al., 1999; Moore et al., 2000). The position of IGN upstream of the portal nervous system has suggested this function could activate the portal glucose signal and its associated benefits. Interestingly, IGN can be induced by specific nutrients or by metabolic surgery to account for about 20%–25% of total endogenous glucose production (EGP) in the post-absorptive state (De Vadder et al., 2014, 2016; Mithieux et al., 2005; Troy et al., 2008). In this situation of glucose release in the portal vein, dramatic improvements in key energy and glucose homeostasis functions take place (De Vadder et al., 2014, 2016; Mithieux et al., 2005; Pillot et al., 2009; Troy et al., 2008). Such improvements include decreased food intake, decreased fat storage and body weight, decreased hepatic glucose production, increased hepatic insulin sensitivity, and improved whole-body glucose metabolism and insulin action (De Vadder et al., 2014, 2016; Mithieux et al., 2005; Troy et al., 2008). It can be assumed that IGN via portal glucose sensing is necessary for these metabolic benefits since no effects take place in mice in which the IGN function has been genetically deleted (by targeted deletion of intestinal G6Pase) or in portal vein capsaicin-treated rats (De Vadder et al., 2014, 2016; Mithieux et al., 2005; Penhoat et al., 2011). Conversely, mice with deficient IGN spontaneously exhibit deregulated glucose control while fed a conventional diet, including elevated fasting glucose and insulin concentrations, glucose intolerance and insulin resistance, and defective insulin secretion in response to glucose. Moreover, they are prone to diabetes since they become diabetic much more rapidly than their control counterparts under a high-fat/high-sucrose diet (Soty et al., 2014). Notably, mice with deficient IGN exhibit increased basal sympathetic tone and hypothalamic resistance to leptin, a hormone that plays a major role in controlling energy homeostasis, secreted by the adipose tissue. This highlights that IGN and associated portal glucose sensing is essential for correct homeostatic hypothalamic functioning. It has been established that the absence of the IGN-glucose signal is causal in these anomalies, since all of the latter, including the deficient phosphorylation of STAT3, a key molecular link in leptin signal, are corrected by portal glucose infusion mimicking IGN (Soty et al., 2014). Therefore, the hypothesis that the IGN/glucose signal could positively interfere with hypothalamic leptin signaling in the control of energy homeostasis is an important issue to be assessed.

Diverging from the benefits conferred by IGN, it must be recalled here that increased hepatic gluconeogenesis (HGN) is deleterious for glucose control. It is increased in type 2 diabetic patients (Granner and O'Brien, 1992; Magnusson et al., 1992), and in genetically manipulated rats, increased HGN (via the adenoviral overexpression of G6Pase) is sufficient to initiate anomalies in the glucose control characteristics of insulin resistance and pre-diabetes (Trinh et al., 1998). Thus, where glucose comes from really matters in glucose control. Glucose stemming from IGN is sensed by portal sensors that signal to the brain and provides metabolic benefits (see above). On the contrary, increased glucose production from the liver has no signaling capacity and only contributes to elevate peripheral plasma glucose and insulin, leading to long-term insulin resistance and further diabetes. Thus, the suppression of HGN by targeted deletion of G6Pase in the liver confers strong protection against the development of diabetes induced by a high-fat/high-sucrose diet (Abdul-Wahed et al., 2014). Therefore, HGN and IGN exert opposite effects on glucose control: increased HGN promotes metabolic anomalies, whereas IGN promotes metabolic benefits via portal glucose signaling.

When Does "Effective" Glucose Sensing of Intestinal Gluconeogenesis Take Place?

It is an important question to know why the induction of IGN is essential for promoting the metabolic benefits of portal glucose sensing. Indeed, the sensing of portal glucose from dietary origin is assumed to occur during postprandial periods, which represent several hours per day in humans and in rodents. Moreover, during the digestion of food rich in starch/carbohydrate, which is the case of modern food in human and of the classical chow diet given to laboratory rodents, the arterio-portal venous glucose gradient is negative, i.e., glucose concentration is higher in the portal blood than in the intestinal artery (by convention, the arterio-venous gradient is calculated as $[glucose]_{artery} - [glucose]_{vein}$) (Strubbe and Steffens, 1977). Portal glucose may be sensed during the postprandial period and may play a role in hepatic glucose uptake and glycogen deposition, for instance (Cardin et al., 1999). However, regarding the modulation of hunger, it must be kept in mind that the portal glucose signal from food is merged with a number of redundant meal-triggered

signals capable of strongly suppressing hunger, e.g., gastric distension, gut motility changes, and blood increase in hunger-curbing gastrointestinal hormones, such as cholecystokinin and glucagon-like peptide-1 (Janssen et al., 2011; Kairupan et al., 2016). A feature of concomitant nervous signals converging on the same targets is that they reciprocally attenuate each other (Melzack and Wall, 1965). It is possible that the portal glucose signal (either from food or from IGN) may not dominate the concomitant strong signals of hunger suppression during the postprandial period. In agreement with this reasoning, reports have shown that the portal delivery of glucose does not determine the duration or the size of an ongoing meal (Baird et al., 1997; Frizzell et al., 1993). (This issue is controversial, however, since a report to the contrary suggests that intrameal portal glucose infusion reduces meal size and duration in rats [Langhans et al., 2001].) Interestingly, portal glucose delivery decreases the size of the next meal (Baird et al., 1997), which is the hallmark of an effect taking place during the post-absorptive and not the postprandial period. Moreover, there is no increase in food intake in rats with periportal capsaicin denervation of the portal vein when they are fed a starch-based diet, suggesting that food glucose does not influence hunger sensation via portal glucose sensing (Mithieux et al., 2005; Zafra et al., 2004). The situation is dramatically different during the post-absorptive periods, in which the aforementioned hunger-curbing signals have ended. Then, the IGN-induced portal glucose signal is the only satiety signal to be sensed by the brain and may be fully efficient for modulating hunger pangs. Similar reasoning may be postulated regarding the efficiency of IGN to modulate the other parameters of energy and glucose homeostasis. In keeping with this rationale, the eventual metabolic benefits in animals with induced IGN are cancelled whenever a periportal capsaicin treatment has been performed previously, irrespective of the triggering process (relevant nutrients or gastric bypass surgery) (De Vadder et al., 2014; Troy et al., 2008).

Slow Onset and Persistence of Intestinal Gluconeogenesis

Interestingly, IGN exhibits features allowing it to be active during the post-absorptive period. Dietary protein induces IGN gene expression via the action of digested peptides on μ-opioid receptors present in the portal vein nerves, which initiates a neural circuit with the brain (Duraffourd et al., 2012). This promotes in the small intestine the induction of the regulatory enzymes of gluconeogenesis (G6Pase and phosphoenolpyruvate carboxykinase-cytosolic form) and also of glutaminase, the enzyme responsible for the metabolism of glutamine (Croset et al., 2001). Enzyme induction progressively takes place during the postprandial period, and the increased enzyme amount persists in the post-absorptive period (Duraffourd et al., 2012; Mithieux et al., 2005). In addition, dietary protein feed the pools of two major IGN substrates, namely glutamine and glutamate, which will be utilized by induced IGN as digestion is ending and afterward (Figure 2). This increases the participation of IGN to about 20% of EGP, as in fasting state (Figure 1).

As for soluble fibers, they are not digested by mammalian digestive enzymes and need some time to traverse the small intestine and reach the distal gut, in which they are fermented by the gut microbiota. The fermentation process stimulates IGN via the complementary effects of several metabolic products: the short-chain fatty acids butyrate and propionate, and also succinate. Butyrate activates IGN gene expression in enterocytes by increasing ATP, which activates adenylate cyclase by a substrate effect. This promotes an increase in cyclic AMP, the intracellular messenger activating gluconeogenesis gene expression (De Vadder et al., 2014, 2015; Gautier-Stein et al., 2006). Propionate binds to free fatty acid receptor 3 in the periportal nerves and initiates a neural circuit that promotes the local release of vasoactive intestinal peptide. The binding of vasoactive intestinal peptide to its receptor elevates the mucosal cAMP content that further activates the expression of IGN genes (De Vadder et al., 2015). In addition, propionate promotes the expression of methylmalonyl-CoA mutase, the key enzyme of its metabolization (De Vadder et al., 2014). What is more, both propionate and succinate serve as glucose precursors for IGN (De Vadder et al., 2014, 2016) (Figure 2). Therefore, soluble dietary fiber behaves as a self-timer of triggering of IGN and a reservoir of gluconeogenesis substrates, depending on microbiota fermentation. Interestingly, this reservoir is expected to endure through refilling, since insoluble fibers of high molecular weight can also be fermented, albeit less rapidly and more distally than soluble ones (Abad-Guamán et al., 2015).

Therefore, under the aforementioned dietary conditions or after metabolic surgery IGN may be induced and persist after the meal digestion and over the night thanks to several complementary mechanisms, including increased expression of IGN enzymes and/or the progressive availability in IGN substrates (Figure 2). This permits the full settle of the metabolic benefits it provides. Lastly, it is noteworthy that IGN is a mechanistic link in the hunger-curbing effect of protein-enriched diets. Interestingly, it has long been known that protein-enriched diets induce satiety effects (hunger curbing during post-absorptive periods) and not satiation effects (hunger curbing during postprandial periods) (Barkeling et al., 1990; Booth et al., 1970; Rolls et al., 1988). The assumption that IGN is a function active during post-absorptive periods and that it is causal in the hunger-curbing effects of dietary proteins fits well with prior knowledge that dietary proteins induce satiety and not satiation effects.

A Negative Arterio-Portal Venous Gradient Is Not Obligatory for Portal Glucose Sensing of Intestinal Gluconeogenesis

It is a widespread belief that an increase in blood glucose in the portal vein versus arterial blood (i.e., arterio-portal venous gradient must be negative) is essential for the portal glucose signal to be effective. Although this may be important for hepatic glycogen storage in the postprandial period (Cardin et al., 1999), it is not what occurs during the post-absorptive period when IGN is induced by specific nutrients or metabolic surgery. In these situations, the arterio-portal venous gradient is null or weakly negative (De Vadder et al., 2014, 2016; Hayes et al., 2011; Mithieux, 2012; Mithieux et al., 2005; Troy et al., 2008). It must be borne in mind that, due to the intense glycolytic activity in the intestine (see above), the portal glucose concentration drops progressively below the arterial glucose concentration at the beginning of the post-absorptive period. This drop amounts to about 0.8 and 0.6 mM in rats and mice, respectively (Croset

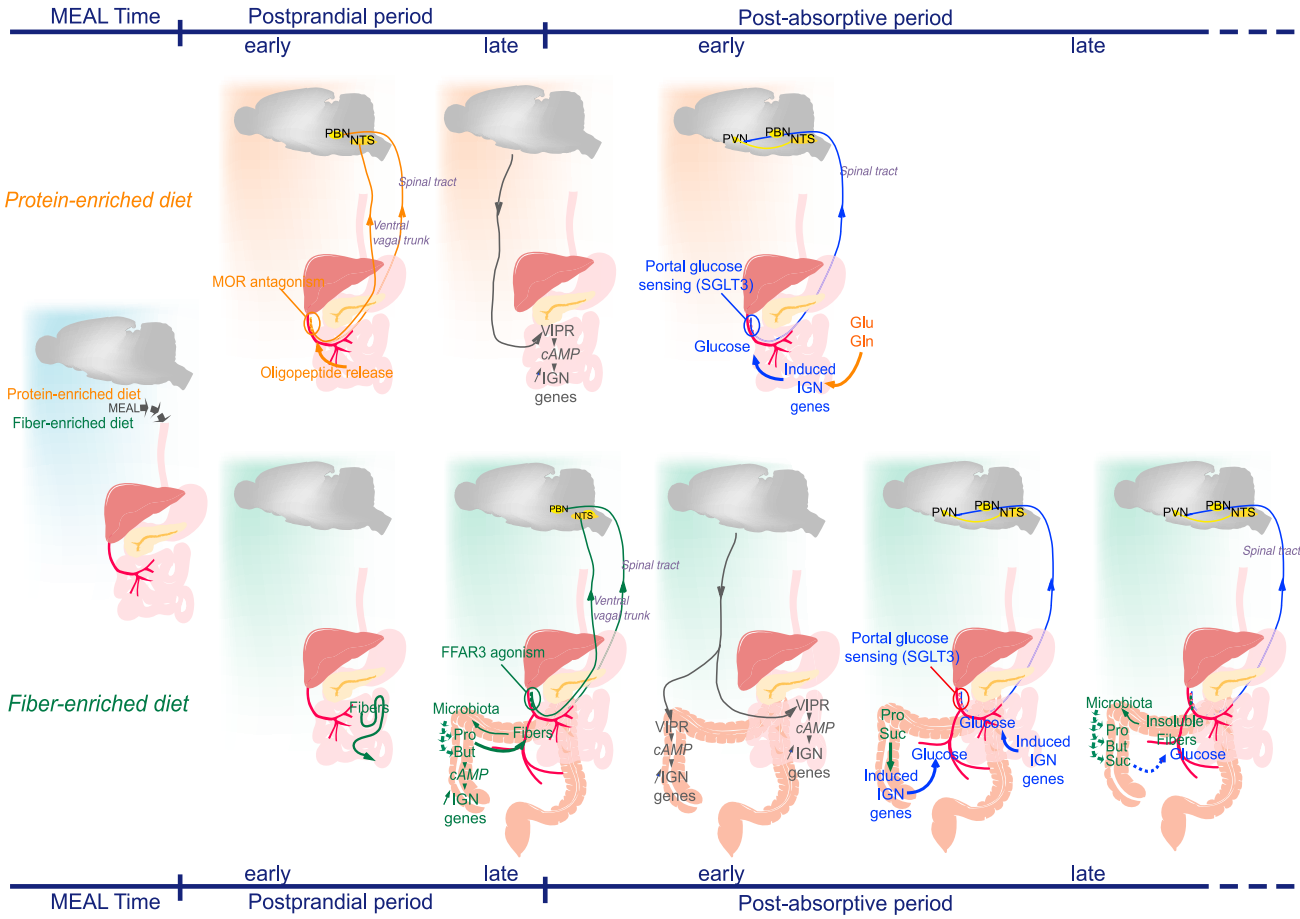

Figure 2. Time Course of IGN-Related Processes Taking Place following the Ingestion of a Protein- or Fiber-Enriched Diet

Upper chain: during the postprandial period, peptides from dietary protein origin act as antagonists on the μ-opioid receptor (MOR) to signal to the brain, which initiates the brain-dependent local release of the neuromediator vasoactive intestinal peptide (VIP). The activation of the VIP receptor (VIPR) activates adenylate cyclase and the production of cAMP that further induces the expression of IGN genes in enterocytes. During the post-absorptive period, glutamate (Glu) and glutamine (Gln) (from digested protein or from the blood) are converted into glucose that signals to the brain via SGLT3 and portal glucose sensing. Lower chain: soluble fibers, which are not metabolized by mammalian digestive enzymes, travel along the proximal intestine to reach the distal gut in the late postprandial period or the early post-absorptive period. They are next fermented by the microbiota in short-chain fatty acids as propionate (Pro) and butyrate (But). Propionate signals to the brain via FFAR3 agonism that induces IGN gene expression in both the proximal and distal gut via neural VIP signaling. Butyrate induces IGN gene expression in the distal gut via cAMP increase consecutive to ATP production. Propionate and succinate then serve as substrates of IGN initiating portal glucose sensing. Later on, insoluble fibers can be fermented, albeit more slowly, and they may promote the same processes. It must be emphasized that these steps are graphically distinguished here for the sake of clarity, but several of them can overlap under physiological conditions of nutrition.

et al., 2001; Troy et al., 2008). This represents physiological portal hypoglycemia, which can be suitably sensed by SGLT3 (see above) (Delaere et al., 2012; O'Malley et al., 2006). It is noteworthy that the beginning of the post-absorptive period fits with the re-onset of hunger (Little and Feinle-Bisset, 2011). Therefore, it may be assumed that the sensing of portal hypoglycemia by SGLT3 promotes the re-onset of hunger when IGN is not activated. Conversely, no portal hypoglycemia occurs when IGN functions. This appears sufficient to blunting hunger or delaying its re-onset (Figure 3).

Intestinal Gluconeogenesis in Literature and Translational Aspects

Animal Studies

In view of the importance of IGN, one may wonder why teams involved in this field have not been more numerous to date. A possible answer is that the technical and conceptual know-how required to estimate glucose production by an organ simultaneously consuming large amounts of glucose is not a widespread skill. The combination of arterio-venous glucose difference (to estimate the net balance of glucose through the organ) with the use of labeled glucose tracers (to quantify glucose utilization by the organ), which is the only approach permitting to deduce glucose production of such an organ, has been developed in the mid-nineties by some groups only. This was aimed at measuring kidney glucose production in various situations in dogs and humans (for a review, see Gerich et al., 2001). We settled this approach in rats to demonstrate glucose production from IGN (Croset et al., 2001).

A major difficulty in the approach is the scattering in tracer data, partly due to the high blood flow through the intestine (a parameter itself variable), which imposes variability on the calculated glucose fluxes. This might explain why a study, published as an abstract then taken up in a review (Previs et al., 2009), failed to

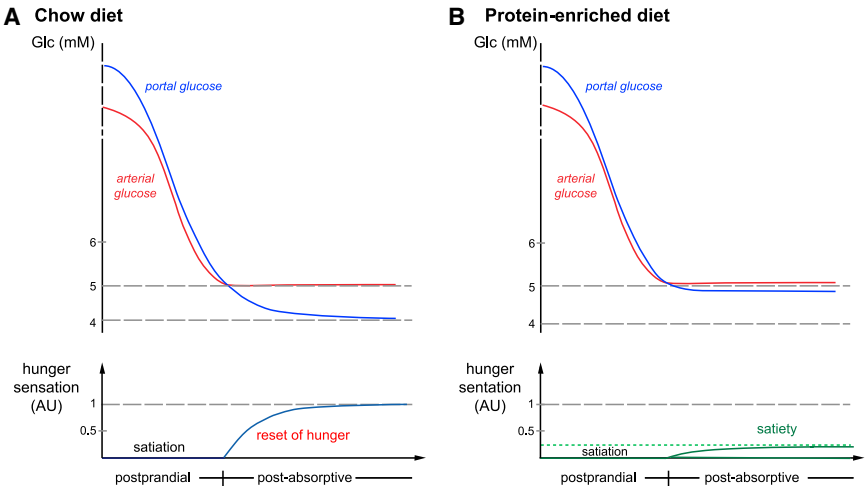

Figure 3. Relationship between Arterial and Portal Plasma Glucose Concentrations and Post-absorptive Satiety

(A) Under classical carbohydrate-enriched diet, IGN is very low during the post-absorptive period. Portal plasma glucose concentration drops below arterial glucose concentration because of high glycolytic activity of the intestine, which translates into the reset of hunger.

(B) Under high-protein dieting conditions, IGN takes place and prevents the drop in portal glucose concentration in the post-absorptive situation. Hunger is then blunted and satiety follows satiation.

AU, arbitrary unit.

reproduce our tracer-based data in 48 hr-fasted rats. Another study argued that IGN is undetectable in 72 hr-fasted rats. The rationale was based on in vivo determination of arterio-portal differences in glucose concentrations (that did not suggest net glucose release, but rather net glucose extraction) (Martin et al., 2007). However, this does not rule out that IGN could have been active and potentially measurable, provided that glucose tracers are utilized (see above), which was not done in this study. Another argument was the failure to detect by ^{13}C-nuclear magnetic resonance (NMR) the formation of ^{13}C-glucose from intestinal pieces incubated in vitro in the presence of ^{13}C-glutamine. Despite the high specificity of NMR, the low sensitivity of the approach is a known weakness. (For a more comprehensive discussion of the strengths and weaknesses of arterio-venous glucose difference and ^{13}C-NMR approaches, see Ekberg et al., 1999 and Pillot et al., 2009). Moreover, glucose (0.3 ± 0.1 mM) was detected by enzymatic assay in the medium at the end of the incubation with ^{13}C-glutamine and qualified of "very small amounts of glucose, accumulated from endogenous substrates." However, no glucose (−0.03 ± 0.04 mM) was detected in the control experiment in the absence of ^{13}C-glutamine. Therefore, an alternative conclusion might be that IGN is detectable (at least in vitro) in the gut mucosa of 72 hr-fasted rats. Accordingly, a more sensitive approach (incorporation of ^{14}C-labeled substrates) allowed other research teams to demonstrate the synthesis of ^{14}C-glucose from isolated intestine and intestinal mucosa preparations in rats (Hahn and Wei-Ning, 1986; Windmueller and Spaeth, 1978), which we could also show from in vivo experiments (Croset et al., 2001). Furthermore, the effective contribution of IGN to plasma glucose concentration in fasted mice was definitely confirmed in vivo from our tissue-targeted mouse models of deletion of G6Pase (Penhoat et al., 2014).

An additional difficulty regarding intestine studies is the high content in degrading enzymes as proteases and nucleases. This renders the study at mRNA and protein levels very delicate to perform and requires specific methods of rapid sampling and tissue homogenization, which are difficult to develop. This issue, combined with the difficulty of the arterio-venous approach and the weakly challenging aspect of only reproducing (or not) our work, could explain why people refrained from engaging further in this field.

Despite these difficulties, our data have now been reproduced at least in part by several independent teams in various contexts. Corroborating our previous findings relating to the nutritional regulation of IGN gene expression, several animal studies reported the increased IGN gene expression upon increasing the protein or fructose content of the diet (Cui et al., 2004; Kirchner et al., 2005; Patel et al., 2015) and after gastric bypass surgery in diabetic rats (Kim et al., 2015; Sun et al., 2013; Yan et al., 2016). (One discrepant study failed to observe increases in IGN gene mRNAs upon protein diet [Azzout-Marniche et al., 2007].) Importantly, that the anti-diabetic effect of IGN is associated with decreased HGN and improved hepatic insulin signaling after gastric bypass surgery (Troy et al., 2008) was also confirmed (Sun et al., 2013).

Translational Aspects

It is noteworthy that, among the seminal studies reporting the presence of G6Pase activity in the intestine, before the identification of the gene (see Rajas et al., 1999 for these references), one of the earlier was performed from human jejunal mucosa (Ockerman, 1965). Moreover, during surgical operations in four patients, the conversion of labeled fructose infused in the lumen in labeled glucose released at the basolateral site was reported, which highlighted the functional character of the enzyme and of the gluconeogenesis pathway (Ockerman and Lundborg, 1965). The presence of IGN enzymes in human mucosa has then been confirmed from enzymatic (Rajas et al., 1999) and histochemistry technics (Yánez et al., 2003).

As for the contribution of IGN to glucose appearance in portal blood, this has now been firmly established during the an-hepatic phase of liver transplantation in human patients, where the kidney could account for about 70% of EGP and the intestine for the remaining 30% (Battezzati et al., 2004), and after gastric bypass surgery in obese patients (Hayes et al., 2011). It could be estimated that IGN could account for at least 25% of EGP in the patients (Mithieux, 2012). Importantly, a recent study suggested that IGN is positively associated with the amelioration of glucose control after bariatric surgery in obese diabetic patients (Gutierrez-Repiso et al., 2016). At last, it is noteworthy that the key role of portal glucose sensing has also been confirmed in the detection of hypoglycemia (triggering counter-regulation) in human subjects (Smith et al., 2002).

Thus, a bundle of arguments is nowadays available in the literature together with our works suggesting that IGN is a key function in plasma glucose control during fasting and, associated with portal glucose sensing, capable of influencing energy homeostasis in fed state in animals and in humans.

Is Intestinal Gluconeogenesis Useful in Natural Selection?

One may tentatively question the usefulness of IGN and associated portal glucose sensing for complex organisms and for what purpose(s) it has continued through natural selection. The IGN function and/or enzymes are not only present in humans (Battezzati et al., 2004; Rajas et al., 1999; Yánez et al., 2003), but also in various mammals including carnivores such as cats (Hübscher et al., 1965), herbivores such as cows (Lohrenz et al., 2011) and rabbits (Bismut et al., 1993), and various rodents including rats, mice, and guinea pigs (Anderson and Rosendall, 1973). It is also present in other animal classes like birds (Palmer and Rolls, 1983) and fishes (trout), a species in which it retains positive regulation through diet protein content (Kirchner et al., 2005).

It is notable that two types of macronutrients appear capable of stimulating IGN: protein, which can be found in abundance in animal meat, dairy products, and certain plants; and soluble fiber, which can be found in abundance in fruit and vegetables. Given the scarcity of sugars and starch in natural foods prevailing before the advent of agriculture and the stringency of plasma glucose control in animals, whole-body gluconeogenesis must have had an even more crucial role than nowadays. As discussed above, both dietary protein and fiber constitute reservoirs of activating factors and of substrates of IGN expected to endure during post-absorptive periods. As for protein, it is noteworthy that a number of amino acids are possible precursors of glucose and can be converted by the other gluconeogenic organs, such as alanine in the liver. Therefore, food proteins constitute a major reservoir of gluconeogenesis not only for IGN but also for the whole body as their assimilation proceeds. Thus, IGN could represent internal information to the brain, telling it that food that has just been assimilated is suitable to satisfy glucose homeostasis for a while. This could be a signal indicating there is no urgency to go back to food foraging, hence its associated post-absorptive hunger-curbing effect. The advantage would be to make the brain better able to arbitrate between, or prioritize, putative concomitant needs.

It is noteworthy that, contrary to the metabolites derived from proteins or fibers, fat derivatives such as triglycerides and free fatty acids infused in rodents in the duodenal lumen (Naville et al., 2012) or in the portal vein (F. Delaere and G.M., unpublished data) suppress hunger rapidly and transiently (i.e., this is in line with a satiation phenomenon but not a satiety phenomenon). However, they have no activating effect on IGN gene expression. Similarly, the infusion of oleoyl-ethanolamide, a hunger-curbing metabolite derived from the intestinal metabolism of dietary lipids (Schwartz et al., 2008) in the portal vein, rapidly and transiently blunts hunger, which requires intact portal nerves. Again, this does not induce IGN gene expression (F. Plessier and G.M., unpublished data). Although lipids represent a key energetic resource, which may be indirectly useful to HGN (an endergonic process, see first paragraph), being oxidized via acetyl-CoA up to CO_2 in the Krebs cycle, they cannot metabolically provide carbon skeletons to build glucose. Continuing from the rationale above, if maintaining plasma glucose is a priority for survival, the need to deal with food renewal to maintain plasma glucose after eating lipid-rich foods should not be delayed as long as with protein- or fiber-rich foods. A more rapid reset of hunger, therefore, is an advantage in this particular situation. What is more, the alteration of intestinal glucose metabolism in rats under high-fat feeding conditions (which may represent what occurs in obesity and associated insulin resistance) makes it incapable of producing glucose from its two main substrates (Mithieux et al., 2006a). The reason is that IGN from glutamine and glutamate proceeds from glutamate-pyruvate transaminase that requires a sufficient pyruvate pool for correct functioning (Mithieux et al., 2004a). However, feeding the pyruvate pool is accounted for by glucose utilization (Watford, 1994). The latter is markedly blunted under high-fat feeding conditions, which in turn dramatically impairs IGN, despite the absence of effect on IGN gene expression (Mithieux et al., 2006a). All of this concurs with the increased hunger and energy intake observed in this specific dietary situation. (It may seem paradoxical that IGN from glutamine or glutamate is stoichiometrically coupled with intestinal glucose utilization; i.e., the production of one mole of glucose produced by IGN requires the utilization of one mole of glucose removed from the arterial blood [Mithieux, 2001; Mithieux et al., 2004a]. One might thus question the usefulness of such an operation for the body. Actually, IGN presents two major advantages. [1] During fasting, it allows the body to engage glutamine and glutamate carbons in gluconeogenesis, which is a crucial process for plasma glucose maintenance that the liver is unable to carry out because the kinetics of the glutaminase enzyme expressed in the liver makes it incapable of using plasma glutamine at physiological concentration [Mithieux, 2001]. [2] In the fed post-absorptive state, this generates one portal glucose molecule with key brain signaling properties to coordinate food intake and glucose homeostasis [Soty et al., 2014].)

Are There Additional Benefits for Intestinal Gluconeogenesis?

It must be emphasized that, in addition to the control of plasma glucose, crucial benefits for survival could derive from the other metabolic functions modulated by IGN, i.e., insulin sensitivity, which is potentiated by induced IGN under highly varied conditions of nutrition: classical starch-based diet (Soty et al., 2014), high-protein diet (Pillot et al., 2009), and high-fat/high-sucrose diets (De Vadder et al., 2014, 2016; Soty et al., 2014; Troy et al., 2008). This could have a beneficial impact for protein synthesis and growth, but also for fertility and reproduction, since insulin is a key positive regulator of these functions (Tamemoto et al., 1994). The positive action of IGN on leptin signaling (see above) could also positively influence fertility, since leptin is a key regulator of this function (Vázquez et al., 2015). Thus, fertility could be impaired in IGN-deficient mice, which could be easily assessed. Moreover, insulin sensitivity associated with the appropriate body weight leads to various pleiotropic benefits in animal models, including protection against metabolic and neurological dysfunctions and extended lifespan (López-Otín et al., 2016). Therefore, IGN could favor healthy aging.

It is remarkable that in addition to the main hypothalamic structures that control food intake and glucose homeostasis, portal glucose delivery during the post-absorptive period activates various brain regions, such as the nucleus accumbens, the central amygdala, the orbitofrontal complex, and the olfactory bulb, all implicated in motivational and rewarding aspects of food (Delaere et al., 2013). This may to some extent be related to the induction of flavor-based food preference, which has been associated with portal glucose infusion (Tordoff and Friedman, 1986). It is noteworthy that food preference associated with IGN could be of interest for a variety of living organisms of the alimentary chain to determine food choices for optimal plasma glucose control. This could relate to omnivorous species of course, and also to vegetarian species, since natural fruit and plants contain highly variable amounts of protein and fermentable fiber, and even to carnivorous species, which could be driven to privilege lean tissues rather than fat tissues, depending on their internal nutritional condition. Therefore, that IGN might have a role to influence emotional or motivational aspects of feeding constitutes an attractive hypothesis. In addition, whether a preference for protein- or fiber-enriched diets could derive from IGN and could be lost in IGN-deficient mice deserves further investigation. Thus, although the latter reasoning may appear somewhat speculative, it is not impossible that the purpose of IGN could extend far beyond the synthesis and release of glucose to maintain plasma glucose concentration in situations of food deprivation or to coordinate food intake and glucose homeostasis in situations of food abundance.

Concluding Remarks

10 years after the first indication that IGN may positively influence hunger sensation and food intake, the key role of IGN in glucose and energy homeostasis has been substantially documented both from nutrient or gastric bypass gains of function and from genetic loss of function. Since IGN signaling involves the brain, especially the hypothalamus, numerous hypothalamic-dependent processes of interest in the energy balance are under its control (Figure 4). A correctly functioning IGN and its regulation mechanisms are therefore keys to metabolic health. We hope this article has shown how IGN and its effects add to our understanding of how metabolism is controlled and to what extent this understanding sheds new light on previous knowledge. In particular, the nutrient-dependent neural induction of IGN extends our vision of the gut-brain axis, classically ascribed to gastrointestinal hormones secreted in blood.

The production of intestinal and hepatic glucose is specific in that both are located in the same blood circuitry, which raises the question of the usefulness of this duplication for the body. This apparent paradox is easily resolved when one takes into account the gastrointestinal nervous system, especially the nerves located at the interface (portal vein), since they sense IGN as a signal to the brain. This explains why, even if IGN represents a lesser amount of glucose than that eventually produced from other sources, it may have important repercussions on whole-body metabolism. Thus, these works on IGN allow us to emphasize the decisive role of the gastrointestinal nervous system (sensitive and efferent) in the control of energy homeostasis. To conclude, it appears remarkable that, among his major contributions subsequent to the discovery of the "glycogenic" role

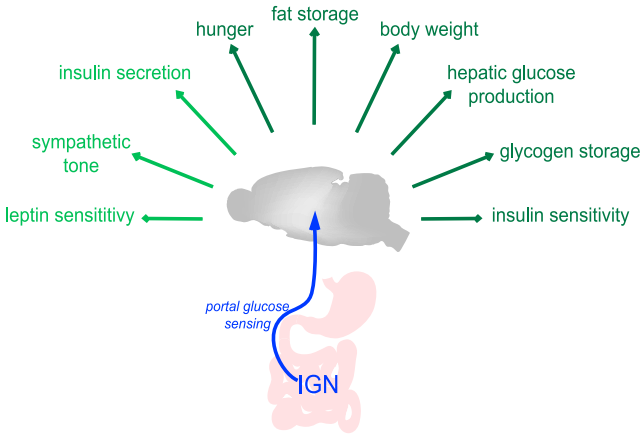

Figure 4. Functions Controlled by IGN via Portal Glucose Sensing and Brain Signaling

In dark green: functions identified from the effects of nutrient-dependent induction of IGN (and absence of effects in IGN-deficient mice). In light green: functions identified from the phenotype of IGN-deficient mice (and correction by portal glucose infusions).

of the liver, Claude Bernard had already envisioned the essential role of nerves in regulating the metabolism of the organs, as he wrote the following on page 65 of his famous notebook, also named the "cahier rouge": "Physicochemical phenomena always start from a vital phenomenon, of which they are merely the evocation subject to the nerves, since the nervous system does not produce but regulates the chemical phenomena of the organism" (Bernard, 1965) (original citation: "Les phénomènes physicochimiques ont toujours un phénomène vital pour point de départ, dont ils ne sont que l'évocation soumise aux nerfs, car le système nerveux ne produit pas mais règle les phénomènes chimiques de l'organisme").

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