Opinion
High Glycemic Index Metabolic Damage – a Pivotal Role of GIP and GLP-1
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When glucose–fructose dimers are supplied as the slowly digestible, completely absorbable, low glycemic index (GI) sugar isomaltulose, the detrimental effects of high GI sucrose are avoided. This difference requires the presence of intact glucose-induced insulinotropic peptide receptor (GIPR) and is mediated by the rapid uptake of glucose and the stimulation of GIP release from K cells in the upper small intestine. GIP promotes lipogenesis, fatty liver, insulin resistance, and postprandial inflammation, and reduces fat oxidation in skeletal muscle, partly by hypothalamic interference with energy partitioning and epigenetic programming. GIP is similarly required for the detrimental metabolic effects of other high GI carbohydrates. We therefore propose that the release of GIP in the upper small intestine is an important determinant of the metabolic quality of carbohydrates.

The Concept of the GI Lacks a Strong Theoretical Basis
The glycemic index (GI) (see Glossary) remains a fervently debated concept regarding potential health benefits of the quality of the carbohydrates as defined by high or low GI of foods [1–5]. Recent studies in non-European populations have suggested increased mortality due to high intakes of refined high GI carbohydrates from polished rice, thereby fueling the discussion [6]. The GI-concept (Box 1) proposes that a slower and lower increase in glucose reduces metabolic and cardiovascular disease [7–9]. The exact reasons why a low GI is beneficial have remained somewhat elusive and the physiological mechanisms are not well defined. The most detailed model assumes that the greater increase in glucose and insulin with high GI foods is unfavorable, by inducing an exaggerated insulin response followed by delayed hypoglycemia and reactive increases in free fatty acids (FFAs), which increase triglycerides and low-density lipoprotein–cholesterol while decreasing high-density lipoprotein (HDL)–cholesterol. The greater insulin responses may increase body fat and weight and lead to insulin resistance and to exhaustion of endocrine pancreatic function and insulin release [8,10].

GI Is Affected by Many Variables
Postprandial increases in glucose differ dramatically between individuals, even to similar foods [11], and are determined not only by the speed and quantity of insulin and glucagon secretion, but also by an array of variables including body composition, age, microbiome, fiber intake, and circadian changes in insulin sensitivity [11–13].

Foods with a low GI tend to contain more fibers and micronutrients that display potent health-promoting properties compared to more processed high-GI foods such as white bread or rice, thereby confounding the results of clinical intervention studies due to their content of non-starch food components affecting sugar and fat metabolism [14–16]. Moreover, some sugars, such as fructose have a low GI but elicit additional metabolic effects on uric acid, liver fat, and blood pressure, which may further confound the outcomes [17].
A Novel Enteroeendocrine Concept of GI Pathophysiology

We propose a novel concept linking the GI to differential responses of the intestinal hormones GIP and glucagon-like peptide (GLP)-1, which are released in different segments of the small intestine (Box 2). In particular, a rapid and pronounced release of GIP in the proximal small intestine by high-GI carbohydrates is proposed to program metabolism for effective energy storage favoring fatty liver, insulin resistance, obesity, subclinical inflammation, and hypertriglyceridemia. This program may have been evolutionarily advantageous in times requiring rapid energy storage. Understanding the pathophysiological mechanisms of high-GI foods provides a basis for developing nutritional and therapeutic solutions.

Foods that have similar composition but differ in GI are required to investigate the physiological impact of the GI under weight-stable conditions in an unambiguous manner. The prototype of such a food is provided by isomaltulose (marketed under the brand name Palatinose), which consists of a glucose–fructose dimer similar to sucrose. However, the two sugars are linked by an α,1,2-glycosidic bond in sucrose and by an α,1,6-glycosidic bond in isomaltulose. The α,1,2 bond is rapidly cleaved by the intestinal glucosidases while the α,1,6 bond is cleaved slowly, resulting in a delayed but complete uptake in the small intestine, which has also been confirmed in human ileostomy patients [18]. The complete uptake in the small intestine is important to distinguish effects on the GI from those caused by changes in gut microbiota that occur when the whole grain will have a lower GI than the milled grains when consumed as flour, due to the slower disintegration of the whole grains in the gut. The same applies to pasta, which typically has a low GI. In mixed meals, other food components such as fat and protein slow gastric emptying and thereby retard the absorption and increase in blood sugar. In addition to the speed of digestion and absorption of a specific carbohydrate, the kinetics and quantity of insulin secretion, the inhibition of glucagon release, and gastric emptying directly determine postprandial glucose levels [3,4,7,8,11,12]. Moreover, GI is highly circadian and increases in blood glucose for similar meals are two to three times greater in the evening as compared to the morning [13].

Intake of isomaltulose results in a slow and delayed increase of blood sugar and insulin and reduced peak concentrations as compared to sucrose, resulting in apparently better glucose response. GIP is released in the upper small intestine in response to food intake from enteroeendocrine K cells [23,25]. GIP is an incretin hormone, which defines it as a gut hormone inducing the release of insulin from pancreatic islet β cells upon food intake but only if blood glucose is elevated [23,24]. GIP is released within minutes upon intake of glucose or rapidly digested carbohydrates such as saccharose or starch from milled flour, and is an important mediator of the early insulin response. GIP is also released by fat and protein but does not induce insulin release in the absence of increased blood glucose. In addition, GIP is an important regulator of postprandial metabolism by acting on receptors on many cell types including insulin producing beta cells, adipocytes, immune cells, endothelial cells, and neuronal cells, but not hepatocytes or striated muscle cells [38]. The whole-body genetic deletion of GIPR renders mice resistant to the development of obesity and insulin resistance in response to high-fat or high-GI diets [9,55]. GIPRs on pancreatic β cells become dysfunctional in chronic hyperglycaemia and do not mediate insulin release in patients with type 2 diabetes, who show a delayed and prolonged insulin response to carbohydrates [22,24]. Another well-characterized incretin hormone stimulating insulin release is GLP-1, which is released from L cells in the distal small intestine and colon upon food intake, particularly by foods that are not resorbed proximally. GLP-1 inhibits gastric emptying and reduces food intake and is a well-characterized principle in the treatment of type 2 diabetes [23,24]. GLP-1 thus rather represents a signal to reduce food intake when digestive capacity is exceeded, such that undigested food reaches the distal small intestine.
tolerance [18–20]. Indeed, using isomaltulose, it is possible to show distinct roles of the GI regarding intestinal hormone responses of incretins and other hormones, insulin sensitivity, hepatic lipid accumulation and fatty liver, and inflammatory responses. A closer understanding is achieved by taking the intestinal hormone responses into account and by determining the responses of humans to postprandial elevations of these hormones.

**Slow (Isomaltulose) versus Fast (Sucrose) Sugars: Different Intestinal Hormone Responses**

Administration of 50 g isomaltulose results in smaller peak increases in glucose than sucrose in healthy individuals [18,19] (Figure 1) and in people with type 2 diabetes [20]. In parallel, there is a smaller peak and total increase in insulin [19]. This is surprising in view of the similar amount of glucose and fructose being absorbed by the organism with either sugar, and indicates an improved insulin action or insulin-independent disposal of glucose. Insulin secretion is partly determined by the intestinal incretins GIP and GLP-1 [21–24]. GIP is produced by K cells, which are predominantly located in the upper small intestine [25], while the GLP-1-producing L cells are located in the more distal small intestine and in the colon [23]. Therefore, it is reasonable to assume that the faster digestion of sucrose and uptake of glucose results in stimulation of the more proximal K cells, while the slowly cleaved isomaltulose may bypass these proximal K cells and therefore release little GIP. Indeed, GIP is rapidly released by sucrose, reaching peak concentrations after 15 min, which coincides and correlates with the early insulin secretion in healthy humans (Figure 1). By contrast, there is little increase in GIP after ingestion of isomaltulose, consistent with bypass of the proximal K cells, and accordingly, little early increase in insulin [26]. Studies comparing the contribution of GIP and GLP-1 to insulin secretion after oral sucrose showed that this is primarily determined by GIP with a lesser contribution of GLP-1 in healthy individuals [27,28].

GLP-1 typically responds to sucrose with a small initial peak with little subsequent secretion [28,29]. Consistent with stimulation of more distal L cells, isomaltulose caused significantly more and sustained GLP-1 release, which peaked after ~60 min [26]. These two sugars thus provide an excellent approach to study the role of incretins in mediating the metabolic responses to low or high-GI foods, without being confounded by differences in either carbohydrate quantity or fiber content.

**Reducing GIP by Nutrition or Deletion of GIPR Prevents Sucrose-Induced Fatty Liver**

Hepatic steatosis has been increasing epidemically worldwide, together with obesity, and is closely linked with the prevalence of metabolic diseases as well as cardiovascular diseases and hepatocellular carcinoma [30]. Increased de novo lipogenesis from sugars contributes to hepatic fat content and is elevated in patients with hepatic steatosis [31,32]. Regarding incretins, increased postprandial release of GIP has been linked to human fatty liver disease [33], while GLP-1 may exert a protective effect [34].

The incretin profile elicited by sucrose and isomaltulose provides an excellent tool to dissect the role of GIP in inducing hepatic steatosis in the context of diets differing only in containing 40% of sucrose or isomaltulose, while fat (40%) and protein (20%) are identical. The hormonal responses in mice closely resemble those of humans regarding glucose, insulin and GIP, that is, isomaltulose elicits only a minimal release of GIP and insulin as compared to sucrose when either sugar is supplied alone (Figure 2) [35]. Importantly, the low release of GIP in the presence of isomaltulose is maintained in the context of a mixed meal, which does not show differences in glucose response (Figure 2) due to the presence of 40% fat and 20% protein, which retard lipogenic and trophic metabolic signals.

- Neuropeptide Y (NPY): orexigenic hypothalamic neuropeptide.
- Orexigenic: appetite increasing (orexis = appetite).
- Phosphatidylinositol 3-kinase: enzyme in the AKT-signaling pathway.
- Postprandial: period immediately after food intake.
- Protein S6: target protein of S6 kinase.
- Saccharose: another term for sucrose, dimer of glucose and fructose which is rapidly cleaved at the α1,2-glycosidic bond by intestinal disaccharidases.
- S6 kinase: kinase immediately downstream of mTOR.
Although fat and protein also stimulate GIP [23], the release of GIP is less in diets containing isomaltulose instead of sucrose, indicating potentiation of GIP release by the combination of fat and sucrose (Figure 2). Notably, in the complex diet, as opposed to the administration of isolated sugars, insulin release is not reduced by the presence of isomaltulose, although GIP release is reduced (Figure 2). Mice receiving such a diet develop fatty liver when the diet contains sucrose but not with isomaltulose. It is also important that mice do not differ in insulin secretion, weight gain, circadian activity patterns, intestinal fermentation, or energy expenditure, thus eliminating alternative explanations for increased liver fat [35]. Notably, in humans a reduction of the GIP release by reducing glucose uptake with the α-glucosidase inhibitor acarbose reduces liver fat in humans [36].

Mechanistic assessment of the role of GIP in causing these differences has been provided by using genetic models with a deletion of GIP receptors (GIPR−/−). In GIPR−/− mice, there is no
difference between sucrose and isomaltulose with respect to hepatic fat accumulation. In fact, the GIPR–/– mice are protected from developing fatty liver upon consumption of high-sucrose diets [35]. Thus, a functional GIP system is required to develop fatty liver in response to sucrose, glucose, and fructose, and the sugar components by themselves are not sufficient.

**Insulin Sensitivity**

A polymorphism in the GIPR gene is related to the risk of impaired glucose metabolism in humans [37], and expression of GIPR mRNA in human subcutaneous adipose tissue is closely correlated with insulin sensitivity, fasting insulin and glucose levels, waist circumference, as well as fasting levels of triglycerides and HDL–cholesterol, that is, all components of the metabolic syndrome [38]. GIP appears to increase fat storage in adipocytes [39,40] and participates in adipose tissue immune regulation [41–43]. The expression of the GIPR transcript in human adipose tissue is higher in abdominal than in subcutaneous fat and decreases with increasing waist circumference. Moreover, weight loss leads to increased expression of GIPR in human subcutaneous fat, which may be posited as a counter-regulatory mechanism [38]. The GIPR
mRNA thus is downregulated by obesity and weight gain and vice versa. Further support for a role of GIP and its receptor is provided by the Pounds Lost Trial, which linked the less functional genetic variant of the GIPR to greater weight loss and improvements of insulin sensitivity in high-carbohydrate, low-fat diets [44].

In humans, circulating levels of GIP are inversely correlated with insulin sensitivity [33] and a GIP antagonist improves insulin sensitivity when co-infused with GIP [45]. This raises the question whether lowering of GIP release by intake of isomaltulose improves metabolic parameters in humans. Indeed, the intake of isomaltulose for 4–20 weeks in controlled diet studies improved insulin sensitivity in humans with metabolic diseases, while sucrose showed no such effect [18,46,47]. Improvements of insulin sensitivity (homeostatic model assessment–insulin resistance; HOMA-IR) were observed in a randomized controlled double-blind prospective study in patients with metabolic syndrome [48]. This is also in line with the mouse data showing the development of insulin resistance with sucrose but not palatinose [35]. Moreover, GIPR−/− mice do not become insulin resistant with a high-sucrose diet, indicating again a pivotal role of GIP [35].

Central Hypothalamic AKT-Signal Pathway Regulated by GIP
GIPR mRNA and GIPR-binding sites are widely expressed in the brains of mice and rats [49,50] and play a role in neurogenesis [51] and locomotor behavior [52]. The hypothalamic injection of GIP upregulates expression of neuroendocrine peptides such as neuropeptide Y (NPY), oxytocin, CART (cocaine- and amphetamine-regulated transcript), and arginine vasopressin, and of components of their receptor coupling systems, while GIPR−/− mice have decreased levels [53].

GIP appears to modulate central AKT signaling in response to dietary interventions. In 6-month-old mice exposed to a high-fat diet, the hypothalamic phosphorylation of mTORSer2448 is decreased significantly in GIPR−/− mice. Further downstream, phosphorylation of S6-kinaseThr389 is nonsignificantly reduced, while its target protein S6Ser235/236 again shows significantly reduced phosphorylation [54]. At the transcript level, hypothalamic phosphatidylinositol 3-kinase mRNA is decreased in GIPR−/− mice, again supporting hypothalamic actions of GIP. GIPR−/− mice have an increased metabolic rate and are more active than control mice on a high-fat diet [55] or on high-GI diets [56], which supports central sites of action regulating physical activity [52].

GIP increases expression of the orexigenic hypothalamic NPY [53], which is reduced in ovariectomized female GIPR−/− mice compared to sham-operated controls. The reduced hypothalamic NPY expression leads to lower food intake, which completely prevents weight gain typically observed upon ovariectomy, even on a normal chow diet [57]. This model of menopause also implies that the typical menopausal weight gain in humans may involve increased appetite triggered by GIP. However, genetic evidence for a role of hypothalamic GIPRs in metabolic regulation is still missing and requires the generation of conditional hypothalamic GIPR−/− mice.

Inflammation
GIPRs are expressed in human adipose tissue [38] and on human monocytes, as well as several macrophage cell lines [41]. GIP is reported to induce expression and release of inflammatory cytokines including interleukin (IL)-6 and IL-1β from isolated human [43] and mouse [58] fat cells. Increased expression of IL-6 and monocyte chemoattractant protein (MCP)-1 has been reported in human adipose tissue upon infusion of GIP in vivo, which also results in elevated circulating levels of MCP-1 [42]. The release of MCP-1 by GIP in
cultured primary human adipocytes requires coculture of macrophages with adipocytes [42], which is also observed in mouse cells [58], suggesting that GIP triggers crosstalk among these cell types. GIP is reported to induce expression of osteopontin, a cytokine related to insulin resistance [59]. Thus, there is evidence that GIP induces a moderate immune response locally in adipose tissue that may also play a role in inducing insulin resistance [42,58,59].

Nutrition with a low GI is linked to reduced serum **C-reactive protein (CRP)**, an established clinical marker of inflammation, in different weight-stable intervention studies in patients with obesity [60] or diabetes [61]. This association is compatible with a role of GIP in relaying the increased levels of CRP. Since CRP and subclinical inflammation are induced by obesity and independently linked to the risk of diabetes and cardiovascular disease, low-GI foods that reduce the increase in GIP may reduce inflammation, particularly in humans with a metabolic syndrome (Figures 3 and 4, Key Figure).

**GIP and Vascular Responses**

Food intake increases splanchnic perfusion and there is strong evidence that GIP is involved in this response [62]. GIP increases superior mesenteric arterial but not celiac artery blood flow in anesthetized dogs, and increases portal blood flow in conscious dogs, while hepatic arterial blood flow is decreased [62]. Infusion of GIP in lean healthy men in the presence of hyperinsulinemic and hyperglycemic clamps increases adipose tissue blood flow [39], which is blocked by co-infusion of a GIP antagonist, which moreover reduces fat storage in adipose tissue [45]. The presence of GIPR in endothelial cells from mice, rats, and humans has been confirmed and shown to induce an inflammatory response involving the cytokine osteopontin [63]. GIPR gene polymorphisms are associated with cardiovascular disease [63,64], and upregulation of GIPR expression has been reported in plaques of arterial endothelial cells [63]. Endothelial GIPRs thus may also be involved in nonsplanchnic arterial regulation and play a role in the risk of stroke and myocardial infarction, which is increased by elevated circulating levels of GIP [63].

**GIP and Metabolic Programming**

Nutritional exposure may lead to metabolic programming, which is best shown for the intrauterine and postnatal periods. Does GIP play a role in metabolic programming as may...
be deduced from its strong associations with the metabolic syndrome? GIPR−/− mice are known to be protected from obesity and insulin resistance in response to a high-fat or high-GI diet [55,56]. However, the intrauterine and postnatal exposure of GIPR−/− mice to a high-fat diet abolishes this protection, leading to similar obesity and insulin resistance upon exposure to a high-fat diet after 6 month as in control mice. The intrauterine programming involves changes in hypothalamic phosphorylation and mRNA expression of the AKT-signaling pathway, as
described above [54]. The most striking alterations are observed in enzymes involved in increased fat oxidation in skeletal muscle cells, which do not express GIPRs. An investigation of the epigenetic signature showed increased methylation of functional response elements in the promoter of carnitine palmitoyltransferase (CPT)1α, which reduced the interaction with regulatory transcription factors [54]. This suggests that central GIP-related pathways are involved in programming of peripheral gene expression related to a reduction of fat oxidation (Figure 4 and see Outstanding Questions). Overall, these findings support a role of GIP to preserve energy stores. While intrauterine and postnatal programming contributes to obesity in later life, this raises the question whether GIP may also be involved in the regulation of energy metabolism after weight loss in adults. The reduction of the basal metabolic rate after weight loss is an unresolved issue, and a putative role of GIP may open new therapeutic approaches [65]. In fact, the postmenopausal and age-associated reductions of physical activity, food intake, and energy metabolism may partially be mediated by GIP, as indicated by studies of the weight gain induced by ovariectomy in GIPR−/− mice, which involved the hypothalamic expression of appetite-regulating hormones and thus central pathways (Figure 4) [56,57].

Concluding Remarks
In summary, high-GI carbohydrates differ from low-GI carbohydrates, specifically by releasing GIP. There is ample evidence for metabolically unfavorable effects of GIP regarding insulin sensitivity, fatty liver disease, subclinical inflammation, and promotion of diabetes and cardiovascular disease (Figure 4). The hormonal responses of the intestine to a sugar with low GI, which induces little release of GIP but greater amounts of GLP-1, result in metabolic improvements in healthy individuals and in people with impaired glucose metabolism or overt type 2 diabetes, providing strong evidence that GIP plays a central role in mediating the deleterious effects of high-GI foods, while reducing the release of GIP may explain much of the health benefits of low GI foods.

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