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Risk of postprandial insulin resistance: The liver/vagus rapport

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Abstract

Ingestion of a meal is the greatest challenge faced by glucose homeostasis. The surge of nutrients has to be disposed quickly, as high concentrations in the bloodstream may have pathophysiological effects, and also properly, as misplaced reserves may induce problems in affected tissues. Thus, loss of the ability to adequately dispose of ingested nutrients can be expected to lead to glucose intolerance, and favor the development of pathologies. Achieving interplay of several organs is of utmost importance to maintain effectively postprandial glucose clearance, with the liver being responsible of orchestrating global glycemic control. This dogmatic role of the liver in postprandial insulin sensitivity is tightly associated with the vagus nerve. Herein, we uncover the behaviour of metabolic pathways determined by hepatic parasympathetic function status, in physiology and in pathophysiology. Likewise, the inquiry expands to address the impact of a modern lifestyle, especially one's feeding habits, on the hepatic parasympathetic nerve control of glucose metabolism.

Keywords

postprandial insulin resistance; liver; vagus; nitric oxide; glutathione; glucose intolerance

1- Introduction

Type 2 Diabetes Mellitus (T2DM) is rapidly expanding worldwide. According to the International Diabetes Federation, in 2012 there were 371 million diabetics—8.3% of the adult population—of which 50% were undiagnosed. During 2012, 4.8 million people died of T2DM, half of them under the age of 60 years. Furthermore, by 2030, approximately 552 million people are likely to have diabetes, corresponding to a 76% increase.

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Further, prediabetes is estimated to affect almost 350 million people worldwide [1]. Its importance is highlighted by increased associated medical costs [2], with a considerable percentage of prediabetics already showing microvascular and cardiovascular complications [1]. Most common among prediabetic subjects are those with impaired glucose tolerance, who exhibit high postmeal glucose excursions and whose diagnosis is more difficult due to methodological limitations, resulting in an high predominance of undetected cases [3,4]. This unchecked progressive rise in glucose excursions has been tightly associated mainly with defects in postprandial insulin sensitivity [5,6].

Additionally, a major recognized modulator of postprandial glucose metabolism is the autonomic nervous system (ANS) [7,8]. Indeed, ANS imbalances have been related to disruptions in insulin action, leading to several complications that culminate in T2DM [8,9]. Specifically, vagal tonus impairment has been shown to be the primary change in autonomic dysfunction, and is associated with increasing insulin resistance [10-12].

Of course, insulin action is ubiquitous, and several organs are commonly implicated in the progression of normal glucose tolerance to glucose intolerance and diabetes. However, in recent years the liver has gained recognition as a maestro among them, working to achieve optimal plasma glucose levels and appropriate tissue glucose disposal. Herein, we will discuss the dogmatic role of the liver on postprandial insulin sensitivity and its rapport with the vagus nerve.

2- Postprandial glucose regulation: A livercentric hypothesis

At first, the idea that the liver orchestrates global glycemic control is not an easy concept to accept. Although it is widely reported that hepatic dysmetabolism is associated with increased glucose excursions, this is normally attributed to a dysfunction of inherent hepatic glucose fluxes. However, a new picture has arisen in which the liver controls glucose homeostasis due to its ability to uptake and produce glucose, but also by determining plasma insulin levels reaching systemic circulation, as well as directly determining optimal peripheral insulin sensitivity during the postprandial state, through hormonal and parasympathetic nervous system cues.

The liver, for its anatomical location (receiving blood from the portal vein, directly from the gut's outgoing circulation), is in a prime position to act not only as a buffer for blood glucose [13] but also as a center of information and effector of the management of energy. Even the processes that happen before, such as gut nutrient absorption, are seen to act through the same parasympathetic vagus avenues. As glucose reaches the gut, this is sensed by enterochromaffin cells that release serotonin, which, together with incretins, activate the vagus, regulating glucose homeostasis, insulin secretion, and food intake in the postprandial period [14].

As for insulin secretion, the parasympathetic autonomic nervous system mediates the secretion of the first peak of insulin from the pancreas, called the cephalic phase [15]. The initial cephalic phase is complemented by responses induced by the arrival of nutrients to the stomach, their absorption in the intestine and delivery to the bloodstream and, subsequently, to the local effects of nutrients at the pancreas. Hence, the incretins

(specifically, GLP-1 and GIP) are released upon food arrival. This, in addition to the rise in blood-glucose concentration in the hepatoportal circulation (intimately related to the liver and then to central brain control), further stimulates insulin release from pancreatic β -cells. Indeed, the effect of glucose-sensing at the hepatic portal sensors on pancreatic insulin secretion is mediated by the parasympathetic nervous system; first by an afferent, from liver to brain, then by an efferent pathway, from brain to pancreas [16].

The liver is chief among the organs in which the hypothalamus interferes with metabolic homeostasis [17]. Afferent signals from the hepatic region are believed to be related to cytokines and nutrient metabolites sensors. Then efferent vagus nerve signalling to the liver is essential for insulin signalling from the mediobasal hypothalamus [18,17,19]. Moreover, hepatic glycogen synthesis is regulated by the hypothalamus through a mechanism mediated by the vagus nerve [20]. More recently, marked emphasis has been given to the ability of the hypothalamus to regulate not only hepatic insulin sensitivity, activating transcription factor 4, but also insulin sensitivity at other organs [21,22].

Nonetheless, all these are merely overarching indications of the central role of the liver in the processes that impact postprandial glucose tolerance, as depicted in figure 1. Luckily, greater detail has been recently reported regarding glucose homeostasis and insulin sensitivity at peripheral organs, also an object of liver control in the postprandial state [23]. Herein we will discuss major points that address this relation starting by the hepatic parasympathetic nerves, approaching the impact of hepatic nitric oxide and glutathione and a non-classic view of glucagon actions.

2.1 Hepatic parasympathetic nerves

It is well known that insulin-stimulated whole-body glucose uptake doubles after a meal, compared to the fast state. This effect has been linked to an increase in insulin secretion, with a subsequent rise in circulating insulin, available to promote glucose uptake at the peripheral tissues. Thus, the classic role of the liver on peripheral insulin action is a direct consequence of how hepatic insulin extraction determines the insulin concentration that reaches the peripheral tissue [24]. However, it was observed that this postprandial-induced increase in insulin sensitivity can be abolished without changing peripheral insulin levels [25]. This discovery led to a new hypothesis that involves the liver as a key effector in the modulation of peripheral insulin sensitivity. Specifically, this hypothesis relates the hepatic parasympathetic nerve tonus to insulin sensitivity at the periphery, mainly in skeletal muscle, through the action of a hepatic factor called hepatic insulin sensitizing substance (HISS).

In the 1980s, it was proposed that hepatic autonomic dysfunction could result in a decrease in glucose uptake and glycogen synthesis. A link between liver disease and T2DM was emerging and autonomic neuropathy was being proposed as an etiological factor to diabetes development [9].

Thirteen years after, it was shown that parasympathetic hepatic nerve (HPN) ablation leads to a decrease in the hypoglycemic effect of insulin. The neutralization of hepatic sympathetic innervation had no additional detrimental effect [24]. Additionally it was shown

that administration of an antagonist of muscarinic receptors, atropine, produced the same degree of impairment in insulin sensitivity observed with the hepatic parasympathetic denervation [26], at a lower dose when given through the portal vein rather than intravenously [27]. Likewise, administration of acetylcholine through the portal vein was able to restore insulin-stimulated glucose uptake, previously abolished with denervation [28]. As expected, peripherally administered acetylcholine was unable to restore insulin-stimulated glucose uptake after denervation.

Surprisingly, when arteriovenous glucose gradients were measured, hepatic vagal surgical denervation or atropine administration were shown not to impair insulin-stimulated glucose uptake in the liver, but in skeletal muscle [26].

By that time, some high variability seen in previous studies prompted the study of the importance of prandial status to the HISS pathway on insulin sensitivity, if experiments were conducted either in the fast or fed state [29]. This study showed that insulin sensitivity was higher immediately after feeding and decreased gradually with time. Furthermore, it was shown that the component of insulin sensitivity independent of HISS (the one preserved after atropine administration) did not change in rats from the fed to a 24h fasting period [29]. The HISS pathway was revealed as responsible for the maximal insulin sensitivity observed after feeding and decreased gradually with fasting until being practically nonexistent. [29]

Additionally, our group showed that in fed animals, hepatic parasympathetic nerve ablation induces insulin resistance at soleus and extensor digitorum longus skeletal muscles, heart, and kidney, but not at liver or adipose tissue [23] (Figure 2). By this data, skeletal-muscle postprandial glucose clearance was shown to change between 38 and 69% of whole-body clearance, depending on the integrity of the hepatic parasympathetic nerves. This supports the concept that the skeletal muscle is the major organ responsible for whole-body glucose clearance [30].

This decrease in skeletal muscle glucose clearance after hepatic parasympathetic denervation resulted in a 51% increase in plasma glucose concentration. As the skeletal muscle uses both glucose and free fatty acid (FFA) as fuel sources for energy production [31,32], this result may indicate increased FFA influx for energy needs. Indeed, in obesity and T2DM patients, FFA flux is chronically increased, and this permanent increase in FFA availability is considered to exacerbate skeletal muscle insulin resistance [33].

Although both heart and kidney play a minor role in whole-body glucose clearance with an overall contribution between 1% to < 0.5%, in the particular case of the ablation of hepatic parasympathetic nerves the impact on postprandial glucose clearance in these organs was 35% and 67%, for heart and kidney respectively, suggesting that any alteration in tissue glucose uptake may lead to dysfunctional mechanisms in those organs [23].

In the heart, although glucose is not the major source of energy, the relative contribution of the glucose utilization pathways is significant, allowing the plasticity necessary for steady ATP production [34-36]. Accordingly, high rates of fatty acid use are described in diabetic patients, leading to the accumulation of lipid intermediates and excessive oxygen consumption [34,35,37]. The mechanisms that regulate kidney glucose use after a complete

meal are less well known. Postprandial glucose use by the kidney has been shown to increase in an absolute sense [38]. By contrast to the renal cortex, which uses FFA as the major source of energy, the renal medulla has low levels of oxidative enzymes, and therefore requires glucose for its energy requirements [38]. Thus, HPN-dependent insulin resistance may induce decreased glucose uptake, shifting substrate use and chronically leading to cardiac and kidney functional abnormalities.

The described studies highlight how the liver/vagus rapport impairment may contribute to an early progression from normal glucose tolerance to diabetes, leading to an increase in glucose excursions. Looking downstream of the HPN, additional steps of the HISS hypothesis were uncovered, as hepatic nitric oxide (NO) production.

2.2. Hepatic nitric oxide

The cascade through which the HPN promotes postprandial glucose clearance and disposal involves the release of acetylcholine and subsequent activation of muscarinic receptors [39] leading to the liver production of NO, shown to be critical for secretion of HISS from the liver [40,41]. The importance of NO for peripheral insulin action has been shown extensively through different strategies. Blockage of hepatic NO synthase (NOS) activity or administration of an NOS antagonist induces insulin resistance [25,42]; using the opposite approach, insulin resistance after hepatic parasympathetic denervation can be overcome by intraportal administration of an NO donor [42]. However, while the absence of NO was shown to impact negatively on postprandial insulin sensitivity by itself, it was unable to act alone to fully express HISS action, but only as a cofactor of hepatic glutathione, as described below.

2.3 Glutathione (GSH)

GSH is a tripeptide synthesized from glutamate, cysteine, and glycine through the enzymes γ -glutamylcysteine (GSC) synthetase and GSH synthetase. Under normal physiological conditions, the rate of GSH synthesis is determined by cysteine availability, which is derived from the diet and from protein breakdown. Glutathione exists in thiol reduced form (GSH) and disulfide oxidized form (GSSG), with GSH as the predominant form in most cells and with the liver as the principal organ for GSH biosynthesis. The main function of glutathione is to act as an antioxidant, preventing cellular damage caused by reactive oxygen species such as free radicals and peroxides [43,44]. Also of particular relevance is the ability of GSH to regulate NO homeostasis, with the formation of nitrosothiols [45].

GSH status has been argued to modulate glucose homeostasis in a direct way, independently of antioxidant activity. Indeed, depletion of GSH has been reported to decrease insulin sensitivity and to cause impairment in insulin signaling in rats, without an increase in oxidative stress markers [46]. Supporting this hypothesis, GSH infusion was reported to increase total glucose uptake in type 2 diabetes patients [47].

The aforementioned potentiation of peripheral insulin sensitivity in the postprandial state, through a mechanism dependent on the integrity of the hepatic parasympathetic nerves/NO axis was shown to be also dependent on increased hepatic GSH levels [48,42].

The necessity of the presence of the two signals (NO and GSH) was elegantly shown in fasted animals. Here, 24h-fasted rats were able to show increased insulin sensitivity to normal postprandial insulin sensitivity only when both GSH and NO were administered to the liver [48]. The prior infusion of any one of them produced no effect on insulin sensitivity; the combined hepatic administration was indispensable to mimic normal postprandial HISS action [48].

This raises the hypothesis that, by reacting together to form S-nitrosothiol (RSNO), GSH and NO are directly involved in the synthesis of HISS [42]. This has been subsequently corroborated by the observation that intravenous S-nitrosoglutathione (GSNO) administration is able to mimic postprandial insulin sensitivity in fasted animals [49]. Interestingly, if GSNO is perfused directly into the portal vein, it induces insulin resistance rather than augmenting insulin sensitivity. This suggests that RSNO has a role in promoting peripheral insulin-stimulated glucose uptake; and that negative feedback may be present if the RSNO concentration reaching the portal vein is too high. If the elusive HISS factor is indeed an RSNO, or another nitrosylated molecule for that matter, remains to be shown [50,51].

2.4 - Glucagon

Another interesting point is the impact of hormones such as glucagon on GSH levels and how hyperglucagonemia seen in diabetes can indirectly affect peripheral insulin sensitivity. In addition to glucagon's well-known physiological function, Lu and colleagues showed that glucagon's effects, mediated via cAMP, decrease hepatic GSH levels due to an inhibition of GSC synthase [52,53]. In the fast state, when glucagon levels are high, cAMP levels are increased and GSH levels are decreased [42]. Upon feeding, the liver receives low glucagon levels, allowing an increase in GSH as cAMP decreases.

We observed that in the postprandial state, when the liver was infused with a dose of glucagon that will not produce glucose output, there was a decrease in GSH levels with consequent peripheral insulin resistance [54]. Moreover, if GSH was supplemented into the liver by administering it as glutathione ester, concomitantly with glucagon, the latter did not induce peripheral insulin resistance (Patarrão and Macedo, unpublished results). Therefore, sustained high levels of glucagon, usually seen in type 2 diabetes, could produce a decrease in hepatic GSH levels, culminating in a state of insulin resistance.

3– Integrated view of the underlying hepatic factors on health and disease

It is well established that liver disease is accompanied by defects in whole-body glucose homeostasis [55] and that it can be a determining factor in the metabolic syndrome [56]. Surprisingly, the initial stages of liver dysfunction are related not to hepatic insulin resistance, as it would be expected, but to a decrease in peripheral insulin sensitivity; mainly due to a decrease in glucose uptake and glycogen synthesis in skeletal muscle [57].

Regarding ageing, it was shown that the hepatic parasympathetic function is gradually impaired, in parallel to insulin resistance [125]. Here, the administration of drugs typically used to prevent oxidative stress were also able to maintain parasympathetic nervous system

tone and insulin sensitivity [58]. Interestingly, in humans, while parasympathetic function was shown to decrease with age [59,60], healthy centenarians showed preserved parasympathetic function [59], which supports the notion that activities that promote parasympathetic activation of vagal function may contribute to longer maintenance of a proper glucose tolerance.

Hypertension is one of the pathologies most often associated with insulin resistance [61,62] and many times included in the metabolic syndrome cluster, with changes in glycemic and lipid profiles [61]. Data from our group showed that postprandial insulin resistance associated with essential hypertension in animal models is due specifically to HISS impairment [63,64], which is in accordance with reports from Swislocki and coworkers, who describe an impaired reposition of skeletal muscle glycogen after a meal [65], whereas hepatic glycogen does not seem to be affected [66]. Also, dysfunction of the parasympathetic-NO axis in hypertension is widely described [67,68] and may constitute an etiological link between hypertension and associated postprandial insulin resistance.

Obesity, independent of its etiology, is probably the pathology more consensually associated with insulin resistance, glucose intolerance, and type 2 diabetes. Several hypotheses have been proposed to explain such an association. For example, increased delivery of FFA from visceral adiposity to the portal vein was proposed to reduce glucose use [69,70] and induce alterations of the autonomic nervous system through an increase of the sympathetic/parasympathetic ratio [71], which could be related to impairment of hepatic-dependent insulin action, and therefore, with postprandial insulin sensitivity. However, data from our group suggests that whole-body fat is highly correlated with the development of postprandial insulin resistance [72], discarding a specific role for visceral fat [72-74].

In contrast, independent of fat distribution, increasing adiposity implies adipocytes hypertrophy and concomitant increased secretion of humoral and inflammatory factors; many authors claim that these adipokines are responsible for obesity-associated insulin resistance: TNF- α , IL-1, or IL-6 [75,76]. An interesting adipose-derived hormone is leptin, which seems to decrease ectopic lipid accumulation in liver and muscle and thereby ameliorate insulin sensitivity [77,78]. Our experiments on a genetic model of obesity characterized by a defective leptin receptor, the obese Zucker (fa/fa) rat, suggested that the observed postprandial insulin resistance is caused by a defect in the insulin signaling pathway itself, as both hepatic-dependent and hepatic-independent components of insulin action were equally impaired [79].

On the contrary, experiments performed by our group on obesity induced by high-fat feeding, a more “physiological obesity,” showed that early insulin resistance is observed only in the postprandial state and not in the fasting state [72]. This fat-induced postprandial insulin resistance is caused specifically by impairment of hepatic-dependent insulin action [72]. Another conclusion from those experiments was that whole-body adiposity correlates specifically with hepatic-dependent insulin action (postprandial), but not with hepatic-independent insulin action (fasting), in accordance with early disturbances in the postprandial state [72].

In a way, one can say that diet-induced alterations in glucose homeostasis, through insulin action, affect firstly and mostly hepatic-dependent insulin sensitivity, since, as observed with high-fat feeding [72], our group also observed that a sucrose enriched diet leads to impaired hepatic-parasympathetic function, resulting in postprandial insulin resistance [12]. High-sucrose diets induce insulin resistance, particularly in skeletal muscle [80,81], without hypertension or obesity [12,82]. Additional reports on elevated oxidative stress, associated with decreased hepatic GSH content [83,84], further corroborate the link between high-sucrose feeding and postprandial insulin resistance. Accordingly, administration of drugs that mimic both hepatic signals—parasympathetic and GSH—were able to reverse insulin resistance in animals fed a high-sucrose diet [85].

Recently, using an obese model prone to diabetes at a young age, we observed that loss of hepatic parasympathetic-NO function occurs at a very early stage in the development of diabetes and is accompanied by low hepatic GSH synthesis, which simultaneously explains the impaired postprandial insulin action and the compromise of the oxidant status in prediabetes [86]. These experiments provided a pathophysiological link between glutathione impairment, autonomic dysfunction, altered NO production, and loss of postprandial glucose homeostasis in obesity-related prediabetic states.

4-Meals and glucose excursions: Does it make a difference what we eat?

In the past decade, the importance of managing postmeal glycemia in the diabetic patient has been given higher relevance than fasting glycemia [87-91] (International Diabetes Federation Atlas 2008), as compelling evidence suggests that high peaks of hyperglycemia, more commonly obtained in the postprandial state, occur before and are more dangerous than dysregulation of fasting glycemia [92,90]. Since the beginning of this century, several groups have shown that postprandial glucose excursions are the major contributors for HbA1C levels in diabetic patients with HbA1C < 7.3 % [89] and that managing postprandial glycemia in type 2 diabetic patients has a greater impact on metabolic control than managing fasting glycemia [87].

More recent reports further suggest that both in the course toward diabetes and even after frank diabetes is installed, the loss of postprandial glycemic control precedes abnormalities in fasting glycemia [90]. Indeed, induction of acute hyperglycemia similar to glucose intolerance in healthy subjects seems to affect their oxidant status [88,91]. Furthermore, Zheng *et al* reported that glucose excursions in type 2 diabetic and in impaired glucose-regulation patients correlate with oxidative stress markers [93] suggesting that daily peaks of glucose excursions are associated not only with the loss of glucose metabolism control, but also with diabetic-related complications [94,95,93]. In a more fundamental approach, it was also observed that cell exposure to intermittent high glucose levels triggers apoptotic pathways in a more pronounced manner than sustained high glucose levels [96], which also seems to be associated with oxidative stress [91].

Considering this, it is worthwhile to discuss how meal composition can affect glucose homeostasis, and concomitantly can affect postprandial glucose excursions.

More than 30 years have passed since Owens and coworkers reported for the first time that glucose excursion is more pronounced after ingestion of a glucose meal than after a mixed meal [97], allowing researchers to conclude that meal composition affects glucose excursions. Recent data further suggest that mixed meals lower postprandial glucose excursions [98].

It is known that insulin-dependent glucose uptake by peripheral tissues increases following a meal, in humans and in animal models [99,100], through a mechanism that depends on nutritional composition of the meal, since neither glucose nor sucrose by themselves are able to increase fasting insulin action [100]. Indeed, supplementation of glucose with protein or amino acids results in higher oral glucose tolerance [101,102], and recent data from our group suggest that a meal is required to contain both amino acids and glucose to trigger the postprandial increase of insulin action. Indeed, it was further shown by our group that after a meal, the observed increase in whole-body insulin sensitivity can be produced by the intestinal administration of a combination of glucose and amino acids (essential to boost liver GSH content), an effect that is abolished if hepatic parasympathetic nerves are impaired (Afonso and Macedo, personal communication).

Based on the fact that GSH and some amino acids can regulate insulin sensitivity, we recently hypothesized that cysteine is an important amino acid as a source of glutathione that, in conjunction with glucose, increases peripheral insulin sensitivity (Gaspar and Macedo., personal communication). In this work, we administered directly into the intestine N-acetylcysteine (NAC) and glucose and observed a significant increase in peripheral insulin resistance, which was not due to an increase in plasma insulin levels (Gaspar and Macedo personal communication). Emerging literature supports that indeed amino acids play a role in glucose homeostasis, and some have the ability to lower blood-glucose levels and improve glucose tolerance, through an increase of skeletal muscle glucose uptake [103-105].

Also, NAC or a diet rich in whey protein and α -lactoalbumin (cysteine rich proteins) was shown to lower oxidative stress and insulin resistance induced by sucrose or fructose in rats and streptozotocin-treated diabetic mice [106]. Also, administration of N-acetylcysteine in the presence of bethanechol (to mimic the activation of the parasympathetic nerves) reinstated the necessary feeding signals, resulting in a complete restoration of postprandial insulin sensitivity in an animal model of insulin resistance [85].

Concerning the mechanism(s) by which amino acids contribute to the rise in insulin action after a meal and thereby contribute to controlling postprandial glucose excursions (figure 3), two major hypotheses should be considered.

The first, more traditional hypothesis is based on the classic precursor role of essential amino acids in the synthesis and activation of both enzymes and substrates in metabolic pathways. One of these key players on postprandial insulin action is hepatic glutathione [42], highly present in the liver, which increases in concentration following a meal [107,42]. Indeed, synthesis of hepatic glutathione requires glycine, glutamate, and cysteine, the last of which is obtained mostly from the meal, either directly or through the essential amino acid

methionine. In this way, for the meal to trigger the increase in insulin action, it must provide substrates for hepatic glutathione synthesis, along with parasympathetic activation, which has been suggested to be a role for glucose in the gut [14]. Recently, it has been suggested that the presence of glucose in the gut is also sensed by enterochromaffin cells that release serotonin, which activates a vagal reflex involved in the regulation of several gastrointestinal functions [108,109]. Thus, glucose in the gut triggers a vago-vagal reflex that stimulates hepatic parasympathetic nerves, whereas amino acids serve as substrates for hepatic glutathione synthesis, both of which are required to produce maximal postprandial insulin action.

In contrast, a second hypothesis is related to the observation that gut-absorbed amino acids also lead to serotonin-dependent activation of afferent parasympathetic fibres, producing centrally-mediated vagal reflexes that control several gastrointestinal-related functions [110]. Although this second hypothesis for the role of amino acids in postprandial insulin action was presented separately from the first, there is nothing in the literature that indicates the two mechanisms cannot occur simultaneously.

Concerning lipid meal content, although most authors today consider that high-fat diets induce glucose intolerance [111], insulin resistance [112,72] and postprandial glucose excursions, there is still some debate on this subject, particularly concerning glucose excursions [113]. Indeed, Farrow and coworkers reported that feeding cats with either high-fat or high-protein diets for 8 weeks resulted in lower postprandial glucose excursions than cats fed a high-carbohydrate diet [113]. Such an observation can be explained by the fact that high-fat feeding, even in smaller periods, leads to higher insulinemia, which temporarily compensates for insulin resistance [72] [114] and, thereby prevents the significant increase in glucose excursions [72] that occur in other models of obesity [79]. In accordance with these observations, other authors reported that higher fat content in the diet leads to significant impairment of either insulin sensitivity in healthy individuals, or β -cell function in patients with impaired fasting glucose [115]. Interestingly, high-fat diet deleterious effects on glucose tolerance seem to be reversed by switching to a high-protein diet [116].

5- Conclusion and implications

Today, type 2 diabetes is a global problem [117]. The present review argues that a crucial risk factor for metabolic dysregulation, an impaired hepatic vagus/NO/GSH axis, emerges well before alterations in blood glycemia are noticed. The early detection of this dysfunction in asymptomatic individuals would most likely decrease the morbidity, mortality, and costs, that derive from type 2 diabetes and the overall metabolic syndrome.

The role of the liver as an integrator and effector of information on glucose homeostasis must be recognizably extended to not only the liver itself but also skeletal muscle, heart, kidney, and liver/vagus dysfunction, to be further investigated at the onset of insulin resistance, and of the alteration of postprandial glucose fluxes, highlighting its importance at the origin of type 2 diabetes. Furthermore, the continued investigation of the physiological and pathophysiological mechanisms involved have strengthened the notion that this is an

attractive target for behavioral and pharmacological interventions; especially those able to, directly or indirectly, preserve/ameliorate autonomic parasympathetic nervous function.

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Figure 1.

The postprandial livercentric hypothesis interplays the relationship of organs and how the liver acts as a maestro for the regulation of plasma glucose levels and of insulin sensitivity. The gut responds to a meal by realizing hormones and by activating the vagus to the hypothalamus. Thereafter, efferent vagus nerve signalling can be triggered by sensing metabolic alterations in the brainstem and the hypothalamus regulating hepatic glucose production glycogen synthesis as well as pancreatic endocrine function (insulin). The liver is subsequently responsible for insulin clearance, regulating the levels of the hormone that reaches the periphery. Vagal activation to the liver in the postprandial state allows hormonal communications from the liver to skeletal muscle, heart, and kidney to increment glucose clearance by these organs.

Figure 2.

This figure depicts the postprandial percentage of glucose clearance in whole-body tissue distribution. (A) The total amount of glucose cleared by tissues after a meal in control animals and after hepatic parasympathetic denervation. In control-animal skeletal muscle glucose clearance, adipose tissue and liver accounts for 69% and 7%, respectively. The parasympathetic hepatic denervation major effect was on skeletal muscle, decreasing glucose clearance to 38%. Other tissues, almost certainly the brain, account for 16% of postprandial glucose clearance and remained unchanged after hepatic parasympathetic denervation. (B) Hepatic parasympathetic nerves affect postprandial glucose disposal at kidney, heart, and skeletal muscle, accounting for 67%, 35%, and 45% of glucose clearance, respectively.

Figure 3.

Proposed mechanism for the increment of insulin-dependent glucose disposal following a mixed meal. Intestinal absorption of glucose and amino acids, following ingestion of a mixed meal containing carbohydrates and proteins, leads to pancreatic insulin secretion, which acts in peripheral tissues—skeletal muscle—to promote glucose uptake. Additionally, absorbed glucose and amino acids also induce the release of serotonin (5-HT) from enterochromaffin cells, which activates parasympathetic afferent terminals and triggers a centrally-mediated parasympathetic reflex that results in nitric oxide (NO) production in hepatocytes. Finally, this efferent hepatic parasympathetic-dependent NO, along with increased hepatic glutathione (GSH) synthesis resulting from amino-acid absorption, potentiate insulin action in peripheral tissues, resulting in higher glucose uptake and concomitant reduction of postprandial glucose excursion. GI, gastrointestinal; 5-HT, serotonin; CNS, central nervous system; Cys, cysteine.