Regulation of Hepatic Glucose Uptake and Storage In Vivo[1,2]

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ABSTRACT

In the postprandial state, the liver takes up and stores glucose to minimize the fluctuation of glycemia. Elevated insulin concentrations, an increase in the load of glucose reaching the liver, and the oral/enteral/portal vein route of glucose delivery (compared with the peripheral intravenous route) are factors that increase the rate of net hepatic glucose uptake (NHGU). The entry of glucose into the portal vein stimulates a portal glucose signal that not only enhances NHGU but concomitantly reduces muscle glucose uptake to ensure appropriate partitioning of a glucose load. This coordinated regulation of glucose uptake is likely neurally mediated, at least in part, because it is not observed after total hepatic denervation. Moreover, there is evidence that both the sympathetic and the nitrergic innervation of the liver exert a tonic repression of NHGU that is relieved under feeding conditions. Further, the energy sensor 5′AMP-activated protein kinase appears to be involved in regulation of NHGU and glycogen storage. Consumption of a high-fat and high-fructose diet impairs NHGU and glycogen storage in association with a reduction in glucokinase protein and activity. An understanding of the impact of nutrients themselves and the route of nutrient delivery on liver carbohydrate metabolism is fundamental to the development of therapies for impaired postprandial glucoregulation. *Adv. Nutr. 3: 286–294, 2012.*

Introduction

The liver plays a unique role in postprandial nutrient metabolism because it has first access to most ingested nutrients by virtue of their absorption into the hepatic portal vein. As a result, the liver is exposed to higher nutrient levels than are peripheral tissues. Moreover, it is able both to store and to release glucose to minimize changes in glycemia between the fed and fasted states. In the normal individual, the intake of a mixed meal results in modest hyperglycemia, accompanied by substantial storage of glycogen in the liver. The postprandial period is characterized by carefully titrated changes in hormone secretion and neural signals, as well as changes in nonglucose substrates, that combine to direct the partitioning of the glucose load among the various tissues (1–4). In contrast to the individual with normal glucose tolerance, the person with poorly controlled type 1 or 2 diabetes exhibits marked postprandial hyperglycemia and impaired hepatic glycogen accumulation (4–6). This review focuses on the current understanding of the signals involved in the control of hepatic glucose uptake and glycogen synthesis in vivo.

Current status of knowledge

In response to ingestion of glucose or a mixed meal and the resulting hyperinsulinemia and hyperglycemia, the fasting liver shifts from net output to net uptake of glucose. It is clear, however, based on the measurement of net splanchnic glucose balance in humans (6–8) and net hepatic glucose balance in dogs (9,10), that neither hyperinsulinemia nor hyperglycemia can independently induce much net hepatic glucose uptake (NHGU[6]). NHGU remains modest (2.8–11.1 μmol·kg^{-1}·min^{-1}) even when hyperinsulinemia and hyperglycemia (resulting from glucose infusion into a peripheral vein) are combined (6,7,9,11,12). On the other

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[6] Abbreviations used: ACC; acetyl-CoA carboxylase; AMPK, 5′AMP-activated protein kinase; cGMP, cyclic guanosine monophosphate; GK, glucokinase; GKRP, glucokinase regulatory protein; GLP-1, glucagon-like peptide 1; GS, glycogen synthase; HFFD, high-fat and high-fructose diet; L-NAME, N_{ω}-nitro-L-arginine methyl ester; NHGU, net hepatic glucose uptake; NO, nitric oxide; NOS, nitric oxide synthase; ODQ, 1H-[1,2,4] oxadiazolo[4,3-a] quinoxalin-1-one; sGC, soluble guanylate cyclase; SIN-1, 3-morpholinosydnominine HCl.

hand, when similar levels of hyperinsulinemia and hyperglycemia are brought about by oral or enteral glucose delivery, the resulting rates of NHGU are as great as 25–27.8 $\mu mol \cdot kg^{-1} \cdot min^{-1}$ (13,14). Thus, it is clear that oral glucose delivery triggers a unique hepatic response and that the liver has an important role in disposing of ingested glucose.

Direct measurement of hepatic glucose uptake in humans is hampered by the technical difficulty and ethical concerns regarding portal vein blood sampling. Using splanchnic balance measurements and tracer techniques, however, investigators have estimated that the human liver disposes of ~25 to 35% of an oral glucose load (15,16). In the dog, a model in which it is possible to measure hepatic balance directly, NHGU accounts for 25–40% of the administered glucose, with the exact percentage being determined by the load of glucose and insulin reaching the liver (14,17). Thus, the data from human and canine experiments are in general agreement that, when presented with a moderately sized oral glucose load, the liver extracts approximately one third of the glucose, together the muscles and fat take up approximately one third, and the noninsulin-sensitive obligate glucose–using tissues dispose of the remaining one third (**Fig. 1**). In fact, the liver not only takes up glucose but also curtails its release of glucose postprandially. Thus, these proportions underestimate the role of the liver in glycemic control because the glucose consumed by the obligate glucose-requiring tissues has to be derived from the absorbed glucose, as a result of the cessation of hepatic glucose production. Consequently, the liver is actually responsible for the disposal of the equivalent of ~60–65% of an oral glucose load. Any impairment in its function, therefore, can lead to excessive postprandial glycemia. Because elevated postprandial glucose levels are associated with adverse outcomes including increased risk of death (all cause and cardiovascular), major cardiovascular events, and progression of diabetic retinopathy (18), an understanding of the regulation of hepatic glucose uptake is of great importance.

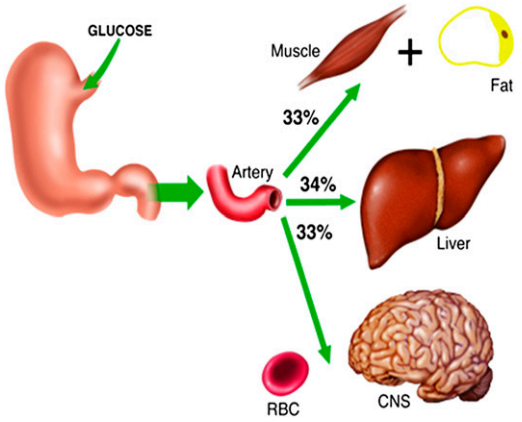

Figure 1 Distribution of a glucose load among the liver, insulin-sensitive tissues, and noninsulin-sensitive tissues. CNS, central nervous system; RBC, red blood cell. Reproduced from Reference 97 with permission.

Portal glucose signal

Originally it was postulated that a gut factor could explain the ability of combined increases in insulin and glucose to cause greater splanchnic or hepatic glucose uptake when associated with oral glucose delivery (7). However, such a gut factor was subsequently ruled out by studies in dogs in which hyperglycemia was created via an intraportal glucose infusion that mimicked the absorption profile of oral glucose. In this manner, several laboratories demonstrated that NHGU was not different after intraportal and oral glucose entry (17,19,20). Using the hyperglycemic clamp technique along with the pancreatic clamp (basal glucagon replacement with either euinsulinemia or hyperinsulinemia) in dogs, it was possible to ensure that the load of glucose and the pancreatic hormone concentrations at the liver were maintained equivalent, whether glucose was given via a leg vein or the hepatic portal vein. In this way, it was conclusively demonstrated that entry of glucose into the portal vein stimulated NHGU and hepatic glycogen synthesis to a significantly greater extent than glucose delivery via a peripheral vein (12,21). Thus, a portal vein signal, rather than a gut factor, was demonstrated to be responsible for enhancement of NHGU during oral, enteral, or portal venous glucose delivery. It is this factor, together with the insulin concentration and the load of glucose reaching the liver, that determines the rate of NHGU (12,22) (**Fig. 2**). The portal glucose signal does not, however, enhance whole-body glucose clearance (11,21). Instead, it is associated with a suppression of nonhepatic (primarily muscle) glucose uptake concomitant with the increase in liver glucose uptake (23). Thus, as a result of its reciprocal actions, the portal signal ensures that a glucose load is appropriately distributed among the skeletal muscle, the liver, and the other tissues of the body.

Although the portal glucose signal has been demonstrated to operate in species other than the dog (24,25), its importance in the human has been more difficult to evaluate because of an inability to catheterize the portal vein and the difficulty in controlling the insulin and glucagon levels reaching the liver. Two investigations in humans are particularly relevant. DeFronzo et al. (7) compared splanchnic glucose uptake in 2 groups of human subjects in whom peripheral vein glucose infusion was used to create a combination of hyperglycemia and hyperinsulinemia. One group then consumed an oral glucose load (1.2 g/kg), with the peripheral glucose infusion rate subsequently being adjusted so that glycemic levels were similar in the presence and absence of the oral glucose load. Glucose ingestion augmented net splanchnic glucose uptake approximately 5-fold, compared with peripheral venous glucose infusion alone. The design of their study was such that the liver in the group receiving oral glucose was exposed to a somewhat larger hepatic glucose load and somewhat higher insulin levels, however, complicating data interpretation. In the second study, Vella et al. (11) used a pancreatic clamp to fix insulin and glucagon concentrations while infusing glucose into either the duodenum or a peripheral vein. Intraduodenal glucose

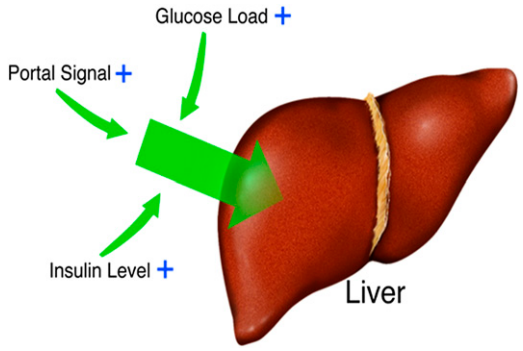

Figure 2 Factors affecting the magnitude of net hepatic glucose uptake (NHGU). In the physiologic range, increases in the amount of insulin reaching the liver and the hepatic glucose load stimulate NHGU. When the insulin concentrations and hepatic glucose loads are equivalent with the 2 routes of delivery, NHGU is approximately 2-fold greater when glucose is delivered via the portal versus a peripheral vein.

delivery was associated with a 40–125% enhancement of hepatic glucose extraction. It is worth noting that whole-body glucose kinetics in humans did not differ, whether glucose was given via the intravenous or intraduodenal route (26), consistent with findings in the dog and mouse (21,25). In summary, the available evidence strongly suggests that the portal signal functions across mammalian species.

A meal contains not only carbohydrate but also fat and protein, and thus it is of interest to know what effect these substrates have on hepatic glucose disposal. The impact of lipids on NHGU has been examined with pancreatic hormones clamped and the portal signal present, as well as infusion of nicotinic acid to suppress endogenous lipolysis. Under these conditions, peripheral infusion of a lipid emulsion to maintain nonesterified fatty acid concentrations at their basal levels was associated with a significant (~50%) reduction in NHGU compared with a control group that received no lipid infusion. The suppression of NHGU in the lipid-infused group was attributable to a combination of stimulation of hepatic glucose production and blunting of hepatic glucose uptake (27). The number and diversity of amino acids have made the examination of interactions between carbohydrate and protein more complex. Under hyperinsulinemic hyperglycemic clamp conditions, portal but not peripheral infusion of a gluconeogenic amino acid mixture (serine, threonine, glutamine, glutamate, glycine, and alanine) significantly blunted NHGU (~50%) in the presence of the portal glucose signal but not in its absence (28,29). On the other hand, when a mixture containing the 20 common dietary amino acids was delivered under hyperinsulinemic hyperglycemic clamp conditions in the absence of the portal signal, it brought about a blunting of NHGU (30); interaction between the 20 amino acid mixture and portal glucose delivery has not been examined. Both glucose and amino acids in the hepatoportal region are known to initiate neural signals that are transmitted to the brain, with some of the amino acids having stimulatory effects and others having suppressive effects on afferent firing rates (31–33). It is thus likely that competition or interaction among the various amino acids and glucose alter the transmission of a neural signal responsible for modulating hepatic substrate extraction. In summary, both fat and amino acids affect the liver's response to glucose delivery, but much work remains to be done to understand the relationships among the macronutrients and their components in the regulation of NHGU.

Mediators of the portal glucose signal. The liver is innervated by parasympathetic, sympathetic and nonadrenergic, noncholinergic (including nitrergic) nerves (34–37). A role for the central nervous system in the control of liver glucose metabolism is generally supported by the literature (38–40). Electrophysiologic data confirm that glucosensors in the hepatoportal region transmit signals to the hypothalamus (41), and total hepatic denervation ablates both the hepatic and muscle responses to portal glucose delivery (42). The manner in which the portal glucose signal is sensed and signals to muscle and liver remains unclear, however. One possibility is that afferent nerves carry information from the hepatoportal region to the brain, which then signals muscle and liver through efferent nerves. Alternatively, the information sent to the brain could bring about a neural signal to one organ or the other, with the subsequent release of a hepatokine or myokine to coordinate the response between tissues.

In regard to afferent signaling, it has been established that a negative arterial-portal vein glucose gradient (i.e., portal vein glucose concentration higher than that in the artery) triggers the response to portal vein glucose delivery (43). Further, it is clear that the arterial and portal vein glucose levels are compared within the liver and not within the central nervous system (44,45). Afferent fibers from the hepatoportal region travel with both the spinal and vagus nerves (35). Data from vagal nerve cooling experiments do not support involvement of vagal afferents in the portal glucose signal because inhibition of vagal firing brought about by cooling the vagus nerves in the conscious dog under hyperglycemic, hyperinsulinemic conditions did not lead to a decrease in NHGU, whether portal glucose delivery was present or not (46,47). The spinal afferent nerves have been shown to function in the detection of hypoglycemia in the portal vein (48), and thus their involvement in the response to a glucose load appears likely, although it has not been examined.

With regard to the efferent limb of the response, again there is little support for a key role for the parasympathetic system. In addition to the evidence from the vagal cooling experiments described earlier, it has been observed that, under hyperinsulinemic euglycemic conditions, hepatic parasympathetic denervation in the rat brings about a reduction in glucose clearance in the skeletal muscle, heart, and kidney but does not affect glucose clearance by the liver (49,50). On the other hand, data do support a role for sympathetic and nitrergic neural input in regulating NHGU. Surgical ablation

of the hepatic sympathetic nerves resulted in an increase in NHGU during glucose infusion into a peripheral vein (51). Likewise, increasing hepatic nitric oxide (NO) using the NO donor 3-morpholinosydnominine HCl (SIN-1) or lowering it using the NO synthase (NOS) inhibitor N_{ω}-nitro-L-arginine methyl ester (L-NAME) brought about reduced and enhanced NHGU, respectively (52,53). Taken together, these data suggest that both adrenergic and nitrergic input to the liver exerts a basal restraining effect on NHGU that is removed in response to feeding or portal glucose delivery.

The pathway or pathways bringing about the nonhepatic response to the portal signal remain undefined. Neural signals represent 1 possibility because electrical stimulation of the ventromedial hypothalamus enhances muscle glucose uptake, an effect that can be prevented with sympathetic blockade (54). In addition to receiving neural signals from the periphery, the hypothalamus is sensitive to circulating hormones and substrates, including insulin and glucose (39,55). Both insulin and glucose modulate the phosphorylation of cerebral 5′AMP-activated protein kinase (AMPK), which can play a role in the regulation of muscle glucose disposal (55).

Glucagon-like peptide 1 (GLP-1) has been suggested as a mediator of the enhancement of NHGU by oral glucose delivery (56). However, physiologic concentrations of GLP-1 have no impact on NHGU when studies are conducted during the infusion of somatostatin (57,58). Somatostatin prevents endogenous release of GLP-1 as well as glucagon and insulin, eliminating the possibility that differences in concentrations of key glucoregulatory hormones account for the findings. Thus, although numerous possibilities exist with regard to the identities of the afferent and efferent limbs associated with the portal glucose signal, it is unclear at present which are crucial for the response. Nevertheless, the available data point toward the involvement of the nervous system.

NO and hepatic fuel sensing. AMPK, a metabolic fuel sensor with numerous targets, is activated by an increase in the AMP:ATP ratio, an indicator that tissue energy reserves are low. Activation of AMPK stimulates energy-producing pathways, i.e., glucose utilization and lipid oxidation, while reducing the activity of fuel storage pathways such as glycogenesis and lipogenesis in muscle and other tissues (59). These roles of AMPK suggest that an increase in hepatic glycogen concentrations might be expected to reduce AMPK activity and consequently blunt NHGU and hepatic glycogen storage. Under steady-state conditions and in the presence of physiologic levels of hepatic glycogen (55–72 mg/g tissue), the rate of hepatic glycogen synthesis is directly related to the rate of NHGU (60). However, proposed newer pharmacologic approaches to the management of postprandial hyperglycemia in type 2 diabetes, such as glucokinase (GK) activators, glucagon receptor antagonists, and glycogen phosphorylase inhibitors, might be anticipated to increase hepatic glycogen content. For this reason, studies were carried out on dogs whose livers had been "supercompensated" with glycogen (100 mg/g liver) (61). These high glycogen concentrations were achieved by infusing a small amount of fructose intraportally under hyperglycemic conditions to stimulate hepatic GK. GK is regulated by both long-term and acute mechanisms (reviewed in reference 62). Long-term mechanisms are largely mediated by insulin, which stimulates GK transcription and translation. Acute regulation (inactivation) occurs via binding of GK to its nuclear regulatory protein, GK regulatory protein (GKRP); this binding normally occurs in the presence of low glucose. Under postprandial conditions, elevated glucose levels stimulate dissociation of GK from GKRP, resulting in the translocation of GK in its active form to the cytosol. Enterally or portally delivered fructose is rapidly taken up by the liver and phosphorylated to form fructose-1-P, an extremely potent stimulator of GK/GKRP dissociation and GK translocation. This, in turn, induces supraphysiologic rates of NHGU and glycogen deposition (63). In contrast to a modest increase in the hepatic glycogen content, which had little apparent effect on liver glucose metabolism, the animals with supercompensated hepatic glycogen exhibited reduced glycogen synthesis in response to hyperglycemia, hyperinsulinemia, and the portal glucose signal (60,61). This was associated with impaired hepatic insulin signaling, increased AMPK phosphorylation, and marked reduction in glycogen synthase (GS) activity coupled with enhanced glycogen phosphorylase activity. McBride and Hardie (64) proposed that glycogen loading increases the binding of AMPK to the nonreducing ends of the glycogen molecule's outer chains, and this close proximity to GS, which is also glycogen bound, increases the likelihood of GS phosphorylation by AMPK. Thus, although our data do not allow us to draw conclusions about cause-and-effect relationships, they are consistent with a role for AMPK in the regulation of hepatic glucose disposal.

A role for AMPK in the regulation of hepatic energy metabolism has been suggested by a number of different laboratories. In the presence of basal glucagon and high physiologic levels of insulin, whether or not hyperglycemia, euglycemia, or hypoglycemia existed, intraportal infusion of the AMPK activator 5′-aminoimidazole-4-carboxamide-1-β-D-ribofuranoside in dogs led to an increase in hepatic glucose output attributable to an increase in glycogenolysis (65–67). This is in agreement with data indicating that AMPK can activate glycogen phosphorylase and inactivate GS (68), as well as inhibit GK translocation and glucose phosphorylation in hepatocytes (69).

Interaction between AMPK and NOS in the regulation of glucose metabolism has been observed in numerous tissues (70–72). Nevertheless, the nature of this interaction remains unclear. Treatment of isolated mouse or human skeletal muscle with NO donors (sodium nitroprusside or spermine NONOate, respectively) increased glucose transport, concomitant with an increase in activation of the AMPK α-1 subunit (73,74). Moreover, spermine NONOate increased glycogen synthesis and AMPK Thr^{172} phosphorylation in L6 myotubes, and the effects were not observed in the presence of a guanylate cyclase inhibitor (73). On the other

hand, there is also evidence suggesting that AMPK is an upstream activator of NOS (75,76). Regardless of the exact relationship between AMPK and NOS, the role of both molecules in the regulation of hepatic glucose metabolism is intriguing and deserves further investigation.

Whole-body insulin sensitivity is decreased by intraportal but not peripheral venous administration of L-NAME, and this effect can be reversed by intraportal but not peripheral delivery of SIN-1 (77–79). As mentioned previously, intraportal infusion of SIN-1 and L-NAME had suppressive and stimulatory effects, respectively, on NHGU (52,53). Thus, we were interested in determining the mechanisms(s) by which changes in NO levels affected liver glucose uptake.

Many of the metabolic actions of NO are mediated via its activation of soluble guanylate cyclase (sGC) and subsequent stimulation of cyclic guanosine monophosphate (cGMP), which modulates the activity of protein kinase G, cGMP-dependent phosphodiesterases, and cyclic nucleotide–gated ion channels (73). Therefore, we infused the sGC inhibitor 1H-[1,2,4] oxadiazolo[4,3-a]quinoxalin-1-one (ODQ) intraportally during a hyperinsulinemic, hyperglycemic clamp in the absence of the portal glucose signal in 1 group of dogs, whereas control dogs received the vehicle via intraportal infusion. Two additional groups were examined, 1 receiving vehicle plus intraportal SIN-1 and 1 receiving both ODQ and SIN-1 intraportally. Infusion of the sGC inhibitor resulted in a 55% enhancement of NHGU compared with control, along with a 48% increase in the liver glycogen content at the end of study (**Fig. 3**). Concomitant infusion of SIN-1 and ODQ did not alter the ODQ-stimulated rate of NHGU. Moreover, intraportal SIN-1 and vehicle administration resulted in NHGU at a rate no different from that in the control dogs. Intraportal ODQ infusion was associated with a 30% decrease in phosphorylation of hepatic AMPK and its downstream target acetyl-CoA carboxylase (ACC), compared with controls, and this was not altered by co-infusion of SIN-1 and ODQ. On the other hand, infusion of SIN-1 plus vehicle resulted in a 25% increase in phosphorylated AMPK/total AMPK and a 30% increase in phosphorylated ACC/total ACC compared with the control group (80). In a follow-up study, the cGMP analogue 8-bromo-cGMP was administered intraportally in the presence of the portal glucose signal, and NHGU was determined to be significantly blunted (81), providing further support for a role of the NO→sGC→cGMP pathway in the regulation of NHGU and glycogen storage (Fig. 3). The data suggest that this pathway could impose an inhibitory signal during fasting that would reduce glucose uptake by the liver. Conversely, a feeding signal that reduced signaling through the pathway might result in enhancement of NHGU and glycogen storage (**Fig. 4**).

Impact of long-term consumption of a high-fat and high-fructose diet on NHGU

The U.S. diet is high in fat, particularly saturated fat, and in simple carbohydrates (82,83). In part because of the increased use of high-fructose corn syrup in beverages and foods, fructose accounts for >10% of energy consumed by the average U.S. child or adult, with the 95th percentile of U.S. fructose intakes totaling ∼20% of total energy (84). Fructose intakes have increased along with increases in the prevalence of obesity, metabolic syndrome, and type 2 diabetes. Epidemiologic and cross-sectional data link high-fat and high-fructose diets (HFFD) with these metabolic

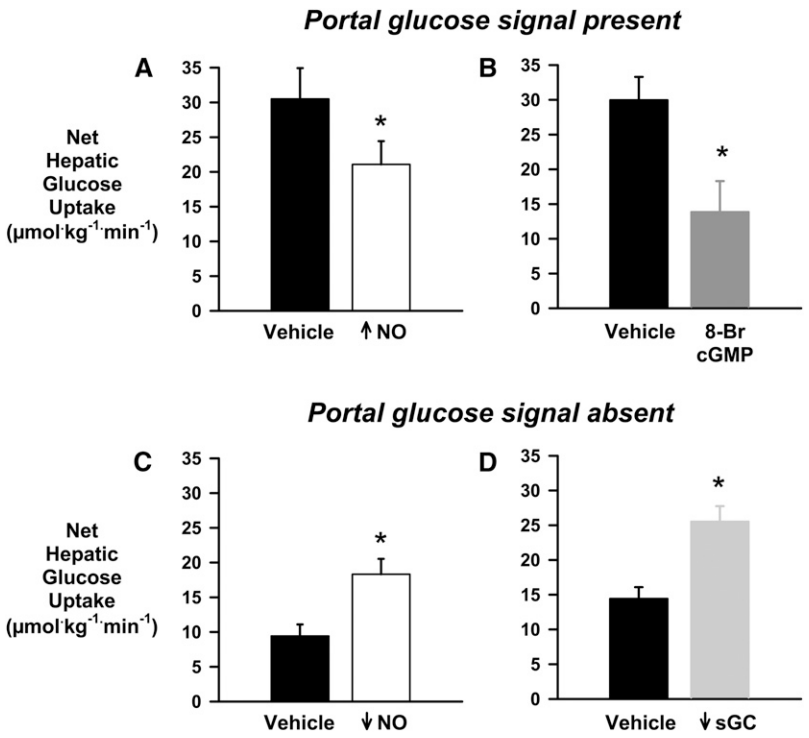

Figure 3 The relationship of nitric oxide (NO) and net hepatic glucose uptake (NHGU). In the presence of the portal glucose signal, increasing hepatic NO by intraportal infusion of 3-morpholinosydnominine HCl (*A*) or mimicking NO activation of the soluble guanylate cyclase (sGC)/cyclic guanosine monophosphate (cGMP) pathway by infusing the cGMP analogue 8-Br-cGMP intraportally (*B*) blunted NHGU. On the other hand, in the absence of the portal glucose signal, reducing hepatic NO by intraportal infusion of the NO synthase inhibitor N_{ω}-nitro-L-arginine methyl ester (*C*) or blocking the activation of the sGC/cGMP pathway with the sGC inhibitor 1H-[1,2,4] oxadiazolo[4,3-a]quinoxalin-1-one (*D*) enhanced NHGU. *$P < 0.05$ vs. vehicle. Data from References (52,53,80,81).

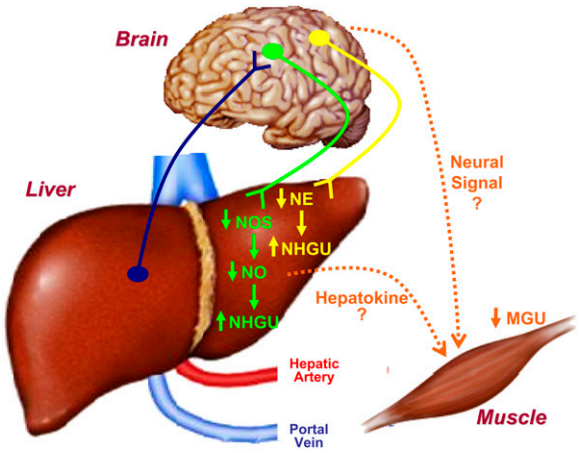

Figure 4 The distribution of a glucose load between the liver and insulin-sensitive tissues (primarily skeletal muscle) is finely controlled. Ingestion of glucose or infusion of glucose into the portal vein creates a negative arterial-portal glucose gradient (portal vein concentration higher than that in the artery) that is sensed within the liver, giving rise to the portal glucose signal, which is associated with an increase in net hepatic glucose uptake (NHGU) coupled with a decrease in muscle glucose uptake. Afferent signals regarding hepatoportal glucose levels can be transmitted from the liver to the brain, particularly the hypothalamus. The efferent limbs of the response apparently rely on neural and/or humoral signals. Both selective sympathetic denervation of the liver and reduction in hepatic nitric oxide (NO) by inhibition of NO synthase (NOS) activity (mimicking a reduction in nitrergic neural signals) stimulate NHGU in the presence of hyperinsulinemia and hyperglycemia brought about by peripheral glucose infusion. In addition, electrical stimulation of the hypothalamus stimulates muscle glucose uptake, and sympathetic blockade prevents the increase in uptake. It is also possible that a humoral factor released either by the liver or muscle (a hepatokine or myokine) regulates glucose uptake by the opposing tissue. MGU, muscle glucose uptake; NE, norepinephrine.

derangements (85–87). Although it is not clear that there is a causal relationship between fructose intake and these disorders, there is strong evidence of stimulation of de novo lipogenesis, visceral adipose tissue deposition, and dyslipidemia by high-fructose diets (88,89). Moreover, women consuming a diet high in fructose versus glucose (25% of total energy intake) for 10 wk exhibited increases in de novo lipogenesis and in fasting plasma glucose and insulin concentrations, along with impairment of glucose tolerance (90).

Animal models exposed to HFFD quickly develop evidence of the metabolic syndrome, including weight gain/overweight, hypertriglyceridemia, and insulin resistance (91–93). The effect of such diets on postprandial hepatic glucose metabolism is incompletely understood, and therefore we examined NHGU and hepatic glycogen deposition in the dog model (94). Adult male dogs were initially fed a balanced meat and chow diet (31% protein, 26% fat, and 43% carbohydrate, virtually all in the form of starch). After baseline assessment, they were either maintained on the meat and chow diet (control group) or switched to an HFFD (HFFD group; energy composition: 22% protein, 52% fat, and 26% carbohydrate, with fructose contributing 17% of the total dietary energy). The insulin and glucose responses to an oral glucose tolerance test conducted at baseline and at 4 and 8 wk of follow-up were stable over time in the control group. Glucose tolerance deteriorated during consumption of the HFFD diet, however, with the area under the curve of the glucose response at both 4 and 8 wk being more than 2-fold that at baseline. Despite the increase in glycemia during oral glucose tolerance testing, there was no compensatory increase in the areas under the curve of the insulin concentrations in the HFFD group. Insulin sensitivity, assessed with a hyperinsulinemic euglycemic clamp at baseline and at 10 wk, also decreased significantly (approximately one third) in the HFFD but not the control dogs. During week 13, a hyperinsulinemic (4 times basal) hyperglycemic (hepatic glucose load 2 times basal) clamp was performed after an overnight fast. For the first 90 min of the clamp, glucose was infused only via a peripheral vein. For the subsequent 90 min, glucose was also infused via the portal vein with the peripheral infusion adjusted as necessary to maintain the hepatic glucose load equivalent in both periods. In response to hyperglycemia of peripheral origin, the control dogs shifted from net hepatic glucose output in the basal state to NHGU at a rate of 10.5 $\mu mol \cdot kg^{-1} \cdot min^{-1}$, and during portal glucose infusion, their NHGU nearly doubled (19.4 $\mu mol \cdot kg^{-1} \cdot min^{-1}$). In the HFFD group, NHGU did not occur with either route of glucose infusion. Concomitant tracer measurements indicated that this was due to defects in both suppression of hepatic glucose output and stimulation of hepatic glucose uptake. Net hepatic glycogen synthesis was suppressed ~80% in the HFFD group.

Subsequently, separate groups of control and HFFD (8 wk of HFFD) dogs were studied after ingestion of a liquid mixed meal. Despite the presence of greater hyperinsulinemia and hyperglycemia after the meal in the HFFD versus control dogs, the HFFD group again failed to exhibit any significant NHGU, and glycogen storage was reduced ~75% in that group (95). Thus, diets rich in fat and fructose impair NHGU and thereby contribute to postprandial hyperglycemia.

Further work has shown that HFFD dogs exhibit substantial decreases in both GK protein and activity in the liver (Δ58% and 71%, respectively) with no decrease in GK mRNA (96), suggesting that the defect in NHGU in the HFFD dogs is likely related to a deficit in GK. This is consistent with an important role for hepatic GK in the regulation of hepatic glucose uptake and glycogen storage (62).

Conclusions

Under normal conditions, the liver plays a critical role in disposing of orally or enterally delivered carbohydrate and therefore in limiting postprandial hyperglycemia. This response involves both a decrease in hepatic glucose production and a stimulation of hepatic glucose uptake. The latter is dependent on a number of inputs: circulating concentrations of glucose, nonesterified fatty acids, and amino acids; hormones

(insulin); and neural mediators (NO and norepinephrine). The route of glucose delivery is responsible for determining as much as 50% of NHGU. The oral, enteral, or portal vein route of delivery brings about a negative arterial-portal vein glucose gradient that elicits a coordinated response of liver and muscle in glucose disposal such that NHGU is enhanced and muscle glucose uptake is suppressed. The portal glucose signal appears to be associated with a change in afferent signaling from the liver to the brain, resulting in a modification of efferent signaling to the liver, likely via sympathetic and/or nitrergic innervation. These signals apparently alleviate a tonic inhibition of NHGU. In response to a HFFD, both hepatic glucose production and glucose uptake in the postprandial period are abnormal, in association with a defect in hepatic GK. An improved understanding of the physiologic and pathophysiologic responses in the postprandial period will improve our ability to design appropriate treatments for individuals with impaired glucose tolerance and type 2 diabetes.

Acknowledgments

All authors have read and approved the final manuscript.

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