Mini-Review

Pathophysiological Mechanisms That Alter the Autonomic Brain-Liver Communication in Metabolic Diseases

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Abbreviations: AGE, advanced glycation end-product; ANS, autonomic nervous system; CNS, central nervous system; HbA1c, glycated hemoglobin A1c; HFD, high-fat diet; RAGE, receptor for advanced glycation end products; SAR, sorbitol-aldose reductase; SNS, sympathetic nervous system; SORD, sorbitol dehydrogenase; T2D, type 2 diabetes; TNF, tumor necrosis factor

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Abstract

The brain influences liver metabolism through many neuroendocrine and autonomic mechanisms that have evolved to protect the organism against starvation and hypoglycemia. Unfortunately, this effective way of preventing death has become dysregulated in modern obesogenic environments, although the pathophysiological mechanisms behind metabolic dyshomoeostasis are still unclear. In this Mini-Review, we provide our thoughts regarding obesity and type 2 diabetes as diseases of the autonomic nervous system. We discuss the pathophysiological mechanisms that alter the autonomic brain-liver communication in these diseases, and how they could represent important targets to prevent or treat metabolic dysfunctions. We discuss how sympathetic hyperactivity to the liver may represent an early event in the progression of metabolic diseases and could progressively lead to hepatic neuropathy. We hope that this discussion will inspire and help to frame a model based on better understanding of the chronology of autonomic dysfunctions in the liver, enabling the application of the right strategy at the right time.

Key Words: neuropathy, sympathetic nervous system, catecholamine, type 2 diabetes
several neuroendocrine and autonomic ways of influencing energy and glucose metabolism. These processes depend on many hormonal and neural factors controlling several pathways that have evolved to protect the organism against starvation and hypoglycemia (1, 2). Unfortunately, these sophisticated homeostatic processes can be impaired in metabolic diseases such as obesity and type 2 diabetes (T2D).

The brain consumes about 120 grams of glucose daily, accounting for nearly 60% of the utilization of glucose by the whole body in the resting state (3). Thus, it is no surprise that physiological, counterregulatory mechanisms have evolved that are very effective in preventing or correcting hypoglycemia. Defenses against hypoglycemia include, among others, changes in pancreatic hormone secretions (reduced insulin and increased glucagon), activation of the hypothalamic-pituitary-adrenal axis (increased glucocorticoids), increased sympathoadrenal outflow (increased epinephrine), mobilization of the parasympathetic nervous system (reduced vagal outflow), activation of the sympathetic nervous system (SNS, increased norepinephrine release by the nerves) and changes in brain permeability to facilitate the entry of circulating energy-related signals (4, 5). The net effect of the activation of these mechanisms of defense is an increase in metabolic substrates availability, such as increased hepatic glucose production and lipolysis, together with sparing of energy dissipation (6). These mechanisms of defense are so effective that severe hypoglycemia is uncommon in the general population. However, this effective means of preventing death from starvation has become dysregulated in modern obesegenic environments (7-13), although the pathophysiological mechanisms behind metabolic dyshomeostasis are still unclear. Moreover, half of people living with diabetes develop peripheral neuropathy (14), suggesting that interferences in the routes of communication between the brain and organs may be contributory to the development of metabolic alterations. There is also evidence that metabolic diseases are characterized by a state of autonomic hyperactivity, at least at the levels of certain organs (15, 16).

In this Mini-Review, we describe potential mechanisms leading to liver neuropathies and how autonomic dysfunctions can alter brain-liver communication, leading to the development of metabolic diseases. We also describe how metabolic diseases themselves may result in, or exacerbate, miscommunication between the brain and the liver. We hope that this discussion may help framing a model to define and understand the pathophysiological mechanisms that alter brain-liver communication in metabolic diseases.

Peripheral Neuropathy
The peripheral nervous system is responsible for bidirectional communication between the central nervous system (CNS) and organs through a vast network of nerves (17). These nerves can be motor (conscious control of the movement of muscles), sensory (transmission of sensory information to the CNS) or autonomic (unconscious control of the activity of organs and glands). Neuropathy consists in dysfunction or damage of the peripheral nervous system resulting in loss of signals, inappropriate signaling, or distorted message. It is estimated that up to 50% of Americans living with diabetes will be affected by a neuropathy, highlighting the importance of this condition (14). Mononeuropathy involves damage to only one nerve (eg, carpal tunnel syndrome) (18). However, most neuropathies affect many nerves and are therefore referred to as polyneuropathies. Common symptoms of damaged motor and/or sensory nerves include numbness, tingling, impaired sensation, muscle weakness, and pain (18). Autonomic neuropathy is a form of polyneuropathy affecting one of the 2 branches of autonomic nervous system (ANS), namely the sympathetic and parasympathetic (19). Malfunction of the ANS is often referred to as dysautonomia and results in gland or organ dysfunction. Common symptoms of damaged autonomic nerves include heat intolerance, excess sweating, sexual dysfunction, and gastrointestinal symptoms. However, autonomic neuropathy may also lead to alterations in glucose homeostasis, as highlighted in the next sections.

Diabetic Neuropathy
Diabetes is a leading cause of many types of polyneuropathies. Common manifestations of diabetic neuropathy include hypoglycemia unawareness resulting in autonomic failure, tachycardia, orthostatic hypotension, affectations of the gastrointestinal tract, and sudomotor dysfunction, to name but a few. Diabetic neuropathy can also cause extreme pain, lead to disabling foot ulcers, and ultimately cause death. Cardiovascular autonomic neuropathies are highly prevalent in people with a long history of T2D, affecting up to 60% of patients (20-22). They can also affect people with prediabetes (impaired glucose tolerance) and metabolic syndrome (23-25). Although not as prevalent, gastrointestinal neuropathies can also affect people with diabetes and cause important manifestations such as gastroparesis (26-28). The idea that diabetic neuropathy contributes to the pathophysiology of insulin resistance and T2D is supported by evidence of hepatic neuropathy in metabolic diseases.

Hepatic Diabetic Neuropathy
Neuropathy has been described in both alcoholic and nonalcoholic liver cirrhosis (29-31). In particular, autonomic dysfunction appears to develop in chronic liver disease and to be associated with the mortality rate (32-34).
Early work indicates that demyelinating peripheral neuropathy develops in patients with liver diseases and suggests that nerve damage can be the result of alteration in glucose metabolism or secondary to toxic metabolites (35). Considering the extent of affected organs in diabetic neuropathy, there is no reason to think that neuropathy does not affect liver metabolism, but there is currently no defined readout or biomarker of liver neuropathy that can be used in the clinic. However, recent preclinical evidence suggests that diabetic neuropathy also affects the liver. In particular, a recent report indicates that 20 weeks of high-fat diet (HFD) results in hepatic sympathetic neuropathy in mice (36). Mice deficient for the leptin gene (ob/ob) also exhibited a significant reduction of sympathetic axons in the liver (36). Interestingly, the loss of sympathetic innervations was reversible by calorie restriction or leptin supplementation in these models. Furthermore, deleting Sterile Alpha and Toll/Interleukin Receptor Motif-Containing Protein 1 (Sarm1) in mice, which prevented the development of neuropathies, was also sufficient to improve glucose metabolism and energy expenditure, suggesting that hepatic neuropathy may be a contributing factor to the pathogenesis of diabetes. It should be noted that liver neuropathy was not observed after shorter time of diet (12 or 16 weeks), indicating that it develops only when mice are challenged for a long period of time (36). However, many questions remain. In particular, it is unclear whether this progressive liver neuropathy also happens in humans, even though there is evidence that chronic liver diseases lead to such a pathology. In addition, it is still uncertain if hypoglycemic drugs are sufficient at preventing or restoring liver neuropathy. Additional studies are needed to determine the timing and the factors that contribute to diet-induced liver neuropathy, as well as the potential treatments.

**Pathophysiological Mechanisms of Diabetic Neuropathy**

Many processes are thought to be involved in the development of diabetic neuropathy. Here we describe 3 potential mechanisms that could perturb hepatic innervation and contribute to miscommunication between the brain and the liver in diabetes.

**Sorbitol-Aldose Reductase Pathway and Oxidative Stress**

The sorbitol-aldose reductase (SAR) pathway, also known as the polyol pathway, is a 2-step process in which glucose is reduced to sorbitol by the aldose reductase, and then oxidized to fructose by the sorbitol dehydrogenase (SORD) (Fig. 1A). Since glucose is the obligatory substrate of this pathway, hyperglycemia promotes sorbitol accumulation in cells, an effect linked to neuropathy (37). The role of the SAR pathway in neuropathy has been known for a long time, and evidence continues to accumulate that it is involved in diabetic complications such as microvascular damages (38). Supporting the role of this pathway in nerve damage, mutations in the SORD gene were recently shown to represent the most frequent recessive form of hereditary neuropathy (39). SORD is highly expressed in the liver, and its inhibition protects the liver from injury (40). Moreover, hyperglycemia alters Schwann cell biology by causing sorbitol accumulation (37). Considering that Schwann cells are responsible for peripheral nerve myelination, it is likely that these alterations participate to diabetic neuropathies (37). Overactivity of the SAR pathway can induce oxidative stress by increasing reactive oxygen species (ROS) production (41). It has been suggested that localized oxidative stress in kidneys participates in the development of diabetic nephropathy (42, 43). Additional studies are needed to determine whether the SAR pathway and oxidative stress participate in the pathogenesis of liver diabetic neuropathy.

**Hyperglycemia-Induced Glycation**

Glycation is a general term describing the nonenzymatic covalent attachment of a carbohydrate to another biomolecule such as a protein, a lipid, or DNA (44). High levels of glucose within cells can cause glycation of proteins and alter their structure and function. Hyperglycemia also increases and accelerates the production of advanced glycation end products (AGEs, Fig. 1B) (45). One commonly known AGE is glycated hemoglobin (HbA1c), which has become a powerful clinical tool to diagnose diabetes and to follow its progression and the efficiency of treatment. However, protein glycation and AGEs can be detrimental and these have been shown to be implicated in the pathology of diabetic neuropathy (46, 47). In particular, AGEs can modify cellular components through their interaction with a number of extracellular and intracellular proteins, including the receptor for AGEs (RAGE) (48, 49). In addition, AGEs can alter normal neuronal function, leading to oxidative stress and inflammation (50, 51). Clinical evidence indicate that AGEs and RAGE are increased in patients with diabetic neuropathy, whereas diabetic mice deficient for RAGE are protected from deficits of the peripheral nervous system in comparison with wild-type mice (50). Therapeutic strategies exist to reduce either the formation or the toxic effects of AGEs (48, 51). For instance, metformin reduces serum levels of AGEs in patients with T2D (52). Studies performed in diabetic mouse models also revealed that treatment with soluble RAGE or anti-RAGE protects from diabetic nephropathy by decreasing inflammatory signaling.
cascades (53, 54). Interestingly, AGEs can accumulate in nearly all tissues, including the liver. In particular, it was shown using noninvasive approaches in mice that AGE-modified albumins were rapidly captured by scavenger cells and accumulated within the liver (55). Therefore, increased AGEs could alter the normal liver function, which over a long period of time could lead to various disorders (55, 56). Further studies are necessary to better understand the link between increased protein glycation in liver and diabetic neuropathy.

**Inflammation**

Inflammation is likely to be the main contributing factor to hepatic diabetic neuropathy. Recent data indicates that sympathetic and vagal functional status are impaired independent of HbA1c levels in patients with T2D (57). This suggests that the pathogenesis of diabetic neuropathy may not involve increase blood glucose directly. Diabetes can cause neuritis (i.e., inflammation of peripheral nerves), suggesting that inflammation can play a role in the pathogenesis of diabetic autonomic neuropathy (58). Neuropathy of the sensory nerves has been associated with increased pro-inflammatory cytokines, including tumor necrosis factor α (TNF-α) (Fig. 1C) (59). Moreover, anti-inflammatory molecules are effective at reducing neuropathic pain, indicating that inflammation, whether it is a cause or a consequence of peripheral neuropathy, could participate in the pathogenesis of nerve damage (59). Evidence indicates that hepatic sympathetic neuropathy occurring under metabolic challenges is caused by pro-inflammatory cytokines. The expression and circulating levels of TNF-α were shown to correlate with the onset of liver sympathetic neuropathy (36). Moreover, an anti-TNF-α neutralizing antibody was sufficient at reverting the loss of sympathetic nerves in the liver caused by a HFD (36). Interestingly, authors showed

![Figure 1. Potential mechanisms contributing to hepatic diabetic neuropathy. A, The SAR pathway and oxidative stress. Hyperglycemia can promote sorbitol accumulation in cells, leading to oxidative stress. This in turn can lead to microvascular damages and neuropathy. B, Hyperglycemia-induced glycation. Glycation of proteins can alter their structure and function, leading to the production of AGEs. Through their action on RAGE, AGEs contribute to oxidative stress and inflammation. This results in alterations in neuronal functions and peripheral neuropathy. C, Inflammation. Neuropathy has been associated with increased pro-inflammatory cytokines. Abbreviations: AGEs, advanced glycation end products; RAGE, receptor for AGEs; SAR, sorbitol-aldose reductase; SORD, sorbitol dehydrogenase; TNF-α, tumor necrosis factor α.](image-url)
that liver macrophages expressing the marker F4/80 reside adjacent to sympathetic axons in the liver and that their co-culture with celiac ganglia neurons results in the destruction of the nerves in a TNF-α dependent manner (36). Together, these results suggest that anti-inflammatory drugs could be used as a treatment of diabetic liver neuropathy, an idea supported by accumulating evidence that insulin resistance and diabetes are tightly linked to inflammation (60). However, whether these effects on nerves are directly caused by the anti-inflammatory actions or secondary to metabolic improvement needs further investigation. Nevertheless, these data suggest that inflammation could impair the autonomic brain-liver communication.

**Sympathetic Overactivity**

As described in the previous sections, metabolic diseases can be associated with peripheral neuropathy. However, evidence also indicates that other forms of autonomic dysregulations also develop in obesity and T2D. Whether these dysregulations precede or participate in the development of neuropathies is unclear. Moreover, these dysregulations can be bidirectional and tissue dependent. For instance, George Bray’s MONA LISA (Most Obesities kNown Are Low In Sympathetic Activity) refers to the reduced sympathetic tone to adipose tissue often observed with obesity, which participates to the decrease in lipolysis (thus more lipid accumulation) and reduction in thermogenesis (thus less energy expenditure) (61). On the other hand, obesity-associated sympathetic overactivity to the kidney and vasculature is a well-known contributor to the pathophysiology of hypertension (62). Moreover, the enhanced sympathetic tone in hypertension is associated with insulin resistance and dyslipidemia (62). As for the liver, available evidence suggests that obesity and T2D are associated with increased sympathetic tone, which may participate, at least earlier in the pathology, in the development of hyperglycemia and dyslipidemia.

**Liver Sympathetic Overactivity Can Contribute to Hyperglycemia**

Many mechanisms can explain how metabolic diseases associate sympathetic overactivity can result in insulin resistance (62). Using the euglycemic insulin clamp technique in combination with tritiated glucose to evaluate the effect of adrenaline on tissue sensitivity to insulin, Deibert and DeFronzo reported that adrenaline inhibits the ability of insulin to suppress hepatic glucose production in human subjects (63). Importantly, this approach allowed them to avoid an adrenaline-induced fall in plasma insulin and adrenaline-induced hypoglycemia, to study the direct impact of adrenaline on liver metabolism. This study suggests that increased catecholamines during sympathetic overactivity may prevent the ability of insulin to suppress hepatic glucose production, contributing in turn to hyperglycemia. Adrenoceptors expressed on hepatocytes modulate several aspects of metabolism, including hepatic glucose production and fatty acid metabolism (64). This suggests that liver adrenoceptors could be involved in the pathogenesis of obesity and T2D. In fact, Deibert and DeFronzo have shown that the nonselective beta-adrenergic antagonist propranolol could prevent the effects of adrenaline on the liver (63), suggesting that a beta-adrenoceptor mediates the effects of the SNS on liver glucose production. However, recent transcriptomic data suggest that human hepatocytes express very low, if any, levels of beta-adrenoceptors, but high levels of alpha-adrenoceptors (65). Pharmacological evidence supports these data. For instance, treatment with alpha blockers improves insulin sensitivity and lowers both HbA1c and triglyceride levels in hypertensive patients with T2D (66-68) and moderately obese patients without diabetes (69). Evidence in rodents also indicates that alpha-adrenoceptors are likely to participate in the autonomic brain-liver communication. For instance, the use of phentolamine (a synthetic imidazoline with alpha-adrenergic antagonist activity), but not propranolol, was shown to abolish the increase in glucose production in rat livers (70, 71). Similar observations were made by Exton and colleagues, showing that adrenaline-induced the activity of the enzyme responsible for glycogenolysis was dependent of an alpha, but not a beta, adrenoceptor (72). It is therefore clear that sympathetic overactivity can drive hepatic glucose production and affect insulin sensitivity, but additional studies are needed to better define the receptors and mechanisms mediating these effects and whether their expression and activity are impaired in metabolic diseases. Species differences may also exist in terms of receptors involved and localization. Studies are also needed to better determine if alpha blockers hold significant potential, alone or in combination with antidiabetic drugs, to improve metabolic health. However, as the research progresses with drugs targeting adrenoceptors, one needs to consider the potential that catecholamine resistance may represent an obstacle using and developing molecules targeting liver adrenoceptors.

**Catecholamine Resistance**

Evidence indicate that chronic sympathetic overactivity can lead to catecholamine resistance (73). Catecholamine resistance refers to the inability of adrenaline or noradrenaline to induce a defined response. Just like insulin resistance, catecholamine resistance may result from
default adrenergic signaling but could also involve a reduction in the number or affinity of these receptors to catecholamine. Evaluation of catecholamine resistance has been widely documented in obese adipocytes. For instance, the lipolytic action of catecholamines is blunted in obesity (73). In this particular example, the resistance is defined as an inability of the catecholamines to induce a well-known, easy-to-measure parameter, that is the release of free fatty acids from the adipocyte. However, when it comes to the liver, what defines catecholamine resistance? As described in the previous paragraph, one easy readout could be the glucose output, with the prediction that obesity and T2D may blunt the ability of noradrenaline to stimulate hepatic glucose production. However, how can we conclude that liver catecholamine resistance exists in a context of neuropathy or sympathetic overactivity? These questions highlight the need of developing new strategies to define catecholamine resistance in hepatocytes, that could be applicable both in vitro and in vivo. Further studies are therefore warranted to define liver catecholamine resistance.

Does Sympathetic Overactivity Precede Liver Neuropathy in Metabolic Diseases?

The number of sympathetic axons was shown to be significantly reduced in the livers of mice challenged with a HFD for a long period of time, suggesting that obesity causes hepatic sympathetic neuropathy in the long term (36). However, another study has previously shown that increased hepatic sympathetic nerve activity mediates liver steatosis during diet-induced obesity (13). In particular, an increase in sympathetic outflow to the liver was associated with accumulation of triglycerides after 10 weeks of HFD. Pharmacological ablation of sympathetic nerves using 6-hydroxydopamine or phenol-based hepatic sympathetic nerve denervation prevented liver steatosis (13). Moreover, evidence from obese Zucker (fa/fa) rats indicate that surgical denervation of the sympathetic hepatic nerve lowers plasma triglycerides independent of changes in circulating free fatty acids and insulin or changes in food intake, suggesting that sympathetic hyperactivity may contribute to dyslipidemia in this model (74). However, these data need to be cautiously interpreted, as denervation can result in several secondary changes that may have been overlooked. Nevertheless, these observations are supported by evidence that overactivation of the SNS is implicated in a number of pathophysiological conditions that are associated with nonalcoholic fatty liver disease, such as hypertension and insulin resistance (15, 16). Together, these studies suggest that a bimodal response of the SNS during the progression of metabolic diseases exists. In particular, obesity and T2D may first lead to increased sympathetic outflow to the liver (compensation), followed by a progressive decrease in the number of hepatic sympathetic fibers (neuropathy) (Fig. 2). This would implicate that the

![Figure 2](image-url). Bimodal hypothesis of the autonomic control of liver during metabolic diseases. We hypothesize that obesity and type 2 diabetes may first lead to increased sympathetic outflow to the liver, followed by a progressive decrease in the number of hepatic sympathetic fibers and ultimately the development of hepatic neuropathy. Therefore, autonomic control of liver during metabolic diseases is a “moving target” and a better understanding the chronology of autonomic dysfunctions in the liver may help applying the right strategy at the right time. Preventing sympathetic overactivity early on may be a viable strategy to prevent the development of metabolic complications.
autonomic control of liver during metabolic diseases is a “moving target.” Additional studies are needed to test this possibility with important clinical implications. An important consideration for future studies is the inclusion of functional assessment of the SNS activity in addition to evaluation of morphological changes.

Conclusion
In this Mini-Review, we discussed the pathophysiological mechanisms that alter brain-liver communication in metabolic diseases. Many pathogenic mechanisms can lead to hepatic neuropathy, including hyperglycemia-induced increases in sorbitol synthesis and glycation, as well as inflammation. Moreover, obesity-associated sympathetic overactivity appears to precede liver neuropathy and could contribute to hyperglycemia and lead to catecholamine resistance. Based on the evidence from the available literature, we suggest that enhanced sympathetic outflow to the liver occurs early on during the development of obesity and diabetes, which is progressively followed by a decrease in the number of hepatic sympathetic fibers (Fig. 2). This highlights the importance of better understanding the chronology of autonomic dysfunctions in the liver in order to apply the right strategy at the right time. We believe that preventing sympathetic overactivity early on is a viable strategy to prevent metabolic complications. We also hope that the scientific community will make significant discoveries in autonomic pharmacology in the years to come, enabling prevention and treatment of diseases developing from miscommunication between the brain and peripheral organs.

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