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Review

The role of the autonomic nervous liver innervation in the control of energy metabolism

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ABSTRACT

Despite a longstanding research interest ever since the early work by Claude Bernard, the functional significance of autonomic liver innervation, either sympathetic or parasympathetic, is still ill defined. This scarcity of information not only holds for the brain control of hepatic metabolism, but also for the metabolic sensing function of the liver and the way in which this metabolic information from the liver affects the brain. Clinical information from the bedside suggests that successful human liver transplantation (implying a complete autonomic liver denervation) causes no life threatening metabolic derangements, at least in the absence of severe metabolic challenges such as hypoglycemia. However, from the benchside, data are accumulating that interference with the neuronal brain–liver connection does cause pronounced changes in liver metabolism. This review provides an extensive overview on how metabolic information is sensed by the liver, and how this information is processed via neuronal pathways to the brain. With this information the brain controls liver metabolism and that of other organs and tissues. We will pay special attention to the hypothalamic pathways involved in these liver–brain–liver circuits. At this stage, we still do not know the final destination and processing of the metabolic information that is transferred from the liver to the brain. On the other hand, in recent years, there has been a considerable increase in the understanding which brain areas are involved in the control of liver metabolism via its autonomic innervation. However, in view of the ever rising prevalence of type 2 diabetes, this potentially highly relevant knowledge is still by far too limited. Thus the autonomic innervation of the liver and its role in the control of metabolism needs our continued and devoted attention.

1. Introduction

The autonomic nervous system is the unconscious part of the peripheral nervous system and comprises the motor system for viscera, smooth muscles and exocrine glands. The scientific interest for the innervation of the liver by the autonomic nervous system and its function in the control of energy metabolism can be traced back to a time when the need to understand the pathophysiology of metabolic diseases like type 2 diabetes mellitus may have been less urgent than in our modern affluent society. The great French physiologist Claude Bernard was the first to discover and describe that the liver can store and release glucose, and he named this stored form of glucose glycogen. At that time in history the general assumption was that the body could not synthesize glucose de novo (gluconeogenesis). However, Claude Bernard believed that hepatic glucose production was under the control of autonomic nerves and carried out the earliest study on the autonomic innervation of the liver and glucose metabolism in 1848. He observed a decrease in hepatic glucose output after peripheral vagotomy, but failed to show increased glucose output by electrically stimulating the vagal nerves. He then tried to punch the floor of the fourth ventricle, i.e., the place of origin of the vagal nerves. The short-term "artificial diabetes" he induced in this way (the well-known piqûre diabetique) was not blocked by cutting the vagal nerves, but it could be blocked by transection of the spinal cord, i.e., the origin of the sympathetic nerves that innervate the liver. Although this earliest functional study did not mean he could distinguish the glucoregulatory function of the liver from that of other visceral organs, it was the first indication of a brain mechanism controlling peripheral glucose homeostasis and of the involvement of the autonomic nervous system. Despite this inspiring starting point, the role liver innervation plays in the control of energy metabolism is still not fully uncovered today, especially regarding metabolic sensing by the liver.

After insulin was discovered by Banting and Macleod in the 1920s, physiologists and biochemists focused their attention on the control of liver metabolism by hormones, and in subsequent years only little attention was paid to the involvement of neuronal signaling in liver metabolism. In the 1950s Mayer put forward the "glucostatic theory", the "lipostatic theory" and the "glucoreceptor" conception [1–3] as

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explanatory brain mechanisms involved in the control of feeding behavior and glucose metabolism. Although these theories renewed interest in neuronal sensing mechanisms involved in the control of liver function, the "glucostatic theory" itself was soon rejected based on experimental studies by others [4]. In the early sixties the existence of glucose-sensitive neurons in the ventromedial hypothalamus (VMH) and lateral hypothalamus (LH) was proven by Anand [5] and Oomura [6]. Russek then proposed the existence of glucose receptors in the liver [7]. Soon after, a change of vagal activity was recorded by Niijima upon glucose infusions into the portal vein [8].

The term "glucoreceptor" was gradually replaced by "glucose sensing". Glucokinase (hexokinase) (GK) [9] and glucose transporters (GLUT) [10,11] are considered to be the main molecular components of neuronal glucose sensing [12], while other mechanisms such as sodium/glucose cotransporter type 3 (SGLT3) [13] and twik1-related acid-sensitive K^+ channel subunit (TASK) 1 and 3 [14,15] could be also involved.

In contrast to glucose sensing, a mechanism for lipid sensing by the liver was strongly doubted at the beginning of last century. It was thought that, of the three macronutrients, only hydrophilic glucose and amino acids could enter the liver via the portal vein after absorption from the intestine into the mesenteric veins. Fatty acids were thought to be absorbed in the intestinal lymph and to enter the heart through the thoracic duct and the superior vena cava. Compared with other organs and tissues, the liver was thus thought to have only nutritional input via glucose and amino acids, but not via lipids. It was Frazer [16] who discovered that indeed neutral fat globules will only enter the systemic circulation, but that fatty acids do pass into the portal capillaries and enter the liver. Thereafter, short- and medium-chain fatty acids were confirmed to be transported into the portal vein [17,18], and this was later confirmed for long-chain fatty acids and triglycerides as well [19].

As was the case with glucose, lipid was proven to be a metabolic signal that can be sensed by vagal nerves as well [20]. More importantly, however, it became clear that the brain too, is an important metabolic sensing organ. Today, there is no doubt that the brain (especially the hypothalamus) and liver, as well as the gastrointestinal tract, can independently detect glucose, lipids and other metabolic information. The relative importance, however, of each of these components separately has only recently become the subject of both animal and human studies.

This review will start with an overview of the anatomical and physiological approaches used to identify the pattern of autonomic liver innervation. Then we describe the different roles played by the spinal and vagal afferents and efferents in liver metabolic sensing as well as in liver glucose and lipid production. The review ends with a description of the different levels of integration of metabolic information followed by a discussion of the current status of the known connections and missing links between the brain and liver in the control of energy metabolism.

2. Neuroanatomy of the hepatic innervation

The liver is innervated by sympathetic and parasympathetic nerves, both containing afferent as well as efferent fibers. The sympathetic splanchnic nerves innervating the liver originate from neurons in the celiac and superior mesenteric ganglia, which are innervated by pre-ganglionic neurons located in the intermediolateral column of the spinal cord (T7–T12). The parasympathetic nerves innervating the liver originate from pre-ganglionic neurons in the dorsal motor nucleus of the vagus (DMV) located in the dorsal brainstem. Unlike other visceral organs, no clear intrahepatic postganglionic neurons have been identified [21].

The distribution of sympathetic and parasympathetic nerves in the liver is markedly species-dependent. Histochemical and immunochemical studies have been performed using a variety of markers for autonomic liver innervation. For instance, vasoactive intestinal peptide (VIP), tyrosine hydroxylase (TH) and neuropeptide Y (NPY) have been used as markers for sympathetic efferent fibers [22,23]. In addition, α-adrenergic and β-adrenergic receptors for the sympathetic neurotransmitter noradrenaline are present in the hepatic artery and portal vein [24,25]. On the other hand, acetylcholinesterase (AChE) and vesicular acetylcholine transporter (VAChT) [26], located in parasympathetic postganglionic cells [21], tend to be the vagal efferent markers of choice [27,28]. Calcitonin gene-related peptide (CGRP) has been used as a spinal afferent marker, since the nodose ganglia express much less CGRP than the dorsal root ganglia (DRG) [29]. Finally, substance P (SP) has been used as a marker for both vagal and spinal afferents [30,31]. Different combinations of these markers have been applied to hepatic tissues of human, monkey, dog, rabbit, rat, hamster, guinea pig, mouse, carp, bullfrog, and turtle. Some results are not firmly established as they could not be repeated in later studies, but this is probably due to non-specific technical limitations, such as those encountered using earlier histochemical methods for the demonstration of acetylcholinesterase (AChE) in rat parenchyma [32]. Generally, in most of the examined species, sympathetic and parasympathetic markers (either neurotransmitters or synthesizing enzymes) could be detected in the hepatic artery, the portal vein region and the area around the bile ducts. Differences mainly exist in the interlobular area and parenchyma. In several studies, TH and NPY showed co-localization, and both kinds of terminals have been observed in the connective tissue of the interlobular septum and parenchyma from human, monkey, and guinea pig, but not from rat, hamster and mouse. In rabbit liver parenchyma, TH is expressed without co-localization of NPY. AChE fibers were not found in human liver parenchyma, or in any other species studied [22,23,33–37]. Although NPY is sometimes also considered a neurotransmitter for postganglionic parasympathetic nerves [38,39], no study has shown co-localization of NPY and AChE in liver tissue. A major difference between sympathetic innervation of humans and the most commonly used animal models, i.e., rats and mice, is that the latter have no clear parenchymal sympathetic innervation, while in human liver (also in guinea pig), sympathetic noradrenaline-immunoreactive fibers penetrate deep into the lobule to end of hepatocytes [40]. However, the functionality of the sympathetic efferent innervation of species with parenchymal sympathetic innervation could still correspond to that of species without [41] as information from aminergic and peptidergic nerve terminals can be relayed electrically to individual cells by structures such as cell-to-cell connecting gap junctions [42,43]. Indeed, signal propagation through gap junctions, i.e., via electrotonic coupling, can compensate for the sparse direct inputs to the hepatocytes, especially with respect to sympathetic signal transduction [43,44]. Also, there is considerable homology between the rat and human liver gap junctions [45]. This brought about the idea of additional functions of the gap junctions, such as the relay of hormonal signals from the periportal area to the hepatocytes [46]. Furthermore, the sympathetic signal may be propagated via the release of prostaglandins from Ito cells [47,48] (the Ito or stellate cells are located in the space of Disse, which is separated from the lumen by the fenestrated endothelium, while Kupffer cell and dendritic cell face the sinusoidal lumen [49]).

Only few approaches are available to investigate and differentiate the intrahepatic neuroanatomy of the autonomic innervation, such as neuronal tracing or neuronal denervation in combination with physiological interventions. In rats, liver vagal afferents mainly ascend to the left nodose ganglion [50,51], with the axon processes from the nodose ganglion projecting to the nucleus of the solitary tract (NTS). Sympathetic afferents from the liver enter the dorsal root ganglion (DRG), with the DRG axons terminating in the dorsal horn of the spinal cord [21]. The remarkable lack of either vagal efferent or afferent innervation of liver parenchyma as indicated by the (immuno)histochemical studies was confirmed by neuronal tracing studies in rats, as no anterograde labeling was found in the parenchymal liver tissue from anterograde tracer injections in either

the nodose ganglion or the dorsal motor nuclei [50]. In addition, it was reported that the hepatic vagal nerve is only a sub-branch from the common hepatic branch that terminates in the upper duodenum, pancreas, pyloric sphincter, and antral stomach [50] (Fig. 1). This observation was not in line with the assumption that vagal nerve fibers derived from the common hepatic branch and the periarterial plexus of the hepatic artery proper exclusively innervate the liver. The anatomical observation that the gastroduodenal vagal branch joins the hepatic vagal branch to form the so-called "common hepatic branch" complicates the interpretation of data from experiments in which the common hepatic vagal branch is disrupted or its neural activity is recorded. This is well evidenced by the separation of the gastroduodenal branch from the common hepatic branch by means of denervation, as it turns out that an electrical signal of the common hepatic branch that is sensitive to serotonin is blocked by transection of the gastroduodenal branch [52]. In other words, stimulation of the intestinal tract may affect recordings of the hepatic branch, and "hepatic parasympathetic denervation" will in fact denervate the common hepatic branch.

Retrograde tracing from liver parenchyma close to the hilus (i.e., where all nerve bundles enter the liver) only results in a limited amount of DRG labeling from Th7–11, indicating that only very few DRG afferents innervate the hepatoportal system [21].

As just mentioned, the classic anterograde and retrograde tracers are only able to reveal the location of first order sensory and motor neurons. The location of second-order motor neurons in the central nervous system can be revealed with the multi-synaptic viral tracing technique. After injection of the pseudo-rabies virus in rat liver, several hypothalamic areas are highlighted (in addition to the brainstem) as containing second-order neurons, such as the lateral hypothalamus (LH), the paraventricular nucleus (PVN) and the retrochiasmatic area [53]. Combining the viral tracing technique with selective denervations of either sympathetic or parasympathetic liver innervation clearly demonstrated the presence of separate populations of, respectively, parasympathetic and sympathetic motor neurons, both first and second [54].

Human liver nerve fibers show a strong plasticity in their distribution. Pathological challenges related to autonomic hyperactivity, such as (pre)cirrhosis and noncirrhotic portal hypertension, cause a decreased parenchymal innervation [55], whereas nerves are proliferating in the portal region [56,57] as indicated by an increased number of NPY fibers [58]. Whether this redistribution is related to a change in liver metabolism is not clear.

Summarizing it is evident that, despite the clear evidence for both a sympathetic and parasympathetic innervation of the liver, many details still have to be filled in and a lot is still to be learned about the autonomic innervation of the liver. Technical limitations still prevent a clear mapping of some parts of the liver neuronal network, such as, for instance, the location of parasympathetic postganglionic cell bodies. This lack of more detailed knowledge is a major obstacle for functional studies on the role of the autonomic innervation in the control of liver metabolism as they very much depend on the existing knowledge on its neuroanatomy. Also the difficulty of separating the sensory and motor branches still provides a profound obstacle to differentiate the various functional aspects. Despite these neuroanatomical difficulties, the evidence presented below clearly shows that the liver is a powerful metabolic sensor, and a crucial link in the brain control of energy metabolism.

3. Afferent pathways and metabolic sensing

All macronutrients absorbed from intestinal digestion will be "sensed" first by the gastrointestinal tract [59], before entering the liver via the portal vein. Cephalic, postprandial and post-absorptive gastrointestinal secretions will also reach the liver via the portal vein. With the large variety of chemoreceptors located in the hepatoportal system, it is more than likely that these metabolic signals will also be sensed by the liver and reported to the brain. For a long time,

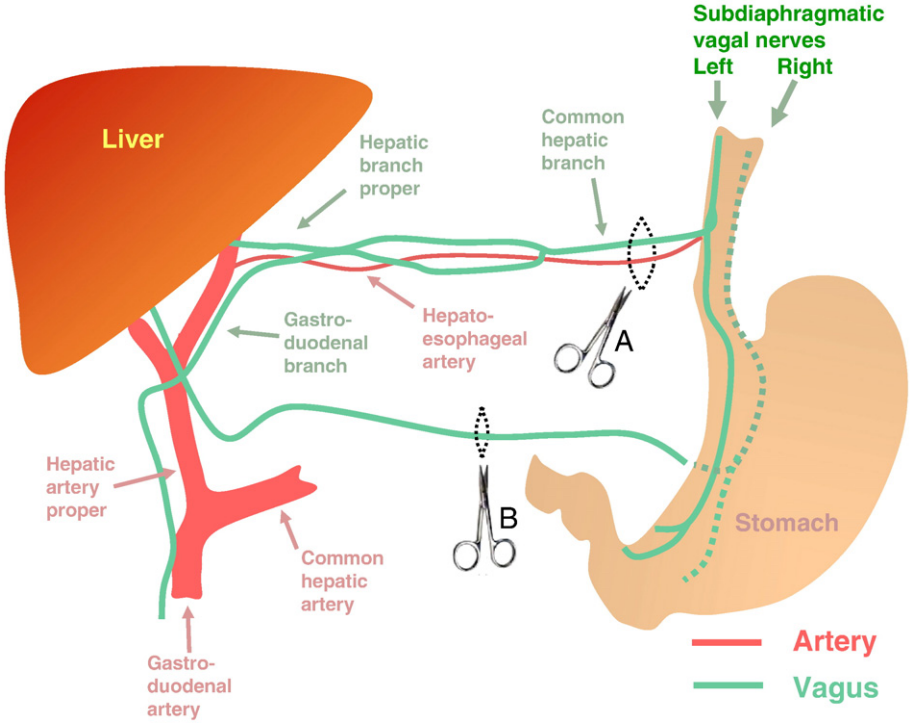

Fig. 1. An illustration of the relationship between the hepatic common vagal branch, the hepatic vagal branch proper and the gastroduodenal vagal branch (which terminates further up in the upper duodenum, pancreas, pyloric sphincter, and antral stomach) (partly adapted from [21,282]). Hepatic parasympathetic denervation includes denervation of the left branch (site A) and the right branch (site B) originating from the right posterior subdiaphragmatic vagal nerve (the nerve branch running behind the stomach is illustrated by a dotted line). It is not feasible to selectively remove the hepatic branch proper and therefore left branch denervation is routinely performed at the common hepatic branch and not by transecting the hepatic branch proper.

metabolic sensing by the liver (or hepatoportal system) was therefore considered to be the primary source of information for the brain to regulate metabolism. However, in the last two decades, the prominent role of liver metabolic sensing has been challenged, since it has become clear that the brain is able to sense metabolic information from many more sources than just the liver. For instance, the presence of insulin [60], leptin [61,62], adiponectin [63], ghrelin [64] and neuropeptide Y [65] receptors in the brain makes it very likely that the brain can also sense metabolic information coming from organs such as the pancreas, adipose tissue, stomach and gut directly. The liver releases a number of factors that function as paracrine and endocrine regulators of glucose and lipid metabolism, such as adropin [66] and fibroblast growth factor 21 (FGF21) [67,68]. Remarkably, to date, none of these circulating factors have been reported to convey metabolic information from the liver to the brain. Therefore, the brain and liver are probably specialized in collecting different types of information, and this information is converging into integration centers, such as the nucleus of the solitary tract (NTS) in the hindbrain [69] and the paraventricular nucleus (PVN) in the hypothalamus [70]. The studies on glucose and lipid sensing provide some of the best examples to illustrate this complex network. In addition, a different type of metabolic sensing is relayed within the afferent fibers from intrahepatic metabolic sensors such as the liver X receptor (LXR) [71] and the carbohydrate response element binding protein (ChREBP) [72], as these intrahepatic sensors mainly work as coordinators between glucose sensing and lipid synthesis at the intracellular level. Recently, the peptide adropin, secreted by the liver and brain, was identified as a downstream signal regulated by LXR. Adropin mainly functions as a paracrine factor, but it also works as an endocrine factor to regulate glucose homeostasis and lipid metabolism [66]. Whether adropin acts locally on its targets or via an autonomic neuronal connection has not been elucidated yet. Finally, there is the hepatic insulin sensitizing substance (HISS), a substance released from the liver by parasympathetic stimulation, but not yet identified at the molecular level, that seems to be involved in the remote control of skeletal muscle glucose uptake [73].

3.1. Glucose sensing

The brain is unable to either synthesize or store the amount of glucose required for its normal cellular function, therefore it accurately keeps track of the whole process of glucose metabolism, from the initial stages of glucose intake, through absorption, storage, production and ultimately utilization. The mechanism of glucose detection, or glucose sensing, takes place in different areas of the brain [5,6,12,74–76], as well as in the periphery. Moreover, in the brain, not only neurons can detect glucose levels, but glial cells expressing glucose transporter type 2 (glut2) are also involved, especially in the hypoglycemia-stimulated glucagon secretion mechanism [77,78]. The primary places of peripheral glucose sensing are located in the taste bud cells [79], the intestinal lumen [80,81], the carotid body [82], and the best studied locus, the hepatoportal area [83–86]. For an up to date review on this issue the reader is referred to the recent review by Watts and Donovan [87].

In the earliest study of liver glucose sensing, using fairly high concentrations of glucose, Niijima [8] proposed three different locations for the "glucose receptor": 1) the wall of the portal vein, 2) the parenchyma of the liver, and 3) the wall of the hepatic vein. Nowadays it is generally accepted that glucosensors are mainly located in the portal area [83–85], which is innervated by both sympathetic and vagal afferents [88,89]. The functional meaning of glucosensing by these two types of afferents is still under investigation. High concentrations of glucose presented in the portal vein by a positive porto-arterial glucose gradient are mainly sensed by the vagus nerve and inhibit its activity [8]. The signal transduction from portal vein glucose infusion to the NTS can be blocked by hepatic vagotomy [90,91].

One hypothesis is that hepatic glucosensors participate in the control of food intake, by sensing the flow of digested glucose when its concentration is high. However, total liver denervation does not seem to affect feeding behavior in any significant way [92,93]. Possibly the portal–peripheral glucose gradient alone is not sufficient to inhibit feeding, but when joined with brain glucose sensing it may be able to reduce food intake. On the other hand, decreasing the portal–peripheral glucose gradient will activate vagal afferent activity [94], and this activation has been proven to be essential for the initiation of food intake [86,95–97]. Therefore, in the control of feeding behavior, hepatic glucosensing might play a more important role in triggering the initiation of feeding than in its termination.

In more recent studies, hypoglycemia sensed by the portal vein has received increased attention especially in the setting of insulin therapy in view of its essential role in tight glycemic control in diabetes patients. The occurrence of frequent and severe hypoglycemia may partially originate from defective glucose counterregulation [98]. Hypoglycemia detection is not mediated by vagal afferents [99,100], but does involve the capsaicin-sensitive primary spinal afferent nerves [101]. It has also been suggested that portal vein glucose sensors only play a key role in the response to slow-onset hypoglycemia [102], but that the primary place of detection shifts to other loci such as the brain when hypoglycemia develops rapidly [103,104].

In animal studies, a selective sympathetic or parasympathetic hepatic denervation is not sufficient to prevent the counterregulatory response resulting from an insulin-induced hypoglycemia [100,105,106]. On the other hand, contradictory results were found when a total denervation was applied [100,105], and apparently the results are very much dependent on the denervation method.

The hypoglycemia counterregulatory response has also been investigated in patients who received a liver transplantation. In this "model", all direct neural connections but not the neurohumoral factors are lacking. In clinical studies carefully excluding bias from immunosuppressive treatment such as prednisone [107] data from chronic uveitis patients are compared with data from liver transplant patients. During a hypoglycemic clamp, liver transplanted patients appeared to have impaired hypoglycemic counterregulation as shown by less epinephrine and a cortisol release and a blunt recovery of endogenous glucose production (EGP) to basal levels [108]. These defects indicate that neuronal inputs from liver to brain (and/or brain to liver) are important to elicit the appropriate hypoglycemic counterregulation. The exact intrahepatic mechanism of glucose sensing is not clear yet, but it has similarities with the pancreatic β-cells, as it needs activation of the glucagon-like peptide-1 (GLP-1) receptor [109–114], and is GLUT-2 dependent [115].

3.2. Lipid sensing

Although normal feeding behavior does not require intact liver innervation, overingestion of lipids can affect food intake through the autonomic innervation of the liver. Experimentally administered free fatty acids (FFAs) in the small intestine can be directly transported to the portal vein to enter the liver. Gastrointestinal primary sensory nerves have been reported to be involved in mediating the suppressive effect of intestinal lipid on feeding behavior [116,117]. Further studies specifically differentiating general abdominal vagotomy from hepatic vagotomy suggested that the hepatic vagus has a major involvement in this mechanism [118]. Hepatic portal infusions of lipids significantly increase hepatic vagal afferent activity [20]. The inhibitory effect on feeding behavior induced by hepatic lipid sensing has also been confirmed under diabetic conditions in experimental animals. A high-fat diet normalizes food intake in STZ-diabetic rats [119–121], but common branch hepatic vagotomy can completely

block both the fat-induced decrease in caloric intake as well as normalize the increased hypothalamic NPY and CRF mRNA expression [120,122].

Still, in some studies, the inhibitory effects of FFAs on food intake cannot be simply blocked by subdiaphragmatic bilateral vagotomy [123]. Thus, in addition to FFA, high fat diets might contain information that affects feeding. Alternatively, FFAs may be able to manipulate feeding via other mechanisms such as the hypothalamus [124].

Under physiological conditions not only food-derived lipids will enter the liver. Fatty acids are also the metabolically most important product of adipose tissue lipolysis, and especially triglycerides stored in the abdominal adipose tissue will release FFAs into the portal vein. The hepatoportal vagal sensing of lipids may therefore not only be important for the "reflexive" regulation of feeding behavior, but it may also play a role in the pathophysiology of metabolic abnormalities such as hepatic insulin resistance. Physiologically, abdominal adipose tissue only contributes a small part of the total amount of FFAs entering the portal vein, but an increased release of FFAs from the adipose tissue can be triggered by stress, anger, frustration, and other factors, such as smoking [125]. Elevated levels of FFAs in the portal vein have been suggested to be the cause of insulin resistance, as they might directly reduce insulin clearance by the liver [126–128]. Furthermore, since the anti-lipolytic effect of insulin on omental adipose tissue is minor, due to the low insulin receptor number [129], insulin resistance will result in a further increase of the amount of FFAs released. The overloading of the liver by FFAs may finally cause an increased synthesis of triglycerides and an excess secretion of very low density lipoprotein (VLDL).

As with glucose sensing, a specific lipid receptor has not yet been identified, but lipids are natural ligands for the peroxisome-proliferator-activated receptors (PPARs) [130] that are also involved in glucose metabolism. A knock-out of the lipogenic enzyme fatty acid synthase (FAS) will not only induce hypoglycemia and a fatty liver, but also a defective expression of PPARα. Furthermore, PPARα deficiency prevents glucose intolerance caused by diet-induced obesity [131,132]. Unlike glucose sensing, splanchnic nerve afferent activity is not affected by jejunal lipid administration [118], and no study so far has shown spinal afferent responses to any other kind of adiposity information.

3.3. Protein sensing

Protein digestion will elevate portal vein amino acid levels and high protein feeding has been reported to stimulate glucagon release independently of amino acids blood levels [133]. It is hard to say whether this is due to a special portal amino acid sensor, because surprisingly, only few studies on hepatoportal protein sensing are available. A high protein diet is able to inhibit food intake [134,135] but this effect might not be due to a direct hepatoportal protein sensing mechanism, but rather to the stimulation of intestinal gluconeogenesis [136–138] which may consequently activate portal glucose sensing [139]. This high glucose loading may then eventually result in inhibited feeding.

3.4. Hormone sensing

Not only nutrition itself can be sensed by the liver, but the nutrition and absorption process will elicit the release of a variety of hormones (so-called incretins), that can also be sensed by the liver. Glucagon-like peptide-1 (GLP-1) is one of the best studied signals in this class of hormones.

Besides its brain origin and its involvement in the control of food intake by a central mechanism [140,141], GLP-1 is also secreted from the intestines during meal absorption. Its stimulatory effect on insulin secretion and its depressive effect on glucagon secretion implicate a remote control on the pancreas [142,143]. Because of its low postprandial plasma levels and its rapid degradation, the action of GLP-1 is probably close to its site of release [144]. The action of GLP-1 most likely also involves a neuronal pathway. Indeed, GLP-1 receptors are expressed in the hepatoportal area [145]. Infusion of a truncated form of GLP-1(7-36)amide (tGLP-I) into the portal vein increases hepatic vagal afferent activity and pancreatic vagal efferent activity [113], while it augments glucose-stimulated insulin secretion [146]. Peripheral GLP-1 is also able to influence feeding behavior. Its effects on meal size are mediated by the vagal nerve, but this effect does not involve the hepatoportal mechanism [147], which we will discuss later.

The brain has been proven to be the main sensor of the adipokine leptin, affecting hepatic vagal afferent activity directly in a dose-dependent manner, with low doses inhibiting its activity and high doses increasing it. In addition, the activity of glucose-sensitive units is inhibited by low concentrations of leptin [148]. The gastrointestinal peptide cholecystokinin (CCK) released from the duodenal mucosa also has satiety effects, which are mediated by the gastric branch of the vagus [149]. CCK can be sensed by hepatoportal regional terminals [52], but whether its inhibitory effect on feeding is mediated by the hepatoportal vagal branch or via the gastric vagal branch is not clear. The fact that lesions of the termination centers of the common vagal afferents, i.e., area postrema and NTS, do not impair the satiety induced by CCK [150], further complicates the understanding of the central processing of peripheral CCK information. Portal infusion of somatostatin, yet another one of the gastroenteropancreatic hormones, also increases hepatic vagal afferent activity [151]. How this signal is processed further, within the brain, is not yet known.

The inhibitory effect of illness on feeding activity is thought to be mediated by inflammatory factors [152]. The cytokine interleukin-1 (IL-1) released during immune activation, has been studied in great detail. Intraperitoneal administration of IL-1β inhibits food intake [153], and this effect is proposed to involve hepatic vagal sensing since its afferent activity is increased by IL-1β stimulation [154]. Peripheral administration of IL-1α has similar anorexic effects [155]. However, hepatic vagotomy is unable to block this effect [156].

In conclusion, the contribution of metabolic sensing in the liver to the overall whole body energy balancing network is still under discussion. Unlike the brain, where the glucose concentration is sensed by glucose excitatory and inhibitory neurons (and glia), in the liver the glucose concentration is more likely to be monitored by the sympathetic and parasympathetic nerves. The glucose sensing mechanisms in the brain and liver clearly interact, but many details still need further clarification. Unfortunately, very little is still known about the cellular mechanism of glucose sensing in the liver.

4. Efferent pathway and the control of hepatic metabolism

4.1. Neuronal signals in control of liver glucose and lipid metabolism

After the initial findings of Bernard, numerous efforts have been made to understand in more detail the brain mechanisms responsible for the control of liver metabolism, be it with some delay. First of all, Bernard's findings on the control of liver glucose output by the autonomic nerves were confirmed and extended. For instance, liver glycogen content can be changed by neuronal inputs independent of influences from circulating glucoregulatory hormones, such as the catecholamines, insulin and glucagon. Follow-up studies focused on specific brain–liver connections, such as the information from different brain regions and their output pathways to the liver via specific autonomic nerves.

Early studies often used surgical removal of other metabolic organs or a total isolation of the liver. For instance, it was shown that in adrenalectomized and/or pancreatectomized animals, electrical stimulation of the splanchnic nerve decreases liver glycogen content and causes an increased release of glucose by increasing the activity of the liver glycogen phosphorylase and glucose-6-phosphatase enzymes [157,158], as well as a partial inactivation of phosphorylase

phosphatase activity [159]. Stimulation of the vagus nerve, alternatively, accelerates glycogen synthesis, and this effect could be completely counteracted by a simultaneous stimulation of the splanchnic nerve [160,161]. Later on, the independence of this neuronal pathway in the control of liver glucose production was also confirmed in an eviscerated animal model. In these experiments the authors showed that the reduction of blood glucose concentrations induced by insulin administration to the brain (via the carotid artery) was conserved after a total pancreatectomy together with the removal of the entire gastrointestinal tract and the spleen [162]. Recently, the original data on the inhibitory effects of central insulin on plasma glucose concentrations were confirmed when insulin was applied directly into the cerebral ventricle. In addition, it was shown that the inhibitory effect of central insulin on hepatic glucose production could be blocked by both hepatic vagotomy and sympathectomy, and that this central insulin effect only needs vagal efferents (not afferents) without affecting glucose uptake [163,164]. Very recently, it became clear that the vagal efferents to the liver are vital for the CCK signal generated in the gut to regulate hepatic glucose production and maintain glucose homeostasis. In this study, it was shown that the intraduodenal administration of CCK-8 can enhance hepatic insulin sensitivity and inhibit glucose production, and that these effects can be negated by hepatic vagotomy [165].

Lipid metabolism in the liver mainly includes the synthesis and secretion of VLDL, ketone bodies and fatty acid oxidation. Reducing liver noradrenaline by phenol-induced hepatic sympathetic denervation can decrease carnitine palmitoyltransferase (CPT), which is responsible for transferring long-chain fatty acid into the mitochondria [166]. The hepatic sympathetic input is also involved in regulating the secretion of apoB-containing lipoproteins, including VLDL [167]. In the perfused liver model, noradrenaline is able to inhibit the secretion of triglyceride and apoB as well as the release of VLDL at a post-transcriptional level [168,169]. In line with this, hepatic sympathetic denervation results in lower VLDL secretion, and higher concentrations of plasma cholesterol and VLDL-cholesterol [170]. The sympathetic innervation to the liver also influences ketone body metabolism. In the perfused liver model, sympathetic stimulation inhibits hepatic ketogenesis [171], resulting in a reduced ketone body output from the liver [172].

Perfusion of isolated liver has also been used to highlight the importance of the autonomic innervation of the liver and eliminate the possibility of extra-liver humoral inputs. In the perfusion model, splanchnic nerve stimulation caused an increased glucose and lactate output, whereas decreased urea, glutamine formation and ketone body production were observed [173,174]. These effects mainly involved activation of the α1-adrenergic receptors [175], and to a much lesser degree that of the β-receptors [176].

However, the physiological significance of the sympathetic innervation for hepatic glucose production is constantly being questioned. For instance, in systemic α1-adrenergic receptors deficient mice higher liver glycogen content was found together with a higher parasympathetic tone [177]. However, blocking the portal α1 and β-receptors during heavy exercise does not change the hepatic glucose production [178].

In the perfusion model, effects of neuronal manipulation on liver hemodynamics are inevitable. For instance, acetylcholine (Ach) applied into such an isolated model causes vasoconstriction and a reduction of blood flow and oxygen supply to the liver [179]. However, the early liver perfusion studies provided convincing evidence that the metabolic changes observed in the liver were not caused by hemodynamic changes in the liver or an overflow of noradrenalin into the hepatic vein [180,181].

4.2. Brain areas involved in liver control of glucose metabolism

Stimulation of several brain areas has been shown to induce similar changes in liver glucose metabolism as produced by direct stimulation of sympathetic or parasympathetic nerves. These brain areas are either proposed or proven to be able to affect liver glucose metabolism via their effect on autonomic neuronal output. For instance, electrical stimulation of the VMH causes an increased activity of the liver gluconeogenic enzyme phosphoenolpyruvate carboxykinase (PEPCK), and a marked suppression of hepatic pyruvate kinase (PK) activity, a key glycolytic enzyme [182]. These responses could not be abolished by adrenalectomy [183]. Stimulation of the LH, on the other hand, resulted in a decrease in PEPCK activity but did not alter PK activity [182]. Physiologically, it seems that cholinergic, but not noradrenergic, dopaminergic or serotonergic receptors in the LH are selectively involved in the stimulation of liver glycogen synthesis [184]. These early proposals for putative direct neuronal pathways were only recently supported by evidence from more detailed studies on the effects of brain insulin signaling on liver glucose metabolism. Brain insulin signaling inhibits liver gluconeogenesis (GNG) via neurons in the mediobasal hypothalamus that contain ATP-sensitive potassium (KATP) channels [185], an effect that can be largely blocked by hepatic vagotomy [163], but also involves NPY signaling to sympathetic pre-autonomic neurons [164].

Electrical stimulation of the suprachiasmatic nucleus (SCN) has also been reported to induce hyperglycemia [186]. This hyperglycemia might involve both direct hepatic and indirect (i.e., pancreatic) stimulatory effects on glycogenolysis [187]. Blocking the GABA-containing projections from the SCN to the PVN by bicuculline also induces hyperglycemia, and this hyperglycemia could be eliminated by hepatic sympathetic but not parasympathetic denervation [54]. The autonomic innervation of the liver is also involved in the hepatic insulin resistance and in increased hepatic glucose production induced by thyrotoxicosis, again an effect that seems to be mediated via a PVN mechanism and is independent of circulating glucoregulatory hormones, including the thyroid hormone itself [188,189]. Among the aforementioned hypothalamic peptidergic systems, NPY is well defined as a target of several circulating factors, due to its location in the arcuate nucleus (ARC), i.e., the “metabolic window of the brain”. For instance, the adipokine resistin can modulate lipid metabolism and increase glucose production via its action on NPY neurons [190–192]. Considering the well-established role of NPY in the control of hepatic insulin sensitivity via the hepatic sympathetic innervation [164,193], it is very likely that autonomic nerves will also mediate the central effects of resistin on liver metabolism. The involvement of NPY and other hypothalamic neuropeptides in the control of glucose homeostasis will be discussed in more detail in the next paragraph.

Virtually nothing is known about brain areas that are in control of hepatic lipid metabolism. Two recent papers have described effects of the i.c.v. administration of glucose and NPY on hepatic lipid metabolism [193,194], but no information is available about the possible location of these effects.

4.3. Hypothalamic neuropeptides involved in the control of liver glucose metabolism

4.3.1. Neuropeptide Y (NPY)

Best known among the hypothalamic neuropeptidergic networks are the NPY-containing neurons in the ARC with their projections to several hypothalamic brain areas including the PVN. The first report on the glucoregulatory effects of the hypothalamic NPY system appeared in the mid nineties when it was shown that i.c.v. administration of NPY increases endogenous glucose production in rats, probably by decreasing hepatic insulin sensitivity [195,196]. Later on these results were confirmed in mice [193]. In view of the inhibitory effects of hypothalamic insulin receptors on hepatic glucose production [185,197], the abundant expression of insulin receptors in the ARC [198], the inhibitory effect of insulin on NPY neuronal activity [199], and the effects of i.c.v. NPY on sympathetic activity [200–202],

studies in our group by combining the euglycemic–hyperinsulinemic clamp technique with the i.c.v. administration of NPY, and hepatic sympathetic-, parasympathetic- and sham-denervated in rats, confirmed once again that i.c.v. NPY is able to block (partially) the inhibitory effects of hyperinsulinemia on hepatic glucose production, but it also showed that a specific denervation of hepatic sympathetic nerves blocks the effect of NPY. Therefore, the brain-mediated inhibitory effect of insulin on hepatic glucose production is probably effectuated via an inhibition of NPY neuronal activity in the ARC. Subsequently, the resulting diminished release of NPY will decrease the stimulatory input to the sympathetic pre-autonomic neurons in the PVN and thus reduce the sympathetic stimulation of hepatic glucose production. The results of Pocai et al. [163], however, show that also the parasympathetic innervation of the liver is involved in the inhibitory effect of insulin on hepatic glucose production. This means that in addition to the effect of NPY on the sympathetic pre-autonomic neurons there is probably another neurotransmitter that is responsible for the transmission of insulin's effects in the ARC to the parasympathetic pre-autonomic neurons in the PVN. Moreover, the effects of NPY also seem to be specific for glucose production as in none of the above experiments was there a significant effect on whole body glucose disposal.

4.3.2. Pro-opiomelanocortin (POMC)

Next to the orexigenic NPY/AGRP neurons, the ARC also contains a population of anorexigenic POMC/CART-containing neurons. The most important POMC-derived peptide with respect to feeding and metabolism is alpha-MSH. The antagonistic function of the NPY/AGRP and POMC/CART cell populations is most clearly illustrated by the fact that AGRP acts as an endogenous antagonist of the melanocortin receptors 3 and 4 [203]. The antagonizing mechanism of these neuropeptides are extremely important to adapt the hypothalamic–pituitary–thyroid (HPT) axis to the prevailing food/energy status, i.e., the fasting-induced suppression of TRH mRNA in the PVN needs the reduction in alpha-MSH and the increase in AGRP [204]. Surprisingly, this antagonistic cell population does not seem to be involved in the inhibitory effect of hypothalamic insulin on glucose production, as co-administration of a melanocortin antagonist failed to block the decrease in glucose production induced by central insulin [205]. Blocking alpha-MSH signaling via i.c.v. infusion of the melanocortin 3/4 receptor (MC3R/MC4R) antagonist SHU9119 has no effects on glucose metabolism, but i.c.v. infusion of alpha-MSH itself has a clear stimulatory effect on glucose production via GNG which can be antagonized by SHU9119. In the liver, the stimulation of GNG is confirmed by the increased expression of glucose 6-phosphatase (G6Pase) and PEPCK. In addition, all these central manipulations had no effects on peripheral glucose uptake. It has been proposed that the hypothalamic MC3R/MC4R signaling pathway mediates the effects of systemic leptin on glucose production. Central administration of leptin has been proven to be involved in liver GNG regulation, by redistribution of intrahepatic glucose fluxes, in which GNG is increased and glycogenolysis was suppressed. However, unlike the central action of insulin to inhibit glucose production [185], this redistribution action of leptin does not change total glucose production by the liver [206,207]. Although systemic leptin alone did not alter hepatic insulin sensitivity, it can enhance the hepatic insulin sensitivity by the i.c.v. co-infusion of SHU9119 [205]. Indeed, just like insulin, also the effects of systemic leptin on glucose production are mediated via a hypothalamic mechanism. Recently, it was nicely shown that the adenoviral-induced expression of leptin receptors in the ARC of leptin receptor knock-out animals improves peripheral insulin sensitivity via enhanced suppression of glucose production [208]. The ARC-induced expression of the leptin receptor was associated with a reduced hepatic expression of G6Pase and PEPCK, but again, no significant changes in the insulin-stimulated whole body glucose utilization were apparent, which is different from the leptin action in the VMH on stimulating glucose uptake via an insulin-independent way [209]. Moreover, the effects of hypothalamic leptin signaling on hepatic insulin sensitivity could be blocked by a selective hepatic vagotomy, providing further supportive evidence for the idea that ARC projections to pre-autonomic neurons (in the PVN) are important for the transmission of the effect of leptin on glucose production.

4.3.3. Orexin

The neuropeptides orexin-A and orexin-B (also known as hypocretin-1 and hypocretin-2) were initially identified as the endogenous ligands for orphan receptors involved in the pathogenesis of narcolepsy [210,211]. They were recognized as regulators of feeding behavior and energy metabolism because of the exclusive localization of their cell bodies in the lateral hypothalamus (LH), the induction of feeding upon their i.c.v. administration, their responsiveness to peripheral metabolic cues such as leptin and glucose, and the metabolic phenotype of the knock-out animals. More recent studies suggest that the orexin system is particularly important for the maintenance of wakefulness. However, recent data from our group also clearly revitalize the metabolic function of the orexin system. We showed that an increased availability of orexin in the central nervous system, either by i.c.v. infusion, or by local activation via removal of GABA inhibition, increases plasma glucose concentrations through an increase in hepatic glucose production. As with NPY also the stimulatory effect of orexin on glucose production could be blocked by a hepatic sympathetic but not parasympathetic denervation. Although it is not entirely clear yet where in the brain orexin is acting to stimulate glucose production, the i.c.v. infusion experiments and the presence of a pronounced orexin-containing fiber network in the PVN suggest that its main action is again at the level of the sympathetic pre-autonomic neurons in the PVN, but in view of the electrophysiological data of Van Den Top et al. [212], a direct effect of orexin at the level of the sympathetic pre-ganglionic neurons in the intermediolateral column of the spinal cord can also not be excluded.

4.3.4. Pituitary adenylate cyclase activating peptide (PACAP)

PACAP is a 38-amino acid, C-terminally α-amidated neuropeptide that was originally isolated from the ovine hypothalamus on the basis of its ability to stimulate adenyl cyclase activity in rat anterior pituitary cells [213]. Studies conducted in rodents have shown that PACAP exerts a wide array of biological activities both in the CNS and in peripheral organs. Again the results from knock-out studies indicated the involvement of PACAP in glucose metabolism. However, these studies did not reveal which part of the metabolic phenotype should be attributed to central signaling pathways of PACAP, although some evidence for central effects on energy metabolism was available. Among others it has been shown that in the brain PACAP decreases food intake [214,215] and increases plasma glucose [216]. Data obtained in our lab clearly show that i.c.v. administered PACAP has a strong effect on glucose production [217]. This effect is very likely mediated through the pre-autonomic neurons in the hypothalamus, since i.c.v. infusion of PACAP-38 induced c-Fos is expressed by sympathetic pre-autonomic neurons in PVN, and sympathetic but not parasympathetic hepatic denervation can eliminate the hyperglycemic response to i.c.v. infusion of PACAP-38.

4.3.5. Glucagon-like peptide 1 (GLP-1)

Besides the above mentioned effects of GLP-1 as a metabolic signal sensed by the liver portal vein nervous system, GLP-1 is also known to decrease food intake in rodents and humans [218,219]. The anorectic effects of GLP-1 are probably mediated through both peripheral and central mechanisms, as a population of GLP-1 positive neurons is located in the brainstem and projects to hypothalamic and brainstem areas important in the control of energy homeostasis [220,221]. GLP-1 is also involved in glucose metabolism and may lower plasma glucose

levels through multiple mechanisms [222], including central mechanisms. First, Knauf et al. [223] demonstrated that during hyperglycemia i.c.v. administered GLP-1 decreases non-insulin-dependent muscle glucose uptake. Although the hypothalamic GLP-1 projections from the brainstem target both the PVN and the ARC [220], it was shown that direct administration of GLP-1 in the ARC, but not in the PVN, reduces glucose production [141]. On the other hand, GLP-1 administration in the PVN causes a decrease in food intake. Interestingly, GLP-1 receptor mRNA is also expressed in ~70% of the ARC-POMC neurons. These data seem to suggest that both central and peripheral GLP-1 can regulate food intake and glucose homeostasis, and provides a nice example of how the peripheral and central effects of a hormone/neurotransmitter can work synergistically to regulate glucose homeostasis.

Most of the above mentioned neuropeptides share a common effective hypothalamic area i.e., the PVN, but not for all of them has it been fully proven yet that they regulate specifically glucose metabolism via the PVN. In our studies and studies of others, central administration of orexin-A, PACAP-38, NPY [224] and synthetic MC3R and MC4R agonists [225] are all associated with Fos immunoreactivity in this nucleus. Moreover, for the PACAP-38 induced Fos-ir neurons in the PVN we have shown that they project to the sympathetic preganglionic neurons in the spinal cord. Since some of these peptides are orexigenic (orexin, NPY, and MCH), while others (POMC and PACAP) are anorexigenic, this suggests that the mechanism of feeding regulation is separated from that of glucoregulation. Secondly, sympathetic and parasympathetic pre-autonomic neurons in the PVN are separated [226]; this brings about the question, whether the neuropeptidergic effects we just described can be categorized into two groups, depending on their specific effects on either the sympathetic or parasympathetic output pathway. In our studies, the orexin-A and PACAP-38 induced hyperglycemia can only be blocked by hepatic sympathetic but not parasympathetic denervation. Also in the case of NPY, although it does not influence basal glucose turnover, the suppressive effect on hepatic insulin sensitivity is only blocked by hepatic sympathetic denervation. On the other hand, it has been shown that insulin and leptin signaling in ARC influence hepatic insulin sensitivity also via the vagal nerves, supposedly via another type of neurotransmission from the ARC (to the PVN) to influence pre-autonomic neurons in the hypothalamus. Clearly, further studies combining neuroanatomy and physiology are necessary to reveal this "parasympathetic pathway".

4.4. Liver innervation and the balance between glycogenolysis and gluconeogenesis

Sympathetic stimulation of glycogenolysis is enhanced further via Ca^{2+} release from mitochondria, the stimulation of phosphorylaseβ kinase activity, and the subsequent activation of phosphorylase activity [227–230]. Vagal efferent activity is thought to regulate gluconeogenesis (GNG) [163] by targeting liver IL-6 and STAT3 signaling [231] via SirT1 [232]. One important issue in liver glucose metabolism is how the balance between glycogenolysis and GNG is regulated, or under which conditions GNG can be augmented. Clarification of this issue is of direct importance for understanding the mechanisms that underlie the development of the metabolic syndrome and, maybe more importantly, how obesity can trigger the development of type 2 diabetes. One of the hallmarks of type 2 diabetes is the excessive hepatic glucose production. Hepatic insulin resistance has been considered to be central to the pathophysiology of the excessive glucose production, especially via an increased GNG through the increased activity of PEPCK and G6Pase [233]. However, this change in GNG is not explained by an alteration in glucoregulatory hormones. An acute increase or decrease in the insulin concentration mainly influences the rate of glycogenolysis but has little effect on GNG in non-diabetic subjects and/or in type 2 diabetic patients [234–236], and infusion of glucagon in non-diabetic subjects does not increase the rate of GNG either [237]. In addition, a clear organization of GNG based on zone can be observed in the liver, with higher rates of GNG being found in the periportal zone of the rat as compared to the pericentral zone, both under fed [238] and fasting conditions [239].

The involvement of brain signaling was thus considered and most of the evidence highlights the importance of hypothalamic mechanisms. Electrical stimulation of the VMH and LH changes the activity of the gluconeogenic enzyme PEPCK [188], whereas increased insulin signaling in the mediobasal hypothalamus inhibits liver GNG via the hepatic vagal innervation [163]. In addition, central administration of leptin has been shown to redistribute intrahepatic glucose fluxes, in such a way that GNG is increased and glycogenolysis suppressed. However, unlike the inhibitory action of central insulin on total glucose production [191], leptin does not change total liver glucose production [212,213]. When one of the downstream signaling components of the leptin—the melanocortin pathway—is interrupted, total glucose production is decreased due to abolishment of GNG. In addition, activation of melanocortin receptors can stimulate GNG [211].

In addition to leptin and insulin, evidence is accumulating that FFAs are also sensed by the hypothalamus directly. It has been shown that fatty acids within the hypothalamus stimulate liver GNG [124]. However, it remains to be elucidated where and at what level FFAs elicit this effect.

Although there are indications that K(ATP) channels in the mediobasal hypothalamus are involved, the (neuronal) pathways from brain to liver that control GNG are still poorly defined. In the hypothalamus, ARC NPY/AGRP neurons, LH orexin neurons and PVN neurons (in the lateral magnocellular subdivision) are all activated during fasting [240,241]. Activation of the parvocellular division of the PVN including the sympathetic pre-autonomic neurons by the neuropeptide PACAP-38 [223] mainly stimulates glycogenolysis and hardly changes GNG. Therefore, either there is a cellular differentiation within the PVN with respect to the control of the balance between GNG and glycogenolysis, or other signaling pathways than the PVN have to be considered.

In summary, in recent years major progress has been made in the unraveling of the hypothalamic circuitry that is involved in the control of hepatic glucose production. This progress involves both the awareness that many peripheral nutritional and metabolic signals may "use" the central nervous system as an intermediate to affect hepatic glucose metabolism, as well as more detailed information on neural pathways and neurotransmitters able to affect hepatic glucose production. The main challenge in the years to come will be to connect all these peripheral signals to the appropriate hypothalamic pathways.

5. Metabolic integration in the liver and brain

5.1. Intrahepatic interaction of neuronal and humoral signals that control metabolism

Sympathetic and parasympathetic liver efferent nerves contain the classic aminergic (epinephrine and norepinephrine) and cholinergic neurotransmitters, as well as peptidergic components such as NPY which can be co-released with the classic neurotransmitters from both sympathetic and parasympathetic terminals [242,243]. At the same time, the liver also receives a large amount of humoral information via the portal vein or arterial inputs. One of the unsettled issues is the interaction between the humoral signals and the neuronal signals that the liver receives during different energetic situations. First of all, insulin has an antagonizing effect on sympathetic (adrenergic) stimulation of glucose production [244], probably by interrupting the Ca^{2+} flux into the mitochondria of the

hepatocytes [245]. Secondly, sympathetic nerve stimulation in the presence of glucagon increases the output of glucose further and reduces the enhanced lactate uptake by glucagon [244]. These data implicate that the stimulatory effects of hepatic nerves on glucose output can be modulated by circulating glucoregulatory hormones. The opposite pathway, i.e., neuronal signals modulating a hormonal signal, does not seem to exist since in dogs complete liver denervation has no clear effects on the glucose production-increasing properties of glucagon [246].

NPY may interact with both humoral and neuronal signaling in the liver. In dogs, NPY infusion into the portal vein stimulates hepatic glucose uptake without significantly altering whole body glucose disposal [247]. On the other hand, although NPY per se is not able to directly regulate hepatic glucose production, it can inhibit the stimulatory effects of glucagon and noradrenaline on glucose production [248]. In contrast to NPY, galanin, the other neuropeptide released from the celiac ganglion as a sympathetic neurotransmitter, has no effects on its own when infused into the portal vein, but it does potentiate the action of norepinephrine to stimulate hepatic glucose production [249].

It has been hypothesized that insulin induces liver glucose uptake and storage into glycogen when the glucose level is higher in the portal vein than in the hepatic artery (portal–artery gradient). Thus this gradient sensing is involved in the stimulatory action of insulin on liver glucose uptake [250]. This process can be augmented by vagal stimulation as mimicked by an intraportal infusion of acetylcholine [251]. Type 3 muscarinic receptors in the hepatocyte possibly mediate these effects [179]. In contrast, blocking vagal efferent signals by atropine can inhibit insulin-mediated glucose uptake under the portal–artery gradient situation [252]. Not surprisingly, the effects of vagal activation on the effects of glucagon are opposite to its synergistic action on insulin, i.e., the glucagon-stimulated glucose release is antagonized by either vagal nerve stimulation or Ach [253]. Whether these interactions take place at the level of receptor sensitivity or are due to a direct influence on the fractional extraction of these hormones is not clear.

5.2. The brain as an intermediary for the outflow of metabolic liver information to other organs

The increased PPAR activity in the liver needs intact vagal afferents to the brain in order to result in the expected systemic effects [254]. Interestingly, vagal inputs seem to be mediating strikingly different signals, since on the one hand disruption of vagal afferent fibers can prevent PPARα mediated glucocorticoid-induced metabolic derangements including insulin resistance [255], whereas on the other hand they are also essential for hepatically expressed PPARγ2 to increase insulin sensitivity [254]. Again, this brings back the topic of the location of vagal sensing: due to the apparent lack of vagal afferent innervation in parenchyma, the above-described mechanisms seem to depend mainly on sensors located in the portal region. Within the brain–liver circuit, hepatoportal afferents and efferents form an autonomic feedback loop. This circuit could be “built” as a simple sensory-motor reflex, but most likely involves a complex brain mechanism [87].

Net hepatic glucose uptake is more pronounced when glucose is loaded directly into the portal vein instead of into the general circulation, despite controlled insulin and glucagon levels [256–259]. This means that the hepatoportal signal evoked by glucose has to be sensed by a specific pathway. Indeed, it was reported that an intact nerve supply to the liver is vital for this response. First, after a complete liver denervation the extra uptake by the overload of glucose into the portal vein was blocked [256]; second, after hepatic vagotomy liver glucose uptake was decreased by approximately 40% under euglycemic–hyperinsulinemic conditions during portal glucose infusions [260]. It is therefore logical to expect that the storage of glucose in the liver will be changed by interruption of liver innervation. However, a complete denervation only changes the variability of both glycogen synthesis and GNG but not its absolute level [261,262]. The central pathway can thus influence these processes, but the liver also contains a strong autoregulatory mechanism. Interestingly, under hyperinsulinemic conditions, total hepatic glucose production can be increased during portal glucose loading [260]. This raises the possibility that the autonomic nerves interact with insulin signaling as discussed before.

Stimulation of the hepatoportal glucose sensors by glucose infusions can stimulate glucose uptake in the heart, brown adipose tissue, and muscle. These portal glucose-induced changes in glucose utilization involve both an insulin-dependent and an insulin-independent mechanism [263]. The insulin-independent mechanism possibly relates to GLUT-4 and AMP-activated protein kinase (AMPK) signaling in muscle [264]. Besides glucose, high physiological doses of GLP-1 infusion in the portal vein are also able to stimulate glucose clearance in non-hepatic tissues [110].

5.3. CNS integration of liver and blood borne metabolic information

The brain controls energy metabolism by balancing energy expenditure and energy intake and/or production. In order to maintain the right balance, the brain, liver, gastrointestinal and other metabolic sensing mechanisms, either via the neuronal or the humoral pathway, cannot be separated from each other.

From the information provided above it is clear that a multilevel network is dedicated to receiving and relaying the liver and other visceral metabolic information to the brain via both hormonal and neuronal routes. The first order of convergence for the neural information from metabolic sensing from the different visceral organs is found at the level of the nodose and dorsal root ganglia. Hereafter, the second level for convergence of information is in the NTS and the dorsal horn of spinal cord. Although this has never been investigated specifically for the liver, there is the possibility of an ultrashort feedback loop via projections from the dorsal horn to IML, or from NTS to the dorsal motor nucleus of the vagus (DMV). Interestingly, although spinal ascending pathways and the NTS both project into the parabrachial nuclei (PB), the topographic separation of spinal and NTS inputs into PB [265] does not make this area a likely integration place for spinal and vagal inputs. One of the possible integration sites in the midbrain is the periaqueductal gray matter (PAG), which receives inputs from both the general-visceral recipient part of the NTS and the thoracic spinal cord [266]. How this sympathetic–parasympathetic integration overlaps or “interferes” with the proposed columnar organization of the PAG [267] in the control of liver metabolism is not yet known.

Within the hypothalamus, the lateral hypothalamus (LH) has been reported to respond to portal vein infusions of glucose or CCK [268,269]. The responses to glucose were not found in other hypothalamic areas like the supraoptic nucleus, PVN or ventromedial hypothalamus [270]. Furthermore, the excitability of LH neurons seems to follow the rhythm of the day/night cycle [271]. Interestingly, splanchnic denervation eliminates the LH responses to glucose, whereas vagal denervation exaggerates this response [270]. These data suggest that the LH receives both spinal and vagal liver glucose sensing information and thus may be one of the main hypothalamic integration areas for these neuronal inputs.

Regarding the integration of neuronal and humoral sensing information, the arcuate nucleus, which is the unique metabolic sensor for almost all circulating metabolites and their relatives, is a strong candidate for the integration of humoral and vagal inputs via the NTS-ARC projection [272]. Another major candidate is the PVN, as both sympathetic and parasympathetic metabolic sensing information reaches the PVN by direct and indirect pathways [70]. Moreover, other forebrain areas, such as the bed nucleus of the stria terminalis

and a number of hypothalamic nuclei also innervate the PVN. This unique position allows the PVN to integrate a very broad spectrum of neuronal and humoral metabolic sensing information and to organize its autonomic and neuroendocrine outflow consequently according to these different inputs.

Finally, at the level of the hypothalamus probably also the integration of information from the metabolic–homeostatic system and the cognitive–hedonic processes involved in the control of energy balance and food intake take place, as information from the limbic system and cortex also reaches the PVN via projections to the BNST and subPVN [273].

Vice versa it is clear that hepatic autonomic afferents transmit glucosensing information to higher brain areas, but how the many different brain regions are involved in accepting and integrating this information is still very ill defined. However, a very recently published anatomical study on the communication within the hypothalamic, cortical and mesolimbic circuitries involved in the regulation of energy balance, provides a clear clue that indeed neuronal pathways do transfer energy sensory information from the hypothalamus to cerebral cortex [274].

6. Discussion and perspectives

6.1. What can be learned from "gain of function" and "loss of function" studies?

Despite all the evidence for manipulation-induced effects of neuronal elements on liver glucose and lipid metabolism, the physiological significance of the afferent and efferent liver innervations is still not clear.

Liver transplanted humans and animals are suitable models to study the consequences of a complete denervation on liver metabolism. In liver transplanted patients, no reinnervation of either hepatic sympathetic efferent or afferent nerves has been observed until 30 months [275]. In transplanted rats, by using growth-associated protein (GAP)-43 as an axonal marker, regenerating axons possibly originating from parasympathetic ganglion cells in the hepatic hilus of liver allografts have been observed [276,277], but a centrally derived reinnervation has never been claimed.

Liver transplanted patients have relatively normal insulin-dependent glucose metabolism, and after a long term recovery from the initial effects of the immunosuppressive treatment, also protein and FFA metabolism return to nearly normal [108,278]. When comparing results from matched healthy subjects and kidney-transplant patients who received immunosuppressive medication similar to that received by the liver transplant patients, exercise data showed that glucose production increased to a similar extent in control subjects as in liver transplanted patients [279].

In mice, 9 months after orthotopic liver transplantation, body weight and other hepatic and general metabolic parameters are in the normal range, despite an increase in LDL cholesterol, LDL/HDL ratio and in hepatic glucose production. In short-term (2 weeks) completely liver denervated dogs, liver glycogenolysis response to a physiological increase in glucagon is unaltered [246], despite the fact that in the intact situation vagal activity will antagonize the effects of glucagon. A similar observation has been made in other experimental animals [262].

Taken together, these data indicate that the direct efferent liver innervation may not be essential for maintaining normal liver glucose, amino acid and lipid metabolism, and that autoregulatory mechanisms inside the liver are fully able to control liver metabolism in basal (i.e., non-stimulated) conditions. However, the defective hypoglycemic counterregulation observed in liver transplanted individuals, as discussed before, suggests that the autonomic innervation of the liver

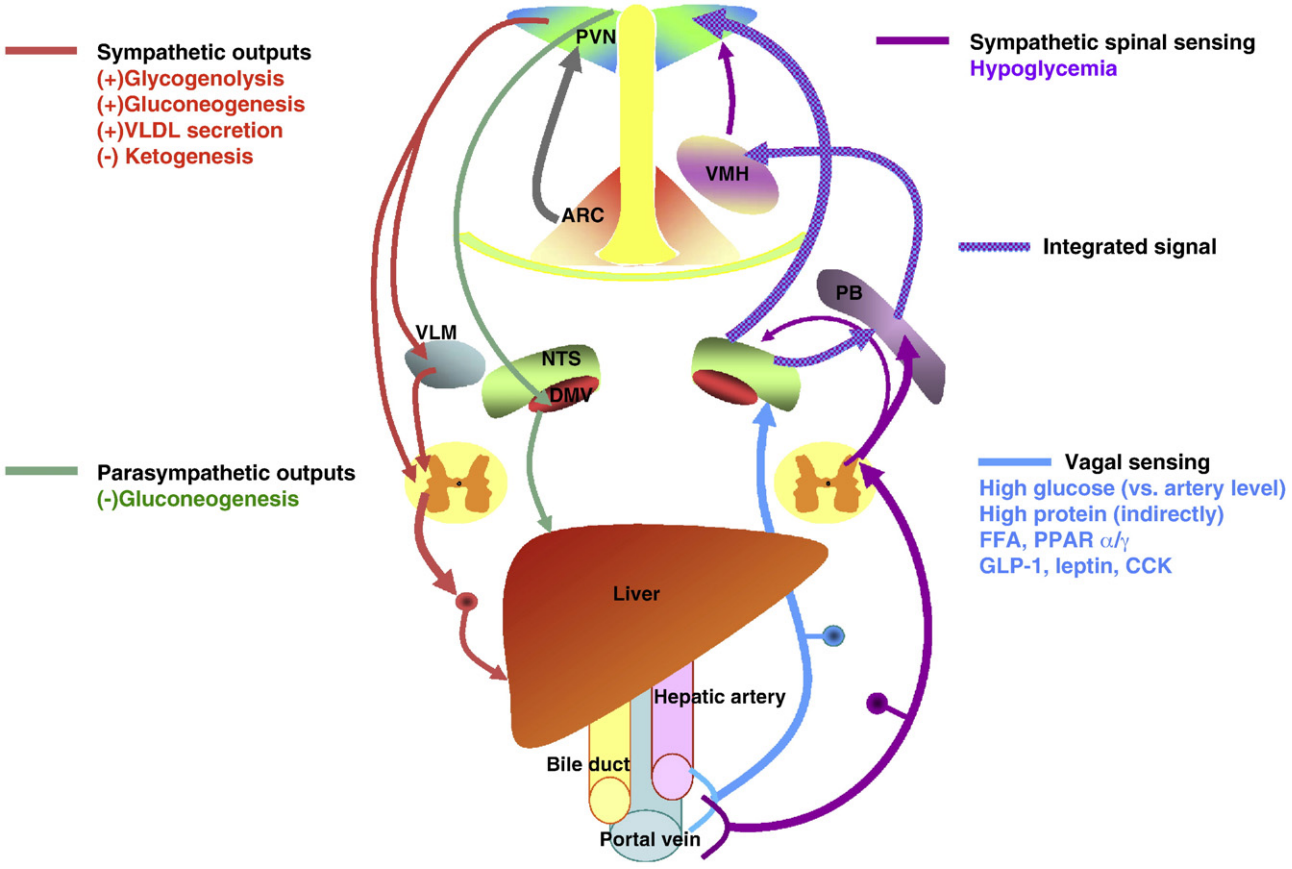

Fig. 2. Summary of the hepatic metabolic sensing and the neuronal pathways involved. Vagal and sympathetic afferents originate from both the liver itself and the portal vein.

might be more essential during "fight or flight" responses, by triggering catabolic responses such as stimulation of glucose output via a fast neuronal pathway, preparing the individual for emergency conditions. Interestingly, if only a sympathetic or parasympathetic liver denervation is performed, the normal daily rhythm in plasma glucose concentrations is eliminated but a complete denervation of both branches simultaneously does not result in such disturbed glucose rhythmicity [280]. Apparently for the remaining humoral and autoregulatory control systems it is easier to maintain a balanced glucose output without any autonomic innervation, than with an unbalanced autonomic input. These findings support the idea that disorders of (hepatic) glucose metabolism are more likely to be derived from an unbalanced autonomic input to the liver than from a complete absence of such inputs.

6.2. Perspective

From the viewpoint of whole body harmonization, afferent liver signaling is important for allowing the brain to synchronize liver physiology with that of other parts of the body. The liver can be considered as a primary nutritional sensor, while the brain serves as an overall energy sensor. Metabolic sensing in the liver is organized in such a way that most of the metabolic signals that indicate "plentifulness" are sensed by the vagal nerves, i.e., high concentrations of glucose and lipid absorbed from food, leptin released from adipose tissue, and lipid-activated PPARs activity (Fig. 2). Continuous high levels of lipid sensed by the portal vein nerves may lead this sensing system to increase its threshold; consequently more lipids are needed to generate the appropriate afferent signal. In a chronic situation this may mean that the brain integration center loses this piece of peripheral information. However, whether this eventually results in a profound loss of feedback about the metabolic situation from periphery to the brain needs to be investigated. Probably, parallel running humoral factors such as the newly defined lipid sensor ghrelin O-acyl transferase (Goat)-ghrelin can also signal to the brain about the availability of energy [281], and this pathway may either complete the neuronal metabolic sensing from liver or even take over when neuronal sensing from the liver is not available, for instance after liver transplantation. Checking the metabolic profile after blocking the (Goat)-ghrelin signaling with hepatic vagal denervation could test this possibility.

In contrast to vagal innervation, spinal nerves predominantly sense the "inadequate" metabolic information, especially the lack of glucose. These opposing roles might also be involved in a dysbalance during pathophysiological states. One of the hypotheses is that a hypoglycemia counterregulation pathway may be activated inappropriately during a euglycemic or hyperglycemic condition, driving the liver continuously to produce glucose, and overriding the inhibition from insulin.

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