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Hepatic Nervous System and Neurobiology of the Liver

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Abstract

The liver has a nervous system containing both afferent and efferent neurons that are involved in a number of processes. The afferent arm includes the sensation of lipids, glucose, and metabolites (after eating and drinking) and triggers the nervous system to make appropriate physiological changes. The efferent arm is essential for metabolic regulation, modulation of fibrosis and biliary function and the control of a number of other processes. Experimental models have helped us to establish how: (i) the liver is innervated by the autonomic nervous system; and (ii) the cell types that are involved in these processes. Thus, the liver acts as both a sensor and effector that is influenced by neurological signals and ablation. Understanding these processes hold significant implications in disease processes such as diabetes and obesity, which are influenced by appetite and hormonal signals.

Introduction

The autonomic nervous system (i.e., visceral and involuntary nervous system) is a part of the peripheral nervous system that plays a key role in the regulation of numerous physiological events in the liver. The autonomic nervous system is subdivided into the sympathetic and parasympathetic arms that relay signals in the brain/liver neural axis. Branches of both the vagal and splanchnic nerves innervate the liver via the portal area, and are closely associated with the portal vein and bile ducts (25, 58). The vagus nerve is comprised of motor and sensory fibers, while the splanchnic nerves consist of both visceral efferent and afferent fibers, as well as sensory fibers. Systematic neural ablation has highlighted the importance of the hepatic autonomic innervation of the liver in both physiological and pathological processes. Also, recent evidence has further defined the role of the autonomic nervous system by identifying the subtype, receptors, and mediators involved in the neural regulation of the liver. Currently, there is considerable interest to further the understanding of the anatomical and functional characteristics of the hepatic nervous system due to the impact it may have on diseases such as diabetes mellitus type 2, obesity and other pathologies.

Anatomy of the Hepatic Nervous System

Extrinsic Anatomy of the Hepatic Nervous System

The liver is innervated by both afferent and efferent autonomic nerves, which are associated with the portal vein, hepatic artery, bile ducts and liver hilus (Fig. 1). The sympathetic innervation is postganglionic and originates in the celiac and superior mesenteric ganglia

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that receive preganglionic fibers from the intermediolateral column of the spinal cord (T7-T12) (104). The parasympathetic nerves branch off the vagus nerve, and are thought to innervate the liver either directly as preganglionic fibers originating in the dorsal motor nucleus of the brainstem, or synapse on ganglia located at the hepatic hilus and within the hilar spaces (27, 59, 104). The anterior plexus forms a network of nerves surrounding the hepatic artery that originates from the left portion of the celiac plexus and the right abdominal branch of the vagus. The posterior plexus is derived from the right portion of the celiac plexus and is located around the portal vein with occasional innervations accompanying the hepatic vein (27).

Intrinsic Anatomy of the Hepatic Nervous System

While it is not fully understood to what extent neural innervation regulates the function of the specific cell types present in the liver, progress has been made in the characterization of the intrahepatic neuroanatomy in humans and other species. These studies have indicated that there is considerable variation in the distribution of intrahepatic nervous fibers between different mammalian species. This can be studied by specific staining with markers for different classes of efferent nerves. In most species, a number of markers for sympathetic and parasympathetic nerves have been observed surrounding the hepatic artery, portal vein, and bile ducts, indicating general innervation of these structures by a variety of neuron subtypes. The expression of sympathetic nerve fibers in species such as the rat is restricted only to these areas, whereas humans express markers of efferent sympathetic fibers extending deep into the connective tissue and hepatic lobules and ending on liver parenchymal cells (Fig. 2) (29). However, it is puzzling that these anatomical differences between species do not alter the parenchymal responses to sympathetic innervation (11, 36, 87). This may be due to the abundance of cell-cell connecting gap junctions in the rat and similar species that compensate for the lack of direct sympathetic innervation (11, 36, 87). Indeed, gap junctions serve a role in the liver to transmit electrochemical and hormonal signals from the periportal area to hepatocytes and the intrahepatic vasculature (40, 87). While the gap-junction mechanism occurs in the human liver, the effects are more pronounced in the rat liver due to the large number of gap junctions between rat hepatocytes (46).

Hepatic Afferent Nerves

Due to an intimate relationship with absorbed substances from digestion of food along the gastrointestinal (GI) tract, the liver serves as an ideal sensor for osmoreception, and the detection of glucose and fatty acid levels. After absorption in the GI tract, macronutrients travel through the portal vein to the liver. A large number of chemoreceptors are present in the liver that sense ions and nutrients and send signals to the brain. Mechanistic information about the hepatic afferent system has been obtained by the ability to trace neural activity and the knockdown of genes for neuropeptides and cognate receptors in animal models. This information may be utilized for the development of promising therapies for the clinical management of diseases including obesity and diabetes. With this in mind, it is of interest to understand how liver afferent fibers regulate appetite and metabolism, beginning with the detection of glucose, lipids and GI hormones. This topic will be discussed in the following subsections.

Hepatic Sensing by Osmoreceptors

The osmolality of mammalian extracellular fluid (ECF) is modulated by an osmosensing system located throughout a number of organ systems. This system balances salt and water intake or excretion by signaling to the brain. The brainstem is a crucial osmosensing organ, and contains osmoresponsive neurons that are excited by hyperosmotic stimuli, and

inhibited by hypo-osmotic stimuli (15, 74). Outside of the central nervous system (CNS), the peripheral osmoreceptors are responsible for detecting disturbances in osmolarity (1, 21). The liver is quite effective at sensing changes in blood osmolality, which is particularly relevant since water intake can be detected in the liver prior to impacting systemic blood osmolality (50). In fact, this system allows the body to make appropriate changes in preparation for osmolar changes.

Hepatic neurons that run adjacent to hepatic blood vessels detect and respond to ionic currents generated by physiological shifts in osmolality (50). The pressor reflex is a neurological reflex that raises blood pressure by engaging the sympathetic nervous system thereby causing arteriolar constriction. The pressor reflex is one outcome of osmosen-sation and can be triggered merely by drinking water (41). Research describing the pressor reflex is ongoing, however, the main role that the hepatic nervous system plays in evoking this reflex has been identified. This includes information on the mechanistic parameters involved in this process (50, 60). Hepatic neurons rely on osmotically-activated ion channels for osmosensation. One such receptor, the transient receptor channel protein vanilloid 4 (TRPV4), has recently been identified for the role it plays in generating ionic currents in response to changes in osmolarity (50). The detection of hypo-osmotic stimuli by the TRPV4 is transmitted to the brain via afferent fibers originating in the thoracic dorsal root ganglia of the spinal cord (Fig. 3). The role of the TRPV4 has been well defined in animal models, but its clinical relevance requires further studies in humans. However, clinical data is supportive of a hepatic sympathetic activation in response to water intake (57). This study revealed that liver-transplant recipients exhibited lower plasma norepinephrine (NE) levels after water intake compared to those of control transplant recipients (kidney transplants) (57). Furthermore, the afferent stimulus is suggested to activate efferent sympathetic nerves inducing the pressor reflex (57, 96). However, it is unclear which nerve fibers function as osmoreceptors (50).

There are several physiological/clinical parameters that are associated with the activation of hepatic osmoreceptors. First, water intake is suggested to regulate the weight loss of overweight individuals (94). This finding is postulated to be independent of dieting and activity (94). Future research should determine the value of water intake in combination with current weight-loss regimens. Second, liver-transplant patients that have denervated livers have elevated plasma osmolality and a decreased sympathetic response to water intake (50, 57). Finally, orthostatic and postprandial hypotension respond to water intake (50).

Hepatic Ion Sensation

The liver contains receptors for monitoring body fluid home-ostasis by detecting key physiological ions (i.e., Na^+) present in the portal blood system. Similar to osmoreception, the hepatic nervous system recognizes changes in ion concentration before they occur in the systemic blood (63). Hepatic nerves have a distinct advantage for the detection of ions compared to other organs since the concentration of absorbed substances in the portal vein is 4–5 times higher than that detected in the systemic blood (62). Thus, the liver is an ideal "predictor" of systemic blood-ion concentration, allowing for predictive compensation of fluid homeostasis.

Studies have shown that the infusion of water into the portal vein results in greater urinary excretion than infusing the same volume of water into the vena cava, a finding also supported by earlier work (2, 62, 66). These findings highlight another powerful mechanism for maintaining fluid homeostasis, which is known as the hepatorenal reflex. This reflex is characterized by increased Na^+ concentration in the portal vein triggering a decrease in renal sympathetic tone and excretion of Na^+ (Fig. 4) (62). Loss of this reflex may be partially responsible for the increased Na^+ concentration seen in cirrhotic patients (62). Future

research will help uncover whether it is possible to activate the hepatorenal reflex during disease states with high serum Na^+ concentrations such as hypertension.

Metabolic Sensing of the Liver

Glucose Sensing—Glucose sensing is known to occur in different cell types and areas of the brain (53). In the CNS, cells expressing glucose transporters (glut), such as neurons and glial cells, are triggered during hypoglycemic conditions to stimulate processes such as glucagon release (55). Peripherally located glucose sensors are located in taste buds, intestines, the carotid body and liver areas (37, 85, 92, 101, 102).

A number of studies have demonstrated glucose sensing by the liver. Evidence has suggested that the wall of the portal vein is a likely location for this (67). Studies on glucose sensing in the liver have helped establish that the portal vein (but not the hepatic artery) is responsible for glucose sensing (37, 38). While the relative contribution of both autonomic arms (sympathetic and parasympathetic) remains to be fully elucidated, each arm has been demonstrated to play a role in glucose sensing by the liver (8, 72). Decreased portal glucose concentrations activate vagal afferent activity, triggering increased food intake (68). This mechanism appears to be critical for the initiation of food intake, rather than the termination of feeding upon its inhibition (104). However, in hypoglycemic conditions the vagal branch does not appear to trigger feeding except in slow-onset hypoglycemia (56). Rapid-onset hypoglycemia is detected by the brain but, not by the liver (19, 86). While much can be learned from these studies, it remains uncertain as to what degree these effects contribute to the regulation of human hypoglycemia since the method for denervation may affect the results (23, 104).

The mechanism for hepatic glucose detection appears to be similar to that demonstrated during pancreatic β-cell activation. In the pancreas, GLUT2 controls the uptake of glucose and activation of insulin secretion (33). In the liver, GLUT2 acts as a hepatoportal glucose sensor and plays a role in the detection of hyperglycemia (16). In a $GLUT2^{-/-}$ model, knockout of GLUT2 resulted in a failed hypoglycemic response to portal glucose infusion (16). While glucose intake/hyperglycemia is sensed in the liver by a direct mechanism involving GLUT2, other molecules and peptides that increase during meal intake may exert insulin-tropic actions via liver afferent fibers. Glucagon-like peptide-1 (GLP-1) is released into the portal circulation in response to food ingestion and initiates firing of vagal nerves (69). This will be discussed further in the section “Hormone Sensing.”

Essential clinical applications can be developed from research involving glucose sensing. In diabetic patients, glucose sensing is crucial during hypoglycemia induced by insulin therapy. On the other hand, the modulation of glucose sensing by the GLUT2 transporter may be significant during hyper-glycemia as seen in the case of insulin resistance. Finally, it has been reported that liver transplant patients have lower physiological levels of glucose compared to controls undergoing the same immunosuppressive therapy (prednisone) (80). Liver transplant patients had an impaired counter-regulatory response to hypoglycemia. Here, hypoglycemia failed to increase epinephrine/cortisol levels (80). Furthermore, liver-transplant patients had increased insulin and glucagon levels. Thus, the liver is necessary for an appropriate counter-regulatory pathway, and insulin response to glucose during feeding, which requires further investigation for the development of clinical applications for liver transplantation and diabetes. Future research is necessary to determine the exact mechanism for intrahepatic glucose sensing.

Lipid Sensing—Afferent fibers in the liver are responsible for a negative feedback loop involving feeding behavior, and alterations in glucose production. Studies performed to differentiate the effects of general abdominal, and hepatic vagotomy, have suggested that

vagal afferent fibers detect the levels of free fatty acids (FFA) in the liver, and play a role in feeding behavior (22). Infusion of linoleic acid, liposyn II, corn oil, or caprylic acid into the portal vein resulted in vagal afferent stimulation from the liver (84). The vagal response was strongest in response to linoleic acid or triglycerides (84). In addition, animals fed a diet high in fat displayed a negative feeding behavior, which is blocked by vagotomy of the common hepatic branch (100). Another study confirmed that these effects were mediated through afferent signaling and not efferent signaling by damage induced to the afferent fibers by exposure to capsaicin (100). These studies emphasize a role for a reflexive decrease in feeding associated with activation of hepatic afferent fibers (Fig. 5). In addition, activation of afferent neurons is crucial for directing fat deposition and regulating plasma metabolite levels (100).

The molecular pathway responsible for lipid sensing in the liver remains undefined. One potential pathway involves the activation of protein kinase C (PKC) δ, θ, and ε (18). Activation of these PKCs reduces the inhibitory actions of insulin on glucose production in liver cells. Lipid activation of PKCs is not unique to the liver, as activation of PKCδ occurs during lipid sensing by duodenal cells. The activation of this pathway regulates glucose production by a gut-brain liver mechanism. A combination of afferent signals from both the gut and liver may trigger hypothalamic increases during food intake (Fig. 5). Future research needs to evaluate the potential overlap between lipid-induced signaling in the liver, gut and other tissues.

Perhaps even more important than the reflexive role of hepatic lipid sensing, are its effects on insulin resistance. In the liver, lipid-sensing directly conflicts with that of the GI tract and the brain in that it reduces the inhibitory actions of insulin on gluconeogenesis, and/or glucose production by the liver (18). Under normal physiological conditions, a mutually-balancing circuit triggered by lipids regulating gluconeogenesis exists in which the brain/GI tract are in opposition to the liver (18). Lipid sensation by the brain directly inhibits glucose production, whereas lipid sensation by the liver acts by increasing insulin resistance (18). Thus, in disease states characterized by insulin resistance such as diabetes type 2, this balance is offset. Here, lipids sensed by the liver increases insulin resistance in obesity-associated diabetes, which contributes to disease pathology (18). There is a critical need to develop new strategies to delineate the relative roles of the liver and other organs in the initiation of insulin resistance and the resultant diabetic pathology.

Hormone Sensing—In the liver, the afferent sensory neurons detect nutritional, and absorptive hormones called incretins. One major incretin, glucagon-like peptide 1 (GLP-1), is secreted in the brain as well as GI organs (76). The visceral secretion of GLP-1 occurs primarily in the intestine during food absorption. GLP-1 stimulates the pancreas to secrete insulin and inhibits glucagon secretion (77). GLP-1 is thought to have a local action in the GI tract due to its low postprandial plasma levels and rapid degradation (3). In the liver, GLP-1 is sensed by afferent nerves in the portal vein via GLP-1 receptors (98). Here, activation of GLP-1 receptors stimulates hepatic vagal afferent nerves, triggering changes in insulin release from the pancreas via signals from the efferent sympathetic nerves originating in the brain (6). There is a great need for the development of a clear understanding of the lipid sensing-metabolism circuit, and a high clinical demand for new therapies. Currently, the research supports the role of the liver as a regulator of lipid sensing and glucose production. It is possible that the GLP-1 system can be targeted to control feeding behavior in humans with metabolic disorders. Future research should investigate whether modulation of the GLP-1 system can be useful for the management of type 2 diabetes and obesity.

Liver afferent fibers also express receptors for a number of hormones secreted by the GI tract. Cholecystokinin (CCK) is released from I cells in the duodenum in response to food intake, and stimulates GI-tract organs such as the liver and bile ducts (93). Receptors for CCK are expressed in the portal vein, which stimulates afferent nerves (39). However, denervation of the nucleus tractus solitarious (NTS) or area postrema does not impair the satiety effects of CCK, indicating a possible autonomic reflex or alternate route to the brain (39). Other GI hormones sensed by the hepatic vagal afferent fibers include somatostatin and leptin (65, 91).

Interleukins (IL-s) are cytokines secreted by inflammatory cells that are involved in disease processes such as cancer and fibrosis. In addition to hormones, IL-s may also be sensed by hepatic afferents. It has been demonstrated that IL-1β increases hepatic vagal activity (66). Currently, it is believed that IL-1β functions as a chemical messenger from the immune system to the brain through the hepatic nervous system, although the precise role is still unclear (66). IL-1α produces changes in liver cells, and has been suggested to signal through hepatic afferent fibers (61, 103). More research into how the afferent signaling of cytokines may affect disease processes is necessary.

Efferent Hepatic Nerves

Regulation of Hepatic Vasculature

Early work studying the innervation of the liver identified that autonomic signaling plays a key role in the regulation of liver blood volume. Electrical stimulation of hepatic nerves caused a decrease in blood flow through the hepatic artery (49). This vasoconstriction was mediated by alpha adrenergic receptors as demonstrated by alpha blockade using phentolamine (49). This pathway involving the hepatic artery was not involved in arterial basal tone, but rather was primarily a sympathetic response (47, 48). Altogether, constriction of the hepatic artery, microvasculature, and decreases in trans-sinusoidal filtration could be responsible for the large decreases in total hepatic blood volume seen during activation of the sympathetic nervous system (12). This physiological process assists in maintaining adequate blood volume in the circulation during hemorrhage, where expelling blood from the liver is needed (12).

The sinusoids of the liver participate in the filtration of blood from the portal vein to the circulation. Sinusoids are capillary-like structures maintained by sinusoidal endothelial cells (SEC), surrounded by hepatic stellate cells (HSC) that produce contraction and relaxation of the sinusoidal walls. In humans, intrahepatic efferent nerves terminate at Disse's space in close proximity to HSC, SEC and hepatocytes (13, 79). Within the sinusoids, Kupffer cells are the macrophages that are involved in inflammation and autocrine/paracrine signaling (96). It has been demonstrated that nerve endings containing aminergic, peptidergic, and cholinergic nerves terminate near HSC of the sinusoidal walls. Here, hepatic efferent innervation is suggested to regulate sinusoidal contractility (97). Sympathetic release of adrenalin and substance P (SP) causes contraction of the liver sinusoids, whereas parasympathetic release of acetylcholine and vasoactive intestinal peptide (VIP) causes relaxation (Fig. 6) (97). These molecules are thought to act on HSC and SEC inducing the contraction of the sinusoids (96). In conjunction with the larger vessels, the stimulation of contraction can help to expel blood during hemorrhage or other sympathetic activation. Autonomic regulation of the sinusoids may also assist in hepatic blood flow during chronic liver diseases such as fibrosis/cirrhosis (97). In this setting, the importance of autonomic nerves may be lessened due to the increase in the vasoactive molecules endothelin (ET-1) and nitric oxide (NO) and the decreased density of neurons in the sinusoids (96). Further research is needed to determine whether modulation of this pathway would be beneficial for

patients with cirrhosis. It would also be useful to understand the relationship between Kupffer cells and the hepatic nervous system.

Regulation of Metabolism

Over a hundred years ago, Claude Bernard discovered that the liver stores and releases glucose (104). At that time, it was hypothesized that autonomic nerves control liver glucose and metabolism. Since then a number of studies have helped explain mechanistically how the brain regulates metabolism. For example, stimulation of the splanchnic nerve increases glucose production (GP) and decreases glycogenesis, whereas stimulating the vagus nerve decreased GP and increased glycogenesis (88–90).

Regarding the signals by which the brain regulates GP in the liver, a hypothalamic brain-liver circuit has been proposed to participate in this process. One way the brain monitors nutrient abundance is by sensing fatty acids. The brain detects fatty acid levels by responding to leptin, insulin, and fatty acids themselves (82, 99). These molecules activate ATP-dependent potassium channels (K_{ATP}) in selective hypothalamic neurons (82). It was demonstrated that central inhibition of fatty-acid oxidation via inhibition of the fatty-acid enzyme carnitine palmitoyltransferase (CPT)-1 causes activation of selective hypothalamic nuclei in the brainstem, and downstream decreases in GP via vagal efferent fibers (82). While the decrease in GP was a direct effect, an indirect pathway via increased insulin sensitivity was also present, further decreasing GP (82). Understanding the signaling mechanism for hypothalamic activation of hepatic metabolism has been a topic of immense interest and may provide novel treatment options for diabetes and obesity. A number of central neuropeptides have been studied for their potential clinical use in modulating obesity including: neuropeptide Y (NPY), pro-opiomelanocortin (POMC), pituitary adenylate cyclase activating peptide (PACAP), and glucagon-like peptide (GLP-1) (24, 35, 54, 64, 75, 82).

A neuronal network between the gut, brain and liver offers an additional level of glucose control. Cholecystokinin (CCK)-8 locally stimulates gut-brain afferents traveling through the nucleus tractus solitaries (NTS), and decrease GP in the liver (20). This effect was inhibited by hepatic vagotomy (20). It was further hypothesized that a change in this axis during high-fat feeding may result in CCK and insulin resistance (20).

Fatty acid metabolism by the liver is also under the regulation of the autonomic nervous system. Fatty-acid metabolism occurs in the mitochondria of hepatocytes, and is dependent on the lipid transport protein, carnitine palmitoyl transferase (CPT) I and CPT II (83). The expression of these transporters is regulated by hormones such as insulin and the autonomic nervous system (14). In hepatocytes, catecholamines increase CPT gene expression (9). Similarly, adrenalin, noradrenalin, and dopamine induce ketogenic effects (45). Stimulation of sympathetic nerves around the portal vein decreased very low-density lipid (VLDL) and ApoB (a major component of VLDL) levels (103). This decrease is probably due to post-transcriptional processes (103). In line with this, a later study demonstrated that liver denervation decreased both CPT I and II (17). These data suggest that the sympathetic nervous system participates in the hepatic regulation of lipid levels by decreasing the secretion of lipids by hepatocytes.

Regulation of Liver Repair and Regeneration

Since the discovery that subdiaphragmatic vagotomy in rats severely impaired liver regeneration after partial hepatectomy, the autonomic nervous system has been implicated in liver regeneration (43). Studies have reported findings for parasympathetic activation of liver regeneration (28, 95). After partial hepatectomy, hepatic vagotomy delayed liver

regeneration, which was characterized by a decrease in hepatic aspartate transcarbamoylase and salvage pathway enzyme thymidine kinase in vagotomized rats compared to control animals (44, 73, 95).

The sympathetic nervous system's intimate relationship with HSC and hepatic oval cells (HOC) makes it a candidate for augmenting liver repair. In the normal liver, both HSC and HOC are in a quiescent state, but are activated during liver damage. HSC are the fibrogenic cells of the liver that take on a myofibroblastic phenotype during repair characterized by proliferation, synthesis of matrix proteins, and expression of α-smooth muscle actin (α-SMA) (28). HOC are activated and form new hepatocytes when the number of hepatocytes becomes so low that hepatocytes are no longer able to perform their function. HSC are involved in disease processes such as cirrhosis and may interfere with the growth of HOC during regeneration. HSC have been shown to express α and β adrenoceptors (71). Stimulation of these receptors allows growth of HSC in culture and upregulation of TGF-β1 and collagen (71). It is suggested that HSC are themselves hepatic neuroglia that are regulated directly by the sympathetic nervous system and produce their own catecholamines (70). Additionally, the sympathetic nervous system was shown to be involved in the proliferation of HOC (70). It was demonstrated that chemical inhibition of sympathetic neurotransmission by antagonists caused an increase in HOC number (70). This indicates that the sympathetic nervous system inhibits HOC and activates HSC. Inhibitors of the sympathetic nervous system are potential drug targets for the treatment of cirrhosis. Future research should determine whether sympathomimetics could be used in the management of cirrhosis.

Regulation of the Biliary System

The biliary epithelium is highly innervated, and its function is regulated by a number of known neuropeptides and neurotransmitters. Cholangiocytes are the epithelial cells lining the bile ducts. They modify the bile as it passes through the bile ductules by secreting and absorbing bile salts and bicarbonate (42). Following a meal, when the parasympathetic branch of the nervous system predominates, biliary secretion is enhanced to secrete a maximum amount of bicarbonate (5). Cholangiocytes are the target cells of cholangiopathies, characterized by a dysregulated balance in proliferation/apoptosis (4). During cholangiopathies and cholestatic disease, cholangiocytes undergo rapid proliferation termed "the ductular reaction. If left unabated, the ductular reaction may eventually lead to biliary pathologies such as fibrosis and cancer.

Studies have described an efferent role for sympathetic and parasympathetic nerves innervating the biliary epithelium (5, 51). Cholangiocytes have been shown to express receptors for the M3, but not the M1 acetylcholine receptor (5). Stimulation with acetylcholine enhanced secretin-induced activation of the Cl^-/HCO^{2-} exchanger by Ca^{2+} signaling (5). *In vivo*, vagotomy ablated secretin-stimulated bile flow (51). Furthermore, ACh has been demonstrated to promote the growth of cholangiocytes (51). A bile-duct ligation (BDL) model was used to stimulate proliferation in rats, and study the effects of vagotomy (51). Here, vagotomy decreased the amount of cholangiocyte proliferation and enhanced apoptosis (51). These data suggest a physiological role for cholinergic nerves in cholangiocyte secretion and proliferation.

The adrenergic system also plays a role in cholangiocyte secretion (7). Cholangiocytes express alpha and beta adrenergic receptors (52). In the isolated perfused rat liver, the α1 receptor has been shown to decrease ductal secretion (10). Another study demonstrated that stimulation of the α1-adrenergic receptor with phenylephrine increased secretin-induced ductal secretion, and the proliferation of cholangiocytes by activation of Ca^{2+}- and cAMP-dependent signaling (52). Furthermore, stimulation of the α1-adrenergic receptor by

phenylephrine did not affect basal secretion (52). It was suggested that α1-adrenergic receptor activation coordinates with secretin-dependent signaling to induce maximal ductal bicarbonate secretion (52). A counter-regulatory mechanism is suggested with the α2-adrenergic receptor (26). It has been demonstrated that stimulation of the α2-adrenergic receptor reduces secretin-induced choleresis by downregulation of cAMP signaling in cholestatic rats (26). During biliary disease α1- and α2-adrenergic receptor agonists prevent biliary injury induced by adrenergic denervation by stimulation of cAMP and Akt signaling (30). Another counter-regulatory balance of the sympathetic branch is suggested via a dopaminergic pathway (31). The dopaminergic system counter-regulates secretin-stimulated choleresis in experimental cholestasis (31). The concept that the proliferative capacity of cholangiocytes is under neurological regulation opens new opportunities for research. First, it is critical to know whether regulation of neural signaling may be useful for treating cholangiopathies. In addition, liver regeneration is an expanding field, and it is critical to determine the role of the hepatic nervous system during biliary regeneration.

Hepatic Nervous System and Fibrosis

During liver injury, HSC are activated to a myofibroblastic phenotype that produces collagen. Recent data support that this response is under autonomic control. One study demonstrated that HSC express adrenoceptors and respond to NE by increased proliferation and fibrogenesis (70). Inhibition of the NE by antagonists resulted in decreased growth, collagen deposition, and expression of α–SMA (70). Furthermore, a link between obesity and the sympathetic activation of fibrogenesis was demonstrated (70). It was shown that leptin activates HSC if NE is present (70). In NE-deficient mice, leptin was unable to activate HSC (70). Intriguingly, leptin-deficient mice treated with NE were able to stimulate HSC, suggesting that leptin may act upstream of NE (70). As mentioned in the subsection “Regulation of Liver Repair and Regeneration,” the sympathetic nervous system has been demonstrated to inhibit HOC (69). It was demonstrated that chemical inhibition of sympathetic neurotransmission by antagonists caused an increase in HOC number (69). This indicates that the sympathetic nervous system inhibits HOC and activates HSC. Inhibitors of the sympathetic nervous system are potential drug targets for the treatment of cirrhosis. More research into the basic mechanisms of the liver’s sympathetic activity during fibrogenesis is important.

Regulation of Circadian Rhythms

Circadian rhythms participate in many physiological processes involving the nervous system and GI tract (78). These rhythms are thought to be regulated on a molecular level by transcriptional-feedback loops controlled by clock genes. Two major clock proteins CLOCK and BMAL1 dimerize to promote the translation of Per1/2, Dec 1/2 and Cry1/2. The body’s master clock, the hypothalamus, expresses these genes, but local clock genes are expressed in other tissues. The liver is innervated by nerves originating in the master clock, and locally expresses a robust circadian pattern of its own clock genes (32). Microarray analysis of the mouse liver transcriptome demonstrated that approximately 9% of the genes expressed by the liver are expressed in a circadian pattern, many of these being metabolic regulators (105). Destruction of the suprachiasmatic nucleus (SCN) causes a loss of circadian feeding behavior in rats (34, 81). Endogenous expression of Per1 has been shown to be flattened by restricted feeding (34). Future studies are necessary to elucidate the regulation of liver function via circadian rhythms, such as the regulation of both metabolism and detoxification of drugs. For example, the time of day chemotherapeutic drugs are administered may affect the efficacy of the therapy.

Conclusion

The autonomic nervous system of the liver plays a key role in the maintenance homeostasis, and a number of disease processes. It contains receptors for glucose and lipids that trigger a negative feedback system to modify physiological responses such as satiety and metabolism. Recent advances have touched on the importance of the liver in metabolism, and regulation of insulin and glucagon. Since obesity and diabetes are prevalent in the U.S., it is necessary to understand the mechanisms whereby the liver controls metabolism and feeding. The studies reviewed in this work suggested that glucose and energy homeostasis were highly affected by the hepatic nervous system. These processes are potential drug targets for clinical practice. With the increasing number of individuals affected by liver fibrosis, the role of the autonomic nervous system in liver regeneration is becoming more prominent. It is now known that various niches within the liver control liver regeneration by interplay of multiple cell types including HSC, Kupffer cells, HOC and inflammatory cells. It would be of immense importance to learn how these cells are innervated, as it could hold clinical importance. Future research should be directed towards an understanding of the neurotransmitters, signaling molecules and cell types innervated by the hepatic nervous system.

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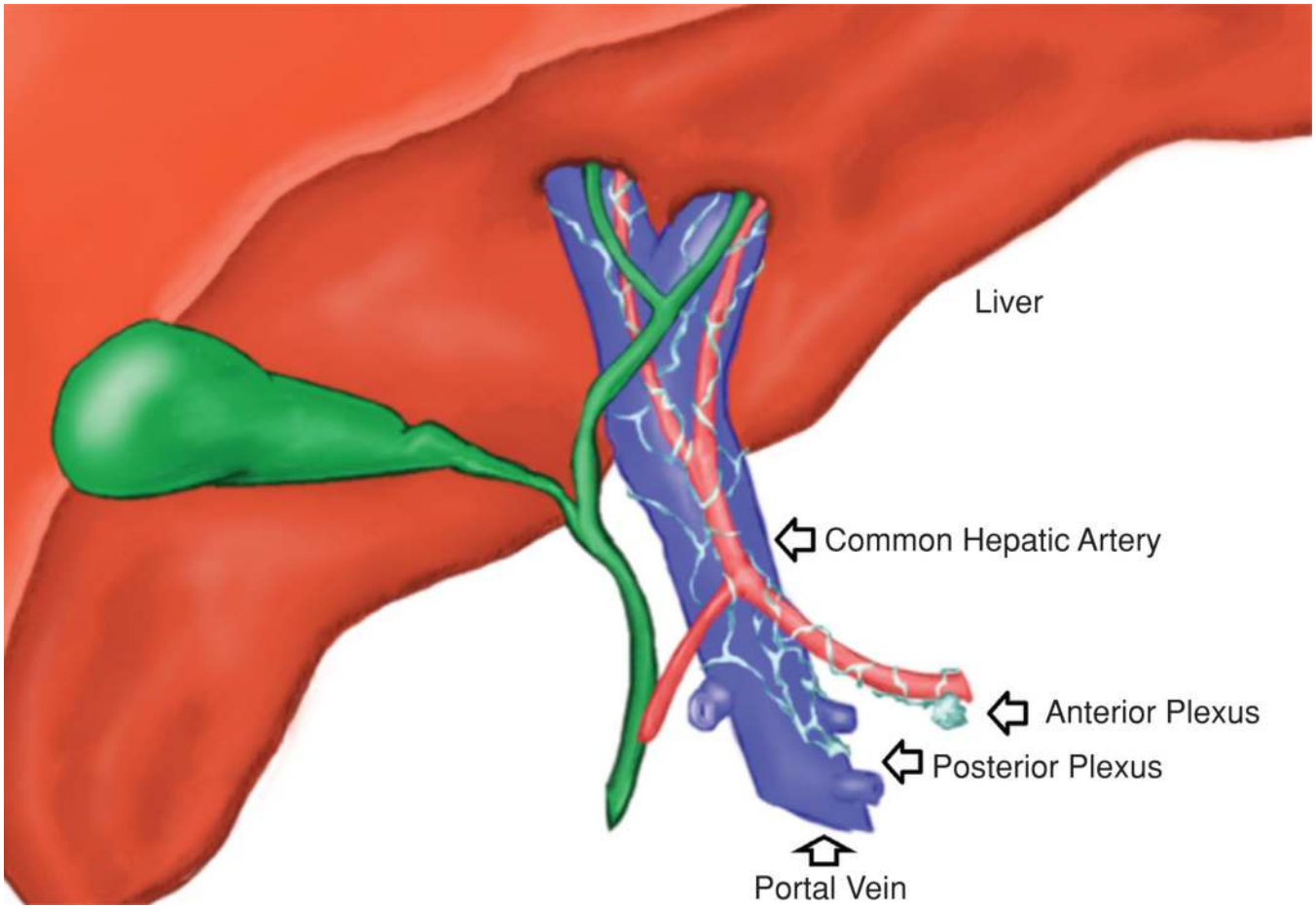

Figure 1. Gross anatomy of the hepatic nervous system

The anterior plexus forms around the common hepatic artery, and the posterior plexus forms around the portal vein. These plexuses follow these structures to enter the liver hilus with the accompanying portal structures and carry afferent and efferent fibers of both sympathetic and parasympathetic origin.

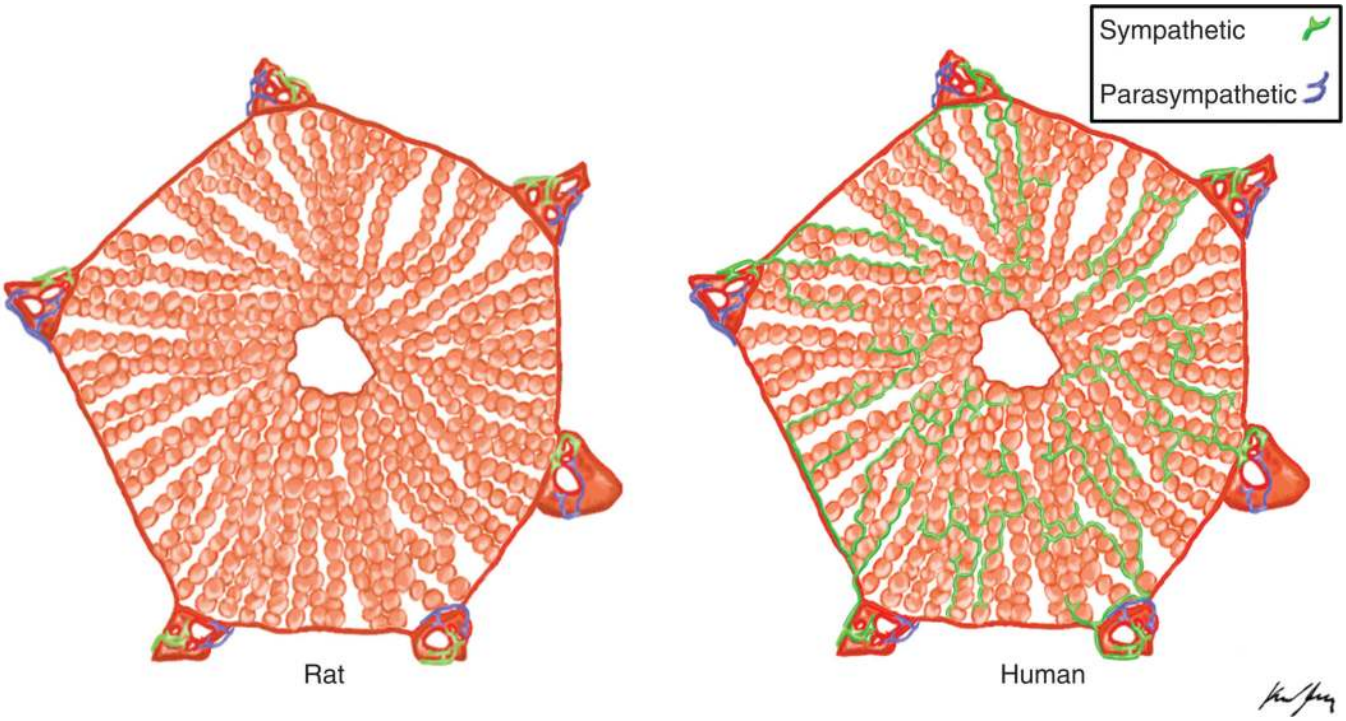

Figure 2. Anatomy of the intrinsic sympathetic and parasympathetic nerve fibers

In all mammalian species, sympathetic and parasympathetic fibers surround the portal area. In humans and guinea pigs but not rats, sympathetic fibers course into liver sinusoids.

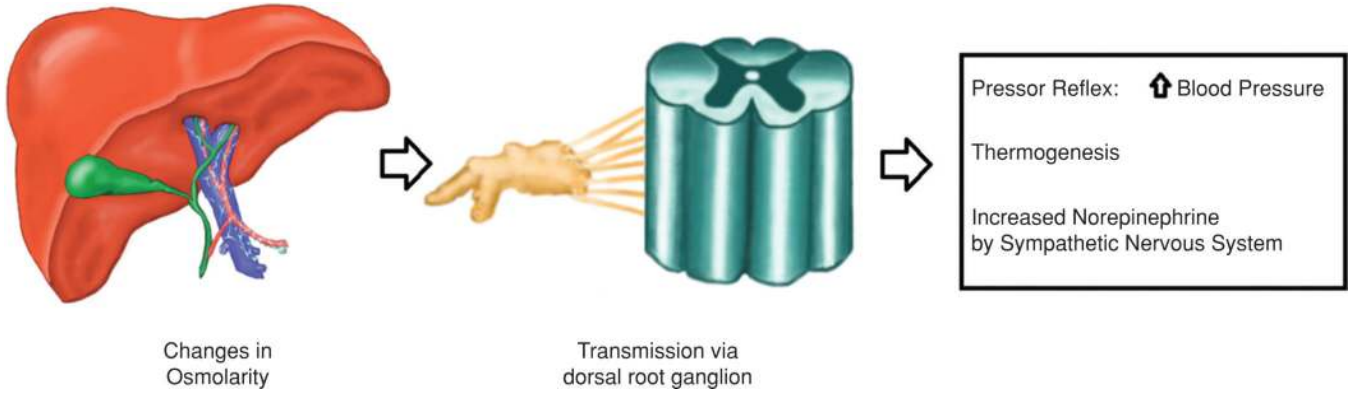

Figure 3. Osmosensation by hepatic afferent nerves

Afferent nerves surrounding the liver vasculature sense hypo-osmolar signals and trigger the pressor reflex via the dorsal root ganglion, and increased sympathetic activity. Like other reflexes, this process is thought to act independent of the brain.

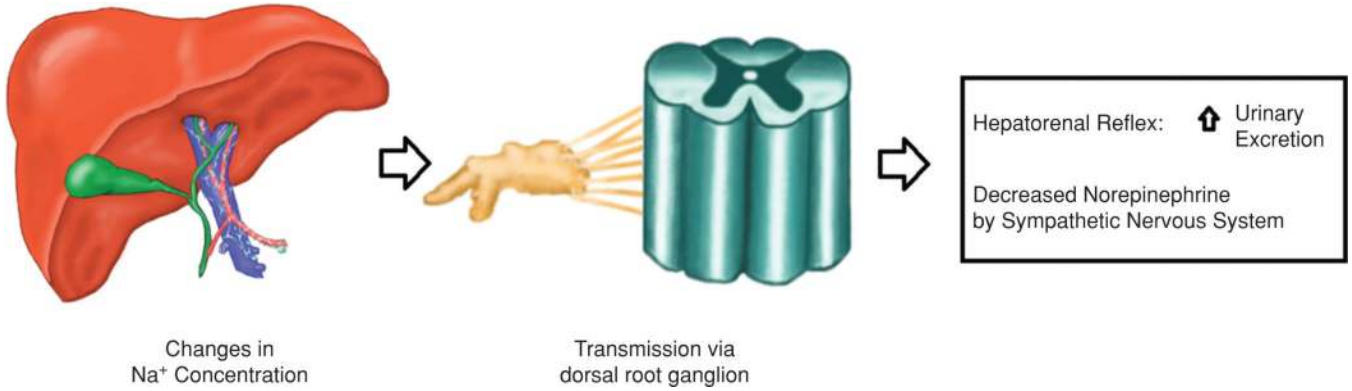

Figure 4. Sensation of Ions by hepatic afferent nerves

Afferent nerves surrounding the liver vasculature trigger in response to hypernatremia and act on sympathetic fibers in the dorsal root ganglion to reflexively decrease sympathetic output to the kidney.

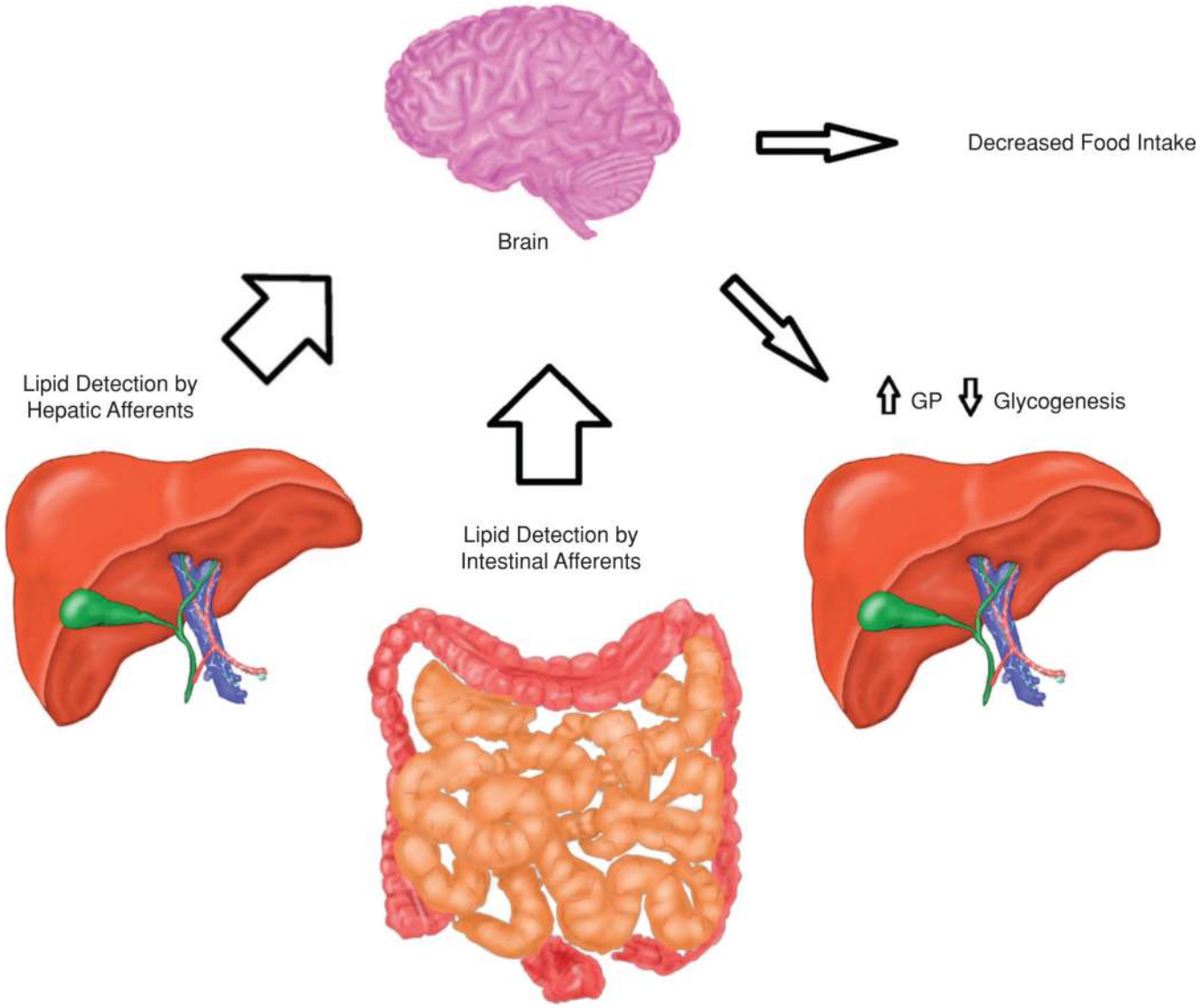

Figure 5. Lipid sensation by liver and gut

Lipid sensation by both the liver and the gut, leads to vagal afferent activation. The hypothalamus of the brain responds by signaling the liver to increase glucose production and decrease glycogenesis.

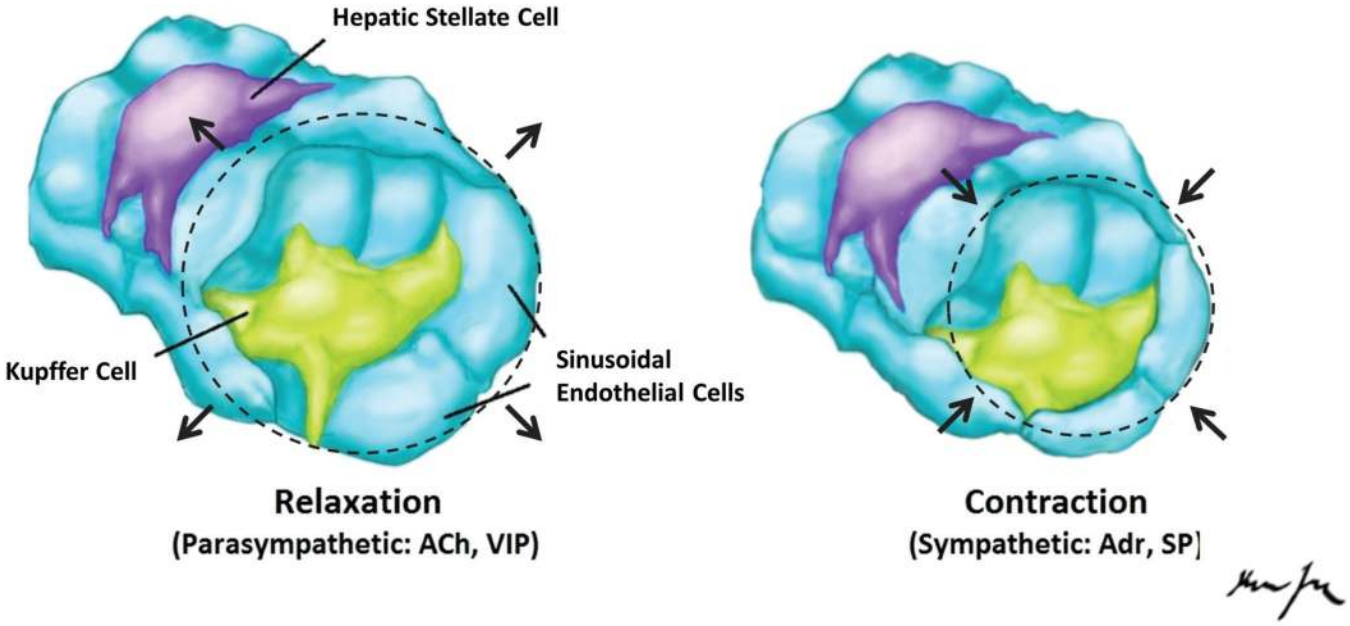

Figure 6. Effects of efferent neurotransmitters and neuropeptides on hepatic sinusoids

Release of parasympathetic neurotransmitters such as acetylcholine or vasoactive intestinal peptide causes relaxation of the sinusoids. Release of sympathetic neurotransmitters such as adrenalin or substance P causes contraction of the sinusoids. Sympathetic activation is seen during hemorrhage or physical activity, where blood is diverted from the liver to the systemic circulation.