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MINIREVIEWS

Role of intrahepatic innervation in regulating the activity of liver cells

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Abstract

Liver innervation comprises sympathetic, parasympathetic and peptidergic nerve fibers, organized as either afferent or efferent nerves with different origins and roles. Their anatomy and physiology have been studied in the past 30 years, with different results published over time. Hepatocytes are the main cell population of the liver, making up almost 80% of the total liver volume. The interaction between hepatocytes and nerve fibers is accomplished through a wealth of neurotransmitters and signaling pathways. In this short review, we have taken the task of condensing the most important data related to how the nervous system interacts with the liver and especially with the hepatocyte population, how it influences their metabolism and functions, and how different receptors and transmitters are involved in this complex process.

Key words: Liver innervations; Hepatocytes; Neurotransmitters; Cellular receptors

Core tip: Liver innervation comprises sympathetic, parasympathetic and peptidergic nerve fibers, organized as either afferent or efferent nerves with different origins and roles. Their anatomy and physiology have been studied in the past 30 years, with different results published over time. Hepatocytes are the main cell population of the liver, making up almost 80% of the total liver volume. The interaction between hepatocytes and nerve fibers is accomplished through a wealth of neurotransmitters and signaling pathways.

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INTRODUCTION

Innervation of the liver comprises efferent and afferent nerves containing sympathetic, parasympathetic and peptidergic fibers. Sympathetic nerve fibers derive from splanchnic nerves and the parasympathetic counterparts have a vagal origin. Fibers derived from splanchnic, vagus and sometimes the phrenic nerves enter the liver through the hilum, together with the hepatic artery, portal vein and bile duct. Some nerve fibers do not accompany hepatic vessels and enter the liver *via* the small omentum or the hepatic vein. Sympathetic and parasympathetic nerves form two separate plexus but communicate with each other: the anterior plexus placed around the hepatic artery, consisting of nerve fibers with their origin in the celiac ganglion and posterior vagus nerve, and the posterior plexus located around the portal vein and bile duct,

formed by fibers from the celiac ganglion and the right vagus[1]. Nervous fibers which are distributed to the hepatic parenchyma derive from a corresponding nervous plexus and their intrahepatic distribution differ according to species[2,3].

In the human liver, nerve endings are located in the hepatic lobules[4], which consists of hepatocytes and non-parenchymal cells. Unlike hepatocytes, which occupy almost 80% of liver volume and have numerous functions, non-parenchymal liver cells occupy only 6.5% of the liver, although representing 40% of total liver cells[5].

Hepatocytes are arranged as cellular cords with a radial disposition that converges towards the centrilobular vein, being separated by sinusoidal capillaries. Between hepatocyte cell cords and sinusoid capillaries there is an interstitial space, a perisinusoidal called a Disse space. This space is formed by a fine network of reticulin fibers, a support for the sinusoids, non myelinated nerve fibers and mesenchymal type cells[6]. Non-parenchymal cells are located in the liver sinusoidal compartment. The hepatic sinusoidal wall consists of three cell types: sinusoidal endothelial cells (SECs), Kupffer cells (KCs) and hepatic stellate cells (HSCs)[5]. Most nerve endings from intralobular spaces are located in Disse spaces[4,7-12], where they make close contact with HSCs, SECs and hepatocytes[7,8,10].

NERVOUS INFLUX TRANSMISSION MECHANISM INTO HEPATOCYTES

Hepatocytes serve multiple functions, such as synthesis, storage, metabolism and transformation of carbohydrates, amino acids, proteins, lipids, vitamins and detoxification, conjugation and excretion of exo- and endogenous substances. During liver regeneration, hepatocytes initiate cell proliferation, maintain metabolic function of the liver, secrete interleukin-6 (IL-6), proteases, protease inhibitors and hepatocyte growth factor[13].

The liver receives both sympathetic and parasympathetic nerve fibers; however, the innervation that hepatocytes receive varies by species. Thus, in the cat, rabbit, guinea pig liver as well as primate liver, it appears that nerve endings are connected to all hepatocytes, unlike rats and mice in which only hepatic cells in the portal region appear to be in contact with intrahepatic nerve endings[14].

Nerve fiber communication with hepatocytes can be accomplished by several mechanisms (Figure 1): (1) hepatocyte direct innervation mediated by norepinephrine and acetylcholine, neuropeptides [neuropeptide Y, galanine (NPY), vasoactive intestinal peptide (VIP), calcitonin gene-related peptide (CGRP), *etc.*], purines [adenosine triphosphate or adenosine (ATP)]; (2) signals intercellular transmission using gap type junctions; and (3) sinusoidal capillary cells innervation which interact with hepatocytes through eicosanoids (prostaglandins, leukotrienes), cytokines (necrotic factor, IL-6, IL-1) and other chemical mediators (endothelin, nitric oxide).

Direct innervation of hepatocytes

Nerve transmission to hepatocytes is achieved through neurotransmitters such as norepinephrine and acetylcholine, neuropeptides, such as NPY, galanine, VIP and CGRP, or purine derivatives as ATP and adenosine.

The liver is stimulated by norepinephrine and epinephrine released from intrahepatic nerve endings but also derived through the blood from the adrenal glands. Catecholamines act in the liver on α1-, α2- and β2-adrenergic receptors[15-17]. Norepinephrine is removed from the site of action by intrahepatic nerve ending uptake, being degraded by liver cells and diffused through the vascular bed[1].

Experiments on rat liver have shown that stimulation of the autonomic nerve plexus around the hepatic artery and portal vein causes increased production of glucose and lactate[1], urate and allantoin formation[17], decreased ketogenesis[18], increased ureogenesis and ammonia uptake[19], as well as increased oxygen utilization[20,21]. Also, hepatic nerve stimulation leads to decreased[16,17,20,22,23] and redistributed intrahepatic flow[21], as well as raised noradrenaline levels in the hepatic vein[15-18]. All these effects of hepatic nerves are only possible in the presence of extracellular calcium[22,24].

NPY, galanin, SP, CGRP, VIP and purine derivatives (ATP, adenosine) act as neurotransmitters, both in adrenergic and cholinergic nerve fibers, as well as in the related hepatic nerves. These neurotransmitters are released locally and are involved in regulating hepatic microcirculation. NPY and ATP act as vasoconstrictors, while VIP, CGRP, SP and adenosine produce vasodilation[14].

Some neurotransmitters also have a metabolic function. Thus, sympathetic hepatic nerve stimulation causes the release of noradrenaline but also of galanin[25], suggesting that galanin potentiates the action of norepinephrine to stimulate hepatic glucose production under stress[14].

Yamamoto *et al*[26] revealed the metabolic activity of ATP, which potentiates the action of hepatic sympathetic nerves suppression action on the formation of ketone bodies in the liver, the effect probably being due to ATP interaction with norepinephrine[14].

Intercellular transmission of signals through gap type junctions

Intrahepatic innervation varies by species. In some species, most hepatocytes are not directly innervated but there is an indirect mechanism for transmitting nervous inflow. One such mechanism is the intercellular communication carried out between adjacent hepatocytes *via* specific channels known as gap type junctions (GJ), which allow the passage of ions and small molecules[14].

GJ density is different among species[27]. Thus, hepatic GJ are more numerous in rats and mice compared to rabbits and guinea pigs[14].

GJ are membrane channels that allow intercellular communication between neighboring cells. GJ consists of two hemichannels, one hemichannel belonging to each

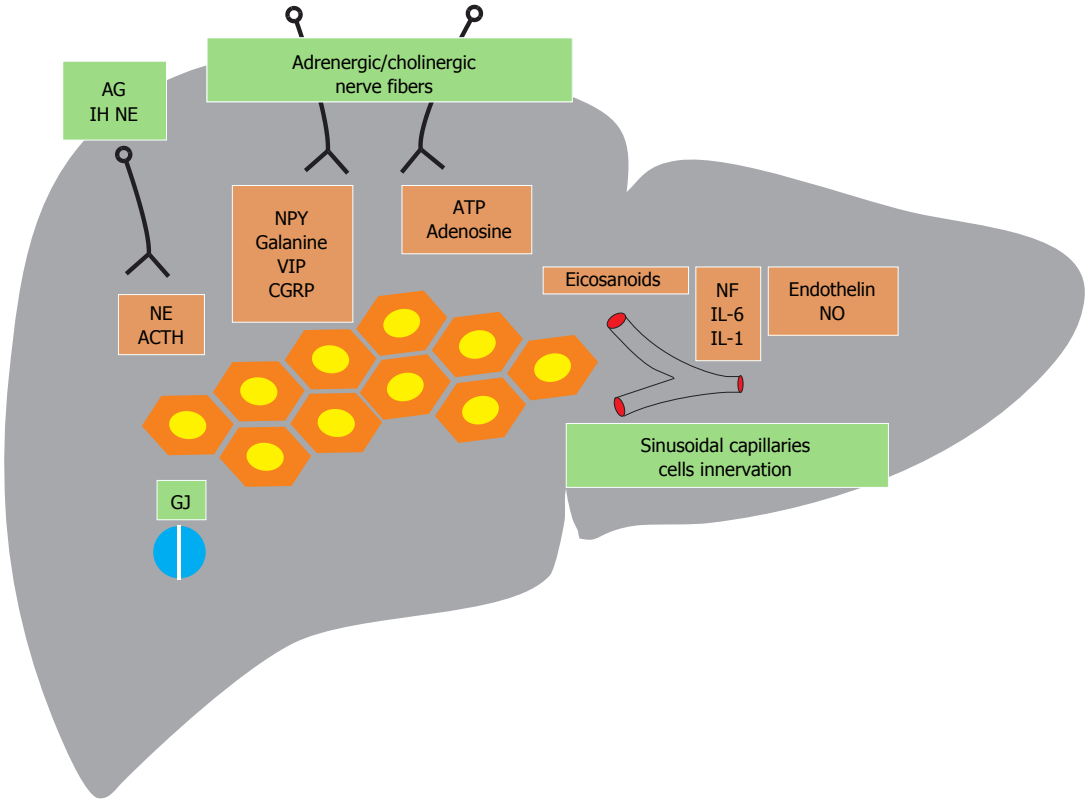

Figure 1 Schematic representation of the communication pathways between nerve fibers and hepatocytes. AG: Adrenal gland; IH NE: Intrahepatic nerve endings; ATP: Adenosine triphosphate; NPY: Neuropeptide Y; VIP: Vasoactive intestinal peptide; CGRP: Calcitonin gene-related peptide; IL: Interleukin; NF: Necrotic factor; NO: Nitric oxide; GJ: Gap junction.

of the two adjacent cells. A hemichannel consists of six subunits or connexins. Connexin 32 (Cx32) is the major protein component expressed in murine hepatocytes. Cx32 plays an essential role in signal propagation induced by the norepinephrine released from sympathetic nerve endings in hepatocytes[28].

GJ ensure the transmission of information to neighboring cells, achieving functional integration of hepatocytes, and thus functioning as a body and not as a mere cluster of cells[28].

GJ have an important role in transmitting nervous impulses from sympathetic nerve endings in parenchymal and non-parenchymal cells of the liver, in some species of mammals. There is an inverse relationship between sympathetic nerve fiber density and number of intrahepatic GJ[14]. Research on rat liver, which contains numerous GJ[15,29], showed that sympathetic nerves innervate only a part of parenchymal and non-parenchymal cells of the periportal area[15]. Metabolic and hemodynamic effects of hepatic sympathetic nerves are achieved by α1 receptor stimulation[17,23,30], are abolished by prostanoids synthesis inhibitors, and are mimicked by prostaglandins but not by thromboxanes[31]. Norepinephrine, as well as F2α prostaglandin, stimulates the release of glucose from isolated hepatocytes with increased inositol 1,4,5-triphosphate and glycogen formation[32].

Sending signals through GJ is involved in the metabolic effects of sympathetic nerves[14]. The norepinephrine released from sympathetic nerve endings binds to α1 receptors of parenchymal and non-parenchymal cells. The release of glucose from the proximal parenchymal cells from the periportal region under the action of norepinephrine initiates a signal which propagates through GJ to distal parenchymal cells, which in turn releases glucose. Norepinephrine stimulates contraction of proximal non-parenchymal cells (sphincters), reducing the flow in the sinusoid capillaries. It also causes the release of prostaglandins (PG) into the Disse space. PG, in turn, bind to prostanoid receptors of parenchymal and non-parenchymal cells. PG released from non-parenchymal cells are rapidly degraded in the liver[32] and so do not reach the distal cells. PG increase glucose release in the periportal parenchymal cells and perhaps initiate a signal that propagates to the other cells by GJ. PG stimulate contraction of proximal non-parenchymal cells, thus reducing the flow to sinusoid capillaries[15,33].

Sinusoidal capillary cells innervation

Sinusoidal capillaries are located between the cell cords and have a 9 to 12 micrometers diameter. The sinusoidal capillary wall is discontinuous and is formed out of a basement membrane and a capillary endothelium. Sinusoidal endothelium consists of flattened endothelial cells and phagocytic Kupffer cells in a ratio of 5/3. In addition to these two main types of cells in the sinusoid capillaries, there are also stellate cells and lymphocytes[6]. Capillary walls have an important role in the regulation

of the sinusoidal microcirculation[34,35].

Endothelial cells are flat and have elongated, hyperchromic nuclei and reduced cytoplasm. Junctional complexes are lacking. There are very small spaces of 0.5 micrometers between the cells. The apical membrane of the endothelial cells has transcytoplasmic fenestrations which are small holes arranged in nests with a diameter of 100 nm, with a role in controlling cholesterol, lipoprotein and vitamin A metabolism. In the cytoplasm of endothelial cells, a small number of cell organelles and pinocytosis vesicles were revealed. Endothelial cells produce prostaglandins, endothelin, IL-1 and IL-2[6,13].

Hepatic stellate cells (Ito cells, lipocytes) are located in the Disse space in small niches, among hepatocytes. They are in contact with the liver cells and through their microvilli and cytoplasmic processes have contacts with endothelial cell microvilli[6]. Well developed organelles and lipid droplets were found in the HSC cytoplasm. HSCs store vitamin A, containing factors related to retinoid acid and retinol, and produce extracellular matrix. Under normal conditions, HSCs have a deposit function, while in pathological ones it transforms into myofibroblastic type cells[6,13,36,37].

Research has shown that the distribution of intrahepatic innervation varies by species[29,38-43]. Guinea pig, cat and tupaia have an intralobular innervation similar to the human one[11,12,29,40], in contrast to mice and rats where it differs from the human[39,41-43].

In human liver, nerve endings are located in the Disse space[4,11,12], closely connected to hepatocytes and non-parenchymal cells, particularly HSCs[7,8,10,11].

Non-parenchymal cells are the only ones that can synthesize eicosanoids (prostaglandins, thromboxanes and leukotrienes) from arachidonic acid released from phospholipids by the action of phospholipase A_2 and converted to prostaglandins and thromboxanes *via* the cyclooxygenase path and leukotrienes *via* the lipoxygenase path[1]. Experiments on perfused rat liver have shown that the synthesis and secretion of prostanoids in non-parenchymal liver cells is influenced by a number of physiological stimuli, pathological and chemical. These stimuli also determine an increased release of glucose and lactate, as well as increased vascular resistance in the liver[1]. Of these stimuli, the most important are: extracellular nucleotides[44], nucleosides[45], zymosan[46,47], endotoxins[48], aggregates of immunoglobulins[49], anaphylatoxins[50,51], phorbol esters and calcium ionophores[44]. Norepinephrine and/or other chemical mediators released from nerve endings can stimulate the formation of prostanoids in non-parenchymal liver cells. Prostanoids, in turn, can modulate hepatocyte metabolism[1].

Of eicosanoids, only PG, without thromboxanes and leukotrienes, play a role in the events triggered by nerve stimulation[1].

PG participation in the chain of events initiated by nerve stimuli in the liver depends on hepatocellular receptors for PG. Research conducted so far confirms the existence of these receptors[1].

HSCs are indirectly involved in nerve fiber communication with hepatocytes, through PG. Noradrenaline may lead, by means of α1-adrenergic receptors, to increased synthesis of PG in the HSC, and PG, in turn, stimulate glycogenolysis in the hepatocytes. Unlike KC, producing predominantly PGD_2, HSC secret PGF 2 alpha released in increased amounts compared with PGD_2, as a result of sympathetic stimulation[52].

Intrahepatic nerve fiber terminations, often containing vesicles which contain neurotransmitters like substance P (SP) and vasoactive intestinal peptide (VIP), are closely related to HSC. It is considered that HSC that surround CECS, forming sinusoidal capillary walls, have a role in the contraction and relaxation of sinusoidal walls, thus intervening in the regulation of the sinusoidal microcirculation[4].

HSC contraction is stimulated by a number of substances such as endothelin-1 (ET-1), angiotensin II, norepinephrine, prostaglandin F_2, thromboxane A_2 and thrombin. In contrast, vasoactive substances such as acetylcholine, VIP, nitric oxide (NO), carbon monoxide, prostaglandin E_2 and adrenomedulin produce HSC relaxation[4].

ET-1 produces contraction of HSCs through ET receptor stimulation on autocrine or paracrine pathways. HSC contraction appears to be related to the increase of intracellular Ca^{2+} and inositol phosphate. For the sinusoid microcirculation control role of the HSC, the presence in the HSC cytoplasm of α smooth muscle actin, which is a contractile protein, also stands, such that the contraction of the HSC can be compared with that of smooth muscle cells in the vessel wall structure. On the other hand, prostaglandin E_2, adrenomedulin and other vasoactive substances determine HSC relaxation by increasing intracellular cAMP. In addition, HSC produces NO and inhibits contractility by an autocrine mechanism linked to NO[8].

Of the mentioned vasoactive substances, ET-1 and NO have an important role in the regulation of sinusoidal microcirculation. ET is a peptide consisting of 21 amino acids with a strong vasoconstrictive effect on the smooth muscle fibers. It has three isoforms, ET-1, ET-2 and ET-3[4,53].

Two receptors have been identified for ET: ET_A and ET_B, both belonging to the superfamily of G-protein-coupled receptors[54]. ET_A receptor has a higher affinity for ET-1 and ET-2 than for ET-3, while the ET_B receptor has a similar affinity for all three isoforms of ET. ET_A receptors stimulation increases intracellular cAMP levels, whereas ET_B receptor stimulation leads to inhibition of the adenylate cyclase system[55]. Also, ET_B receptor stimulation activates Ca^{2+}-dependent NOS[56]. Douglas *et al*[57] described two ET_B receptor subtypes: ET_{B1} and ET_{B2}. Stimulation of ET_A and ET_{B1} receptors causes contraction of smooth muscle fibers, while ET_{B2} receptor stimulation causes dilation by increased synthesis of NO[58].

ET-1 receptors from intralobular spaces predominate in the juxtaportal region. About 35% of ET-1 receptors

are located in the HSCs, a smaller number are located in the CECS and KCs[59]. Both ET_A and ET_B receptors are found in the liver. All cells of the sinusoidal capillary walls have ET_B receptors but only HSCs have ET_A receptors. Mallat *et al*[60] have identified 20% ET_A receptors and 80% ET_B receptors on activated HSCs.

NO is synthesized from L-arginine by the NO synthetase path (NOS). Three NOS isoforms have been identified: two are calcium-dependent, one produced by the neurons (nNOS or NOS I) and other by the vascular endothelial cells (eNOS or NOS Ⅲ), and one calcium-independent isoform, cytokine-induced (iNOS or NOS II). Rat HSCs shrink under ET-1 or SP action and relax, causing vasodilatation, under NO action produced by HSC under the influence of IL-1[4,61].

In normal liver, sinusoidal contraction is inhibited by ET_A receptor antagonists[62,63] but, according to some authors, not by ET_B receptors antagonists[4,62-64]. Other researchers believe, however, that ET_B receptor stimulation results in constriction of sinusoid capillaries[65]. It is possible that this discrepancy between the results obtained by different authors is due to coupling ET_B receptors with NOS, which masks the vasoconstrictor effect[63,66].

The various subtypes of endothelin have different effects on hepatic microcirculation. The relationship between NO and endothelin is extremely important in the control of vascular tone[63].

Liu *et al*[58] have shown that ET-1 binding to ET_B receptor leads to eNOS activation on the Akt phosphorylation path, thus reducing the phosphorylation of eNOS and NO synthesis. The same researchers highlighted the crucial role of βγ subunits of the G protein in triggering endothelin/NO reactions. The stimuli which regulate the ET expression and vascular sensitivity to ET also adjust the NOS and heme oxygenase-1 activity. Both enzymes catalyze the production of substances which, by guanylate cyclase activation, produce vasodilation[67].

CONCLUSION

Liver innervation is one of the most complex control systems in the human body; therefore, a better understanding of its inner workings is of paramount importance for developing future therapies and procedures for ameliorating the metabolic function of the liver. Being able to manipulate nerve impulses and synaptic mediators can possibly allow direct control over the functions of hepatocytes. Direct acting agents with excellent control over specific liver functions could become a reality, with direct implications for drug therapy, surgery or liver transplant.

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