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Research review

Liver innervation and hepatic function: new insights

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ARTICLE INFO

Article history:
Received 18 August 2014
Received in revised form
4 November 2014
Accepted 3 December 2014
Available online 8 December 2014

Keywords:
Hepatic innervation
Metabolism
Liver regeneration
Transplanted liver
Liver repair

ABSTRACT

The hepatic nervous system has a well-known impact on the regulation of liver function and organism homeostasis. The aim of this review is to summarize the new available data regarding the role of hepatic nerves. In the last decade, studies have shown that hepatic nerves exert subtle but significant modifications on the regulation of glucose and lipid metabolism, food intake, and liver regeneration. They also play a role in liver disease pathogenesis, and hepatic denervation has beneficial results to liver graft ischemia–reperfusion injury. Available data are still limited, and further research toward neural pathways involving the liver that can modify response to disease is required.

1. Introduction

The role of the hepatic nervous system in the maintenance of normal liver function and overall organism homeostasis has long been minor, since after orthotopic liver transplantation (OLT) and, therefore, denervation of the organ, liver continues to function well without serious consequences. This perspective has changed over the last two decades, after publication of detailed reviews, emphasizing the morphologic and functional aspects of liver innervation [1,2].

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0022-4804/$ – see front matter © 2015 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.jss.2014.12.006

The liver receives afferent [3] and efferent [4] nerve fibers of both sympathetic and parasympathetic origin. Hepatic nerve distribution is highly species dependent, with the human liver exhibiting both intra-acinar and portal tract innervation, whereas in mice and rats hepatic innervation is evident only in portal tracts (Fig. 1) [5]. During embryonic development, the liver is poorly innervated and does not contain intrinsic neurons derived from the neural crest cells, in contrast to the developing gastrointestinal tract [6]. Furthermore, in the first two trimesters of gestation, neural distribution in the human liver predominates in the portal tracts, with intra-acinar innervation appearing only toward term [7]. These data suggest that fetal human liver does not need extensive neural control to exert its functions, mainly hematopoietic, whereas after gestation its role changes as reflected in its more extensive innervation pattern. In the adult liver, therefore, hepatic nerves have been shown to play an important role in the regulation of the hepatic neuroendocrine compartment [8], glucose metabolism [9], circadian rhythm [10], liver cell hydration and osmolyte content [11], liver regeneration [12], and liver repair [13].

The scope of this review is to summarize and critically appraise new available data on the role of hepatic innervation on liver function and organism homeostasis, focusing on experimental studies of surgical and pharmaceutical liver denervation or the administration of neuromodulator agents (Fig. 2). Relevant literature was searched using the PubMed database with emphasis on studies after 2004, when the anatomy and function of liver innervation had been extensively reviewed [2].

1.1. *Liver innervation and progenitor cells*

Hepatic progenitor cells (HPCs) in human liver and oval cells (OCs) in rodents are two equivalent terms for the same stem cells, differentiating into hepatocytes and cholangiocytes in severe acute and chronic liver injury [14,15]. These cells are localized in four possible locations as follows: canals of Hering, intralobular bile ducts, periductal "null" mononuclear cells, and peribiliary hepatocytes [16]. The combination of selective hepatic branch vagotomy and galactosamine-induced hepatitis results in significant reduction of OCs in comparison with sham-operated rats exposed only to galactosamine intoxication. Furthermore, in transplanted human liver with hepatitis, the number of HPCs is significantly decreased in comparison with that of control livers with hepatitis and normal innervation. Cassiman *et al.* have shown that hepatic vagal nerves activate HPCs in the injured liver, probably through acetylcholine release to type-3 muscarinic (M3) receptors present on these cells [17]. On the other hand, denervation of normal rat liver results in increase of the number of OCs between 5 and 14 d after two-thirds partial hepatectomy (PH) in comparison with partially hepatectomized rats that did not undergo denervation [18]. Thus, hepatic nerves may play a role during liver regeneration, although the regenerative response after PH is known not to involve OCs, but rather the other hepatic cellular populations [14,15]. In addition to M3 receptors, HPCs also express vasoactive intestinal peptide receptor type 2 and receive nerve endings as well [19].

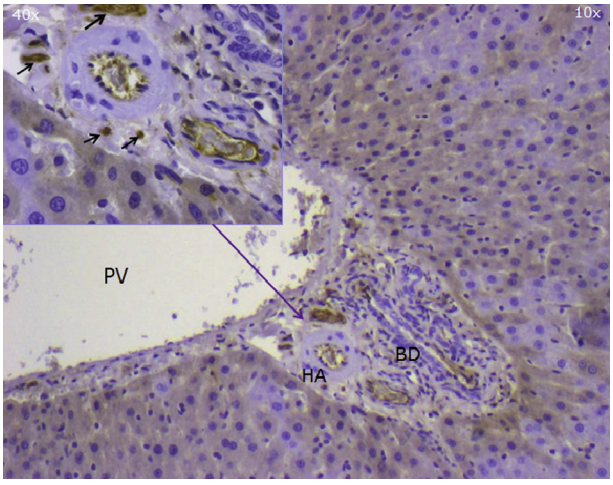

Fig. 1 – Immunohistochemistry of rat liver section positive for the pan-neuronal marker PGP 9-5. Nerve bundles/fibers (small black arrows) are only present at the portal tracts, in close proximity to the terminal hepatic artery and interlobular bile duct. BD = bile duct; PV = portal vein; HA = hepatic artery. (Color version of figure is available online.)

1.2. *Liver innervation and metabolism*

Liver innervation plays a critical role on the regulation of carbohydrate and lipid metabolism. A thorough review on the interaction between liver innervation and metabolism has recently been conducted by Yi *et al.* [20].

1.2.1. *Glucose metabolism*

Hepatic parasympathetic denervation, either surgically induced or through hepatic muscarinic receptors or nitric oxide synthase blockade, results in 50% decrease of the glucose disposal effect of insulin from the blood after a meal and may reduce insulin corresponding levels in the normal fasting state. The glucose disposal effect of insulin was attributed to both insulin direct action and also to hepatic insulin sensitizing substance (HISS), released from the liver and acting on skeletal muscles, stimulating storage of glucose as glucogen. A critical factor for the release of HISS is hepatic parasympathetic innervation and, therefore, its blockade may lead to HISS-dependent insulin resistance [21], also found in an animal model of hypertension [22]. Liver parasympathetic innervation is responsible for 45%, 35%, and 67% of skeletal muscle, heart, and kidney postprandial glucose clearance respectively, and hepatic parasympathetic denervation leads to a significant decrease in skeletal muscle glucose clearance and consequent 51% increase in plasma glucose concentration, implicating deregulation of the parasympathetic neural component of the liver in the pathogenesis of type 2 diabetes [23]. Chronic partial sensory denervation, through 2% capsaicin administration around the anterior hepatic plexus, also results in decreased insulin sensitivity and diabetes in rabbits [24]. As far as muscarinic receptors are concerned, Li *et al.* [25] found that lack of M3 receptors in genetically modified mice do not result in significant metabolic alterations after