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CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

COMMENTARY

The Potential Implication of the Autonomic Nervous System in Hepatocellular Carcinoma

Liver cancer casualties are increasing worldwide despite the recent advent of adequate hepatitis B virus and hepatitis C virus therapies. Though extensive effort has been made in the past 20 years to study the effects of nonviral comorbidities on hepatocellular carcinoma (HCC), the unexplained heterogeneity of clinical evolution among patients in terms of traits and speed remains problematic for clinicians. After almost two decades of intense molecular profiling, the overall understanding of HCC development at the level of cells and tissues remains incomplete. Despite many potential therapeutic options, several drugs have failed to exceed the efficacy of the currently available compounds in phase III trials, indicating a need for novel targets[1] and renewed approaches for studying the disease.[2]

Indeed, although the major contribution of hepatocytes, and the implication of activated hepatic stellate cells and immune cells, is well documented in HCC, other cell types including intrahepatic neurons have seldom been studied. These latter lie at the interface between neurobehavioral traits of the patient and the pathology of the organ, and may thus improve prediction of disease prognosis and response to personalized (ie, tailor-made) therapy. Furthermore, keeping in mind that, in general oncology, 60% of patients develop cancers for reasons as yet unknown, once likely risk factors (eg, predisposing congenital mutations, smoking, alcohol consumption) have been considered,[3] this novel research approach may identify as yet unsuspected HCC risk factors.

Brief Neurobiological Considerations in the Liver: Potential Influence on HCC-Predisposing Chronic Liver Disease

Succinct Anatomical Notions Pertaining to the Hepatic Autonomic Nervous System

The autonomic nervous system (ANS) (ie, visceral and involuntary sympathetic and parasympathetic nervous systems, or sympathetic nervous system and parasympathetic nervous system, respectively) is part of the peripheral nervous system, which plays a key role in regulating numerous physiological events, in synergy with the central nervous system (CNS). The sympathetic and parasympathetic nervous systems relay signals along the brain-liver neural axis. In 1924, it was shown that branches of the vagal nerve innervate the liver via the portal area, and are closely associated with the portal vein and bile ducts.[4] In most species, a number of markers of 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. Intriguingly, the expression of sympathetic nerve fibers in species such as the rat is restricted to these areas, whereas in humans the expression of markers of ANS fibers extends deep into hepatic lobules and reaches liver parenchymal cells.[5–7] This suggests a bidirectional and permanent connection between liver pathophysiology and the CNS, through afferent and efferent ANS fibers that sense and respond to relevant signals.

Pathophysiological Implication of the ANS in Chronic Liver Disease

CNS- or neural-derived events have recently been associated with chronic disease[8] and cancer survival rates.[9] Psychosocial factors independently and significantly predicted cancer prognosis in a meta-analysis of over 150 studies.[10] Systematic hepatic neural ablation highlighted the importance of autonomic innervation in both physiological and pathological contexts, including metabolism, liver regeneration, and liver fibrosis. Indeed, afferent hepatic nerves of the ANS ensure liver sensing of glucose (via the GLUT2 receptor), lipids (through several protein kinase C isoforms), hormones (eg, GLP-1 and CCK), and owing to its well-known implication in liver pathology, interleukin (IL)-1β, which in turn increases hepatic vagal activity.[11] Efferent hepatic nerves, linking the CNS to hepatic physiology, regulate the hepatic vasculature through its adrenergic and cholinergic arms.[12] The impact of the parasympathetic system on sinusoidal contractility, through its neurotransmitter acetylcholine, has also been reported[12] with likely consequences on blood supply regulation.

The influence of such processes on tumor metabolism is very likely, as nutrients and metabolites are delivered and excreted via the bloodstream, and their implication on the evolution of cirrhosis, the gateway to HCC, has been experimentally established.[13] Such efferent nerves also alter hepatic metabolism in real time, after CNS sensing of circulating amino acids. This occurs through the implication of hypothalamic nuclei and the brainstem, themselves influencing the local secretion of different neurohormones, such as neuropeptide Y, pro-opiomelanocortin, pituitary adenylate cyclase-activating peptide, and glucagon-like peptide 1.[14]

Regarding HCC onset in the context of chronic liver disease (CLD), the efferent nerves of the ANS were shown to be implicated in liver repair and regeneration. One study proposed that after partial hepatectomy, liver regeneration was severely impaired by vagotomy in rats,[15] while two others indicated that adrenergic signaling encouraged regeneration[16, 17] via hepatocyte growth factor induction[18]

and moderation of transforming growth factor β1 activity.[19] Hepatic stellate cells express adrenoreceptors, the stimulation of which increases transforming growth factor β1 and collagen production, and fosters their orientation toward a profibroblastic phenotype.[20] However, unlike vagotomy, sympathetic inhibition by chemicals causes an increase in hepatic oval cells, which are considered to be potential HCC precursors.[20] Efferent hepatic vagal activity has anti-inflammatory effects through its action on local IL-1β and IL-6 secretion.[21] Hence, an important part of the beneficial association of vagal activity with cancer outcome[9] may involve this anti-inflammatory pathway. Such findings are summarized in Figure 1.

Heart Rate Variability as an Interesting Marker in CLD

Heart rate variability (HRV) is a systemic marker of vagal activity,[22] and high HRV is predictive of survival in pancreatic cancer via its association with reduced inflammation.[23,24] Concerning the systemic level of vagal nerve activity, HRV significantly and independently predicts cancer prognosis,[22] where it is predictive of longer overall survival or reduced tumor marker levels over time in breast, colon, pancreatic and prostate cancers.[9,22,24,25] With respect to CLD, HRV significantly predicts mortality and liver transplantation in cirrhotic patients, independently of confounders (eg, disease severity).[26,27] Finally, HRV frequency domain parameters were significantly and positively correlated with time to death in patients with terminal HCC.[28] In line with this finding, from the adrenergic arm perspective, a meta-analysis of 23 randomized trials carried out on >2600 patients with cirrhosis indicates that nonselective sympathetic beta-blockers lead to reduced risk of HCC.[29] The hepatic tissue of HCC patients is innervated by both sympathetic and parasympathetic nerves. Though little is known on the role of the ANS in HCC, nerve fiber density seems to be associated with poor prognosis.[29] The sympathetic nervous system was speculated to promote hepatocarcinogenesis by modulating inflammation through activation of α_1-adrenergic receptors of proinflammatory Kupffer cells.[30] Such findings including those mentioned in the previous sections are innovative and are especially appealing given the paucity of adequate predictive and curative approaches for HCC.

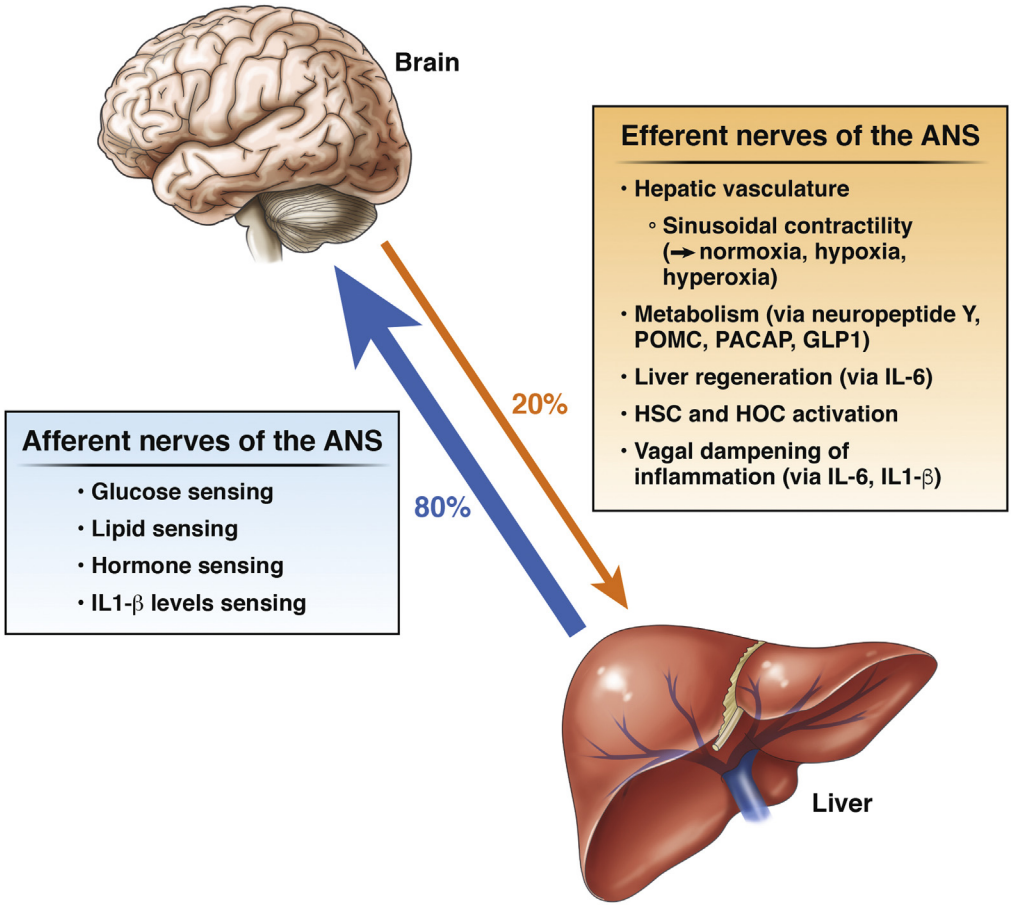

Figure 1. Pathophysiological functions conveyed both ways by autonomic nervous system (ANS) fibers along the brain–liver axis. GLP1, glucagon-like peptide 1; HOC, hepatic oval cell; HSC, hepatic stellate cell; IL, interleukin; PACAP, pituitary adenylate cyclase-activating peptide; POMC, pro-opiomelanocortin.

Future Directions: Pharmacology, Cell Biology, Animal Models, and Clinical Studies

Despite their potential interest, these new results often rely on correlative studies, and are sometimes conflicting. The precise roles of the sympathetic and parasympathetic branches of the ANS and their causal implication in HCC onset and growth from a biological and mechanistic perspective at the intra-organ level remain unknown. Intriguingly, an acetylcholine-secreting memory phenotype splenic T cell population was shown to regulate inflammation and immune responses,[31] likely affecting cancer immunosurveillance and immunotherapy. In this context, a number of interesting projects could be proposed. First, in vitro experiments could evaluate the influence of cholinergic and adrenergic signaling on the major pathogenic processes (eg, inflammation, fibrogenesis, loss of differentiation and transformation) related to carcinogenesis on each isolated hepatic cell type, including hepatocytes and hepatocyte-like cells, Kupffer cells, endothelial cells and stellate cells, as well as liver mononuclear cells. In particular, hepatic stellate cells in normal liver are arranged in a network of interconnected processes, making contact with sinusoidal endothelial cells and hepatocytes. They are a likely possible portal for mediating effects of the ANS throughout the liver.[32] Of note, following liver transplantation, the newly implanted liver is a denervated organ. The implications of such could also be fruitfully considered in clinical investigations in the HCC field, although confounding factors such as immunosuppression need to be taken into consideration. Second, in the event of causal effects observed in the previously mentioned experiments, preclinical in vivo models of CLD and HCC could be used to evaluate the sensitivity of HCC onset, evolution, and growth to sympathetic and parasympathetic signaling. Third, retrospective and prospective studies could be implemented at the level of the patient in order to evaluate the prognostic and correlative potential of ANS-derived circulating or resident markers regarding HCC onset and outcome. Finally, pharmacological synergy could be examined between current standard-of-care molecules used for HCC and agonists or antagonists of ANS-related receptors, several of which are present in the tumor local environment and in the liver.[14]

Overall, combined with the recently demonstrated anti-inflammatory effects of vagal-stimulating implantable devices in cancer predisposing inflammatory diseases of the GI tract,[33,34] these findings strengthen the potential interest of liver neurology considerations in future HCC research.

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Conflicts of interest
This author declares the following: Thomas Decaens has shared interests with AstraZeneca, Bayer, BMS, BTG, Ipsen, and Sirtex (consulting, member of advisory board and/or teaching), as well as Arqule, Genoscience, and Roche (research). The remaining authors disclose no conflicts.

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