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Role of Peripheral Inflammation in Hepatic Encephalopathy

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A growing body of evidence now highlights a key role for systemic inflammation in altering behavior and mood in patients with liver disease. How inflammation occurring in the periphery in the context of liver disease, communicates with the brain to mediate changes in neurotransmission and thereby behavior is incompletely understood. Traditional routes of communication between the periphery and the brain involve neural (i.e. vagal afferent nerves) and humoral (blood-borne) pathways, with increased circulating levels of endotoxin and cytokines (especially Tumor Necrosis Factor α, TNFα) that occur during systemic inflammatory responses, as being primarily implicated in mediating signaling via these pathways. However, in recent years communication via peripheral immune-cell-to-brain and the gut-microbiota-to-brain routes have received increasing attention in the context of liver disease for their ability to modulate brain function, and generate a spectrum of symptoms ranging from fatigue and altered mood to overt Hepatic Encephalopathy (HE). In this review, we discuss periphery-to-brain communication pathways and their potential role in mediating systemic inflammation-associated alterations in behavior, that are in turn ultimately part of a spectrum of brain changes linked to the development of clinically apparent HE. (J Clin Exp Hepatol 2018;xx:1–5)

INTRODUCTION

Hepatic Encephalopathy (HE) is a serious complication of acute or chronic liver failure and includes a spectrum of neuropsychiatric disturbances. The pathogenesis of HE remains a topic of discussion in the scientific community with several theories proposed, including the central concept that hyperammonemia is a key driving factor.[1] However, serum concentrations of ammonia often correlate poorly with the severity of HE in cirrhotic patients. Other proposed mechanisms involve disruption of the blood–brain barrier, changes in neurotransmission, neuroinflammation, oxidative stress, Small Intestinal Bacterial Overgrowth (SIBO), and brain blood flow abnormalities.[1] More recently an important contribution of peripheral inflammation as a significant contributor to HE has been suggested.[2,3] Moreover, it is increasingly recognized that a synergistic mechanism exists between ammonia and peripheral inflammation in regulating the onset and severity of HE.[4] This review outlines how systemic inflammation may contribute to HE and the changes in behavior associated with this condition.

SIGNALING PATHWAYS LINKING THE PERIPHERAL IMMUNE SYSTEM AND THE BRAIN

Patients with chronic liver disease commonly exhibit peripheral inflammation and experience altered brain function giving rise to symptoms that adversely affect their Quality of Life (QoL).[5,6] How liver disease-related systemic inflammation and immune activation leads to remote changes in brain function remains unclear. A number of general signaling pathways have been described that link systemic inflammation to changes occurring in the brain, which in turn give rise to altered behavior.[7] These signaling mechanisms have been divided into three main pathways; namely neural, humoral and immune.[5,6,8]

(1) Neural pathway: Vagal afferent nerves innervate the liver and can be activated through cytokine receptors expressed on vagal nerve endings by proinflammatory cytokines released during peripheral immune responses. After activation, vagal afferents carry stimuli to the brain which in turn activate primary and secondary cerebral projection areas, leading to changes in brain function and behavior.

(2) Humoral pathway: Circulating proinflammatory cytokine levels (e.g. Tumor Necrosis Factor α, TNFα, Interleukin-6, IL-6) are often increased in the setting of peripheral immune activation, and in patients with liver disease.[5,9] Cerebral Endothelial Cells (CECs) express receptors for TNFα and IL-1β, and CEC activation by cytokines has been

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Abbreviations: CECs: Cerebral Endothelial Cells; HE: Hepatic Encephalopathy; IL: Interleukin; LPS: Lipopolysaccharide; MPA: Monocyte Platelet Aggregate; PSGL-1: Anti-P-Selectin Glycoprotein 1; QoL: Quality of Life; SIBO: Small Intestinal Bacterial Overgrowth; TNF-α: Tumor Necrosis Factor-Alpha

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implicated as an important step in periphery to brain signaling,[6–8] and in the development of sickness behaviors in rodents.[6,7] Proinflammatory cytokines, including TNFα, can induce the production of secondary messengers (such as prostaglandins and nitric oxide) in CECs, which can be released into the brain and subsequently lead to changes within the brain.[5–7] Importantly, cytokines within the circulation can also gain access to brain tissue through areas of the brain devoid of an intact blood–brain barrier (called the circumventricular organs).[6,8]

(3) Immune pathway: Peripheral inflammation is commonly associated with increased numbers of circulating activated immune cells. These immune cells can traffic to the brain and adhere to activated CECs.[6,8] Adherence of immune cells to CECs can lead to stimulation of secondary messenger production by CECs, which in turn are released within the brain parenchyma and activate resident immune cells in the brain (e.g. astrocytes, microglia).[6–8] Resident brain immune cells activated in this way, can themselves release inflammatory mediators (e.g. cytokines) that alter neurotransmission and behavior.[10] Alternatively, immune cells may traffic from the blood vessel lumen into the brain parenchyma and subsequently release proinflammatory mediators that elicit these neural changes within the brain.[11]

IMMUNE SYSTEM-TO-BRAIN SIGNALING IN LIVER DISEASE IN THE ABSENCE OF LIVER FAILURE AND HE

Changes in behavior, including decreased cognition ("brain fog"), fatigue, anorexia and altered mood (depression, anxiety) are commonly experienced by patients with liver disease, regardless of liver disease severity.[12] These symptoms can overlap with symptoms reported by patients with HE,[1] suggesting that the peripheral and central drivers of these two symptom complexes are intimately related and therefore must share similarities in their pathogenesis. Systemic inflammation and associated immune system activation occur in both cirrhotic and non-cirrhotic liver disease.[2,3,5] Therefore, a spectrum of differential activation of peripheral signaling pathways that drive central changes in neurotransmission and behavior, may underlie differences in the clinical expression of symptoms in liver disease patients, ranging from common-liver disease associated symptoms to those more typical of HE. An improved understanding of the link between peripheral inflammation-driven changes in the three main signaling pathways, and changes in brain function, may provide novel therapeutic approaches to improve symptoms, QoL, and reduce the severity of HE.

In the setting of liver disease, the importance of neural pathways linking the liver and the brain, resulting in altered brain function, is likely of lesser importance compared to the other signaling pathways. Specifically, liver transplantation which denervates the liver, does not typically improve fatigue severity or neurological dysfunction in patients with primary biliary cirrhosis.[13] Similarly, recurrent HCV infection in a transplanted liver induces behavioral changes that are similar to infection in a non-denervated liver.[14]

An active role for a humoral liver-to-brain communication pathway in the setting of liver disease is possible, as increased circulating proinflammatory cytokine levels have been documented in patients with chronic liver disease.[5,9] However, these circulating cytokine elevations are often low grade, intermittent and often not reproducible.[15,16] Moreover, elevations in circulating cytokine levels typically do not correlate with behavioral changes documented in patients with liver disease.[5,17] In contrast, activated cytokine producing immune cells, including monocytes, have been identified within the peripheral circulation in animal models of liver injury and in patients with liver disease.[11,18] Monocytes have the capacity to produce large amounts of cytokines, including TNFα.[18] Moreover, activated monocytes can roll along and adhere to CECs that express relevant adhesion molecules on their surface.[19,20] Through this mechanism high concentrations of cytokines can be delivered in close proximity to endothelium, driving the subsequent generation of secondary signaling molecules such as nitric oxide from the endothelium.[5,20] The secondary signaling molecules generated in this fashion, can in turn be released within the brain parenchyma where they activate microglia and facilitate changes in neurotransmission that alter behavior.[6–8,10] Importantly, we have previously shown in an experimental model of liver disease that this process occurs, is regulated by TNFα produced by monocytes adherent to cerebral endothelium, and critically drives microglia activation within the brain and the subsequent generation of adverse liver disease-related behaviors.[11,19–21]

Although activation of monocytes within the circulation can be associated with liver injury, the mechanism linking liver damage and monocyte activation to produce TNFα remain unclear. The gut microbiome has been increasing implicated in the regulation of behavior.[22] Moreover, a healthy gut microbiome appears to provide overall health benefits which has led to the broad societal intake of supplements, including probiotics, to beneficially alter the gut microbiome. Furthermore, probiotic consumption has been shown to alter brain function and behavior in healthy humans. Specifically, probiotic ingestion can have beneficial effects on mood and cognition,[23] and is associated with changes in neural activity in brain regions involved in emotional processing.[24] The mechanism whereby probiotic ingestion leads to changes in brain function and behavior remain unclear, but have been linked to changes in gut flora (although not routinely observed), changes in gut permeability, and shifts in systemic immunity with decreased production of proinflammatory cytokines, including TNFα. Gut microbiome changes have been identified in patients with chronic liver disease, and these changes have been implicated in altered behavior and HE through a gut-liver-brain axis.[25]

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