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Mini Review

Neuroinflammation and Hepatic Encephalopathy: Uncovering the Crucial Role of Gut Microbiota Dysbiosis

Dachuan Jin[1†*], Zhongfeng Cui [1†], Shunqin Jin [2†], Peng Gao[3], Guangming Li[3*]

[1]*Medical Laboratory, Henan Provincial Infectious Disease Hospital, China*

[2]*Department of Radiology, Hebei Medical University, China*

[3]*Department of Liver disease, Henan Provincial Infectious Disease Hospital, China*

***Corresponding author:** Dachuan Jin, Medical Laboratory, Henan Provincial Infectious Disease Hospital, China Guangming Li, Department of Liver disease, Henan Provincial Infectious Disease Hospital, China

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Abstract

Hepatic encephalopathy (HE) is a serious complication that can occur in both acute and chronic liver disease, which is a significant cause of human morbidity and mortality. However, the underlying mechanisms of HE is not yet fully understood. While hyperammonemia has long been thought to be the primary cause, recent studies suggest that neuroinflammation may also play a key role in HE. Moreover, it has been shown that gut dysbiosis contributes significantly to the pathogenesis of neuroinflammation and HE. This mini review provides a summary of the emerging role of neuroinflammation as a novel mechanism of HE and highlights the critical role of gut dysbiosis in inducing neuroinflammation and HE.

Keywords: Neuroinflammation; hepatic encephalopathy; gut microbiota dysbiosis

Introduction

Hepatic encephalopathy (HE) is a severe neuropsychiatric disorder caused by acute and chronic liver disease and/or portal shunt. It is the most common complication in patients with cirrhosis [1,2]. As a marker of a disturbance in the body's homeostatic mechanisms, HE is an independent predictor of mortality and is strongly associated with poor prognosis [3] Symptoms of HE mainly involves varying degrees of impairment in sensory, motor, and cognitive function. The exact pathogenesis of hepatic encephalopathy remains unclear. Hyperammonemia was initially thought to be the primary cause of the development of HE. A novel concept of the pathogenesis of hepatic encephalopathy is now the induction of neuroinflammation [4]. It is believed that although hyperammonemia is an important determinant of mortality in hepatic encephalopathy, neuroinflammation is also one of the key mechanisms in the development of hepatic encephalopathy and has an important role in the pathogenesis of both acute and chronic hepatic encephalopathy and may be a key therapeutic target for patients with hepatic encephalopathy [5].

Some clinical trials have found that the development of mild hepatic encephalopathy is not related to blood ammonia levels but is associated with circulating levels of inflammatory factors [6]. In patients with cirrhosis, blood ammonia concentrations do not always correspond to the severity of hepatic encephalopathy. And anti-inflammatory therapy can effectively alleviate hepatic encephalopathy [7]. Therefore, neuroinflammation may play a key role in the occurrence and development of HE2, [8-10]. However, there is still much controversy and uncertainty about the role of neuroinflammation in hepatic encephalopathy. This mini review highlights the importance of intestinal microbiota in neuroinflammation and HE.

Exploring neuroinflammation and its relationship to HE

Neuroinflammation is defined as an inflammatory response in the central nervous system, which is a biological response of the neuroimmune system induced mainly by various biological, chemical, and physical factors, i.e., microglia and astrocytes in the central nervous system through the release of inflammatory mediators (e.g., cytokines, chemokines, reactive oxidants, inflammatory en-

zymes) in response to noxious stimuli [11-14]. Microglia and astrocytes are resident immunoreactive cells distributed in the CNS, and both are immunoreactive cells that play a key role in neuroinflammatory processes. Microglia plays a crucial role in maintaining the homeostasis of CNS tissues in vivo and are therefore also known as housekeeping cells. The most prominent role of astrocytes is to maintain the blood-brain barrier (BBB). Microglia activation and increased pro-inflammatory factors (mainly TNF-α, IL-1β and IL-6) are the main features of neuroinflammation [15].

In addition, microglia also release the anti-inflammatory factor IL-10, which provides neuroprotection and plays an important role in the late resolution of inflammation. This is due to microenvironmental perturbations, microglia polarization can change to either a pro-inflammatory M1 phenotype or an anti-inflammatory M2 phenotype [16]. Microglia plays a central role in the neuroinflammation of hepatic encephalopathy, as it is a major source of reactive nitrogen and oxygen species and pro-inflammatory cytokines. Therefore, reactive microglia are a hallmark of neuroinflammation and a key modulatory factor of neurological dysfunction [17].

Additionally, due to the rapid responsiveness of microglia to neuroinflammation in the brain, it has been used as a diagnostic marker for the progression of neuroinflammation [18-20]. Recent studies have found that the inflammatory process involving cytokines and lipopolysaccharides plays an important role in the pathogenesis of hepatic encephalopathy. Cytokines from the necrotic liver and sepsis can freely cross the blood-brain barrier in normal situations. Therefore, some believe that changes in the peripheral immune system are transmitted to the brain, resulting in neuroinflammation, thereby altering neural transmission, and leading to changes in cognition and movement [21]. Peripheral inflammation in liver disease patients is characterized by an increase in circulating proinflammatory cytokine levels, including IL-1β, IL-6, IL-8, IL-12, and TNF-α, and this change is also associated with a decline in cognitive function in hepatic encephalopathy patients [22].

As lipopolysaccharides cannot cross the blood-brain barrier, the effect of LPS on brain edema may be mediated by cerebral endothelial cells [23]. In acute liver failure, a strong neuroinflammatory response characterized by the activation of microglia and an increase in proinflammatory cytokines is also commonly observed [24]. Therefore, there may be a close relationship between neuroinflammation, and acute hepatic encephalopathy (AHE) caused by acute liver failure. Studies have found that the expression of inflammatory factors in the brains of rats with acute hepatic encephalopathy is elevated, accompanied by the activation of microglia, and the intensity of microglial activation and elevated levels of inflammatory factors are significantly correlated with the severity of liver encephalopathy in acute liver failure rats. However, the specific molecular basis is not yet clear [25].

It has been observed that although hyperammonemia impaired the performance of psychological tests in patients with cirrhosis during the inflammatory state, this did not occur after the elimination of the inflammatory state. This suggests that hyperammonemia and inflammation may play a synergistic role in the development of hepatic encephalopathy, and that blood ammonia can exacerbate the functional impairment of nervous system induced by the inflammatory state [26].Furthermore, it has been demonstrated in animal experiments and clinical studies that anti-inflammatory drugs such as indomethacin can reduce brain edema in hepatic encephalopathy and even normalize intracranial pressure in patients with acute hepatic encephalopathy. This suggests that inflammation occurring in the central nervous system may play a crucial and central role in the development of hepatic encephalopathy.

Currently, there is still controversy regarding the role of neuroinflammation in the development of hepatic encephalopathy. Some studies have found no increase in the levels of inflammatory cytokines such as IL-1β, TNF-α, IL-4, IL-10, and IFN-γ in patients with cirrhosis and hepatic encephalopathy, and the expression of neuroinflammation in different animal models also varies without a clear explanation for this discrepancy [27]. In addition, imaging studies in rat model of hepatic encephalopathy have shown a correlation between hyperammonemia and the severity of neuroinflammation as assessed by positron emission tomography (PET), while the levels of pro-inflammatory cytokines did not change significantly. Therefore, hyperammonemia as a circulating neurotoxin may still play an important role in the pathogenesis of hepatic encephalopathy.

Gut-liver-brain axis: understanding the role of gut dysbiosis and neuroinflammation in HE

The bidirectional communication between the gut, liver, and central nervous system is known as the gut-liver-brain axis. The gut-liver–brain axis is critical for maintaining homeostasis within the body. In liver disease patients, gut inflammation affects liver disease by accumulating inflammation and inhibitory immune cells in the liver, and this relationship between the gut and liver is known as the gut-liver axis [28]. The recently emerged concept of the gut-brain axis refers to the interaction between the central nervous system and the gut microbiota. However, it is not yet clear how the gut communicates with the brain to maintain gut immune homeostasis. In addition, the liver and brain are interconnected and interact through blood circulation and neural signaling [29,30].

In hepatic encephalopathy, enteric-derived neurotoxins are the most common predisposing factor for neuroinflammation [31]. Therefore, neuroinflammation in patients with hepatic encephalopathy may be closely related to disorders of the gut microbiota. Disturbed gut microecology is characterized by decreased diversity, increased harmful microorganisms, and decreased beneficial microorganisms [32]. And this significant gut microecological dysbiosis affects cognitive, mood-related behaviors. This change in gut microbial composition, intestinal mucosal barrier and associated immune function continues to worsen with the progression of liver function disease. It has been suggested that impaired gut-liver-brain axis in patients with liver disease is the main cause of

HE and the gut microbiota has emerged as a key factor affecting gut-liver, gut-brain, and brain-liver communication. Cirrhosis is a definite cause of altered gut microbial structure and function, and alterations in the gut-brain axis function as an intrinsic factor in the development of hepatic encephalopathy [33].

A rodent model of cirrhosis constructed using carbon tetrachloride also shows similar gut microbiota dysbiosis to that of human cirrhosis changes, including an increase in the numbers of Firmicutes and Enterobacteriaceae and a decrease in the numbers of the Ruminococacceae and bifidobacteriaceae [34,35]. Mice receiving microbiota from patients with cirrhosis also show more pronounced neuroinflammation and activation of glial cells, whereas mice receiving control healthy human-derived microbiota show milder neuroinflammation [36]. The abnormal gut microbiota is considered a crucial factor in the systemic inflammation, neuroinflammation, and immune activation observed in hepatic encephalopathy. Studies indicated that changes in gut microbiota are closely related to the secretion of proinflammatory cytokines. In the progression of liver cirrhosis, the normal gut microbiota is disrupted, particularly the Enterobacteriaceae and Streptococcaceae families, while the pathogenic microbiota that produces lipopolysaccharides is significantly increased.

Lipopolysaccharides are strongly immunogenic particles present in the outer membrane of gram-negative bacteria, which can recognize and activate Toll-like receptor 4 (TLR4) and NOD-like receptors (NLRs) in the liver, leading to the production and release of various inflammatory factors through signal cascade activation, thereby causing systemic inflammation [37]. Changes in gut microbiota led to the disruption of the intestinal mucosal barrier, a rise in endotoxins and inflammatory factors, and an increase in blood-brain barrier permeability. In the case of systemic inflammation or oxidative stress, astrocytes release TNF-α and activate microglia. Activated microglia proliferate and produce and release various pro-inflammatory factors, leading to cascading neuroinflammation.

Although LPS released from the gut bacteria cannot cross the BBB, it can increase the levels of IL-6 and TNF-α. By binding to receptors expressed by brain endothelial cells, lipopolysaccharides can activate microglia in the brain and increase the production of TNF-α and IL-1β, inducing neuroinflammation. Therefore, changes in gut microbiota promote systemic inflammation and neuroinflammation. Research suggests that probiotics and fecal microbiota transplantation can effectively alleviate the symptoms of hepatic encephalopathy, demonstrating that gut microbiota reconstruction is effective in treating neuroinflammation associated with hepatic encephalopathy. This indirectly proves that gut microbiota dysbiosis is a key factor in the development of hepatic encephalopathy18,31. However, the current controversy lies in the specific mechanisms of action and the optimization of treatment plans29. For example, when performing fecal microbiota transplantation, it is necessary to ensure the balance of gut microbiota; otherwise, selecting an inappropriate donor can harm the patient [38,39].

Conclusions

In summary, the occurrence of hepatic encephalopathy may be attributed to a complex mechanism involving multiple factors, but the neuroinflammatory mechanism resulting from gut microbiota disturbance may play a pivotal role in this process. The treatment targeting gut microbiota dysbiosis and/or neuroinflammation may become a new therapeutic approach for HE, and investigating the mechanisms underlying how gut microbiota dysbiosis induces neuroinflammation and promotes HE has become a hot topic of research. Transplantation of gut microbiota, probiotics, and prebiotics for controlling gut microbiota have already shown effectiveness as a therapeutic intervention for improving neuroinflammation, alleviating secondary neurological injury, and ameliorating HE in clinical practice [40-42]. However, delving deeper into the mechanisms by which gut microbiota dysbiosis and neuroinflammation lead to the development of HE can provide valuable insights into the identification of more targeted and efficacious therapeutic strategies [43].

Conflicts of Interest

The authors have none to declare.

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