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Liver-induced inflammation hurts the brain

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The immune system is activated following injury or infection. The local response can be accompanied by a systemic response, which includes the synthesis and release of different mediators by innate immune cells. The liver is not an exception and when exposed to an acute or chronic insult generates an inflammatory response that may affect other organs. Liver-induced inflammation is able to cause disturbances in the central nervous system (CNS) including metabolic (hyperthermia, somnolence, loss of body weight) and behavioural manifestations (lethargy, anhedonia, decreased social interaction). These manifestations are collectively termed "sickness behaviour" [1], and are attributed to dysfunction of the CNS.

The underlying mechanisms responsible for this periphery-to-brain inflammatory communication are not fully understood, but include both neural and humoral pathways that act in parallel (Fig. 1) [2]. The neural pathway involves afferent nerves (vagal and trigeminal nerves) that can be locally activated by cytokines present at the site of injury and project to different areas of the brain. The humoral route involves cytokines that interact with the brain diffusing freely from the blood in areas lacking the blood–brain-barrier (the circumventricular organs), or communicate with the brain by activating the endothelium and transmitting signals to brain parenchyma. A key component of this signalling process is the activation of the immune cells resident in the brain parenchyma (microglia), which are usually in a quiescent state. The activation of microglia is considered essential in the innate immune response of the brain and leads to the release of molecules, such as neurosteroids and/or prostaglandins that affect neurons.

Neuroinflammation is a process that has gained increased attention in neurodegenerative diseases, such as Alzheimer's and Parkinson's disease, and has also been described in hepatic encephalopathy [3]. According to the data published in this issue of the *Journal of Hepatology*, neuroinflammation may also participate in more subtle neurological manifestations of liver disease. The article by Nguyen *et al.* investigates the underlying mechanisms of sickness behaviour in a murine model of cholestatic liver injury (bile duct ligation, BDL). In agreement with other studies [4], sickness behaviour is related to an increase in serum interleukin-6 (IL-6). In the current model, the generation of IL-6 was clearly shown to originate in the cholestasic liver and induced IL-6 signalling in the brain via endothelial activation, as suggested by an increase in the expression of p-STAT3 in endothelial cells of the hippocampus. These observations support the notion that systemic symptoms such as fatigue, frequently present in chronic cholestasic diseases, may originate from the effects of liver-induced inflammation on the brain. This is an interesting concept that may initiate a new approach for treating the symptoms associated with chronic liver disorders.

The authors were able to modify the IL-6 immune response by manipulating regulatory T cells (Treg). Sickness behaviour in BDL mice was enhanced by depletion of Treg and diminished following Treg infusion. Treg manipulation did not alter liver injury, but was associated with changes in hepatic levels of *IL-6* mRNA, plasma levels of IL-6 and peripheral blood mononuclear cell expression of IL-6. No remarkable changes were found in TNFα or IL-1β levels. The potential role of IL-6 in sickness behaviour development was further investigated in *IL-6* knockout BDL mice. These animals showed similar baseline behaviours and a resistance to developing neurological sickness behaviour after BDL. However, they exhibited typical sickness behaviours when injected with IL-6. Previously, there have been attempts to modify the course of primary biliary cirrhosis (PBC) using immunomodulatory therapies [5] that may yet be shown to be beneficial. Infusion of Treg's has been used to hasten immune reconstitution in bone marrow transplantation [6]. However, Treg therapy is not currently understood as a treatment to be applied to PBC patients, but rather as a paradigm to investigate its pathogenesis. The current study validates the BDL mice to investigate the systemic manifestations of cholestasis and supports the neurological origin of sickness behaviour. This interpretation is in accordance with data from PBC patients, in whom an increased plasma concentration of neurosteroids, which activate the GABA-A receptor and result in neuroinhibition, has been found [7]. Similarly, abnormalities in central activation and cortical inhibitory and excitatory circuits have been recently described in fatigued PBC patients in a neurophysiology study [8].

Recently, inflammation has been identified as a factor with important systemic repercussions on liver diseases [9]. Cirrhotic

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Editorial

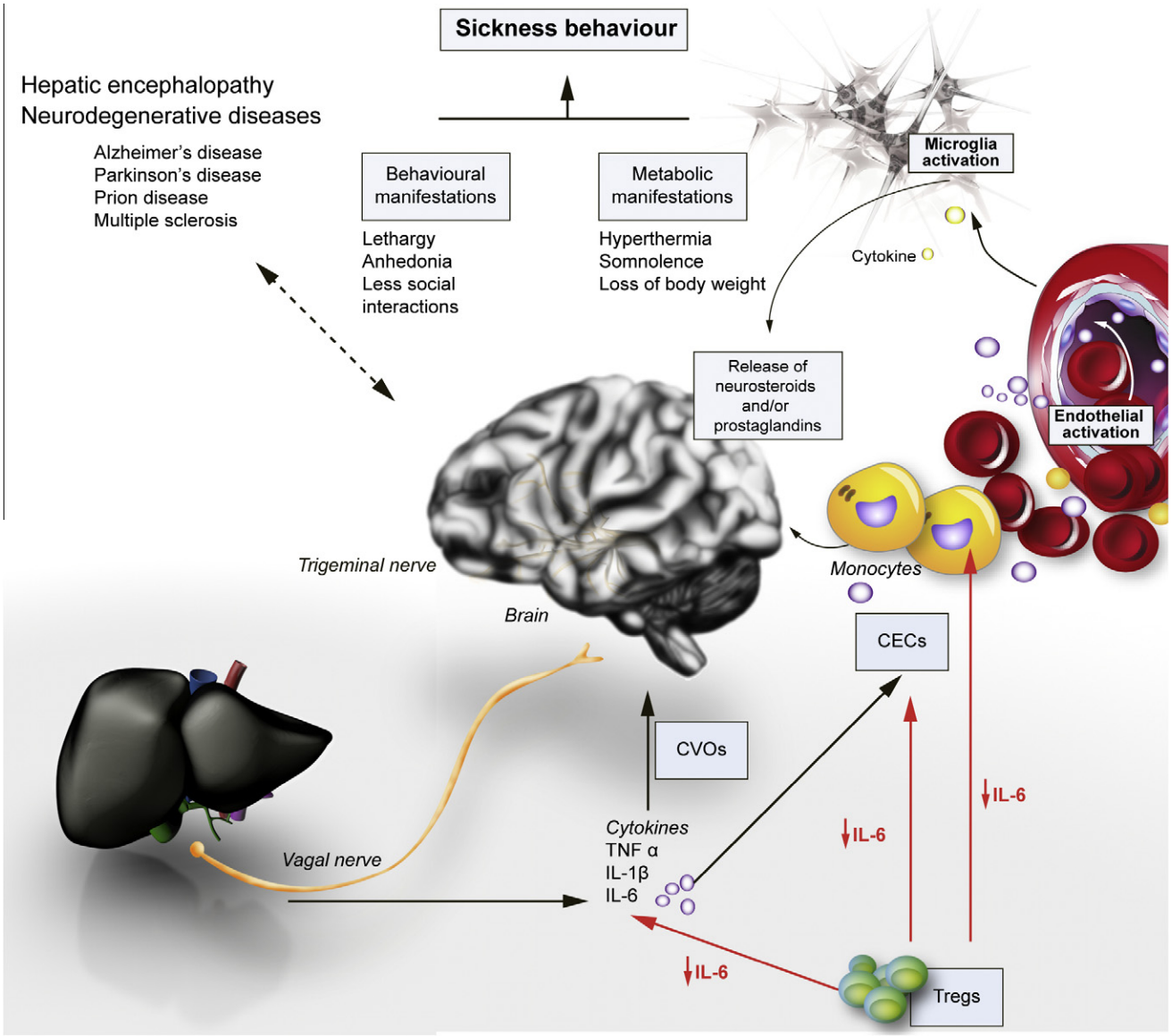

Fig. 1. Potential liver to brain communication pathways. Neural pathway: the liver is innervated by vagal afferents that can be activated by the local immune mediators such as TNFα, IL-1β, IL-6. The activated vagal afferents project to different brain areas including nucleus tractus solitarius and area postrema. Humoral pathway: cytokines synthesised locally are released to systemic circulation and reach the brain. They can either diffuse freely to the brain parenchyma in areas where there is a lack of intact blood–brain barrier such as circumventricular organ – CVOs – or activate cerebral endothelial cells – CECs – and signal the brain. Monocytes can also migrate into the brain in response to an activation of the cerebral microglia. As a result of this, there is a release of cerebral immune mediators such as neurosteroids and prostaglandins that will signal neurons and cause symptoms of sickness behaviour. Peripheral inflammation can also precipitate episodes of hepatic encephalopathy and accelerate the natural course of neurodegenerative diseases.

patients are particularly susceptible to bacterial infections which may be followed by systemic complications [10] that can be responsible for patient's demise, in spite of apparent control of the bacterial infection. The systemic inflammatory response appears to be an important mediator that leads to vasodilatation of splanchnic arterial vessels, circulatory impairment, and hepatorenal syndrome [11]. The brain has long been considered an immune-privileged organ protected from systemic inflammation by the blood–brain-barrier, a concept that has recently changed. Systemic infection can induce delirium without direct bacterial infestation of the CNS and without signs of systemic sepsis [12]. Activation of the peripheral immune system has strong effect on the brain through pro-inflammatory cytokines, which can induce delirium in susceptible subjects. Older people appear to be more sensitive due to a more permeable blood–brain-barrier, over-activation of microglia or insufficient cholinergic inhibition in the CNS. Similarly, systemic inflammation can precipitate hepatic encephalopathy in predisposed patients, due to previous small-vessel cerebrovascular disease [13], activated microglia [14] or brain atrophy [15].

Continuous activation of peripheral inflammation can have long-lasting consequences on the brain, as it has been proposed for chronic hepatitis C [16]. The occurrence of infections does increase the risk of Alzheimer's disease or accelerate the

progression of established dementia [17], probably because peripheral inflammation causes a continuous activation of microglia. The administration of non-steroidal anti-inflammatory drugs (NSAID) may become a new strategy to prevent dementia; in rheumatoid arthritis NSAID protect against the subsequent development of Alzheimer's disease [18]. In experimental models of liver failure, NSAID ameliorate cognitive disturbances [19]. However, NSAID use is not promoted in cirrhosis, because they may be dangerous due to their effects on renal function and enhanced bleeding risk. The explanation for the beneficial effects of NSAID on cognitive function is that they interfere with mediators that can cause persistent damage through bystander injury to neighbouring neurons. Activation of microglia (the "macrophages" of the brain) appears to play a pivotal role in this process. In patients with cirrhosis, infection, and inflammation are frequent precipitating factors for hepatic encephalopathy that may activate microglia [20]. Cognitive decline has been documented following an episode of encephalopathy [21], even after complete recovery of liver function following liver transplant [22]. In addition, patients with history of hepatic encephalopathy that have undergone liver transplant show permanent cognitive impairment and smaller normalised brain volume with reduced N-acetyl aspartate (an indication of neurone loss) [23].

There are multiple data that show that activation of peripheral inflammation may cause injury to the brain in patients with liver disease. The extent and consequences of the CNS damage depends on multiple factors, including the characteristics of the inflammatory response. The work by Nguyen *et al.* shows that this inflammatory process can be initiated in the liver and can cause sickness behaviour associated with cholestasic diseases. Although many questions remain unclear and further investigations are required, this study supports the notion that liver-induced inflammation hurts the brain and justifies the evaluation of new immunomodulatory therapies in liver diseases.

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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