Peripheral inflammation induces neuro-inflammation which alters neurotransmission and cognitive and motor function in hepatic encephalopathy: Underlying mechanisms and therapeutic implications

Vicente Felipo
Centro de Investigación Príncipe Felipe, Spain

Abstract

Several million patients with liver cirrhosis suffer Minimal Hepatic Encephalopathy (MHE), with psychomotor slowing and mild cognitive and coordination impairments that increase accidents, falls and hospitalizations and reduce their quality of life and life span. MHE is an important clinical, social and economic problem. Hyperammonemia and peripheral inflammation act synergistically to induce these neurological alterations. We have identified some alterations of the immune system associated with appearance of the neurological alterations in cirrhotic patients: Increased activation of all subtypes of CD4+ T-lymphocytes and of its differentiation to Th follicular and Th22. Patients died in HE show neuro-inflammation in cerebellum, with activation of microglia and astrocytes and loss of Purkinje cells. We study in animal models the mechanisms by which inflammation leads to neuro-inflammation; how neuro-inflammation alters neurotransmission and how this leads to cognitive and motor alterations. We identify therapeutic targets and assess whether treatments acting on these targets improve cognitive and motor function in rats with MHE. Rats with MHE show neuro-inflammation in hippocampus, with microglia and astrocytes activation and increased IL-1b and TNFa. This is associated with altered membrane expression of NMDA and AMPA receptors which, in turn, impairs spatial learning and memory. Rats with MHE also show neuro-inflammation in cerebellum, associated with altered GABA transporters and extracellular GABA which impair motor coordination and learning in a Y Maze. These alterations may be reversed by treatments that reduce peripheral inflammation: Anti-TNFa, reduce neuroinflammation: Sulforaphane, increase extracellular cGMP. The mechanisms by which inflammation induces neuro-inflammation, how this impairs neurotransmission and leads to cognitive and motor alteration would have common components in different pathologies including chronic diseases associated with inflammation, ageing and some mental and neurodegenerative diseases. Treatments useful to improve these mechanisms in MHE may be also useful in these pathologies.

Current evidence suggests that chronic inflammatory diseases lead to neuroinflammation. Increased neuroinflamamtion can result in neurological impairment with deficits in cognition and motor function. For example, patients with diabetes, rheumatoid arthritis, obesity or chronic kidney disease can develop neurological deficits. Inflammation and neuroinflammation are major contributing factors to cognitive and motor deficits in situations such as postoperative cognitive dysfunction, ageing and in some mental (e.g. schizophrenia) and neurodegenerative (e.g. Alzheimer's disease) diseases. Patients suffering from chronic liver diseases (mainly cirrhosisand/orhepatitis) also show chronic inflammation which can led to hepatic encephalopathy (HE): any alteration in cerebral function which is a consequence of previous liver failure. There are two main types of liver diseases which induce HE: acute liver failure and chronic liver diseases. The effects and mechanisms underlying the cerebral alterations in acute and chronic liver failure are completely different. This review will focus only on the mechanisms involved in HE in chronic liver diseases, mainly in liver cirrhosis.

Chronic liver diseases affect more than 5 million people in USA and a similar number in the European Union. Patients with the chronic liver disease do not show neurological alterations at the beginning of the disease. However, with the progression of liver failure, most of these patients will suffer from some grade of HE. There are two main forms of HE in chronic liver disease: minimal hepatic encephalopathy (MHE), in which the symptoms are not evident but can be unveiled using psychometric tests; clinical or overt HE, in which the symptoms are evident. Once the symptoms are evident, clinical HE is graded in four stages according to the West Haven criteria. Minimal hepatic encephalopathy has important consequences on daily life of patients with chronic liver diseases. Attention, mental processing speed, visuomotor and bimanual coordination are necessary for many daily tasks such as driving cars or dressing. Patients with MHE have impaired driving ability, which is associated with peripheral inflammation, with increased levels of interleukin-6 (IL-6) and IL-18. They also have increased risk of traffic, home and work accidents and more falls, fractures, and hospitalizations, which pose a high economic burden to health systems. In addition, MHE predisposes patients to clinical HE with more serious neurological impairment that can lead to coma and death and reduces life span. Early diagnosis and treatment of MHE would improve the quality of life and survival of patients and economic burden. Inflammation and neu-

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roinflammation in the neurological alterations in patients with chronic liver disease and MHE Inflammation is a main contributor to the changes in cognitive and motor functions found in MHE patients suffering from chronic liver disease. For example, the serum levels of the pro-inflammatory cytokines IL-6 and IL-18 are increased in cirrhotic patients with MHE compared with cirrhotics without MHE. Moreover, the levels of IL-6 and IL-18 correlate with the grade of MHE evaluated using psychometric tests. Hyperammonemia plays a synergistic role with inflammation in the induction of the neurologic impairment. Hyperammonemia developed in cirrhotic patients by ingestion of an amino acid mixture induces neuropsychological impairment during inflammation, but not after its resolution. The contribution of inflammation and hyperammonemia to the neurological impairment in different pathological situations with different grades of inflammation and hyperammonemia was assessed by Felipo et al., who showed that the joint presence of inflammation and hyperammonemia, is enough to induce mild cognitive impairment, even in the absence of liver failure. The studies by Shawcross et al and Felipo et al. support the idea that, as occurs in other chronic diseases, in chronic liver diseases, peripheral inflammation is involved in the induction of the cognitive and motor alterations associated to MHE and to overt HE. The in vivo studies reported above in animal models show that neuroinflammation would be a key therapeutic target to improve the cognitive and motor alterations in MHE and overt HE. However, different approaches can be used to reduce neuroinflammation in chronic liver disease, but it is important to take into account the possible secondary effects of each treatment, which may depend on the type and grade of liver disease in each patient. For example, several studies show that ibuprofen ameliorates cognitive and motor function in rats with MHE. However, ibuprofen is a non-steroidal anti-inflammatory drug (NSAID), and this type of anti-inflammatory is not recommended in cirrhotic patients because they may induce kidney damage and, in patients prone to portal hypertension (a common liver disease complication), the risk of gastrointestinal bleeding is intensified with NSAIDS. Therefore, alternative therapeutic approaches are needed to reduce neuroinflammation that would present no secondary side-effects.

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