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

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 TNF α . 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-TNF α , 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.

Biography

Vicente Felipo is the Director of the laboratory of neurobiology and of the Program on neuro-inflammation and neurological impairment of the Centro de Investigación Príncipe Felipe, Spain. He has 30 years of experience in research on the mechanisms, diagnosis and treatment of neurological alterations in hyperammonemia, hepatic encephalopathy and by exposure to food and environmental contaminants. He has published more than 300 manuscripts, 3 patents, edited 7 books, organized more than 20 international symposia and directed more than 26 doctoral theses. He has been first secretary of International Society for Hepatic Encephalopathy and member of different national and international committees.

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