



PRINCIPE FELIPE

CENTRO DE INVESTIGACION

Seminario CIPF

Effects of hyperammonemia and hepatic encephalopathy on neuronal connectivity in the brain of cirrhotic patients and animal models. Therapeutic implications.

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Abstract: Around 2 million of cirrhotic patients suffer minimal hepatic encephalopathy (MHE) in the European Union with cognitive and motor impairments which are not detected in a routine examination. MHE is associated with increased risk of accidents and of progression to worse clinical HE and with reduced quality of life and lifespan. Hyperammonemia, inflammation and neuroinflammation play a main role in the cognitive and motor alterations in MHE but the mechanisms leading to the neurological alterations are not yet fully understood.

Our group has shown by neurophysiological techniques that the auditory evoked potential mismatch negativity (MMN) is impaired in patients with MHE, showing a reduced MMN wave area correlating with attention deficits evaluated with specific psychometric tests. The mechanisms by which MMN is impaired in MHE are not known. The aim of this work is to identify mechanisms underlying the impairment of MMN in MHE. We hypothesize that 1) hyperammonemia is a main contributor to impairment of MMN in MHE and 2) the functional connectivity between the different areas involved in the generation of the potential may be altered in hyperammonemia. To assess these hypotheses we:

1. Designed and implemented a system with the hardware and software necessary to register and analyze in rats the auditory evoked MMN potential and the connectivity between different areas involved in its generation. We found that hyperammonemic rats show reduced amplitude and area of the MMN wave, especially in hippocampus, thus reproducing the impairment found in MHE patients. The communication between different areas involved in evocation of the potential is altered in hyperammonemic rats. Treatment with the anti-inflammatory Ibuprofen restores the area and the amplitude of the MMN potential and improves the communication between the different areas in the delta band.
2. We also analyzed in cirrhotic patients with and without MHE the structural integrity and functional connectivity in brain in resting-state by magnetic resonance. This sheds light on how altered structural integrity and functional connectivity in the hippocampal system would contribute to impairment of learning ability and long-term memory in patients with MHE. Patients with MHE also show reduced gray matter volume and functional connectivity in some neuronal networks involved in attention and executive functions which correlate with cognitive impairment.

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