Cerebellar inhibition in hepatic encephalopathy - a transcranial magnetic stimulation study

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Abstract:

Hepatic Encephalopathy (HE) is a frequent complication in patients suffering from liver cirrhosis. HE comprises a variety of neuropsychiatric and motor symptoms. Increased ammonia levels have been suggested as a key factor in the disease pathology. Using animal models, Cauli and colleagues reported that hyperammonemia may lead to brain area depending alteration of GABAergic neurotransmission with an increase of GABAergic tone in the cerebellum and a decrease in the cerebral cortex. Consistent with this data, recent work from our group revealed a reduced GABAergic tone in the motor cortex of patients with manifest HE using transcranial magnetic stimulation (TMS). The aim of this study is to probe how GABAergic cerebellar tone is altered in patients at different stages of HE and how this alteration is related to clinical parameters such as the critical flicker frequency and ataxia scoring. Methods: 30 participants [15 patients with HE (5 minimal HE, 6 HE grade I, and 4 HE grade II) and 15 age matched healthy controls] were subjected to the following: 1- Critical flicker frequency (CFF) which is a sensitive and reliable parameter for quantification of low-grade HE in cirrhotic patients. 2- Cerebellar brain inhibition TMS paradigm (CBI): in this paradigm, a conditioning TMS pulse is applied over one hemisphere of the cerebellum followed by a test pulse over the contralateral motor cortex resulting in a motor evoked potential (MEP). In healthy subjects, the MEP is inhibited when the test stimulus is preceded by the conditioning stimulus at an interval between 5-7 ms through inhibition of the fascilitatory disynaptic dentato-thalamo-cortical pathway. 3- Score for assessment and rating of ataxia (SARA) to detect symptoms of cerebellar affection. Results: Cerebellar inhibition at ISI 5 to 7 ms was significantly reduced in patients with HE compared to healthy controls. However, the magnitude of cerebellar inhibition at 7 ms increases with disease severity and correlated with SARA score and with CFF by trend. Conclusion: Overall cerebellar inhibition is significantly reduced in patients with HE, suggesting affection of the dentato-thalamo-cortical pathway in this disease. However, the magnitude of cerebellar inhibition at 7 ms increases with disease severity and correlates with SARA score and with CFF by trend, supporting the hypothesis of disease stage dependent increase of GABAergic tone in the Purkinje cells. Our results are consistent with pervious animal in vitro data suggesting increased GABA-ergic tone in the cerebellum and decreased GABA-ergic tone in the motor cortex.

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