Cerebellum. 2015 Feb;14(1):19-22. doi: 10.1007/s12311-014-0613-0.

IL-1β dependent cerebellar synaptopathy in a mouse mode of multiple sclerosis.

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Abstract

Multiple sclerosis (MS) is considered as an autoimmune inflammatory disease and is one of the main causes of motor disability in young adults. Focal white matter lesions consisting of T lymphocyte and macrophage infiltrates, demyelination, and axonal transection are clear hallmarks of MS disease. However, white matter pathology does not occur exclusively. Clinical and experimental studies have shown gray matter atrophy and lesions occurring in several brain regions, including the cerebellum. Cerebellar-dependent disability is very common in MS patients. Cerebellar deficits are also relatively refractory to symptomatic therapy and progress even under disease-modifying agents. However, the neuropathology underlying cerebellar dysfunction remains largely unknown. We recently demonstrated that the cerebellum is also targeted in experimental autoimmune encephalomyelitis (EAE), the most widely used animal model of MS. Electrophysiological studies, supported by immunofluorescence and biochemical analysis, revealed an imbalance between the spontaneous excitatory and inhibitory synaptic transmission at Purkinje cell synapses. While the frequency of the spontaneous inhibitory postsynaptic currents (sIPSC) during the acute phase of EAE was reduced in correlation with a selective degeneration of basket and stellate neurons, the glutamatergic transmission was enhanced due to a reduced expression and functioning of glutamate aspartate transporter (GLAST)/excitatory amino acid transporter 1 (EAAT1), the most abundant glutamate transporter expressed by Bergmann glia. Of note, we demonstrated that the proinflammatory cytokine interleukin-1β (IL-1β), highly expressed in EAE cerebellum and released by infiltrating lymphocytes, was one of the molecular players directly responsible for such synaptic alterations during the acute phase. Furthermore, other brain regions in EAE mice seem to be affected by a similar inflammatory dependent synaptopathy, suggesting common molecular targets for potential therapeutic strategies. Accordingly, we observed that intracerebroventricular inhibition of IL-1β signaling in EAE mice was able to ameliorate inflammatory reaction, electrophysiological response, and clinical disability, indicating a pivotal role of IL-1β in EAE disease and likely, in MS.

PMID:25326653

DOI:10.1007/s12311-014-0613-0

[PubMed - indexed for MEDLINE]