Presynaptic mechanisms in multiple sclerosis: studies in neuronal cultures and in experimental autoimmune encephalomyelitis

[1]F.C. Guarnieri, [1]R. Cervigni, [1]S. Bellani, [2]D. Pozzi, [1]E. Monzani, [1]E. Fornasiero, [1]L. Yekhlef, [1]S. Taverna, [1]G. Martino, [1]L. Muzio and [1]F. Valtorta
[1] Division of Neuroscience, San Raffaele Scientific Institute, Milan, Italy;
[2] Humanitas Clinical and Research Center, Rozzano, Milan, Italy

The classical view of multiple sclerosis (MS) pathogenesis states that inflammation-mediated demyelination is responsible for neuronal damage and loss. However, recent findings show that impairment of neuronal functions and demyelination can be independent events, suggesting that other mechanisms coexist. It is now clear that more subtle alterations in synaptic function occur, due to the inflammatory milieu, and are probably at the basis of the early cognitive decline that often precedes the neurodegenerative phases of the disorder in MS patients. In particular, it has been reported that inflammation enhances excitatory synaptic transmission while it downregulates GABAergic transmission in vitro and ex vivo. These evidences point to the idea that an excitation/inhibition imbalance establishes in the MS brain, even though the exact molecular mechanisms leading to this synaptic dysfunction are as yet not completely clear.
Along this line, our results point to a possible key role in MS pathogenesis of synapsin I (SynI), a regulator of excitation/inhibition balance in neuronal networks. We observed that acute treatment of primary hippocampal neurons in culture with inflammatory cytokines leads to an increase in neuronal excitability and in SynI phosphorylation. Chronic exposure of neurons reduces the levels of synaptic markers and this effect is much more pronounced in neurons deleted for SynI. In addition, in SynI knock-out (KO) mice the chronic phase of experimental autoimmune encephalomyelitis (EAE) is milder than in wild-type (WT) animals. Our results suggest that synapsin may be a crucial mediator of the neuronal response to pro-inflammatory cytokines.