Preynaptic homeostatic mechanisms in multiple sclerosis: studies in cultured neurons and in mouse models

The classical view of multiple sclerosis (MS) pathogenesis states that inflammation-mediated demyelination is responsible for neuronal damage and loss. However, 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 disabling neurological and cognitive deficits observed 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 points 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.

The aim of the current project is to elucidate the effects of prolonged inflammation on synaptic function/structure and unravel the possible role of synapsins, regulators of excitation/inhibition balance in neuronal networks, in mediating these effects, both in vitro and in vivo, by taking advantage of SynI KO mice available in the laboratory. In particular, we will characterize the functional effects of chronic incubation of hippocampal neurons in culture with inflammatory cytokines, through the use of imaging and electrophysiological approaches aimed at studying synapse remodelling, vesicle exo-endocytosis and presynaptic function in the presence or absence of SynI. In vivo, we will further investigate the consequences of SynI ablation in terms of disease progression, through the clinical evaluation of the experimental autoimmune encephalomyelitis model, and of neurotransmitter release in relevant brain areas, through in vivo electrophysiological recordings. Indeed, the identification of the molecular mechanisms at the basis of neuronal alterations occurring in MS pathogenesis may lead the route for the development of novel therapeutic approaches.

Website: http://www.sanraffaele.org/research/valtorta

Key references: