Synaptic pathology in multiple sclerosis: a role for Nogo-A signaling in astrocytes?

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Multiple sclerosis (MS) is characterized as an inflammatory demyelinating disease that affects the central nervous system (CNS), leading to sensory, motor and cognitive impairments. Ultimately, axonal denudation culminates in axonal lesions and neurodegeneration. Inflammatory demyelinating lesions in MS are associated with infiltration of immune cells, including T-cells and macrophages, with activation of the resident CNS inflammatory cells, astro- and microglia. Recently, synaptopathy has been induced in MS with MS pathophysiology, though, intriguingly, it can occur independently of demyelination (Jürgens et al., 2016). Although inflammation also seems to corroborate with synaptic abnormalities, associated or not with demyelinating lesions, the underlying mechanisms are not fully understood (Mandolesi et al., 2015). In the last decades, the myelin inhibitory protein neurite outgrowth inhibitor-A (Nogo-A) has emerged as a potential mediator of axonal synapseslogenesis (Espírito-Santo et al., 2021), and considering the critical role of astrocytes in regulating synaptic plasticity and function (Allen and Eroglu, 2017), we propose that modulation of Nogo-A pathway in these cells is a new mechanism driving circuitry alterations of MS.

Synaptopathy in MS: Synaptic alterations are hallmarks of MS expressed even in the early stage of the disease both in patients and in animal models of MS, such as experimental autoimmune encephalomyelitis (EAE) and cuprizone-induced demyelination, being directly associated with neurological disabilities. This profile of synaptopathy has been characterized by perturbations of molecular machinery from glutamatergic and GABAergic (γ-aminobutyric acid, GABA) neurotransmission, implicating in excitatory/inhibitory imbalance, with predominant excitability. Sustained activation of glutamate-activated Ca2+ permeable receptors along with reduced glutamate uptake in the synaptic cleft deregulates Calcium homeostasis, leading to synaptic excitotoxicity. Activated micro- and astroglia release inflammatory molecules, particularly tumor necrosis factor-alpha (TNF-α) and interleukin-1 beta (IL-1B), that are implicated with neurotransmission perturbation in experimental MS and patients. Contributing to excitation, TNF-α induces α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor (AMPAR) insertion on the neuronal surface, promoting an increase in AMPAR-dependent excitatory postsynaptic currents. IL-1B signaling, along with its downstream mediator miR-142-3p, promotes reduction in astrocytic glutamate-aspartate transporter expression and activity, impairing glutamate reuptake and leading to the enhancement in the duration of excitatory postsynaptic currents. Other studies still report a reduction in GABAergic transmission by the action of IL-1B, also favoring excitation. The resulting hyperexcitability, which has been related to a higher probability of epilepsy development in MS patients, seems to be adaptive plasticity that aims to restore the impaired neuronal activity due to demyelination (Mandolesi et al., 2015). Despite its importance to reinforce synaptic inputs into target neurons, it may chronically result in excitotoxicity and synaptic loss. Thus, astrocyte and microglia chronic activation is a critical phenomenon to synaptopathy development and maintenance at the MS course and therapeutic approaches targeting its regulation are required.

Along this line, we recently demonstrated that cuprizone-induced acute demyelination increases the density of excitatory synapses in the visual cortex (Espírito-Santo et al., 2021). These results led to the hypothesis that excitatory synaptopathogenesis could represent a mechanism that precedes and contributes to hyperexcitability in MS (Figure 1). Indeed, evaluation of the pre-synaptic protein synapsin 2 in the brain during different phases of EAE revealed enhanced levels in the pre-synaptic phase with progressive decreased levels in posterior phases (Raphael et al., 2017). Aligned with this idea, other studies have reported excitatory contacts loss associated with MS synaptopathy and/or grey matter atrophy as a result of long-term injury, especially during later and progressive phases of MS (Mandolesi et al., 2015). Conversely, at the onset or established phase of the disease from EAE model, pre-synaptic proteins and/or spine density are enhanced in the somatosensory cortex (Poter et al., 2016). Therefore, the confirmation if new excitatory contacts is an early step of MS course which results in hyperexcitability, excitotoxicity and synaptic loss in MS, should benefit from further studies investigating different phases of the disease, and distinct regions of different animal models and MS patients. Considering the actual lack of treatments for the later phase of the disease, unveiling the events underlying synaptic pathology will pave an essential way to the search for novel targets to prevent neurological deterioration during MS course.

Nogo-A in MS: The mechanisms underlying synaptic dysfunction in the MS are still not fully understood, but the Nogo-A protein, a potent neuroplastic inhibitor of adult CNS, has emerged as a candidate in this context. Nogo-A is a component of the myelin sheath that exists as a transmembrane protein expressed by oligodendrocytes, and in a lower degree by neurons. In general, it binds to Nogo Receptor 1 (Ngr1), which, through TROY/p75 and LINGO-1 complex of receptors, activates the RhoA signaling, modulating actin-based morphology (Ineichen et al., 2017). Particularly, Nogo-A inhibits synapse formation, through ROCK-cofilin signaling, downstream to RhoA activation, which leads to the destabilization of the actin cytoskeleton and decrease of dendritic spine density (Kellner et al., 2016).

In the context of MS, studies in animal models have reported that suppression of Nogo-A promotes: clinical improvement, slowed disease progression, reduced demyelination and axonal damage. Despite the lack of consensus of its physiopathological role in MS, both Nogo-A and its receptor neutralization have been employed in different phase I and II clinical trials, with inconclusive results so far (Ineichen et al., 2017). Besides, the last years also described an influx of studies investigating Nogo-A and its receptor as biomarkers for MS and other demyelinating inflammatory diseases in the CNS, both in liquor and blood serum. In fact, both in MS and animal models, the levels of Nogo-A and its receptor are regulated in the course of the disease, by mechanisms still unknown; whereas Nogo-A is reduced in the acute phase of MS, it increases in the chronic phase, mainly in surviving oligodendrocytes and myelin sheath. Interestingly, this MS stage-dependent variation would be a potential target for therapeutic intervention in the MS course.
Nogo-A signaling in astrocytes and synaptopathy in MS: Astrocytes are regulators of synaptogenesis and plasticity in CNS. They can control glutamatergic excitatory synapses mainly through released soluble factors that have been described by our group and others: transforming growth factor-beta 1 and ROCK, the antagonist of ROCK, activates the Nogo-A pathway. The effect on hyperexcitability could be investigated by behavioral analysis and in vivo electroencephalogram evaluation of provoked seizures, which may trigger neurodegeneration. The Nogo-A pathway also seems to be a new target for treatment in MS. Besides, astrocytes regulate synapse formation and function, and it is expected Nogo-A signaling on astrocytes may indirectly contribute to synaptic dysfunction in MS.

Future directions: For a better understanding of the pathophysiological events of MS, the hypothesis that Nogo-A signaling in astrocytes contributes to increased cortical excitability through excitatory synaptogenesis and excitotoxicity needs to be tested. This question can be answered using animal models of MS submitted to astrocyte conditional deletion of proteins belonging to the Nogo-A-activated pathway. The effect on hyperexcitability could be investigated by behavioral analysis and in vivo electroencephalogram evaluation of provoked seizures, which may trigger neurodegeneration.

Another remaining question is whether synaptic loss and neurodegeneration during the chronic phase of MS, in which inflammation is less relevant, is associated to increased Nogo-A levels and astrocyte dysfunctions. Also in this case, astrocytic conditional deletion of proteins belonging to the Nogo-A-activated pathway would be helpful. These results can clarify a new field of investigation, that might contribute to the identification of novel targets to fight the synaptic-related symptoms of MS.

Finally, the available treatments for MS are based on immunomodulation, which is effective for the inflammatory, but inefficient for the neurodegenerative phase [Ineichen et al., 2017]. Besides, current treatments end up neglecting synaptic plasticity, an aspect of synaptogenesis mediated by Nogo-A. A successful depression of Nogo-A pathway should provide a more efficent response.

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