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EDITORIAL HIGHLIGHT

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New actors in optic neuritis pathogenesis

An Editorial for "Influence of retinal NMDA receptor activity during autoimmune optic neuritis" on https://doi.org/10.1111/jnc.14980

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Abstract

The aim of the present report was to analyze the involvement of glutamate neurotoxicity in retinal ganglion cell loss and optic nerve damage induced by experimental optic neuritis. For this purpose, the authors used an optic neuritis model induced by immunisation with myelin oligodendrocyte glycoprotein (AON). The authors describe a correlation in the timing of retinal ganglion cell (RGC) loss with alterations in the optic nerve actin cytoskeleton dynamic, and visual dysfunction. In addition, they show that an intravitreal injection of glutamate mimics, and an NMDA receptor antagonist avoids the effect of pre-clinical AON on visual functions and RGC number, as well as on optic nerve actin cytoskeleton. Taken together, their results support that avoiding glutamate neurotoxicity could become a new therapeutic approach for optic neuritis treatment.

Optic neuritis, a neuropathy which affects mainly young adults and children, provokes primary inflammation, demyelination, and optic nerve axon injury, leading to retinal ganglion cell (RGC) death and visual dysfunction (Aranda, Dorfman, Sande, & Rosenstein, 2015; reviewed by Toosy, Mason, & Miller, 2014). Alterations in visual acuity, visual field, visual evoked potentials, and pupillary reflex, peri- or retro-ocular pain increased by eye movement, and color vision diminution are pathognomonic clinical signs of optic neuritis. The visual dysfunction may worsen in 1 or 2 weeks, but usually begins improving along the following weeks; however, visual alterations (visual acuity, visual evoked potentials, pupillary response, visual field, contrast sensitivity, color vision, and stereopsis) might persist in ~40% of the patients. In addition, recurrent optic neuritis episodes can provoke optic nerve atrophy and vision loss, associated with RGC death. Optic neuritis is highly associated with multiple sclerosis, being the initial symptom in 25% of cases, and occurring during the disease in ~70% of patients, mainly in the relapsing-remitting phase (Toosy et al., 2014).

Corticosteroids are the current therapy pillars for optic neuritis treatment. However, although steroids may increase the speed of visual recovery, the overall visual recuperation is not affected by treatment, which does not prevent axonal and RGC loss (Gal, Vedula, & Beck, 2015). Therefore, neuroprotective therapies for optic neuritis are still an unmet clinical demand (Bojcevski et al., 2020).

Based on the clinical association between multiple sclerosis and optic neuritis, the most frequently employed experimental model for studying optic neuritis is experimental autoimmune encephalomyelitis (EAE), a reliable model of human multiple sclerosis, involving an immune-mediated demyelination process. In the present report, Bojcevski et al. induce autoimmune optic neuritis (AON) in female *Brown Norway* rats by immunisation with myelin oligodendrocyte glycoprotein (Bojcevski et al., 2020). Since RGCs are particularly susceptible to glutamate-induced excitotoxicity, the authors examine the involvement of NMDA receptors on RGC loss, visual dysfunction, and optic nerve actin cytoskeleton network dynamics during the induction phase of AON (Bojcevski et al., 2020). The authors show a correlation in the timing of RGC degeneration with alterations in the optic nerve actin cytoskeleton dynamics and visual disturbances. In particular, the authors demonstrate that the optic nerve globular to filamentous (G-F) actin ratio and fractin levels increase, while gelsolin (an F-actin-binding protein) levels decrease along the disease progression (Bojcevski et al., 2020). At advanced (but not early) stages of AON, these findings correlate with transported protein (β amyloid precursor protein, synaptophysin, and kinesin) accumulation. An

Abbreviation: RGC, retinal ganglion cell; EAE, experimental autoimmune encephalomyelitis; AON autoimmune optic neuritis

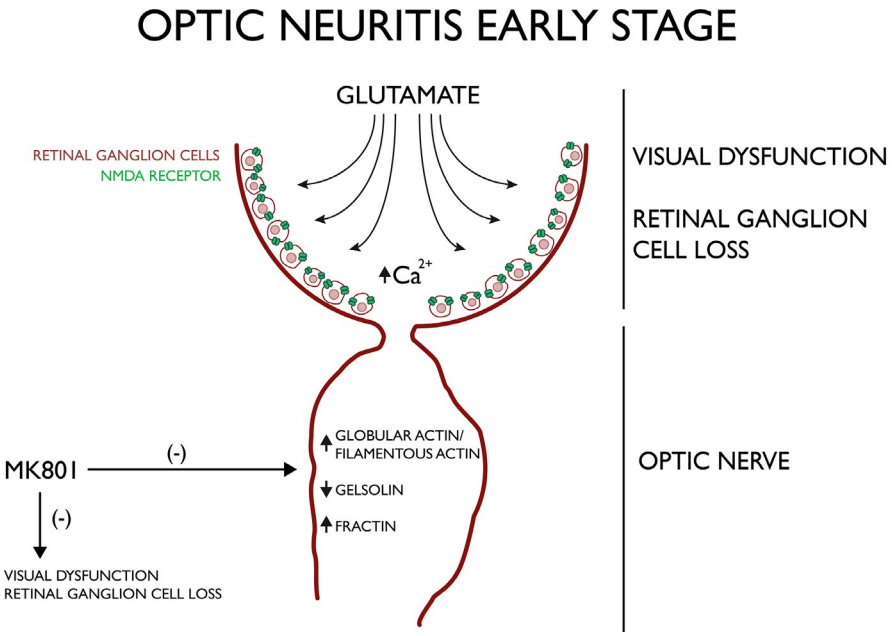

FIGURE 1 In an optic neuritis model induced by immunisation with myelin oligodendrocyte glycoprotein (AON), a correlation in the timing of retinal ganglion cell (RGC) loss with alterations in the optic nerve actin cytoskeleton dynamic, and visual dysfunction, is observed. An intravitreal injection of glutamate mimics, and an NMDA receptor antagonist avoids the effect of pre-clinical AON on visual functions and RGC number, as well as on optic nerve actin cytoskeleton. The increase in calcium levels during the initial stages of AON is prevented by MK-801. Therefore, the impairment of glutamate neurotoxicity could become a new therapeutic strategy for optic neuritis treatment

intravitreal injection of glutamate mimics the effect of pre-clinical AON on RGC number, as well as on optic nerve G/F-actin ratio, and fractin (but not gelsolin) levels, at 24 hr post-injection. In addition, glutamate intravitreal injection induces a decrease in pattern visual evoked potential (an index of RGCs-visual cortex pathway), and pattern electroretinogram (an index of RGC activity) amplitudes. In order to analyze the role of NMDA receptors in RGC degeneration and upstream optic nerve actin cytoskeletal changes, the authors intravitreally inject a potent NMDA receptor antagonist (MK-801) into rats with AON (Bojcevski et al., 2020). MK-801 partly avoids RGC dysfunction and loss (Figure 1), and completely prevents G/F-actin ratio, fraction and gelsolin level changes induced by AON (Bojcevski et al., 2020). In agreement with other reports (Das et al., 2013), the authors show an increase in calcium levels during the initial stages of AON (as indicated by manganese-enhanced magnetic resonance imaging) that is reduced by MK-801, supporting that NMDA receptors contribute to alterations in the optic nerve, probably by regulating retinal calcium content (Bojcevski et al., 2020).

It should be noted that in their experimental setting, RGC loss precedes the onset of immune cell infiltration, axon loss, and demyelination of the optic nerve (i.e., a pre-clinical stage of AON), which is in contrast with several reports showing that axonal loss occurs before the loss of RGC bodies in different experimental models of optic neuritis in rats and mice (Aranda et al., 2015; Brambilla et al., 2012; Quinn, Dutt, & Shindler, 2011; Shindler, Ventura, Dutt, & Rostami, 2008). In addition, RGC loss induced both by AON and intravitreal glutamate depicted in this report (between 7% and 11%) is considerably lower than that shown by other groups (Aranda et al., 2016; Brambilla et al., 2012; Quinn et al., 2011; Shindler et al., 2008). Another limitation of this study relies on the fact that the authors cannot establish whether the cytoskeletal changes induced by AON or glutamate occur in optic nerve axons or astrocytes, oligodendrocytes, or microglial cells. Despite these discrepancies and limitations, their results provide strong evidence supporting: (1) the alteration of optic nerve actin dynamics as an early pathogenic event in optic neuritis, and (2) a glutamate-dependent mechanism in retinal/optic nerve damage induced by optic neuritis. Thus, their results support that the impairment of glutamate neurotoxicity could constitute a fertile avenue for the advance in the search of new therapeutic strategies for optic neuritis treatment.

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