Abstract

Autoimmune posterior uveitis (APU) is an inflammatory condition of the choroid, the posterior segment of the uvea. However, given its close proximity to the retina, APU often affects the adjoining retinal tissue, which may ultimately lead to vision impairment. Despite advancements in recent research, current treatments for APU are unable to completely cure the disease or provide strategies for retinal tissue regeneration. Neurotrophins, including brain-derived neurotrophic factor (BDNF), play crucial roles in nervous system development, growth, and regeneration and also regulate the activity of the immune system. Moreover, BDNF increases the expression of the nerve growth factor inducible VGF (non-acronymic), which is also involved in the modulation of neural and immune functions.

This doctoral dissertation aimed to assess the dual effects of BDNF and VGF, specifically their involvement in the neuroprotective and immunomodulatory mechanisms that may control the pathogenesis of APU, using a mouse model of experimental autoimmune uveoretinitis (EAU) and the ocular administration of BDNF and the VGF-derived peptide TLQP-21. The study also explored the neuroprotective and immunomodulatory effects of BDNF and TLQP-21 on Müller cells (MCs) in vitro. Additionally, this study investigated the ability of high-contrast visual stimulation (VS) to naturally induce BDNF and VGF expression in the retina and MCs in healthy and uveitic mice and the possibility of the retrograde axonal transport of BDNF from the visual brain areas to the retina.

Results from this study demonstrated that high-contrast VS in optomotor drum enhanced mRNA and protein expression of BDNF in retinal neurons and MCs but upregulated VGF only on the mRNA level in both healthy and uveitic retinas. Furthermore, high-contrast stimulation with pulsed light as well as, BDNF, promoted the neuroprotective properties of MCs in vitro by suppressing inflammatory reactive gliosis and inducing their dedifferentiation into neural progenitor cells, pointing to the potential therapeutic mechanism for retinal regeneration. When examining in more detail, we revealed that VS increased not only retinal BDNF expression but also induced the expression of BDNF in the neurons and astrocytes of the superior colliculus, from which it was retrogradely transported to the retina.

In addition, ocular administration of the exogenous BDNF to EAU mice in the form of eyedrops produced similar results as in vitro experiments on MCs. BDNF significantly reduced reactive gliosis in the retina and promoted the neurogenic attributes of MCs by stimulating their proliferation and dedifferentiation into neural progenitors. At the same time, we observed

generation of the newly formed retinal neurons in the ganglion cell layer and inner nuclear layer of the retina. These protective functions of BDNF ultimately resulted in improved clinical symptoms of EAU.

TLQP-21 treatment of MCs in vitro also promoted MC neurodifferentiation and inhibited their pro-inflammatory properties like BDNF. Comparably, the topical ocular treatment of EAU mice with TLQP-21 displayed partial protective effects, as evidenced by a moderate improvement of the clinical manifestations of EAU, decreased reactive gliosis, and downregulation of pro-inflammatory mediators in the retina. In addition, TLQP-21 also enhanced dedifferentiation of MCs and supported neuronal proliferation in EAU mice. However, given that BDNF treatment of EAU mice did not influence the expression of VGF in the retina, it can be assumed that the beneficial effects of BDNF were not mediated through TLQP-21, a peptide derived from the VGF precursor molecule.

Our findings suggest that BDNF and VGF play a significant neuroprotective and immunomodulatory role in the retina. Therefore, enhancement of BDNF or VGF activity, whether achieved endogenously by VS or augmented by exogenous administration, holds a promising therapeutic potential in the treatment of neurodegenerative and neuroinflammatory conditions of the retina, such as APU.