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Mitochondrial Targeted Therapy with Elamipretide (MTP-131) as an Adjunct to Tumor Necrosis Factor Inhibition for Traumatic Optic Neuropathy in the Acute Setting

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Abstract

Traumatic optic neuropathy (TON) can occur following blunt trauma to the orbit and can lead to permanent vision loss. In this study, we investigated the effectiveness of elamipretide (MTP-131), a small mitochondrially-targeted tetrapeptide, in conjunction with etanercept, a tumor necrosis factor (TNF) inhibitor, as neuroprotective agents of retinal ganglion cells (RGCs) after optic nerve trauma with sonication-induced TON (SI-TON) in mice. Treatment with intravitreal MTP-131 and subcutaneous etanercept and MTP-131 showed a 21% increase ($p < 0.01$) in RGC survival rate compared to PBS-treated control eyes. Subcutaneous etanercept and MTP-131 had an 11% increase ($p < 0.05$) in RGC survival compared to controls. Subcutaneous etanercept only group showed 20% increase ($p < 0.01$) in RGC survival compared to controls, while subcutaneous MTP-131 alone showed a 17% increase ($p < 0.01$). Surprisingly, we did not observe a synergistic effect between the two drugs in the group receiving both etanercept and MTP-131. One possible explanation for the absence of a synergistic effect is that MTP-131 and etanercept may be acting on different portions of the same pathway.

Keywords

traumatic optic neuropathy; elamipretide; tumor necrosis factor

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Traumatic optic neuropathy (TON) is a rare etiology of permanent vision loss after blunt force trauma to the orbit (Guy et al, 2014; Kumaran et al, 2015). Early on, patients will usually present with either partial or total loss of vision, afferent pupillary defect, and visual field defects (Kumaran et al, 2015). Over time, the optic disc will become pallorous. As of now, no evidence-based therapy exists to effectively treat TON, as observation, corticosteroids, and optic canal decompression have all been shown to be ineffective in improving visual outcomes (Singman et al, 2016; Chaon et al, 2015; Yan et al, 2017; Goldberg et al, 1996; Yu et al, 2016; Kashkouli et al, 2017; Yu-Wai-Man et al, 2013; Yu-Wai-Man et al, 2005; Yu-Wai-Man et al, 2013). This was best demonstrated in the International Optic Nerve Trauma Study which observed no significant difference in visual outcomes of TON patients treated with either corticosteroid therapy or optic canal decompression surgery (Levin et al, 1999; Carta et al, 2003).

Following TON injury, histopathologic changes seen include axonal degeneration and retinal ganglion cell (RGC) death (Singman et al 2016). We have previously developed a TON injury model using ultrasonic shockwaves (sonication-induced TON: SI-TON) that better simulates the most common mechanism of TON seen clinically (Tao et al, 2017). During this process, we found via quantitative RT-PCR significant increases in tumor necrosis factor (TNF), amongst other pro-inflammatory cytokines, in optic nerves after SI-TON (Tao et al, 2017). Subsequently, we demonstrated in the SI-TON animal model that etanercept treatment after TON significantly improved RGC survival, preserved retinal architecture, and improved RGC function, as evidenced by larger a-wave amplitudes on pattern electroretinogram (PERG) (Tse et al, 2018).

Additionally, during the characterization of these acute molecular events in TON, we recorded an elevation in reactive oxygen species (ROS) within the retina using Red Mitochondrial Superoxide Indicator (Tao et al, 2017). Mitochondria play a crucial role not only in the production of ROS but are also the target of oxidative stress (Ott et al, 2007; Lenaz, 1998). Elamipretide (MTP-131 or SS-31) is a water-soluble tetrapeptide that crosses the outer membrane of the mitochondria where it localizes to the inner membrane and associates with cardiolipin (Szeto et al 2014). Cardiolipin, which is solely expressed on the inner mitochondrial membrane, plays a critical role in cristae formation, mitochondrial fusion, mtDNA stability and segregation, and the organization of respiratory complexes into supercomplexes for oxidative phosphorylation (Sabbah et al, 2016; DeVay et al, 2009; Joshi et al, 2012; Luevano-Martinez et al, 2015; Zhao et al, 2004; Birk et al, 2013). Elamipretide has been shown to enhance cellular ATP synthesis to improve electron transport and reduce the formation of ROS, with no negative effects on healthy mitochondria in multiple organs, including heart, kidney, neurons, and skeletal muscle (Dai et al, 2013; Szeto et al, 2011; Talbert et al, 2013; Yang et al, 2009; Brown et al, 2014). Along with its ROS reducing effects, MTP-131 inhibits lipid peroxidation and prevents mitochondrial swelling, aiding in mitochondrial protection (Zhao et al, 2005). MTP-131 has been mainly studied in the setting of ischemia/reperfusion injury. In myocardial infarction animal models, MTP-131 administration reduced experimental myocardial infarct size (Kloner 2017; Kloner et al, 2012). Saad et al demonstrated that MTP-131 improved renal blood flow and kidney function while reducing kidney hypoxia after stent revascularization in patients with atherosclerotic renal artery stenosis (Saad et al, 2017). MTP-131 has been studied in relation

to several eye diseases and has been shown to have neuroprotective effects in an experimental rat glaucoma model (Wu et al, 2019), prevent high glucose-induced injuries on human retinal endothelial cells (Li et al, 2011), and have antioxidant and anti-apoptotic effects on trabecular meshwork, human lens epithelium, and retinal ganglion cell lines when placed under conditions of oxidative stress (Chen et al, 2017; Chen et al, 2011; Cai et al, 2015). The purpose of this study was to evaluate the effectiveness of both systemic and local (via intravitreal injection) administration of MTP-131 in conferring neuroprotection to RGCs after optic nerve trauma with SI-TON in mice. This study also aimed to examine any synergistic effects MTP-131 would have with etanercept, a non-selective TNF inhibitor, on RGC survival. To our knowledge, this is the first study to evaluate MTP-131 for neuroprotection in the setting of TON.

All chemicals and reagents were purchased from Sigma-Aldrich (St. Louis, Missouri, United States) and Thermo Fisher Scientific Inc. (Waltham, Massachusetts, United States). Elamipretide (Stealth BioTherapeutics, Newton, MA, United States) was obtained from Stealth BioTherapeutics through an MTA agreement. Etanercept (Enbrel, Pfizer, NY) was purchased from the medical pharmacy in Bascom Palmer Eye Institute. All animal experiments were performed in compliance with the NIH Guide for the Care and Use of Laboratory Animals and the ARVO statement for the use of animals in ophthalmic and vision research. Animal protocols were reviewed and approved by the Institutional Animal Care and Use Committee of the University of Miami. C57BL/6 J mice were obtained from Jackson Laboratory (Bar Harbor, Maine). Mice were housed under ambient conditions (standard humidity and temperature) with a 12-hour light/dark cycle. 3-month-old mice were used for the study. Twenty-five mice were used. Left optic nerves were injured (SI-TON model) in all animals; the right optic nerves were not injured. Mice were divided into five treatment groups: PBS (control) (n=5), intravitreal MTP-131 plus subcutaneous etanercept and MTP-131 (n=5), subcutaneous etanercept and MTP-131 (n=5), subcutaneous etanercept (n=5), and subcutaneous MTP-131 (n=5). In mice receiving intravitreal injections, a one-time injection of 100 nM MTP-131 (1.3 μ L) was done intravitreally into the left eye fifteen minutes after SI-TON. In mice receiving only subcutaneous etanercept (10 mg/kg body weight) or MTP-131 (5 mg/kg body weight), daily injections were given on days 0-2 after SI-TON. In mice receiving subcutaneous etanercept (10 mg/kg body weight) and MTP-131 (5 mg/kg body weight) sequentially, etanercept injections were given daily on days 0-2 after SI-TON; daily MTP-131 injections were given on days 3-5 after SI-TON. All mice were euthanized at 4 weeks after SI-TON (Tao et al, 2017). Eyes were enucleated and fixed in 4% PFA. Retinas were collected and stained for the RGC marker tubulin- β III (TUJ1). RGCs were quantified as described earlier (Tao et al, 2017). The Student *t*-test was conducted for single comparisons. P value < 0.05 were considered to be statistically significant. We found that in the PBS vehicle control group, the average RGC count in injured eyes was $77 \pm 2\%$ that of the uninjured contralateral eye counts (Figure 1). In the intravitreal MTP-131 plus subcutaneous etanercept and MTP-131 group, percentage of RGC survival compared to contralateral eye was $97 \pm 1\%$ (Figure 1). In the subcutaneous etanercept and MTP-131 group, RGC survival percentage was $88 \pm 3\%$ of the uninjured contralateral eye (Figure 1). In the subcutaneous etanercept only group, percentage of RGC survival compared to contralateral eye was $97 \pm 2\%$ (Figure 1). In the subcutaneous MTP-131 only group,

percentage of RGC survival compared to contralateral eye was $94 \pm 2\%$ (Figure 1). On retinal flat mounts, PBS vehicle treatment after SI-TON leads to reduced RGC immunoreactivity and mild tissue morphological disruptions similar to what we have reported previously (Tao et al, 2017). Comparatively, in all treatment groups, RGC counts and retinal architecture were preserved and indistinguishable from contralateral uninjured retinas four weeks after injury (Figure 2).

Thus, our data indicate that treatment with intravitreal MTP-131 and subcutaneous etanercept and MTP-131 had the strongest neuroprotective effect, with a 21% increase ($p < 0.01$) in RGC survival rate compared to PBS-treated control eyes. The subcutaneous etanercept only and MTP-131 only groups had similar results, although with slightly less improvement in RGC survival. Surprisingly, we did not observe a synergistic effect between the two drugs in the group receiving both etanercept and MTP-131. One possible explanation for the absence of a synergistic effect is that MTP-131 and etanercept may be acting on different portions of the same pathway. It has been previously demonstrated that TNF can lead to neurotoxicity by causing a rapid decline in mitochondrial function (Russell et al, 2016). Lightfoot et al assessed myokine production of skeletal muscle cell in response to TNF and then compared those results to cells that were pre-treated with MTP-131 (Lightfoot et al, 2015). After treatment with TNF, significant increases in pro-inflammatory cytokines IL-6, CCL2, CCL5, and CXCL-1 were seen, which the authors believed to be mediated by mitochondrial superoxide and the redox-sensitive transcription factor NF- κ B. When the myotubes were pre-treated with MTP-131 and then exposed to TNF, release of all four cytokines was subsequently attenuated. Similarly, others have shown that TNF will induce mitochondrial production of superoxide anions, which may in turn, activate NF- κ B pathways (Hennet et al, 1993; Schulze-Osthoff et al, 1992; Li et al, 1998). Thus, it is possible that the TNF blockade in days 0-2 mitigated the benefit of the systemic MTP-131 administered on days 3-5 following SI-TON and led to a more modest increase in RGC survival.

In mice that received both etanercept and MTP-131 systemically, we attribute the higher RGC salvage rate in those receiving intravitreal injections of MTP-131 versus those not receiving intravitreal injections to the early and localized administration of the MTP-131 soon after injury. Previously, we have reported in our SI-TON model the presence of ROS as early as 30 minutes following injury (Tse et al, 2018). However, statistically significant elevations in TNF were not noted at 6 hours following SI-TON and did not become significantly elevated until 24 hours after injury (Tse et al, 2018). Thus, we believe that addressing the mitochondrial dysfunction early on after injury with MTP-131 with localized intravitreal injection appears to maximize its neuroprotective effects on RGCs by targeting the ROS that are seen within 30 minutes of injury. This underscores the importance of early intervention in a clinical setting.

Of course, the translatability of these results are limited by the immediacy with which both elamipretide and etanercept were initiated, which is not realistic in a clinical setting. We demonstrate that early inhibition of TNF and ROS attenuation leads to improved RGC survival following TON. We believe that our results underscore the urgency with which to initiate therapy after TON in order to achieve the most optimal visual outcomes. Our prior

characterization of the cascade of molecular events that ensues after SI-TON has allowed us to target TNF and ROS from mitochondrial dysfunction in an attempt to mitigate tissue damage and improve outcomes (Tao et al, 2017; Tse et al, 2018). Our findings support the rationale for including mitochondrial-targeted therapies in conjunction with TNF inhibition in the acute management of TON – therapies that are based upon our prior molecular characterization of metabolic events occurring after TON (Tao et al, 2017). With this study, we continue to further refine the clinical management of TON.

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Figure 1.

Percentage of RGC lost at 4 weeks following SI-TON in mice treated with intravitreal MTP-131 and subcutaneous etanercept and MTP-131; subcutaneous etanercept and MTP-131; subcutaneous etanercept only; subcutaneous MTP-131 only; and PBS (control) (**P < 0.01, *P < 0.05, n = 5).

Figure 2. MTP-131 and TNF inhibition with etanercept promote RGC survival after SI-TON. Representative confocal images of tubulin- β III (TUJ1)-labeled RGCs (green) in flat-mounted retinas were imaged 28 days after injury.