Vision System Injury Repair and Mitigation

CB2 Receptor Action of the FDA-approved Drug Raloxifene Mitigates Visual Deficits and Visual System Pathology after Mild TBI

Visual deficits after traumatic brain injury (TBI) are common, but interventions that limit post-trauma impairments have not been identified. A recent study found that treatment of closed-head blast TBI with the cannabinoid type-2 receptor (CB2) inverse agonist SMM189 greatly attenuates the visual deficits and retinal pathology produced by mTBI in mice, by modulating the otherwise deleterious role of microglia in the injury process after trauma (*Reiner et al., 2015*). SMM189 is, however, not yet approved for human use, and is years away from the regulatory approval needed for therapeutic use in humans. Raloxifene is, however, an FDA-approved estrogen receptor drug used to treat osteoporosis that was recently found to also show noteworthy CB2 receptor inverse agonism. Given its FDA-approved status as safe for human use, raloxifene could potentially be used to treat TBI in humans.

Researchers at the University of Tennessee Health Science Center (Memphis, TN) sought to determine if raloxifene can reduce visual system injury and dysfunction after mTBI. In a comprehensive series of functional and morphological studies, raloxifene was injected intraperitoneally at either a low (5 mg/kg) or high (10 mg/kg) dose 2 hours after TBI. Deficits in contrast sensitivity and visual acuity; reductions in the electrical activity from the retina; and increases in anxiety, light aversion, and pupil constriction in response to light were evident when functional tests were performed months after the blast. These negative outcomes of blast TBI were completely or nearly completely remedied by two weeks of raloxifene treatment, with the higher dose generally being more effective. Raloxifene also rescued the loss of axons in the optic nerve and neurons in the oculomotor nucleus following the blast, and normalized an increase in retinal ganglion cell melanopsin, a pigment that mediates light aversion and pupil constriction. Raloxifene treatment was still effective even when delayed until 48 hours after TBI. In studies examining non-visual deficits after TBI, the same researchers at the University of Tennessee Health Science Center also found that fearfulness and anxiety caused by closed-head blast TBI in mice was mitigated by raloxifene.

The effects of raloxifene appear attributable to its CB2 inverse agonism rather than its estrogenic actions and are driven by a biasing of microglia after blast TBI from the harmful pro-inflammatory M1 state to the pro-healing M2 state. Due to its action at CB2 receptors, raloxifene effectively mitigates visual system injury and dysfunction after head trauma in mice and could be rapidly repurposed for use in humans for treatment of TBI (Figure 1).

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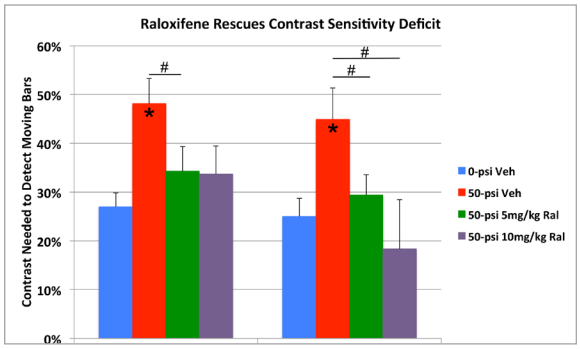

FIGURE 7-22: Contrast sensitivity as measured using Optometry in sham blast and blast mice receiving vehicle, and blast mice receiving raloxifene at either 5 mg/kg or 10 mg/kg. The contrast needed to detect moving stripes was significantly greater for both eyes in blast-vehicle (asterisk) than in sham mice. Contrast sensitivity in the 5 mg/kg raloxifene mice was significantly better than in the blast mice with vehicle for both eyes (bars with pound signs), and for the right eye in the case of 10 mg/kg raloxifene (bar with pound sign). *(Dente et al., 2010*).

REFERENCES:

Reiner, A., Heldt, S. A., Presley, C. S., Guley, N. H., Elberger, A. J., Deng, Y., . . . Moore, B. M., 2nd. (2014). Motor, visual and emotional deficits in mice after closed-head mild traumatic brain injury are alleviated by the novel CB2 inverse agonist SMM-189. Int J Mol Sci, 16(1), 758-787. doi:10.3390/ijms16010758