ABSTRACT

Retinal ganglion cell (RGC) axons relay visual information to the brain via the optic nerves (ONs) and optic tracts of the vertebrate visual pathway. RGC loss leads to irreversible blindness in many optic neuropathies, and is often associated with elevated intraocular pressure (IOP). Studies of experimentally elevated IOP have identified axonal transport (AT) disruption, cytoskeletal modification, and glial activation as contributing factors to RGC death. However, the capacity of these factors to recover following a transient IOP elevation remains unclear. This thesis employed AT tracing and immunological techniques to examine the spatiotemporal progression of RGC and glial responses in rat retina and ON following 30 or 90 minutes of acute elevated IOP, representing a sub-critical or critical insult, respectively. Anterograde AT was examined over 24 hours, and retrograde AT over 14 days, post-injury. Neurofilament (NF) phosphorylation and glial activation were evaluated concurrently with anterograde AT. Thirty minutes of elevated IOP did not cause RGC loss, however, retrograde AT was mildly reduced at all time points. There was a trend towards NF dephosphorylation in the optic nerve head (ONH), and some microglial activation was observed. Conversely, 90 minutes of elevated IOP caused significant RGC loss by 3 hours (40%), followed by a second wave of loss by 7 days (98%). Accumulation of phosphorylated NF was observed in a subset of RGC somas, the proportion of which increased with eccentricity. All AT was significantly disrupted at the ONH, and reduced retrograde AT in the ON suggested dysfunction in the distal axon or terminal. Microglial processes were increased in the inner plexiform layer, and activated microglia became prominent through all retinal layers over 24 hours. Notably, loss of AT function was not recovered following either duration of elevated IOP. These findings suggest that, rather than exhibiting reversible dysfunction following a sub-critical insult, RGCs succumb to high IOP-induced stress in a cell-by-cell manner that is acute and permanent, the degree of which depends on the duration of IOP elevation – short insults (e.g. 30 minutes duration) cause dysfunction and/or loss of a small population of vulnerable RGCs, whereas longer insults affect proportionally more RGCs. Differences in extrinsic and intrinsic risk factors likely contribute to variation in the critical threshold across the RGC population. This work contributes to a timeline of cellular events following acute elevated IOP, and supports the importance of studying critical injury and subtype-specific differences in RGCs.