THE EFFECT OF HYPERGLYCAEMIA ON EXPERIMENTAL SUBACUTE ISCHAEMIC OPTIC NEUROPATHY AND RETINOPATHY

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ABSTRACT

The overarching aim of the work described in this thesis was to address perceived deficiencies in knowledge of the differences between retinal and brain metabolism in order to gain a greater understanding of the mechanisms involved in ischaemic retinal and optic nerve injury. Specifically, the aim of the project was to test the hypothesis that elevated blood and vitreal glucose levels induced by short-term diabetes would attenuate prolonged ischaemic retinal degeneration in the rat.

Simultaneous retinal and cerebral hypoperfusion was achieved by 2-vessel occlusion (2VO; permanent ligation of both common carotid arteries). Prior to testing the stated hypothesis, it was necessary to fully characterize the 2VO model in order to establish the optimal endpoint for analysing neuroprotection. Thus, at various times after surgery, retinas and optic nerves were removed form RNA or Western blot analysis or to be processed for histology and immunohistochemistry. In the retina, 2VO induceda progressive loss of retinal ganglion cells and horizontal cells, thinning of the inner retina, together with macroglial and microglial cell activation. One week was selected as the optimal time point at which to analyse neuroprotection. In the optic nerve, 2VO caused axonal transport disruption, followed by the loss of axonal cytoskeleton proteins, glial cell activation, infiltration of macrophages, upregulation of stress proteins by astrocytes and oligodendrocytes, and finally extracellular matrix remodeling.

To address the major aim of the thesis, rats were divided into 4 groups: normoglycemic and hyperglycemic sham-operated rats; normoglycemic and hyperglycemic 2VO rats. Hyperglycemia was induced 3 days prior to 2VO by streptozotocin injection. Rats were killed one week after 2VO or sham surgery. The retina of one eye were collected for histology/immunohistochemistry, whilst the fellow retina was dissected for real-time RT-PCR. Retinas were analysed for neuronal and glial markers and the inducible stress protein heat shock protein-27. Brains were processed for histology and immunohistochemistry.

Retinas of normoglycemic 2VO animals showed a marked loss of retinal ganglion cells and horizontal cells, thinning of the inner retina, together with macroglial and microglial cell activation. Hyperglycemic 2VO rats displayed a remarkable protection of retinal structure and reduced glial cell activation compared to normoglycemic 2VO animals. There was a significantly greater number of heat shock protein-27-positive retinal ganglion cells in

normoglycemic animals compared to hyperglycemic animals, indicating that a greater proportion of surviving retinal ganglion cells were stressed in normoglycemic animals as compared to hyperglycemic rats. Brains of both normoglycemic and hyperglycemic 2VO animals displayed scattered ischemic infarcts and mild white matter injury.

In conclusion, short-term hyperglycemia afforded a robust protection against retinal hypoperfusion injury, but in the same animals brain injury was not ameliorated. The mechanism of this retinal hyperglycemia-induced neuroprotection requires further study.

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