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ARVO Annual Meeting Abstract | July 2018

Pyruvate protects retinal neurones in culture from nutrient deprivation, excitotoxicity and oxidative stress

John Peter Wood; Glyn Chidlow; Chelsea Guymer; Teresa Mammone; Robert J Casson

+ Author Affiliations & Notes

Investigative Ophthalmology & Visual Science July 2018, Vol.59, 2513. doi:

Abstract

Purpose : The prominent cellular metabolite, pyruvate, has been shown to possess properties which likely endow it with the potential to protect neurons from insults relating to neurodegenerative disease. In order to address this more closely in the context of the retina, we examined whether this compound was able to protect cultured retinal neurons from nutrient deprivation (ND), excitotoxic challenge (EC) or oxidative stress (OxS): all insults which relate to glaucoma.

Methods : Mixed retinal neuron and glial cultures were prepared from 2 day old rat pups via mechanical and enzymatic digestion. After 7 days, cells were treated for 24 hours with medium lacking glucose and amino acids for ND, 200 μM N-methyl-D-aspartate plus 10mM $CaCl_2$ for EC or 100μM t-butyl hydroperoxide for OxS. Viability of neurons was assessed by immunocytochemistry (β-tubulin, calretinin, GABA), Western immunoblot and MTT assay. Mechanisms of potential neuroprotection were assessed by assays for reactive oxygen species and ATP levels.

Results : ND, EC and OxS reduced neuronal viability in cultures by 93.3%, 48.9% and 89.8% respectively. Different classes of neuron generally responded to similar degrees, except that calretinin-immunoreactive (IR) neurons, which comprised a population of small amacrine cells and large ganglion cells (GCs), were relatively more sensitive to EC than were GABA-IR or β-tubulin-IR neurons. Pyruvate (1mM) was able to reduce neuron death induced by ND and OxS by 85.3% and 78.9% respectively, but was less efficacious in counteracting EC, reducing this only by 45.7%. Notably, in the latter case, pyruvate was particularly able to counteract death of the large calretinin-IR GCs. The effects of

pyruvate, which included elevation of cellular ATP and quenching of intracellular reactive oxygen species, were almost entirely counteracted by monocarboxylate transport inhibition.

Conclusions : Pyruvate is able to significantly protect retinal neurons in culture from a panoply of insults. The diverse nature of these insults indicates the potential usefulness of this compound in preserving retinal neurons in diseases such as glaucoma.

This is an abstract that was submitted for the 2018 ARVO Annual Meeting, held in Honolulu, Hawaii, April 29 - May 3, 2018.