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Synthesis and mitochondrial transport of glutathione in the rds mouse

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Abstract

Purpose : Numerous cell death mechanisms have been related with photoreceptor loss in retinitis pigmentosa (RP), including oxidative stress and autophagy. Our group has previously reported alterations in glutathione (GSH) metabolism, the major intracellular antioxidant, in the retina of two different RP animal models, the rd1 and rd10 mice. GSH is synthesized from cysteine, glutamate, and glycine in a two steps process, being glutamate cysteine ligase (GCL) the rate limiting enzyme. De novo synthesis of GSH occurs in the cell cytosol. Though mytochondria is not able to synthesize GSH, it can be transported to these organelles by means of carrier proteins. One of these transporters is the the 2-oxoglutarate (OGC) carrier, that is localized in the inner mitochondrial membrane.
The purpose of this work was to demonstrate if GSH synthesis and mitochondrila transport can be observed in the retina of a different RP animal model, the rds mice. In adition, because oxidative stress may induce autophagy, the expression of several proteins related with autophagy have been determined.

Methods : Animals were treated in accordance to the ARVO statement for the use of animals in ophthalmic and vision research. Retinas from C3H and rds mice at different postnatal days (11, 28, 35 and 42) were obtained. Death of photoreceptors and GSH localization was examined by histochemistry. Western blot analysis was performed to determine the protein content of the catalytic subunit GCL and of the 2-OGC mitochondrla carrier. The expression of two autophagy related proteins (Atg5 and Atg7) was also determined by western blot.

Results : The outer nuclear layer (ONL) was similar in these mutants and in the control at post natal day 11 (P11), however the number of rows of cells in the ONL decreased slowly but significantly at post natal days 28, 35 and 42 (12 rows of cells in the ONL in control retina versus 8 rows of cells in the rds retina at P42). We observed a significant increase in the expression of GCL with age in the rds retinas, that was not observed in control mice (30% and 90% of increase at P35 and P42 when compared to P11). No change in the OGC expression was observed in control and rds mice. Atg 5 and Atg 8 was also increased at P42 in rds mice when compared to control ones, that was not observed at P35.

Conclusions : Therapies that target alterations in GSH metabolism and autophagy may be beneficial in retinitis pigmentosa.

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