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Glyoxalase System as a Therapeutic Target against retinal diseases?

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Abstract

Purpose: Advanced glycation end products (AGEs) are toxic compounds resulting from the non-enzymatic modification of biomolecules by sugars or their metabolites. AGEs are pathologically linked to AMD and diabetic retinopathy and anti-AGEs detoxifying systems are proposed as therapeutic targets to fight pathological dysfunction associated with AGE accumulation. The primary mechanism for detoxifying the reactive intermediates of glycation is the glyoxalase system, the limiting reaction of which is the enzyme glyoxalase 1 (GLO1). Information about the glyoxalase system in ocular tissues is limited.
In this study we evaluate the role of glyoxalase system in retinal tissues and we hypothesize that high level of glyoxalase activity prevents AGE accumulation under non-stressed conditions, and thereby protects against toxicity derived from glycative stress.

Methods: We dissected retina, RPE/choroid and lens along with other non-ocular tissues from 2 month-old wild type C57BL/6J mice. We quantified the GLO1 activity in cytosolic extracts of tissues and carried out a comparative analysis. GLO1 activity was determined spectrophotometrically as the initial rate of formation of S-D-lactoylglutathione. As a positive control, a comparative analysis was also carried out in ocular tissues from transgenic mice overexpressing Glo1 on C57BL/6J (B6) background. Western blotting and immunohistochemistry, using antibodies that specifically recognize GLO1, were performed to quantify protein levels and location of GLO1 in retinal tissue.

Results: Glyoxalase activity was detected in all tissues. The relative order of GLO1 specific activity was retina> liver> kidney> brain> heart> RPE/choroid >lens. Glyoxalase activity is clearly tissue-dependent. When compared to non-ocular tissues, the retinal rate of detoxification was about 2-fold, 8.5-fold, 3.5-fold and 4.5-fold greater than liver, heart, kidney and brain, respectively. Regarding ocular tissues, neuroretinal activity was about 9-fold and 13-fold greater than in the RPE/choroid and lens, respectively. Biochemical and morphological examination of retinal tissues corroborate the highest level of GLO1 expression in neuroretina. GLO1 activity in transgenic mice overexpressing Glo1 was about 3.7-fold and 2.2-fold in retina and RPE/choroid, respectively.

Conclusions: The neuroretina has the highest level of retinal GLO1 activity, suggesting an important protective role against AGEs-derived damage in retina.

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