

## **PROTECTION BY ANTIOXIDANTS AND MITOCHONDRIAL PROTECTIVE COMPOUNDS AGAINST IRON- AND TERT-BUTYL HYDROPEROXIDE-INDUCED OXIDATIVE DAMAGE IN RETINAL PIGMENT EPITHELIAL CELLS**

Voloboueva LA (P), Atamna H, Killilea DW, Liu J, Ames BN

Children's Hospital Oakland Research Institute

Age-related macular degeneration (AMD) is the leading cause of blindness and visual disability in patients 60 years and older in developed countries. Although the pathogenesis of AMD includes different clinical signs, the degeneration of retinal pigment epithelial cells (RPE) is often observed at the early stages of the disease. The most important risk factors for AMD, age and smoking, are both associated with increased oxidative stress. RPE cells might be more susceptible to oxidative damage because RPE functions in the conditions of relatively high oxygen tension, contains an abundance of photosensitizers, and is exposed to intense illumination from focal light. Particularly strong oxidative load is associated with the RPE phagocytosis of photoreceptor outer segments. It has been demonstrated that RPE tissues of AMD patients contain significantly higher levels of cellular chelatable iron—another source of free radicals through a Fenton mechanism. Cellular mitochondria are the primary target of oxidative damage in RPE cells. We hypothesize that oxidative damage to RPE cells, particularly to cellular mitochondria, contributes to retinal degeneration observed in AMD, and that antioxidants and mitochondrial protective compounds may strengthen defense machinery, prevent RPE mitochondrial and cellular damage, and thus might be effective in preventing or treating RPE degeneration in AMD. We investigated the protective effects of lipoic acid (LA) and N-tert butyl hydroxylamine (NtBHA), mitochondrial protective compounds with broad antioxidant activities, against t-butyl hydroperoxide- and iron-induced oxidative damage of RPE cells. Our studies demonstrated that treatments of RPE cells with LA and NtBHA resulted in full or partial protection against the oxidant-induced decrease in mitochondrial function, increased cellular oxidant generation and decreased intracellular antioxidant GSH levels. These results support our hypothesis that mitochondrial protective compounds and antioxidants may be promising in preventing and repairing RPE damage observed in AMD.