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Oestrogens ameliorate mitochondrial dysfunction in Leber's hereditary optic neuropathy.

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Abstract

Leber's hereditary optic neuropathy, the most frequent mitochondrial disease due to mitochondrial DNA point mutations in complex I, is characterized by the selective degeneration of retinal ganglion cells, leading to optic atrophy and loss of central vision prevalently in young males. The current study investigated the reasons for the higher prevalence of Leber's hereditary optic neuropathy in males, exploring the potential compensatory effects of oestrogens on mutant cell metabolism. Control and Leber's hereditary optic neuropathy osteosarcoma-derived cybrids (11778/ND4, 3460/ND1 and 14484/ND6) were grown in glucose or glucose-free, galactose-supplemented medium. After having shown the nuclear and mitochondrial localization of oestrogen receptors in cybrids, experiments were carried out by adding 100 nM of 17β-oestradiol. In a set of experiments, cells were pre-incubated with the oestrogen receptor antagonist ICI 182780. Leber's hereditary optic neuropathy cybrids in galactose medium presented overproduction of reactive oxygen species, which led to decrease in mitochondrial membrane potential, increased apoptotic rate, loss of cell viability and hyper-fragmented mitochondrial morphology compared with control cybrids. Treatment with 17β-oestradiol significantly rescued these pathological features and led to the activation of the antioxidant enzyme superoxide dismutase 2. In addition, 17β-oestradiol induced a general activation of mitochondrial biogenesis and a small although significant improvement in energetic competence. All these effects were oestrogen receptor mediated. Finally, we showed that the oestrogen receptor β localizes to the mitochondrial network of human retinal ganglion cells. Our results strongly support a metabolic basis for the unexplained male prevalence in Leber's hereditary optic neuropathy and hold promises for a therapeutic use for oestrogen-like molecules.

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