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Abstract

Effects of the sigma-2-receptor agonist Siramesine on human lens epithelial cells and implications for treatment of posterior capsular opacification (secondary cataract)

Background
Sigma receptors were originally found in brain tissue and Sigma ligands were developed to treat certain psychiatric disorders. More recently, Sigma receptor antagonists have been shown to inhibit proliferation in mammary and colon carcinoma cell lines, which has lead to an extensive search for applications in cancer treatment. Two isoforms of sigma receptors exist; sigma-1, which is antiapoptotic and sigma-2, which is proapoptic. Normal non-transformed cells are usually quite resistant to Sigma receptor agonists/antagonists, but lens epithelial cells are strikingly sensitive. Proliferation of lens epithelial cells is a clinical problem, causing obscuration of the vision secondary to cataract surgery in many patients. Affecting sigma receptors to prevent formation of PCO is thus an attractive idea.

Aims
I. Effects on proliferation and apoptosis by the sigma-2-receptor agonist Siramesine in cultured human lens epithelial cells – Are these effects mediated through regulation of the cell cycle by the proteasome?
II. What is the role of lysosomes and lysosomal proteolysis in Siramesine-induced apoptosis/proliferation?
III. Does the sigma-2-receptor agonist Siramesine affect intracellular redox-systems?
IV. What is the antiproliferative/proapoptotic effects of Siramesine in a lens capsular bag model and in intact rabbit eyes after cataract extraction?

Methods
Most experiments will be performed on cultured human lens epithelial cells derived from cataract surgery. Methods used to study apoptosis are: morphologic evaluation of cell nuclei and caspase-3 measurements. Proteolytic assays for caspase-3, the proteasome and lysosomal enzymes will use fluorogenic substrates. Immunofluorescence and transmission electron microscopy will be used to study morphology of lysosomes.

Relevance
Cataract extraction is the most common surgical procedure in the western world and posterior capsular opacification is a quite common postoperative complication. Since lens epithelial cells appear to be unusually sensitive to sigma receptor agonist/antagonists, these substances can potentially be used as a drug against PCO in the future.

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Publications (from 2003)


