THE ROLE OF ESTROGEN AND SUPEROXIDE DISMUTASE IN CATARACTOGENESIS

Akademisk avhandling

som för avläggandet av medicine doktorsexamen vid Sahlgrenska akademin,
Göteborgs universitet kommer att offentligen försvaras i hörsal Arvid Carlsson,
Academicum, Medicinaregatan 3, Göteborg

Fredagen den 21 november 2014, kl.09.00

av

Dragana Škiljić

Fakultetsopponent: Professor Alfred Wegener
Department of Ophthalmology, University of Bonn, Germany

Avhandlingen är baserad på följande arbeten:

I. **Dragana Čelojević***, Anne Petersen, Jan-Olof Karlsson, Anders Behndig, Madeleine Zetterberg. Effects of 17β-estradiol on proliferation, cell viability and intracellular redox status in native human lens epithelial cells. *Molecular Vision. 2011; 17:1987-1996*.

II. **Dragana Čelojević***, Staffan Nilsson, Anders Behndig, Gunnar Tasa, Erkki Juronen, Jan-Olof Karlsson, Henrik Zetterberg, Anne Petersen, Madeleine Zetterberg. Superoxide dismutase gene polymorphisms in patients with age-related cataract. *Ophthalmic Genetics. 2013; 34(3): 140-145.*

III. **Dragana Škiljić**, Staffan Nilsson, Mona Seibt Palmér, Gunnar Tasa, Erkki Juronen, Anders Behndig, Jan-Olof Karlsson, Anne Petersen, Henrik Zetterberg, Madeleine Zetterberg. Estrogen–related polymorphisms in Estonian patients with age-related cataract. *Submitted manuscript, 2014*.

IV. **Dragana Škiljić**, Anne Petersen, Jan-Olof Karlsson, Anders Behndig, Staffan Nilsson, Madeleine Zetterberg. Effects of 17β-estradiol on activity, gene and protein expression of superoxide dismutases in human lens epithelial cells. *Manuscript*.

V. **Dragana Škiljić**, Staffan Nilsson, Anne Petersen, Jan-Olof Karlsson, Anders Behndig, Lada Kalaboukhova, Madeleine Zetterberg. Estradiol levels and superoxide dismutase activity in patients with age-related cataract. *Manuscript*.

* Artiklar är publicerade i tidigare efternamnet Čelojević.

UNIVERSITY OF GOTHENBURG

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Dragana Škiljić
Department of Clinical Neuroscience and Rehabilitation, Institute of Neuroscience and Physiology, The Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden

Abstract

Cataract is an opacification of the eye lens, constituting the major cause of blindness globally. Oxidative stress is a key factor in the formation of cataract and female gender is a known risk factor for age-related cataract. The aim of this thesis was to investigate the role of estrogen and the antioxidant enzyme superoxide dismutase (SOD) in cataractogenesis.

Human lens epithelial cells (HLECs) obtained during cataract surgery at the Department of Ophthalmology at Sahlgrenska university hospital in Mölndal (SU/M) were used to study the effects of the major estrogen, 17β-estradiol (E2), on proliferation, cell viability, intracellular redox status, SOD and estrogen receptors (ERs). H_2O_2-induced oxidative stress was used to study the antioxidative properties of E2 in HLECs. Two genetic association studies were performed to investigate if genetic variations in estrogen-related and in SOD genes were associated with increased risk of cataract in an Estonian population, consisting of 492 patients with age-related cataract and 185 controls. Patients and controls were also recruited from the Eye Clinic at SU/M for a study on possible correlations between E2 levels and SOD activity.

The effects of E2 at pharmacological concentrations in HLECs were; increased apoptosis and cell death, reduced cell viability and proliferation as well as increased intracellular levels of reactive oxygen species (ROS). At lower (physiologic) concentrations, increased proliferation, reduced cell death, stabilization of mitochondrial membrane potential and protection against oxidative stress by reduction of ROS were observed. At these concentrations total SOD activity was increased and protein expression levels of ERs were altered. However, no change in neither gene nor protein expression levels of SODs was seen. A linear correlation between increasing age and declining E2 serum levels was evident in cataract patients and controls. Men exhibited higher E2 levels compared to postmenopausal women. However, no correlation between serum levels of E2 and SOD activity was found in our study subjects. The genetic association studies showed that genetic variations in SOD and estrogen-related genes were not associated with increased risk of cataract.

In conclusion, no correlation between SOD activity and E2 serum levels in cataract patients and controls was found and genetic variations in SOD or estrogen-related genes showed no association with increased risk of cataract in our subjects. The observed increase in SOD activity after exposure to E2 and reduction of ROS after preincubation with E2 in oxidatively stressed cells, support a role for E2 in the protection against oxidative stress in HLECs. The antioxidative effect of E2 in lens epithelial cells appears to be induced by non-genomic mechanisms.

Keywords: antioxidant enzyme, cataract, estrogen, gender, lens epithelial cells, oxidative stress, polymorphism, superoxide dismutase

ISBN: 978-91-628-9187-9 http://hdl.handle.net/2077/36756