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DISSERTATION TITLE: *Protection of neurons – glutathione as a key mediator for survival with potential implication for use of estrogens as neuroprotectors*

Glutation (endogen antioksidant) er viktig for overlevelse av nerveceller etter ulike stimuli som induserer til celledød i hjernen (f.eks hjerneslag). Det ble vist at 17 α -estradiol og østrogenanaloger har forskjellig evne til å beskytte nerveceller på grunn av negativ eller positiv interaksjon med glutatoin i pheochromocytoma PC12 celler. 17 α -Estradiol har også en tids- og konsentrasjonsavhengig beskyttelse i en hjerneslagsmodell i kulturer av nerveceller fra kyllinghjerne.

Estrogens are regarded as neuroprotectors, and have been used in clinical applications to protect neurons. However, effects by estrogens may be either beneficial or harmful. This thesis suggests that estradiol analogs have the potential as neuroprotectors and that the endogenous antioxidant glutathione is a mediator for survival. The rat pheochromocytoma cell line PC12 was used to study neuroprotective effects of 17 α -estradiol, a stereoisomer of the natural estrogen 17 β -estradiol, and different estradiol analogs. The findings were that 17 α -estradiol protects against serum deprivation-induced cell death in PC12 cells in low concentration (1 nM), but does not protect in high concentration (10 μ M). The loss of protection at 10 μ M was linked to reduced glutathione synthesis and reduction in total levels of glutathione. On the other hand, chemically modified 2-methoxyestradiol analogs as well as the G protein-coupled estrogen receptor (GPER) antagonist G36 had better profiles as neuroprotectors as they did not interfere with glutathione at 10 μ M. Excessive release of glutamate causes degeneration of neurons and is implicated in various neurological diseases. This thesis also used cerebellar granule neurons from chicken to study glutamate-induced cell death. The results show that 10 μ M 17 α -estradiol, but not 1 nM was neuroprotective against glutamate-induced toxicity when administrated together with glutamate. However, a 24 h pretreatment period with 1 nM protected while 10 μ M failed to protect against cell death. The difference in protection with treatments was linked to calcium response, increase in NR2B protein level and glutathione level. The results provide new knowledge about the neuroprotective abilities of 17 α -estradiol and estrogen analogs and the importance of glutathione as mediator for neuronal survivor. These findings may have implications for the development of estrogen analogs for clinical applications.

