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# ESTROGEN RECEPTORS AND ESTETROL-DEPENDENT NEUROPROTECTIVE ACTIONS: A PILOT STUDY

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Context: Estetrol (E4) has strong antioxidative, neurogenic and angiogenic effects in neural system resulting in the attenuation of neonatal hypoxic–ischemic encephalopathy.
Objective: We aimed to define the role of estrogen receptors in E4-dependent actions in neuronal cell cultures and prove the promyelinating effect of E4.
Methods: In vitro the antioxidative and cell survival/proliferating effects of E4 on H2O2-induced oxidative stress in primary hippocampal cell cultures were studied using different combinations of specific inhibitors for ERÎ± (MPP dihydrochloride), ERÎ² (PHTTP), GPR30 (G15) and palmytoilation (2-BR). LDH activity and cell survival assays were performed. In vivo the promyelinating role of different concentrations of E4 (1 mg/kg/day, 5 mg/kg/day, 10 mg/kg/day, 50 mg/kg/day) was investigated using the hypoxic–ischemic brain damage model in the 7-day-old immature rats before/after the induction of hypoxic–ischemic insult. Myelin basic protein (MBP) immunostaining was performed on brain coronal sections.
Results: Our results show that LDH activity is significantly upregulated in cell cultures where the E4's effect was completely blocked by concomitant treatment either with ERÎ± and ERÎ² inhibitors (MPP and PHTPP, respectively), or ERÎ± and ERÎ² inhibitors combined with 2-BR. Cell survival is significantly downregulated in cell cultures where the effect of E4 was blocked by ERÎ² inhibitor (PHTTP) alone. The blockage of GRP30 receptor did affect neither LDH activity nor cell survival. MBP immunostaining is significantly upregulated in E4-pretreated groups at a concentration of 5 mg/kg/day and 50 mg/kg/day E4, whereas the MBP-positive area OD ratio is significantly increased in all the E4-treated groups.
Conclusions: E4's antioxidative actions mostly depend on ERÎ± and ERÎ², whereas neurogenesis and possibly promyelinating activities might be realized through ERÎ².

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