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Introduction

Estrogens and Neuroprotection

Estrogens exert profound effects on brain differentiation, neural plasticity, and central neurotransmission during development. In adult men and women, accumulating evidence supports a modulatory role of estrogens in the brain and their prime importance in the normal maintenance of brain function during aging. Hence, the multiple activities of estrogens have fueled intense research through the years, which has waned occasionally but been renewed even more intensely with timely publications. Presently, this field of research has been stimulated by the information that estrogen may protect against Alzheimer disease in postmenopausal women and may positively affect symptoms of Parkinson disease and tardive dyskinesia. However, the publication of the Women's Health Initiative trial on the risk of estradiol with progesterone replacement therapy has somewhat mitigated the enthusiasm for estrogen. But should it? Indeed, the combined estrogen plus progestin hormone replacement therapy was terminated after 5 yr instead of 8.5 yr because overall risks outweighed benefits. By contrast, women with a prior hysterectomy receiving unopposed estrogen continue their treatment. In light of this major study, the search for an estrogenic compound without stimulation of the uterus (hence avoiding the combination with progesterone) such as dehydroepiandrosterone (DHEA) or selective estrogen receptor modulators (SERMs) is very promising, timely, and quite relevant. Alternatively, specificity could be obtained by targeting a specific estrogen receptor (ER) subtype or coactivators and corepressors of these receptors. Many of these compounds are already on the market as SERMs (tamoxifen, raloxifene) and dietary supplements (DHEA in some countries, phytoestrogens, and so on).

The investigation of estrogenic activity not only has great clinical potential; it is also a great motivator of fundamental research. Indeed, nature has provided estrogens with numerous effects in the brain via various mechanisms. These are slowly unraveled. This special issue covers the main aspects of estrogenic activity in the brain. First, estrogen activity during brain development, as discussed here, gives clues to possible mechanisms occurring at the other end of life; estrogen developmental programs could be reinstated to rescue injured brain. The recent discovery of a second ER (ERβ) in the brain and its implication in maintenance of aging neurons has stirred much enthusiasm. It is now shown, as discussed in this issue, that ERα and ERβ both are involved in neuroprotection via different mechanisms. For example, ERβ specifically targets dopamine and serotonin activity. The mixed estrogen agonistic and antagonistic activity of SERMs and their potential in neuroprotection is reviewed critically in experimental and clinical studies of stroke and cerebrovascular disease. A unifying hypothesis of estrogen action at high concentration through its antioxidant activity and at low concentration by induction of antioxidative and antiapoptotic thioredoxin is proposed based on cell culture studies. For managing progressive neurodegeneration such as Alzheimer dementia, the proposal that the signaling pathway of NOS1-cGMP-PKG in mediating estrogen-induced cytoprotective genes may foster the development of new estrogen ligands devoid of female hormonal side effects such as carcinogenesis. Considering the numerous targets and activities of estrogens in the brain, it becomes paramount to correlate the in vitro cell culture results as well as the biochemical measures in animal brains with functional correlates. This is reviewed with respect to estrogens and is pushed a step further with the results proposing DHEA as a prodrug for estradiol. DHEA could also target estradiol to the brain considering tissue-specific rate of its metabolism. Novel data showing that endogenous estrogen formation is also neuroprotective in a model of cerebral ataxia is presented. Estrogens have been reported to protect against glutamatergic toxicity in many experimental paradigms. Here it is reported that chronic estradiol also protects against the neurodegenerative effects of *N*-methyl-D-aspartate receptor antagonists. Estrogens could be considered as a buffer to the brain to maintain appropriate glutamate excitation. Much effort has focused on neuronal targets for estrogens; glia is also a target that is presented for neuroprotective effects of estrogens and tamoxifen. Several articles in this issue are devoted to Parkinson disease, which is of utmost importance considering the aging population.

This special issue reports reviews and original data on estrogens and SERM activity with some provocative ideas. They may not all withstand in the long term, but I hope that they will spark your imagination to bring new ideas to this fertile and fascinating field of research.

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