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Neuroprotective action of Estrogen: a brief review

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Abstract

Estrogens have been shown to affect the nervous system in many different ways. As the age advances especially in post menopausal women a significant decline in Cognition is observed. The low estrogen levels in postmenopausal females makes them vulnerable to neurodegenerative disorders. Estrogen has a neuroprotective role and this has been extensively studied in in-vitro or in rodents but the exact mechanism of action especially in humans is not completely understood. Several hypothesis have been documented by scientist to explain the neuroprotective mechanism of estrogens, they either 1) influence levels of neurotransmitter like GABA, Acetylcholine etc. 2) influence cerebral blood flow 3) alter growth proteins levels associated with axonal growth or lower the neurotoxic effects of β-amyloid. In this review, the author has tried to briefly describe the possible mechanism of action of estrogen in the nervous system, which may be significant in protecting against damage caused by ageing.

Keywords: Estrogen, Aging, Brain function

Introduction

Estrogen a sex steroid not only controls the reproductive function but affects the nervous system in many different ways.

17β-Estradiol (E2), the most potent and predominant form of estrogen, has a number of effects on cognition and brain function. Estrogens act via two receptors the ERα and ERβ which are differently expressed throughout the rat brain. Immunohistochemical techniques have shown that in the hypothalamus ERα is present in the arcuate and ventromedial nuclei, whereas ERβ is mostly present in the paraventricular and ventromedial nucle, the cerebellum expresses only ERα and the hippocampus expresses both the subtypes but mainly has ERβ.[1-5] In some brain regions both the receptors have been localised i.e. in preoptic area, the bed nucleus of the stria terminalis, the lower brainstem and the dorsal horn of spinal cord. In females concentration of estrogens in blood decreases with age and the low estrogens levels in postmenopausal stage leads to decline in cognition and which affects the working memory, impairment of focus and attention and slowing of speed of information processing.[6-9] Normal ageing process is accompanied by changes in structure and function of those brain regions that are implicated in neuropsychiatric disorders, such as Alzheimer's disease (AD). Murphy et al[10] in a study measuring glucose metabolism, using positron emission tomography and 18F-2-fluoro-2-deoxy-D-glucose, observed that females had significant age-related decrease in hippocampal glucose metabolism, compared to men. The hippocampus part of limbic system is a crucial structure for the formation and processing of episodic memory and spatial memory.[11] It is also implicated in emotional behaviour.[12] The hippocampus is susceptible to damage during ageing and repeated stress.[13] It is well known that women have a higher age-related prevalence of AD than men and they also have a greater disease severity. In one of the study done on postmenopausal women(n=425) ≥65 years of age it was observed that women with high concentrations of bioavailable estradiol had less decline on cognitive testing thereby, supporting the hypothesis that higher concentrations of endogenous estrogens prevent cognitive impairment.[14]

Several mechanisms have been postulated for neuroprotective role of estrogens, but the exact underlying mechanism of this effect in humans is not completely understood. Several studies on rodents and in vitro studies observed that E2 upregulates the excitatory action of neurotransmitters like acetylcholine.[15] In medial preoptic area levels of GABA increased with E2 levels[16] whereas in hippocampus it decreased GABA levels. E2 can augment neurosteroids synthesis and activity via neuroglia aromatase activity.[17-19] E2 also inhibits accumulation of β-amyloid.[20,21] It also reduces neuronal cell apoptosis mediated through ERβ (Nilsen *et al*., 2000, Meda C et al., 2000).[22,23] Estrogen acts on the mitochondria by stabilising its membrane potentials which prevents ATP depletion and hence reduces the generation of oxygen free radicals(Nilsen and Brinton, 2003).[24] Amongst the various neuroglia, estrogens have been shown to alter microglial expression of cytokines and growth factors and lack or low levels of estrogen, may restrict the immune responses and may hasten brain disorders.[25] One of the best-known processes regulated by estrogen hormone is the formation of excitatory synapses in the hippocampus.[26,27] Estrogen treatment increases dendritic spine density on CA1 pyramidal neurons in the hippocampus and also show cyclic variation .E2 can also influence levels of NMDA receptors ,earlier studies have shown that it down regulates activity of NMDA receptors.[28] and thereby reduces the chances of NMDA-induced neuronal death. In one of the epidemiological study done on postmenopausal women an improvement in verbal memory, reasoning and motor speed was seen when given hormone replacement therapy (HRT).[29] Studies

using Neuroimaging techniques done in females have confirmed that estrogens can increase cerebral blood flow, glucose metabolism.[30-31]

Conclusion and Perspective

From the above review it is clear that estrogens have definite neuroprotective role and can be used as an important therapeutic agent to maintain normal neural function during ageing. Role of hormone replacement therapy in humans is an extensive and controversial subject and will be studied extensively in future studies.

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