

Estrogen's action on cognitive function, memory processes, neuro- degenerative diseases: A Review.

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Abstract

Estrogen has an effect on cognitive enhancing and neuroprotection and in the incidence progress and manifestations of most of central nervous system disorders, including neurodegenerative disease. Estrogen effects on cognition depend on the cognitive task and its dependent brain regions. In hippocampus estrogen induces increased numbers of synapses on multiple synaptic boutons between neurons not previously connected. There are fundamental differences between men and women in the underlying pathophysiology, incidence, manifestation, severity, and/or progression of CNS disorders such as PD, schizophrenia, attention deficit/hyperactivity disorder, and autism.

Key words: Estrogen, neurodegeneration, memory, Parkinson's disease, Alzheimer's disease, hippocampus, Cognition.

1. Introduction

Among the most fascinating effects of estrogen are those on cognitive function, memory processes and their alterations during aging and neurodegenerative diseases [1]. In female rats estrogen regulates synaptogenesis in the hippocampus, a brain region important in spatial and declarative learning and memory. During the estrous cycle of a female rat, these synapses are formed under the influence of estrogens and are then broken down after the proestrus surge of progesterone [2].

Ovarian steroids have widespread effects throughout the brain, including brain stem and midbrain catecholaminergic neurons, midbrain serotonergic pathways, midbrain dopaminergic activity, and the basal forebrain cholinergic system [3]. Estrogen-induced synaptogenesis in the rat hippocampus occurs within several days, yet the effects of estrogen on cognitive function in rats and humans take a number of weeks to be fully manifested [4].

Estrogens have cognitive enhancing and neuroprotective effects. Loss of estrogens as a result of the suppression of ovarian function with gonadotropin-releasing hormone agonists, or the loss of ovarian hormones as a result of surgical and natural menopause, leads to generally reversible decreases in declarative memory and motor coordination that respond to estrogen replacement therapy [5].

Young adult women given GnRH hormone agonist to suppress ovarian function exhibit verbal memory deficits and deficits in task- associated neural activity patterns that can be corrected by administration of exogenous ovarian hormones [6].

2. Estrogen and the hippocampus: cognitive function and memory processes

The hippocampus is a brain region that is involved in episodic, declarative, contextual, and spatial learning and memory and serves as a component in the control of autonomic and vegetative functions such as ACTH secretion [7]. One of the processes regulated by ovarian hormones is the cyclic formation and breakdown of excitatory synapses in the hippocampus [8].

Estrogen effects on cognition depend on the cognitive task and its dependent brain regions. For instance, while estrogen impairs performance on striatum-dependent tasks it enhances performance on prefrontal cortical-dependent learning in female rats. It also enhances performance on hippocampal dependent tasks [6].

2.1.1. Mechanism of excitatory synapse formation in the hippocampus.

Estrogen treatment increases dendritic spine density on CA1 pyramidal neurons and treatment of ovariectomized adult rats with estrogen also induces new synapses on spines and not on dendritic shafts of CA1 neurons. Estrogen did not affect dendritic length or branching [8]. Spines are occupied by asymmetric, excitatory synapses and are sites of Ca^{2+} ion accumulation and contain NMDA receptors. NMDA receptors are expressed in large amounts in CA1 pyramidal neuron. Estrogen treatment upregulates immunoreactivity for the largest NMDA receptor subunit, NR1, on dendrites and cell bodies of CA1 pyramidal neurons, whereas NR1 mRNA

levels did not change after estrogen treatment that induces new synapses. This suggests the possibility that NR1 expression is regulated post-transcriptionally by estrogen [7].

In young female rats, estrogen induction of NR1 is proportional to the induction of new spines, so that NMDA receptor density per spine is not increased; however, in the aging female rat, there is NR1 induction without proportional increase in dendritic spines. This might make the aging hippocampus more vulnerable to excitotoxic damage such as, by stroke or seizures [9].

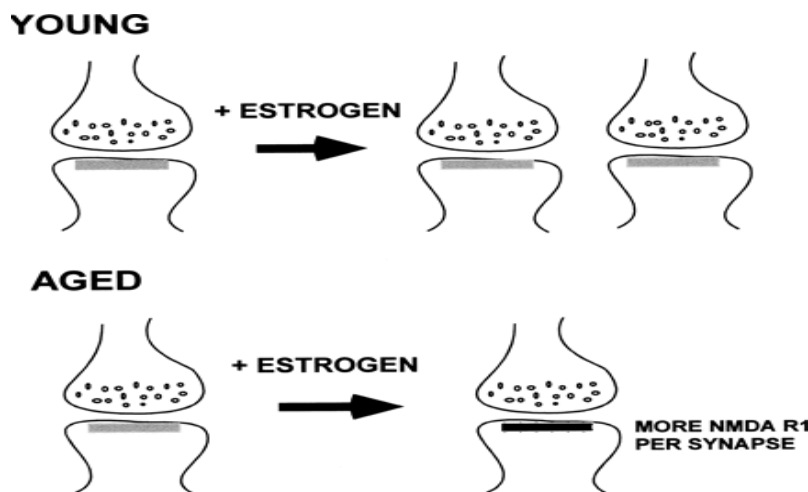


Figure 1. Different Modes of Hippocampal Plasticity in Response to Estrogen in Young and Aged Female Rats [9]

Young adult female rats show upregulation of both NMDA receptors and dendritic spines on CA1 pyramidal neurons in hippocampus, with a proportional increase of NMDA receptors and spines. In contrast, the aging rat hippocampus responds to estrogen by upregulating NMDA receptor R1 subunit expression but not by increasing the number of spine synapses [9].

2.1.2. Cellular and molecular events associated with synapse formation

In hippocampus estrogen induces increased numbers of synapses on multiple synaptic boutons between neurons not previously connected. This implies an active role for the dendrite in forming synaptic contacts. Estrogen increases synaptic connectivity between single presynaptic inputs and multiple postsynaptic CA1 pyramidal cells [10].

Gene products characterizing dendritic spines include spinophilin, a protein that helps to bundle actin filaments in the dendritic spine and regulates many of the properties of spines, the calcium-calmodulin kinase II (CaMKII) is a major protein of the postsynaptic density that plays an important role in long-term potentiation (LTP) and synaptic differentiation. Glutamatergic synapses contain other key proteins in the postsynaptic density besides CaMKII; these include PSD-95, densin-180, and citron, a rac/rho effector protein [7].

2.2. Cell nuclear estrogen receptors in the hippocampus

ER α is sparsely distributed in interneurons in the CA1 region in addition to regions of Ammon's horn and dentate gyrus, with greater density in ventral than dorsal hippocampus [1]. Early in development, more pyramidal cells may have nuclear ER α than in the adult and radioimmune cytochemistry results have shown much stronger estrogen effects on synapse and spine protein levels in ventral, compared to dorsal hippocampus [11].

2.3. Functional significance of estrogen on hippocampus

Estrogen treatment of ovariectomized rats produces delayed facilitation of synaptic transmission in CA1 neurons that is NMDA mediated and leads to an enhancement of voltage-gated Ca²⁺ currents and LTP sensitivity peaks on the afternoon of proestrus in intact female rats at exactly the time when excitatory synapse density has reached its peak. Besides affecting neuronal activity in hippocampus, estrogen treatment affects hippocampal-dependent learning and memory and sustained treatment improves performance in a working memory task [7].

3. Neuroprotective effect of estrogen

Estrogen has neuroprotective effect against a variety of neurodegenerative disorders, including stroke, Alzheimer's disease and Parkinson's disease [12], [13]. The aging brain responds differently to estrogen treatment than the young brain. Fewer spines on CA1 pyramidal cells contain ER alpha in the aging female compared to the young female rat [9]. This suggests that aging may be accompanied by a loss of estrogen sensitivity in the rat hippocampus. Indeed, in contrast to young animals, estrogen treatment does not increase

CA1 axo-spinous synapse density in ovariectomized aging rats, and it fails to alter the distribution of ER alpha in the CA1 of aging rats [6].

Women are “protected” against stroke relative to men at least until the years of menopause, when E2 levels decline and stroke outcome in postmenopausal women has been shown to be worse as compared to males, with postmenopausal women having a significantly higher disability and fatality rate as compared to men. While there may be many reasons for the worse stroke outcome in women, the onset and poor outcome of stroke in women parallels the time period of falling E2 levels that occurs after menopause [12].

E2 neuroprotection in the brain is mediated principally by the “classical” nuclear ER-mediated genomic signaling pathway, which involves E2 interaction with nuclear ER and regulation of transcription of various genes that mediate neuroprotection. E2 increases the expression of the anti-apoptotic gene, *bcl-2*, in the ischemic penumbra following middle cerebral artery occlusion and global ischemia and it also increases *bcl-2* in vitro in rat hippocampal neurons and human NT2 neurons, while it inhibits expression of pro-apoptotic *bcl-2*-antagonist of cell death [13].

Estrogen treatment protected against neural damage following experimental stroke (brain damage caused by an interruption of blood flow to specific portions of the nervous system) and damage induced by beta amyloid (an abnormal protein present in Alzheimer's disease) [14]

There are two ways in which estrogens protect the brain from neurodegeneration. First, estrogens maintain function of key neural structures such as the hippocampus and basal forebrain and the widely projecting dopaminergic, serotonergic, and noradrenergic systems. As estrogen levels decline during menopause, these systems and the cognitive and other behavioral processes that depend on them also decline. Estrogens not only maintain function but also confer resilience against neural damage. Second by directly blocking the actions of neurotoxic agents or inhibiting their generation such as in strokes and Alzheimer's disease [5]

3.1. Neurodegenerative diseases

The midbrain dopaminergic populations are implicated in a number of CNS disorders that show sex differences in their incidence, manifestation, severity, and/or progression, such as PD, schizophrenia, attention deficit/hyperactivity disorder, and autism. This implies fundamental differences between men and women in the underlying pathophysiology, which in turn has implications for responsiveness to treatments [15].

3.1.1. Parkinson's disease

PD is likely to arise from the interplay of environmental and genetic factors. Sex is considered to be an environmental factor and male sex, together with age, is one of the strongest risk factors for PD, men having at least a two-fold higher risk than women for developing the disease at all ages and for all nationalities studied, the protective effects of estrogen in women are likely to contribute to the female advantage [15].

Symptoms and risk of developing PD can be reduced by estrogen treatment and prolonged natural exposure to endogenous estrogens; however, the timing of postmenopausal estrogen treatment may be crucial and the positive effects in women are attributed to estrogen's effects on normal dopaminergic transmission (the surviving neurons in PD), as well as its more generally acclaimed neuro-protective actions, which prevent cell loss [1].

Protective effects of estrogen in women could be mediated via activation of mitochondrial ERs, which are involved in cytoprotection from oxidative stress and regulation of apoptosis [16].

Sex differences in striatal DA responses to estrogen may be mediated indirectly, rather than directly on the DA neurons. The striatal interneuron populations of inhibitory GABAergic medium spiny neurons (MSNs), which play a key role in regulating basal ganglia output in the healthy brain, are one possible target. Estrogenic potentiation of stimulated DA release from the female striatum has been attributed to a suppressive action on the MSNs, which relieves their inhibitory input to the DA terminals. This involves rapid effects mediated by way of ER alpha, which is primarily associated with the membrane but not nuclear fraction in striatal lysates [17].

The serotonergic system of the dorsal raphe is also an estrogen-sensitive foremost regulator of SNc DA neurons that not only demonstrate sex differences in G-protein signaling mechanisms but also has a sexually dimorphic ultra-structure in humans. Estrogen, protect against toxin-induced depletion of DA in the female striatum, and administration of physiological levels of estrogen to ovariectomized females are similarly effective against striatal damage induced by 6-OHDA in rats or MA or MPTP in mice. In male rodents, in contrast to females, gonadal hormones exacerbate the extent of mild or moderate striatal lesions [15].

Estrogen is neuroprotective in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine brought on nigrostriatal lesions, an animal model of idiopathic PD. Estrogen also prevents MPTP-induced depletion of striatal dopamine, dopamine transporter binding and expression and decreases the MPTP-induced tyrosine-hydroxylase-immunoreactive neuron loss and attenuates the glial activation induced by MPTP. More over estrogen interacts with the IGF-1 system to protect NSDA and maintain motor function after 6-hydroxydopamine lesion in animals [12].

3.1.2. Alzheimer's disease

Alzheimer's disease (AD) is the leading cause of dementia in the elderly and is characterized by the presence of extensive plaque deposition and neurofibrillary pathology [12].

Unlike PD, being female rather than male features among a number of risk factors, after aging, for developing the disease. Apparent sex differences in pathological features of AD and its relationship to behavioral disturbances indicate a biological basis for the differences. The loss of estrogens at the time of menopause is a risk factor for women to develop AD. Brain estrogen level is lower than normal in female subjects living with AD. In this context, aromatase expression is altered in AD brains, and single nucleotide polymorphisms in the *CYP19* gene are among genetic factors associated with the risk of developing AD [15], [18], [19].

Estrogen can reduce A β accumulation either by modulating APP processing or by increasing its clearance, which could be due to effects on enzymatic degradation of A β and/or microglial phagocytosis of the toxic peptide; the consequent reduction in A β toxicity prevents the damaging chain reaction of mitochondrial dysfunction, increased production of the perilous reactive oxygen species, and neuronal apoptosis [20].

Estrogen also inhibits hyperphosphorylation of tau. It may also exert its general protective effects that are not necessarily specific to AD, including increased expression of antioxidant enzymes to lower oxidative stress and modify the expression of proapoptotic genes [18][20]. All these processes have generally been shown to depend on ER α / β using both classic genomic and non-classic mechanisms, and both receptor isoforms are important, but each is likely to act against AD-related insults via unique signaling pathways [15] [19].

Human genetic studies have revealed evidence of a relationship between mutations of the aromatase gene and AD risk; this suggests that estrogen depletion in the brain may be a significant risk factor for developing AD neuropathology [12].

ER- α and aromatase expression increases with age in the hippocampus of women, and women with AD had down-regulated expression of these genes, suggesting a potential deficit in local brain production of estrogen and altered estrogen signaling in AD [21]. Estrogen may preserve regional cerebral metabolism and prevent metabolic decline in postmenopausal women, especially in the posterior cingulate cortex, a region found to decline in the early stages of AD [12].

At molecular level, estrogen has been shown to augment activation of the survival factor, Akt, while inducing phosphorylation and deactivation of GSK-3 β and BAD, which are recognized death signals in neurons collectively; these effects could enlighten the reported protective actions of estrogen in AD [12]. Risk of developing AD can be reduced by estrogen replacement therapy, although treatment with estrogens once the disease is established has no beneficial effect [5].

4. Conclusion

These sex differences in connectivity and estrogen responsiveness have important implications for the different vulnerability of men and women to psychiatric and neurodegenerative conditions, especially under conditions of stress, where adaptive responses may result in a different degree of allostatic load in sex specific circuitries. Estrogen-based therapy has considerable promise for brain disorders that affect men and women but beneficial effects found in females are not directly transferable to males so it is important to understand the nature and origins of sex-specific pathological conditions and for designing a hormone based therapeutic agents that will have optimal effectiveness in men and women.

5. References

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