Cellular and Molecular Basis of Estrogen’s Neuroprotection

Potential Relevance for Alzheimer’s Disease

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Abstract

Alzheimer’s disease (AD) is one of the most common types of dementia among the aged population, with a higher prevalence in women. The reason for this latter observation remained unsolved for years, but recent studies have provided evidence that a lack of circulating estrogen in postmenopausal women could be a relevant factor.

Moreover, follow-up studies among postmenopausal women who had received estrogen-replacement therapy (ERT), suggested that they had a markedly reduced risk of developing AD. In addition, studies among older women who already had AD indeed confirmed that a decrease in estrogen levels was likely to be an important factor in triggering the pathogenesis of the disease.

In this review article, we will discuss the evidence suggesting that estrogen may have a protective role against AD, mainly through its action as: a trophic factor for cholinergic neurons, a modulator for the expression of apolipoprotein E (ApoE) in the brain, an antioxidant compound decreasing the neuronal damage caused by oxidative stress, and a promoter of the physiological nonamyloidogenic processing of the amyloid precursor protein (APP), decreasing the production of the amyloid-β-peptide (Aβ), a key factor in the pathogenesis of AD.

Index Entries: Neuroprotection; estrogen; cholinergic neurons; apolipoprotein E; APP processing; oxidative stress; Alzheimer’s disease.

Introduction

Estrogen is a steroid hormone that acts through specific nuclear receptors, ER-α and the recently cloned ER-β (Kuiper et al., 1996; Mosselman et al., 1996), playing an important role in the normal development and differentiation of the brain, as well as in the production and maintenance of sexually dimorphic behavior throughout adult life (Breedlove, 1992;
Jones, 1988). However, the effects of gonadal steroids in the brain are not limited to the control of gonadal function and reproductive behavior. In fact, significant effects on axonal outgrowth, connectivity, and function have been described in a variety of brain regions not directly related to reproductive function (Wieland, 1992; Garcia-Segura et al., 1994; McEwen, 1988). Similarly, the action of estrogen on nonreproductive cognitive functions such as perceptual-spatial skills, learning, and memory has also been described (Breedlove, 1992; Van Harren et al., 1988; Williams and Meck, 1991). Cholinergic neurons, located in the basal forebrain, are involved in learning and memory processes and may be implicated in some of estrogen's effects (Gibbs, 1994).

The mechanism by which estrogen might exert a protective effect upon the aged brain is still unknown, but promotion of neurite outgrowth and synaptogenesis, protection against oxidative stress, and an increase in cholinergic activity, are some of its potential effects. Recent follow-up studies among postmenopausal women who received estrogen replacement therapy (ERT), suggested that they had a markedly reduced risk of developing Alzheimer's disease (AD). This disease is the most common cause of progressive cognitive decline and dementia in the aged population (Yankner, 1996), presenting a higher prevalence in women than men (Blass and Poirier, 1996). In this review article, we will discuss the evidence suggesting that estrogen may have a neuroprotective role and the relevance of this data regarding the AD.

**Estrogen Receptors**

The estrogen receptor is a member of the thyroid hormone/Vitamin D$_3$/retinoic acid steroid receptor superfamily and activates genes by its direct binding to specific regulatory elements in DNA (Evans, 1988). Besides direct transcriptional activation, the estrogen receptor also promotes genetic activation via second messengers and/or via trophic factors or its receptors. It is known that there are at least two estrogen receptors, ER-α and ER-β with similar affinity for estrogenic compounds and highly homologous (Kuiper et al., 1996; Mosselman et al., 1996). Nevertheless both receptors can act quite differently, depending on the particular ligand or antagonist binding to them. The tissue distribution of the receptors is different (Mosselman et al., 1996). Moreover, both receptors can dimerize (Pace et al., 1997), increasing the level of complexity to transcription activation in response to estrogen.

The estrogen receptor was the first neural steroid receptor to be recognized. The in vivo uptake of [³H]-estradiol and its binding to the isolated hypothalamus cell nucleus revealed a steroidal specificity similar to that found in uterus (McEwen, 1981; McEwen et al., 1991). Since then, estrogen receptors have been detected in several brain areas including the hypophysis, preoptic area, amigdala, and the nucleus basalis of Meynert (Torand-Allerand et al., 1992; Miranda and Torand-Allerand, 1992). These receptors are located principally in neurons, although glial cells also express them in certain cerebral regions.

**Estrogen as a Trophic Factor for Cholinergic Neurons**

It has been shown that estrogen treatment significantly increased the neurite outgrowth of acetylcholinesterase-positive fibers from embryonic basal-forebrain tissues transplanted into the anterior chamber of the eye (Honjo et al., 1992), indicating that estrogen may have a direct trophic effect upon basal-forebrain cholinergic neurons. Consistent with this notion was the finding that estrogen was also able to induce or promote the formation of either dendrites in hippocampal neurons or dendritic specializations in PC12 cell neurites expressing both estrogen and neurotrophin receptors; these specializations were also able to induce interneural interactions (Lustig, 1994).

The cholinergic neurons located in the basal forebrain are particularly susceptible to degeneration in AD and have been implicated in age-