Current Trends in Biomedical Engineering & Biosciences
ISSN: 2572-1151

Juniper Publishers
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Review Article
Volume 19 Issue 4 - November 2019
DOI: 10.19080/CTBEB.2019.19.556019

Curr Trends Biomedical Eng & Biosci

Estrogen and Susceptibility of Alzheimer's Disease

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Submission: December 11, 2019; **Published:** December 16, 2019

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Abstract

Estrogen is of great importance in regulating normal reproductive and non-reproductive functions. Aromatase is a key enzyme for the biosynthesis of estrogen in the body. The physiological roles of estrogen is mediated by estrogen receptors (ERs). When estrogen levels and/or the expression of its receptor protein are disrupted in the body, it can lead to diseases such as osteoporosis, and may increase susceptibility to diseases such as alzheimer's disease (AD). This paper reviews the relationship between estrogen and AD susceptibility.

Keywords: Estrogen; Aromatase; Estrogen receptors; Alzheimer's disease

Abbrevations: AD: Alzheimer's Disease; Aβ: Abeta Amyloid Protein; ERs: Estrogen Receptors; LTCC: L-type Ca2+ Channels

Introduction

Alzheimer's disease (AD) is the most common form of dementia, accounting for 50-60%, and is a typical progressive neurodegenerative disease [1,2]. AD is characterized by a number of pathological features, notably extracellular senile plaques formed by the aggregation of Abeta amyloid protein (Aβ) and the neurofibrillary tangles (NFTs) in the neuronal cells formed by hyperphosphorylation Tau protein, accompanied by important pathological changes such as brain neuron death, synaptic loss and reactive gliosis [3]. The clinical manifestations of AD are differ at different disease stages. Clinically, AD is a progressive disorder characterized by loss of early memory discontinuity and decline in overall cognitive function in late advanced stages and by behavioral symptoms such as aphasia, misuse, depression, and anxiety; memory impairment and crystallized abilities are remained [4,5]. In recent years, epidemiological retrospective studies have shown that sex steroids are inversely associated with risk of AD, and estradiol seem to play neuroprotective role in AD. Endogenous estrogens is the most common in women after menopause [6]. Epidemiologic studies have reported that postmenopausal females have increase susceptibility of AD when compared with age-matched males. Studies have also shown that women endogenous estrogen have decreased in early menopause in women, and it is closely related to the incidence of AD [7,8].

Endogenous Estrogen Synthesis

Aromatase is one of cytochrome P450 enzyme systems, which can catalyze androstenedione and testosterone to convert irreversibly to estradiol and estrone, respectively. It is the rate-limiting enzyme for estrogen biosynthesis and is located in the endoplasmic reticulum of estrogen-producing cells [9]. Aromatization of androgen and production of estrogen molecule by aromatase has a double action. However, androgens may have no significant change in concentration by removing androgen molecules, estrogens are mole for mole over 100 times more active than androgens [10]. Studies have shown that there are gender differences in the expression and activity of aromatase, and it is higher aromatization expression in males than females and convert androgens to estrogens to induce masculine sexual behavior [11-13]. Most of early studies were limited to the role of aromatase in the regulation of estrogen in animals. In recent years, there has been a new explanation for aromatase, that is, aromatase plays a role in the regulation of female behavioral end points and physiological [14]. Some studies have shown that the role of aromatase is not only involved in the synthesis of estrogen, but also involved in functional regulation. Early work had shown that aromatase plays an important role in the treatment of neurodegenerative diseases and cancer [15,16]. These studies suggested that aromatase promotes local estrogen production,

which regulates brain function. In addition, aromatase can promote sufficient levels of estrogen in the brain when it exerts antioxidant effects to promote neuroprotective effects [15].

Physiological Function of Estrogen

Estrogen can promote the development of secondary sexual characteristics and sexual organ maturation in female animals. Other broad physiological regulatory roles include bone mature, organic components [17], cardiovascular system, central nervous system and metabolism [18-20]. The main source tissues of estrogenare ovary and placenta in female animals, and granulosa cells are crucialto produce estrogen. It includes three chemically different types in body: estradiol, estrone, and estriol, in which estradiol is the predominant exist [21-25]. The classical active mode of estrogen is through the activation of the receptors [26], by which estradiolas ligand-dependent transcription factors regulate the expression of target genes in the nucleus [27]. Estrogens act through two major categories of estrogen receptors (ERs): the classical nuclear receptor including ER1 and ER2, and another membranous receptors including membranous components of classical nuclear receptors and GPER1 (GPR30) and ER-X. ERs signaling pathway can also be mediated via the activation of some protein kinase cascades, such as MAPK/ERK, PI3K/AKT [28], by which cognitive behaviors is regulated.

Estrogen Receptors

Estrogen plays an important role in the repair of more than one disease, including angiocardiopathy [18,29], osteoporosis [30], spondyloarthritis [31], brest cancer [32], AD and Parkinson disease [33,34]. Recent studies have shown that estradiol replacement therapy in obese model of male mice induced by high-fat diet- and rats ovariectomized were evaluated. The results shown that estradiol activates both ER1 and ER2. Meanwhile, ER2 levels increased in a dose-dependent manner [35,36]. Other studies have shown that the preventive effect of estrogen in osteoporosis is mainly via the regulation of ER1 and ER2 and affects the expressions of related proteins and genes [37,38]. Estrogen can play a neuroprotective role through estrogen receptor-mediated signaling cascade. Recent studies have shown that estrogen replacement therapy can reduce the production of Aβ which impaires neurons in AD model. However, the protective effect of estrogen disappears after using ER inhibitors [39-43]. Studies have suggested that ER1 mutations found in metastatic breast cancer promote ligand-independent receptor activation and react against to estrogen-deficiency therapy in laboratory models [44]. Taken together, estrogen is exerted by binding to a receptor.

Estrogen Receptors in CNS

In the central nervous system (CNS), multiple types of estrogen receptors are widely distributed in different regions and exert different physiological functions. There are two forms of ERs in the CNS, where estrogen nuclear receptors exist as a highlight, and the distribution and functions are poles apart in several brain areas [45], including prefrontal cortex, thalamus, hypothalamus, basal forebrain, amygdala, hippocampus, raphe nucleus, locuscoeruleus, posterior cingulate [46,47]. On account of estrogen to be a momentous regulator of the center neurological systems that generate the symptoms associated with menopause, the location of the estrogen receptor is consistent with the associated neuroanatomy [48]. ER1 and ER2 shows a wide range of distribution in forebrain, where they regulate information processing and short-term memory, emotion and motivation, executive function and working memory, temperature, sleep, energy, balance and food intake and so on [49,50]. In the midbrain, ER2 is predominantly localized to locus coeruleus where it regulates adrenergic system functional activities such as attention, arousal and anxiety [51]. ER1 is more narrowly distributed in the hindbrain and cerebellum, and most ER1 and ER2 immunostaining is within cell nuclei [45].

Estrogen disorder and AD

In 1956, the biochemical structure of aromatic amines was studied, and the experimental sample was obtained from rat liver [52]. Androgen aromatization found in human fetuses by Naftolin and Ryan & Petro in 1971 [53]. In the following years, it was proposed that the conversion of androgen to estrogen is aromatization in the human placenta [54]. Studies have found that aromatase is essential in the induction of male sexual behavior controlled by estradiol [55,56]. Finally, this enzyme has now been discovered in brain regions and other tissues or cells. In the brain of rainbow trout, aromatase genes and proteins are higher, and high expression region of aromatase is consistent with ERs in the neuroendocrine region [57]. In mammals, aromatase activity or protein expression has been detected in the hypothalamus, medial proptic area, bed nucleus of stria terminalis, prefrontal cortex, hippocampus, and cerebellum [53,58]. In other specific tissues, aromatase is mainly expressed in ovarian tissue, and it is also expressed in adipose tissue, gonads, and the like.

Recent experiments have shown that removal of ovaries can affect energy, glucose and lipid metabolism, and impaired cognitive function in rat [19,20]. Shin et al. reported that estrogen levels decrease in ovariectomized model rats, mimicing estrogen deficiency, and an obvious deposition of Aβ in the hippocampus was found [20]. Other studies have shown that endogenous estrogen levels in naturally postmenopausal women also decreased. Therefore, natural menopause increases the risk of AD, estradiol administration in postmenopausal women may go into overtime and decrease the risk of AD [59]. Lack of estrogen can lead to an increased susceptibility to brain insulin resistance and neuroinflammation. As a result, the prevalence of AD increases after menopause women [60,61]. Estrogen is known to improve memory by promoting the degradation of Aβ, which may be due to it stimulating the degradation of Aβ and downregulating neuroinflammation and amyloid genesis.

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Estrogen Receptors and AD

The function of estrogen receptor needs to depend on the ligand estrogen. Studies have suggested that brain estrogen has neuroprotective effects [62], and its protective effect is to affect the expression of Aβ and Tau in the brain by activating estrogen receptors RE1 and ER2. The action of estrogen to degrade Aβ may be mediated by binding to the receptor to regulate the activity of secretase [63].

Cav1.2 is the pore-forming subunit of CaV1 Ca2+ channel. Itis also called L-type Ca2+ channels (LTCC). Cav1.2 accounts for approximately 90% of LTCC in the brain and plays a critical role in calcium overload and cell death in AD [64]. Estrogens are neuroprotective which plays a necessary role in brain aging and AD [65,66]. It has been reported that estrogen deficiency promotes the generation of the toxic Aβ and supports the role of estrogens in AD-like pathologies [67]. Evidence has suggested that physiological calcium concentration of nerve cells is necessary to maintain its normal function and increase of L-type calcium leads to neuronal damage [68]. Recent experiments have shown that brief exposure of estradiol induces a rapid increase in calcium currents, which is mediated by direct interaction of estradiol with LTCC subunit [69], and long-term estrogens can inhibit LTCC in neuronal cells [70,71]. A new research shows that ER1 agonist-induced Cav1.2 reduction may suggest an important role of LTCC in estrogen-mediated neuroprotection [65].

ERs-Singnals Mediated and AD

Estrogen receptors are involved in the estrogen signaling pathway, but ER-independent signaling mechanisms exist. ER-dependent pathways can initiate either in the nucleus (ER1 and ER2) or at the plasma membrane (GPR30 and ER-X). Studies have suggested that non-genomic mechanism involving interactions with the plasma membrane can also be mediated via the activation of different protein kinase cascades [28]. The G protein-coupled receptor bound to the ligand undergoes a conformational change, and the α subunit of the G protein is separated from the β, γ subunit by exchanging the guanosine diphosphate which is originally bound to the G protein by guanosine triphosphate. This process makes the G protein active and participates in the next signaling process including the activation of the adenylyl cyclase and Src, then activation of Src activates MMP, which releases of heparin-binding epithermal growth factor (HB-EGF), and the HB-EGF can activate EGFR by which the estrogen regulate the activation of PI3K, Akt, MAPK [63,72]. The combined effects of these signalings and transcriptional events often promote the regeneration of neurotrophic factors. Some studies have shown that nucleus associated ER1 can also be mediated via the activation of different protein kinase cascades, MAPK/ERK, PI3K/AKT [39]. Estrogen can promote nonamyloidgenic cleavage of APP via modulation of ERK/MAPK and PI3K/Akt-dependent signals, and this effect of estrogen was mediated through activation of ER [39,40,73,74]. Studies have suggested that sAPPα stimulates the survival by signal pathway of PI3K/Akt, but Aβ oligomers block signal transduction pathway, leading to the susceptibility of neurons in special parts [75]. Other studies have found that insulin can regulate the localization of presenilin 1 via the PI3K/Akt signaling pathway, thereby regulating the pathological changes of Aβ, which can regulate the pathological changes of Aβ [76]. Studies have shown that activation of the ERK pathway can increase α-secretase activity and sAPPα release and reduce amyloid production [77].

Estrogen and NF-κB mediated in AD

In the early stages of AD discovery, neuropathologists have recognized that glial cells proliferate significantly in the brains of AD patients [78]. Activation of microglia and astrocytes is also extensively present in the brain of AD transgenic mice [79,80]. In particular, there is obvious reactive hyperplasia of glial cells around the amyloid plaque. Meanwhile, activation and proliferation of microglia in the brain, centrated around amyloid plaques, is a momentous feature for AD [81,82]. On the other hand, there is also significant glial activation around neurons degenerated by TNFs [83]. It is further suggested that neuroinflammation is closely related to the pathological changes of AD characteristics. Activation of NF-κB promotes TNF-α-mediated regulation of BAC1 promoter activity, which increases the production of Aβ and affects the development of AD [84]. Previous studies have shown that estrogen or estrogen-like compounds administration has the potential effect to hinder the progression in mouse model of AD. Furthermore, estrogen is known to regulate the activity of proinflammatory transcription factors, such as Nuclear factorkappa-B (NF-κB) [85,86]. NF-κB plays a critical role in the inducible transcription of various proinflammatory genes. It can selectively or directly effects regulate the expression of many genes, including cytokines (IL-1β, IL-6), chemokines (monocyte chemotactic protein-1), and apoptotic (Fas ligand, BclXL) molecules [87-89]. NF-κB up-regulates the expression of many molecules that in turn modulate immune responses, inflammation, and apoptosis [90]. Furthermore, activation of NF-κB is involved in the treatment of AD. NF-κB signaling is activated and stimulates Aβ production through upregulation of beta-secretase1 expression and β-secretase activity [91,92]. The observation of AD patients supports the role of NF-κB activation in the development of AD. Meanwhile, precursor of estrogen, 10β,17β-dihydroxyestra-1,4-dien-3-one (DHED) which is a brain-selective prodrug of 17β-estradiol, have also been studied for the treatment of AD [93]. Yan, Wu, Song, Luo and Xu [93] has confirmed that learning and memory were significantly ameliorated by prolonged treatment with DHED.

Expectations

The probability of AD development, progression, and severity of the disease exsist significant differences between men and women, and increased risk of dementia after menopause [94, 95]. Epidemiological investigation shows that the incidence of

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AD in postmenopausal women is about 3 times higher than in men of the same age. In the past decade of research, the role of estrogen in neuroprotection has been strengthened, and estrogen replacement therapy has many studies in AD. Early studies performed on neuronal suggested that patients with AD can use estrogen therapy for improving memory and cognitive dysfunction [96, 97]. In addition, some studies have revealed that estrogen therapy can be effective in preventing the illness when the therapy is implemented at earlier ages [98]. It is worth noting that the transform levels of estrogen in plasma do not always reflect levels in the brain. Although estrogen has a protective effect, exogenous estrogens have not yet had a significant therapeutic effect [99-101]. Therefore, the protective effect of local estrogen is crucial in the brain, and the importance of local brain aromatase expression and activity is emphasized as the source of estradiol in the brain [102-104].

Brain estrogen and aromatase are closely related to the reduction of neuronal function. Aromatase controls the biosynthesis of estrogen, which acts to increase neuroprotection by increasing local estrogen. In the current study, the relationship between aromatase and estrogen in AD is rarely studied, and the mechanisms of action between them needs further research.

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How to cite this article: Shengjiao Wei, Wei Zhang, Jingshan S. Estrogen and Susceptibility of Alzheimer's Disease. Curr Trends Biomedical Eng & Biosci. 2019; 19(4): 556019. DOI: 10.19080/CTBEB.2019.19.556019

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DOI: 10.19080/CTBEB.2019.19.556019

How to cite this article: Shengjiao Wei, Wei Zhang, Jingshan S. Estrogen and Susceptibility of Alzheimer's Disease. Curr Trends Biomedical Eng & Biosci. 2019; 19(4): 556019. DOI: 10.19080/CTBEB.2019.19.556019