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Estrogen associated gene polymorphisms and their interactions in the progress of Alzheimer's disease

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ABSTRACT

The extensive neuroprotective effects of estrogen against Alzheimer's disease (AD) have been proven in numerous laboratory studies. However, in clinical studies, the exact role of estrogen in AD is still ambiguous. Some evidences even suggested the high levels of estrogen or estrogen replacement treatment increased the risk of AD. Thus, there must be other factors affecting the neuroprotective effects of estrogen. Multiple enzymes and receptor proteins are involved in the biosynthesis, metabolism and signaling pathways of estrogen, and mediate the beneficial effects of estrogen on AD. Previous studies have suggested some polymorphisms of genes encoding these enzymes and proteins are associated with the risk of AD. In addition to the genes associated with estrogen biosynthesis and metabolism and the genes encoding estrogen receptor proteins, some other genes also modulate the effects of estrogen on AD, or interact with other estrogen-associated genes on the progress of AD. The gene-hormone and gene-gene interactions may be key to unraveling the conflicting results regarding the effect of estrogen on AD. In this paper, we will review and discuss the associations between polymorphisms of these genes and their interactions and the susceptibility to AD. A better understanding of these estrogen-associated genes is significant to explore the pathogenesis of AD.

Contents

Abbreviations: AD, Alzheimer's disease; Aβ, β amyloid peptide; ERT, estrogen replacement therapy; ESR, estrogen receptor; E1, estrone; E2, estradiol; E3, estriol; CYP, cytochrome P450; CYP11A1, cytochrome P450 cholesterol side chain cleavage enzyme; HSD-3β, 3β-hydroxysteroid dehydrogenase; CYP17, 17α-hydroxylase/17, 20-lyase; DHEA, dehydroepiandrosterone; 17β-HSD, 17β-hydroxysteroid dehydrogenase; SULTs, sulfotransferases; UGTs, UDP-glucuronosyltransferases; COMT, catechol-O-methyltrasferase; GSTs, glutathione-S-transferases; ApoE, apolipoprotein E; AAO, age-at-onset; VNTR, variable-number tandem repeat; RFLP, restriction fragment length polymorphism; MMSE, Mini-Mental State Examination; NCD, non-coding deletion; HDL, high density lipoprotein; FAD, familial Alzheimer's disease; VLDLr, very low density lipoprotein receptors; LDLr, low density lipoprotein receptor; LRP, lipoprotein receptor related protein; seladin-1, selective Alzheimer's disease indicator-1; FNC, fetal neuroepithelial cell; ChAT, choline acetyltransferase; BuChE, butyrylcholinesterase; ACh, acetylcholine; ChE, cholinesterase; AChE, acetylcholinesterase.

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1. Introduction

Alzheimer's disease (AD) is a chronic neurodegenerative disease characterized by progressive cognitive impairment sufficient to affect functional capacities and cause altered behavior and language deficit. It is the most common dementia and the major cause for senile dementia. Among people aged over 60, the estimated global prevalence of dementia was 24.3 million in 2001. This number is predicted to double every 20 years, and will reach over 80 million by 2040 (Ferri et al., 2005).With the increase of life expectancy, AD has become a global problem. AD affects patients' quality of life, places a great burden on caregivers, and has serious socioeconomic implications. The annual cost per person with dementia exceeds that for patients with cancer or cardiovascular disease (Hampel et al., 2011). Thus, understanding the pathogenesis and risk factors for AD is of great significance.

In previous studies, AD has been found to be more prevalent in women (Andersen et al., 1999; Bachman et al., 1992; Fratiglioni et al., 1997) and this increase in prevalence has drew the attention of researchers because of the effect of estrogen, which declines rapidly after menopause. Numerous laboratory studies have demonstrated the neuroprotective effects of estrogen against AD. Estrogen may protect against the age-related atrophy of hippocampus, a key area of the brain involved in memory function (Eberling et al., 2003). In addition, estrogen enhances the outgrowth and survival of neurons in culture (Brinton et al., 1997). Previous studies have also reported that estrogen can induce an increase of dendritic spines and synapses in hippocampal CA1 pyramidal cells (Woolley et al., 1997). Using neuronal cell lines, previous studies demonstrated the antioxidant and anti-apoptosis functions of estrogen (Ba et al., 2004; Chiueh et al., 2003). Estrogen regulates multiple neurotransmitter systems, including cholinergic, serotonergic and dopaminergic systems, which have degenerative changes in patients with AD (Craig and Murphy, 2009). The deposition of extracellular β amyloid peptide (Aβ) and the presence of neurofibrillary tangles are the neuropathological hallmarks of AD. Estrogen can inhibit the formation of Aβ plaques (Morinaga et al., 2007, 2011; Yue et al., 2005), accelerate Aβ degradation (Merlo and Sortino, 2012), and protect against Aβ-induced neuronal death (Yao et al., 2007). Previous studies have also shown that estrogen prevents the hyperphosphorylation of tau protein, which forms neurofibrillary tangles (Alvarez-de-la-Rosa et al., 2005).

Taken together, these observations demonstrate that estrogen exerts a broad range of protective effects against AD progression. Therefore, estrogen replacement therapy (ERT) is regarded as a potential treatment for AD. However, in an actual patient population, the precise role of estrogen in AD is still ambiguous. First, not all studies have shown gender differences in the prevalence and incidence of AD. Some recent studies, especially those performed in America, have suggested that males and females have a similar prevalence of AD after controlling for age (Hebert et al., 2001), and the incidence did not differ significantly between genders up to an advanced age (Edland et al., 2002; Ruitenberg et al., 2001). Second, serum levels of estrogen are not always significantly lower in patients with AD compared to controls; some studies reported comparable or even higher levels of estrogen in patients with AD (Cunningham et al., 2001; Paoletti et al., 2004). Furthermore, menopause status and the decline of estrogen levels are not necessarily associated with cognitive impairments (Herlitz et al., 2007). Some previous studies suggested that estrogen levels were not related to cognitive performances in women (Thal et al., 2003; Yaffe et al., 1998). Finally, early studies suggested that estrogen deficiency increased the risk of AD, and that ERT was useful in preventing AD (Paganini-Hill and Henderson, 1994; Yaffe et al., 2000b). However, other evidences showed that high concentrations of estrogen were not necessarily associated with beneficial effects on AD or cognitive ability (den Heijer et al., 2003), but resulted conversely in an increase in the risk of AD and the rate of cognitive decline (Geerlings et al., 2003; Ravaglia et al., 2007; Yaffe et al., 1998). The adverse effects of ERT on the incidence of cognition and dementia was supported by the Women's Health Initiative Memory Study (Espeland et al., 2004; Shumaker et al., 2004), a large multicenter, randomized, double-blind, placebo-controlled clinical trial, which cautioned regarding the application of ERT in AD.

These controversial results indicate that the level of estrogen is not the only factor that determines the effect of estrogen on AD. The synthesis, metabolism and signaling pathways of estrogen are complex. Multiple enzymes and receptor proteins are involved in this process, and affect the levels and physiological effects of estrogen. Thus, the genes encoding these enzymes and proteins may interfere with the effects of estrogen on AD, contribute to the failure of ERT, and furthermore, increase the risk of AD. In addition to these estrogen biosynthesis and metabolism genes and estrogen receptor (ESR) protein genes, some other genes also modulate the effects of estrogen on AD, or interact with other estrogen-associated genes, thereby, contributing to the progression of AD. These gene-hormone and gene-gene interactions may be key to unraveling the conflicting results regarding the effect of estrogen on AD.

A few previous studies reviewed the associations between estrogen related genes and the susceptibility of AD, which mainly focused on aromatase (CYP19, an estrogen synthesis gene), catechol-O-methyltrasferase (COMT, an estrogen metabolism gene), and the ESR1 gene (Hiltunen et al., 2006; Serretti and Olgiati, 2012; Sundermann et al., 2010). We will systematically review the associations between the risk of AD and the estrogen