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Short Communication

Does Estrogen Therapy Prevent Late Onset Alzheimer's Disease?

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Neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, Amyotrophic lateral sclerosis and Huntington's disease remain a major challenge to human. Among the neurodegenerative diseases, Alzheimer's disease (AD) and Parkinson's disease are two major forms. According to the recent survey in US, more than 5.5 million (age 65 or older) people have dementia caused by Alzheimer's and remain the 5th leading cause of death among the elders. World Health Organization (WHO) expected ~ 16.2% prevalence of AD among people over 65 years worldwide by 2050. The median survival of AD patients who diagnosed at age 65 years is estimated to be 9 years. The disease causes ~ 66-75% of household income for the management. Furthermore, due to behavioral disturbances, faecal and urinary incontinence and increase need for personal care of AD patients, prevalence of anxiety and depression were found among caregivers mainly female care givers. Despite large number of studies to find various mechanisms for AD, the exact molecular mechanism in the pathophysiology of this irreversible disease has not yet been established. Formation and deposition of extracellular β-amyloid peptide (Aβ, ~4 kDa protein) in an amyloidogenic pathway in the brain region leading to synaptic dysfunction, disrupting neural connectivity was demonstrated as well [1]. Aβ is formed from the β-amyloid precursor protein after processing by the membrane-bound multi-subunit aspartyl endoprotease, β- (exists in two forms BACE1 and BACE2) and γ-secretase. Presenilin1 or 2 (PS1 or PS2), subunit of γ – secretase was found to be mutated in familiar AD cases. In addition to this, several forms of mutations in the β-amyloid precursor protein were also evidenced. Among the different Aβ species found, the one ending at position 40 (Aβ40) are present in 80 - 90% cases, followed by slightly longer forms Aβ 42 in 5 - 10% cases. Aβ42 are more toxic due to its fibrillogenic and hydrophobic nature.

Sporadic AD is a late onset disease constitutes more than 90% of the incidence in which declined activity of two metalloprotease Neprilysin and insulin-degrading enzyme (IDE) were reported. Neprilysin is for the extracellular degradation while IDE in neuronal and microglial cells is involved in both intra- and extracellular degradation [2,3]. During normal aging, the activity of these two enzymes found decreased [4]. Declined mitochondrial function was found to be associated with the early onset of dementia and hence mitochondria targeted antioxidants are promising area of future research [5]. Extracellular Beta-Amyloids plaque and intracellular neurofibrillary tangles produce low-level of inflammation and oxidative stress both were found to be associated with synaptic plasticity and thus described as the hallmark of AD [6].

Women make up almost 2/3 of seniors living with Alzheimer's disease in the U.S. Episodic memory is found to be affected due to damage of the medial temporal lobe which is involved in the hippocampal formation and associated cortical areas in AD [7]. Recent studies highlighted the prophylactic role of female gonadal steroid hormones in the prevention of AD. Despite the reproductive function of gonadal hormones, they play exceptional functions on Central Nervous System. Many cellular mechanisms are triggered directly or indirectly by these hormones to enhance the brain function. Hormone replacement therapy (HRT) includes estrogen plus progestin therapy and estrogen-only therapy [8]. Among the estrogen hormones 17β-estradiol, a major estrogen hormone is mediated its action through ERα and ERβ receptors. Clinical and experimental studies during the last decade have evidenced several protective effect of 17β-estradiol in late onset AD.

Since 17β-estradiol can prevent the declining of reduced glutathione, a non-protein thiol in nerves the effect was considered as an antioxidant [9]. This might be effective to prevent the oxidative stress and inflammation induced by Aβ. Furthermore, estrogen receptors are distributed on the mitochondrial membrane and thus 17β-estradiol can prevent the accumulation of calcium via efflux of ca++ mediated by activating the Na+/Ca++ exchanger on mitochondrial membrane and thus prevent the decline of mitochondrial membrane potential and apoptosis [10]. The anti-apoptotic effect can also be associated with stabilizing the bax:bcl2 ratio in cortical neurons by increasing the level of bcl-2, an anti-apoptotic protein [11]. 17β-estradiol can inhibit the cdk-5 and prevent the tau protein hyperphosphorylation which later forms intracellular

neurofibrillary tangles. 17β-estradiol can increase the expression of brain derived neurotrophic factor through activation of MAPK/ERK and PI3K signaling. Some of the neuroprotective actions of 17β-estradiol in brain are mediated ERβ than ERα. This includes the degradation of β-amyloid by insulin dependent enzyme. The effect was found to be mediated through PI3K-AKT pathway [12]. Viña and Lloret in their review highlighted that mitochondria of young females are more protected against Aβ toxicity and generate less reactive oxygen species or release less apoptotic signals when compared to males or females of old age [13].

Studies in ERβ knockout mice demonstrated the significant role of 17β-estradiol in brain development. Regional neuronal hypocellularity (mainly in the cerebral cortex) and thus neuronal deficits in the brains was evidenced in ERβ knockout mice [14]. Treatment with 17β-estradiol elevated IDE in the hippocampal region and thus attenuated Aβ plaque formation. This could explain the direct mechanism underlying estrogen-mediated preventative effect against AD when initiated at the onset of menopause [15]. Despite the wide range of activity of 17β-estradiol against the incidence of AD, clinical trials conducted on the protective effect remains inconclusive [16]. Study by Women's Health Initiative failed to find a protective effect. However, Henderson., et al. (2007) demonstrated that women who used hormones at younger ages had lower risks for AD [17]. Long term (more than 10 years) systemic (oral or transdermal) estrogen therapy was found to be protective against AD [18]. Estradiol-based hormone therapy for more than 5 years was associated with a reduced risk of mortality among Finnish women with AD [19]. However, more recent study conducted among the postmenopausal women in Finland concluded that systemic hormone therapy irrespective of hormones (estradiol or oestrogen-progestogen) was fund to be associated with a 9 - 17% increased risk of AD. The OR 1.09 (95% CI 1.05 to 1.14) in estradiol treated group and OR 1.17 (%CI 1.13 to 1.21) in estrogen-progestogen treated group were found [20]. Therefore, some factors are found to be associated with the beneficial effect of 17β-estradiol which includes age at the onset of therapy, dose and regimen of the hormones used, duration of therapy and risk factors associated with the incidence of AD. Nevertheless the beneficial effects of HRT in very early age of elder females, recent clinical trial data have pointed to a slight increase in the number of gynecological cancers among menopause women and prothrombotic effects which increase the risk for stroke [21]. This was found to be mediated by the peripheral estrogen receptors. The risk was found to be associated with the dose, type of medication (high concentration of estrogens or with the third-generation progestogens, cyproterone, drospirenone), age (> 40 years), mode of administration (oral > transdermal patch and vaginal ring) and congenital or acquired predisposition to thrombosis [22]. An oral conjugated equine estrogen, the most used estrogen formulation for postmenopausal hormone therapy for the management of early menopausal symptoms among the women of age 50 - 59 years, was fund to prevent osteoporosis, cardiovascular disease and AD [23]. Hence, analogs of estrogen which act as agonist in brain and antagonist in peripheral cells are promising approach in the prophylactic therapy of AD. Thus, a long term clinical trials in middle aged women with family history of AD is warranted to conclude the protective effect.

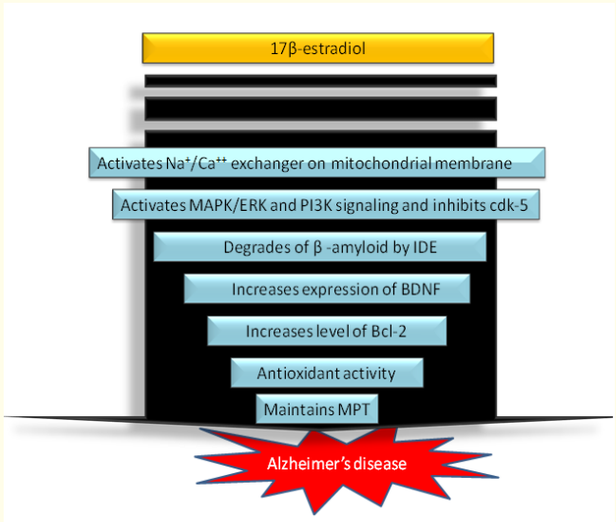

Figure 1: The various effects of 17β-estradiol on nerve cells that blocks/delays the AD. 17β-estradiol prevents the various mechanisms in the pathophysiology of Alzheimer's disease formation. It scavenges the free radical generated by neuroinflammation, scavenge free radicals in mitochondria and increases the degradation of amyloid beta to prevent plaque formation by activating insulin-degrading enzyme (IDE). Enhanced apoptosis is evidenced in AD brain due to the oxidative stress and neuroinflammation. 17β-estradiol decreases the apoptosis by increase calcium efflux from mitochondria by activating the Na+- Ca++ exchange to maintain the mitochondrial membrane permeability transition (MPT) and increase the expression of Bcl-2, an anti-apoptotic protein on mitochondrial membrane. Furthermore, 17β-estradiol increases the expression of Brain derived neurotrophic factor (BDNF) via PI3K/Akt signaling pathway

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