Journal Pre-proofs

Review article

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PII: S0304-3940(21)00599-1
DOI: https://doi.org/10.1016/j.neulet.2021.136221
Reference: NSL 136221

To appear in: *Neuroscience Letters*

Received Date: 31 January 2021
Revised Date: 23 April 2021
Accepted Date: 2 September 2021

Please cite this article as: S. Radaghdam, V. Karamad, A. Nourazarian, B. Shademan, F. khaki-khatibi, M. Nikanfar, Molecular mechanisms of sex hormones in the development and progression of Alzheimer's disease, *Neuroscience Letters* (2021), doi: https://doi.org/10.1016/j.neulet.2021.136221

Molecular mechanisms of sex hormones in the development and progression of Alzheimer's disease

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Abstract

Alzheimer's disease (AD) is a form of brain disorder characterized by various pathological changes in the brain. Numerous studies have shown that sex hormones are involved in the disease. For instance, progesterone, estrogen, and testosterone are well-known steroid sex hormones that play an essential role in AD pathogenesis. The Gender-dependency of AD is attributed to the effect of these hormones on the brain, which plays a neuroprotective role. In recent years, much research has been performed on the protective role of these hormones against nerve cell damage, which are promising for AD management. Hence, in the current review, we aim to decipher the protective role of steroid hormones in AD. Accordingly, we will discuss their functional mechanisms at the genomic and non-genomic scales.

Keywords: Alzheimer's disease; Sex Hormones; MAPK / ERK signaling; brain-derived neurotrophic factor (BDNF).

Introduction

Steroid hormones have different effects on various tissues such as gonads and the nervous system. In addition to their hormonal role in reproductive activity, they have protective functions in the central nervous system (CNS) [26, 37]. Following the binding of the hormone, receptors become phosphorylated, migrate to the nucleus, and activate transcription of specific genes. These hormones can affect different CNS areas, namely the brain, spinal cord, and peripheral nerves, due to estrogen and progesterone receptors in these sites [26]. Previous studies showed that androgen and estrogen levels are higher in the newly-isolated hippocampus of male mice than in the plasma [42]. Steroids play an essential role in maintaining the body's vital balance. Neurosteroids are steroids synthesized in the brain independent of their peripheral production in the adrenal glands. Neurosteroids can regulate neuronal excitability and play a distinct role in anxiety and depression disorders [41]. Although neurosteroids do not directly contact the steroid hormone receptors, their metabolites can occupy intracellular steroid receptors. Neurosteroids can activate signaling pathways and alter cellular behaviour by acting on the steroid receptor. In the current review, we first described the specificity of AD, then examined the role of steroid hormones in signaling pathways to prevent AD. Proper knowledge of these signaling pathways can provide the right treatment for better management of AD patients.

Alzheimer's Disease

Alzheimer's disease is a progressive disease of memory loss with significant sex differences [53]. The high prevalence of AD in women can be due to differences in life expectancy between men and women [16]. The increased risk of AD is significantly affected by sexual steroid hormones in women. Decreased levels of estrogen and progesterone are associated with an increased risk of AD. In men, the risk of developing AD is affected by the male sex steroid hormone, testosterone, too. Although menopause is not seen in men, the rate of testosterone production gradually decreases with age, resulting in an increased risk of developing AD [24]. Low testosterone levels

increase the risk of androgen-related diseases and cause the clinical syndrome termed Androgen Deficiency in Aging Males (ADAM) [18].

Also, AD can be associated with a variety of conditions, including the deposition of specific Aβ proteins that form neuritic plaques in the brain; Tao protein hyper phosphorylation, which causes the accumulation of intricate neurofibrillary filaments outside the nervous cells; and the activation of glial cells, which leads to the loss of synapse and inflammatory responses [48]. Although AD's pathogenesis is not fully understood, the central hypothesis is that the disease can be initiated and directed with a long-term increase in the Aβ level [21]. Identifying the pathways that cause or exacerbate the disorder can help find the treatment options.

Aβ Peptides in AD

Beta-amyloid precursor protein (β-APP) is a membrane protein at the end of pre-synapse axons [63]. This protein has a large extracellular and a small intracellular portion. If the beta-secretase and gamma-secretase enzymes cut the APP, a peptide similar to beta-amyloid is obtained. Secretase enzymes produce the Aβ peptide through subsequent proteolytic processing to stimulate neuronal survival [23]. Aβ peptides are one of the widely-expressed natural products of metabolism composed of 36-43 amino acids. The physiological level of synaptic amyloids leads to the modulation of stimulus messages and the prevention of neurons' excessive activity [47].

Neprilysin proteases and insulin-degrading enzymes control the level of Aβ peptides. Any changes in the β-APPs and their regulatory enzymes lead to premature Alzheimer's disease [58]. Aβ peptides are easily collected in oligomers and fibrils. The production and deposition of monomer (1-42) Aβ play a vital role in developing Alzheimer's disease by deteriorating oxidative stress, inflammation, and membrane damage [69]. Due to its overproduction, Aβ deposition could occur

through abnormal APP processing or a disturbance in removing Aβ through microglia phagocytosis or enzymatic degradation [60].

An increase in estrogen and testosterone levels leads to a reduction in Aβ by regulating and managing APP proteolytic process. Treatment of neurons with sex steroids increases the secretion of β-APPs and reduces the production of Aβ [28]. It is believed that the presence of sex steroid hormones prevents non-amyloidogenic processing. This pathway is triggered by the activation of protein mitogen-activated protein kinase (MAPK) in the signaling pathway [7]. However, testosterone may also mediate these effects by AR signaling [9].

Moreover, testosterone is more potent than estrogen; it is involved in the secretion of β-APPs. The inhibition of aromatase in the presence of testosterone leads to a decrease in β-APP secretion [7]. Sex steroids can modulate the proper context for secretory enzyme activity; for example, estrogen can regulate intracellular pathways for β-APP secretion [76]. Sexual steroids can enhance Aβ secretion by modulating β-APP metabolism. Also, estrogen can increase Aβ breakdown and excretion [43] by expressing Aβ-degrading enzymes such as IDE and neprilysin [39]. Testosterone reduces the secretion of Aβ by activating the proper signaling pathways and affecting neuropilins [13]. Examining the steroid hormone pathways on AB peptide processing can increase our understanding of Alzheimer's disease and propose appropriate treatments.

Neurosteroidogenesis in Alzheimer's disease

Neurosteroidogenesis starts with the transfer of cholesterol into the mitochondria, a rate-limiting step involving steroidogenic acute regulatory protein (StAR) and translocator protein 18 kDa (TSPO) [35]. This step is followed by converting cholesterol to pregnenolone by the mitochondrial side-chain cleavage enzyme, P450scc [38]. Pregnenolone exits the mitochondria and is

metabolized to either progesterone or 17OH-pregnenolone, the latter giving rise to DHEA. DHEA and progesterone can be both metabolized to androstenedione. Androstenedione is subsequently converted to testosterone, which is converted to 17β-estradiol through aromatization [27]. Most of the steroidogenic enzymes expressed in the adrenal glands and the gonads are also present in the CNS. Their expression is cell type-, region-, developmental stage- and gender-specific [4]. Steroidogenesis takes place in both neurons and glia [38]. Astrocytes produce pregnenolone, progesterone, DHEA, androstenedione, testosterone, estradiol and estrone [17]. Oligodendrocytes synthesize pregnenolone and progesterone. Finally, neurons can produce pregnenolone, DHEA, androstenedione, and estrogens[78]. It needs to be stressed out that the steroidogenic capacity of these cell types has been primarily examined in purified cells or in vitro in cell cultures.

Estrogen levels are reduced in the brains of AD patients compared to the brains of non-AD subjects [74]. Estrogen depletion via ovariectomy in the APP23 AD mouse model increases pathological signs of the disease and microglial activation, whereas treatment of ovariectomized mice with 17β-estradiol is protective [64]. Along the same line, aromatase knockout in APP23 female mice induces earlier disease onset and increases Aβ deposition, while microglia from these mice display impaired Aβ clearance [74].

Similarly to estrogens, age-related decline in progesterone levels in women associates with AD risk [44].Aβ25-35 injection into the CA1 hippocampal region of male rats decreases progesterone levels in the prefrontal cortex and the hippocampus. In contrast, progesterone administration improves behavioural performance, increases pyramidal neuron survival and decreases TNF and IL-1β expression in a dose-dependent manner [11]. However, continuous progesterone treatment of female ovariectomized 3xTgAD mice, although reducing tau hyper phosphorylation, does not

affect Aβ accumulation or behavioural improvement, while in co-treatment with 17β-estradiol it reduces the ameliorating effects of the latter [12]. However, most clinical studies conducted so far, enrolling mainly female AD patients, failed to improve cognition or AD symptoms by estrogen or progestogen administration.

Estrogen receptors in Alzheimer's disease

Sex steroids exert their multiple actions through binding to nuclear receptors that act as ligand-dependent transcription factors to regulate the expression of target genes [10]. One mechanism by which estrogens exert their protective effects in the brain is through estrogen receptors. Currently, two estrogen receptor genes have been identified in humans: the original ESR1 (estrogen receptor alpha) and the more recently found receptor, ESR2 (estrogen receptor beta) [10].In addition to its influences on the development, plasticity, and survival of neurons, estrogen affects several neurotransmitter systems in the brain. It is an essential regulator of serotonergic, dopaminergic, and cholinergic neurons [54]. ERα and ERβ are both widely distributed in the brain, and ERα mediates a stimulatory, while ERβ mediates an inhibitory effect of estrogens. Indeed, ERα appears more effective than ERβ in inducing transcription linked to the estrogen response element (ERE) [65].

Removal of ERα has been shown to eliminate the protective effects of estradiol in all areas of the brain. In contrast, the ability of estradiol to protect against brain injury is preserved in the absence of ERβ. As a result, the ERα subtype is a critical mechanistic link in mediating the protective effects of physiological levels of estradiol in brain injury. Therefore, ERα mediates protection of the brain carries far-reaching implications for the selective targeting of ERs in treating and preventing neural dysfunction associated with normal ageing or brain injury [20]. Estrogen

receptor β, independent from estrogen, can reduce inflammatory reactions and amyloid β deposition in the hippocampus of Alzheimer's disease rats and improve learning and memory capacities. This effect may be mediated through activation of the Akt pathway [61]. Epidemiological studies suggest that estrogen replacement therapy decreases the likelihood of developing Alzheimer's disease. Still, estrogen replacement in older women does not affect the incidence or progression of Alzheimer's disease [51]. This probably means that the value of estrogen replacement lies in its prevention or slowing of neurodegenerative processes and not in reversing neurodegeneration.

The effects of sex hormones on signaling pathways in AD

It is essential to identify the signaling pathways associated with AD, increasing our understanding of the disease and providing appropriate treatment strategies.

The Signaling Pathway of Testosterone in AD

Testosterone is an androgen and can be converted to a more potent form called dihydrotestosterone (DHT). Testosterone and DHT activate the androgen receptor (AR). Interestingly, AR is found in both sexes' hippocampus and is part of the pathophysiology of Alzheimer's disease [2]. Testosterone can also be converted to estradiol and have an indirect effect by activating the estrogen receptor. Also, many studies have shown lower testosterone levels in men with AD than in the control group [40]. Direct and long-term functioning of androgens leads to a decrease in Aβ accumulation through the non-amyloid genic APP pathway. It also stimulates the enzymes involved in the destruction of Aβ. Studies have shown that testosterone levels in the brain are inversely related to the level of Aβ [3].

Previous studies showed that mTOR signaling pathways play a role in disease progression, ageing, and neuron regeneration. mTOR is a serine/threonine kinase that combines with different proteins to form two complexes, mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2) [19]. mTOR signaling is crucial for synaptic flexibility, learning, and memory formation in the adult brain [59]. The accumulation of Aβ in AD stimulates an mTOR signaling pathway that leads to cognitive impairment [68]. Preclinical studies have shown that mTOR activation increases the production of Aβ by modulating APP's progressive metabolism, while inhibition by rapamycin improves conditions such as AD [1].

Increased expression of ß and γ activates the MAPK hyperactive signaling pathway in AD. As this pathway is activated, an increase in the neurons' apoptosis and the Aβ levels is observed [5]. Testosterone and DHT physiological levels rapidly and temporarily affect MAPK / ERK signaling in the hippocampal nerve cells. Phosphorylation at the bottom of the ERK leads to apoptosis inactivation, resulting in increased cell survival [75]. The reduction of cell death and decreased activation of caspase-3 or by interaction with g-aminobutyric acid (GABA) receptors were observed due to the treatment of primary hippocampal neurons with testosterone or DHT [33]. Besides, testosterone and DHT protect nerve cells against other insults, such as the lack of serum in the culture medium and oxidative stress [34]. Studies have shown that lower levels of androgen increase the vulnerability of neurons in the hippocampus after injury. If a testosterone supplement is used, it may improve the lesion to some extent [55]. The effect of testosterone in modulation in Alzheimer's diseases showed in figure 1.

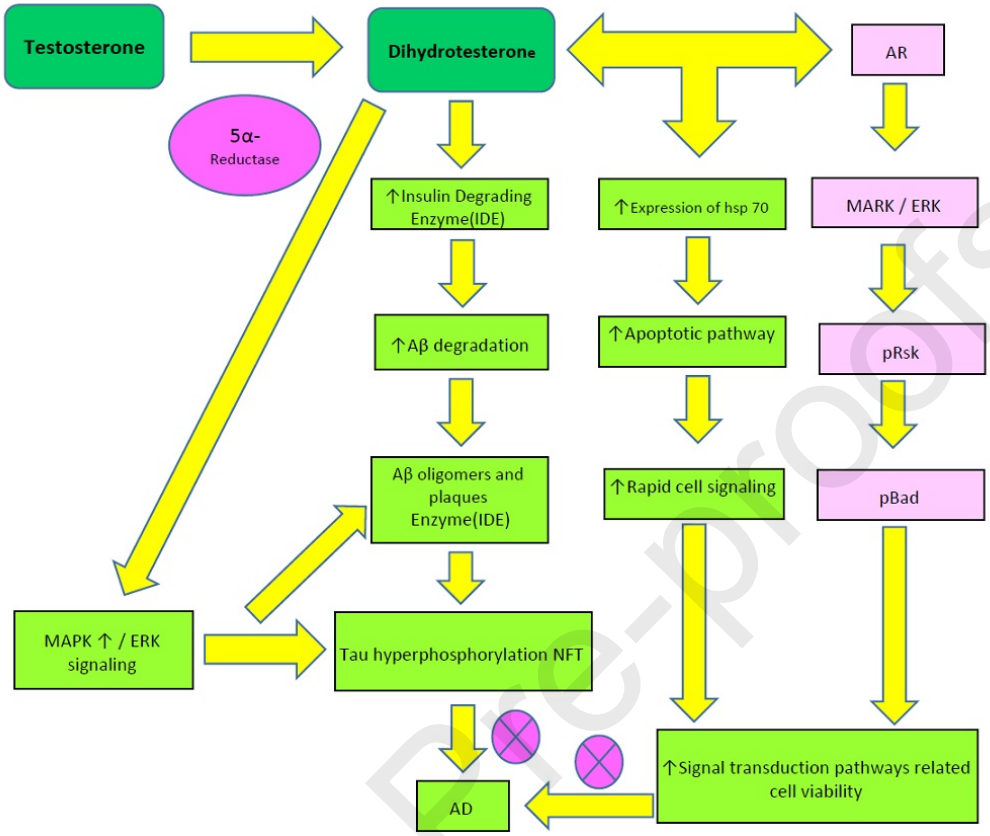

Fig 1. Effects of testosterone in the modulation of Alzheimer diseases

The Signaling Pathway of Estrogens in AD

Estrogen function is regulated by the estrogen receptor (ER) [72].Estrogen exerts its neuroprotective effects at the cellular and molecular levels through several mechanisms dependent or independent of ER [57].

Estrogen regulates APP processing through amyloid genic and non-amyloid genic pathways. Estrogen further regulates the level of Aβ through the non-amyloid genic pathway [62]. Estrogen regulates APP processing by activating the signaling pathways of regulated extracellular kinases

1 and 2 (ERK1 and ERK2) and also through protein Kinase C (PKC) pathways [25]. PKC signaling pathway is a potent activator of the non-amyloid genic APP processing [45].

The signaling pathways stimulated by Aβ activate the downstream proteins that shift the nerve cells into the apoptosis cycle. Activation of JNK signaling can lead to the apoptosis of the nerve cells. This pathway is regulated by estrogen to protect the nerve cells from Aβ [67]. Estrogen is involved in regulating the Bcl-2 family. It exhibits neuroprotective actions against Aβ toxicity by increasing the expression of Bcl-xL and Bcl-w (anti-apoptosis) and suppressing Bim-expression (apoptosis-inducing) [71]. Recent studies have shown that 17beta-estradiol (E2) can also increase Bcl-2 by activating CREB-dependent Akt [66]. Estrogen can also activate the ERK / CREB signaling pathway, thereby regulate Bcl-2 [66].

Glycogen synthase kinase-3 (GSK-3) controls various physiological processes in neurons and plays a vital role in regulating transcription factors, including steroid receptors [8]. Estrogen inhibits GSK-3 activity by activating the Akt-related signaling pathway [49]. Estrogen can regulate kinases and phosphatases' activity to regulate tau phosphorylation using E2 and P4 and through the glycogen synthase kinase-3 (GSK-3) pathway [14]. Estrogen can also reduce tau phosphorylation through the Wnt signaling pathway and the dickkopf-1 gene [52].

Of note, Aβ deposition can activate the microglia and deteriorate the inflammation. Estrogen is a potent inhibitor of nerve cell death and oxidative damage [52]. Estrogen has antioxidant effects through ER-independent mechanisms. In contrast, the anti-inflammatory effects of estrogen are regulated by ER-dependent mechanisms [57]. Therefore, it may be beneficial to prevent or treat several neurological diseases in which inflammation is a significant contributor to nerve cell damage. Removal of microglia is one of the mechanisms that increase the Aβ level. Therefore, the amount of Aβ increases dramatically in this case [15].

Interestingly estrogen is unable to regulate inflammatory reactions after the activation of microglia [46]. The effect of testosterone in modulation in Alzheimer's diseases showed in figure 2.

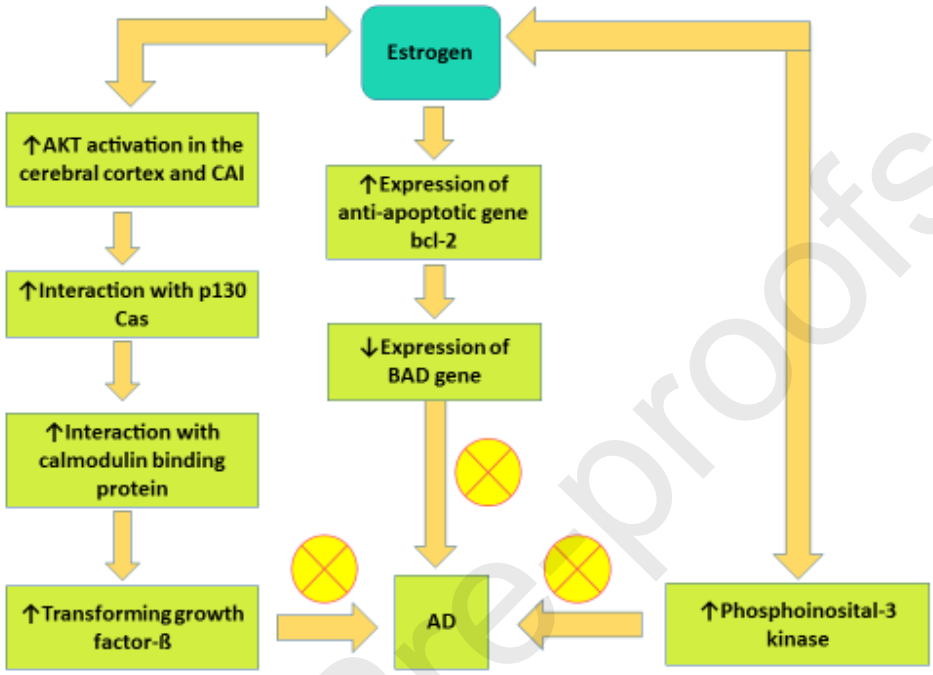

Fig 2. Effects of estrogen in the modulation of Alzheimer diseases

The Signaling Pathway of Progesterone in AD

Progesterone and its equivalents, dihydro progesterone (DHP) and tetrahydro progesterone (THP), may have neuroprotective effects on the damaged CNS [31]. Although progesterone receptors (PR) are expressed in the hippocampus and frontal cortex, previous studies on mice without progesterone receptors showed that the hormone's effects are not exerted only through this receptor. In this way, a new protein was identified to bind to the membrane [77].

Progesterone performs its function in the brain through three cellular pathways, gene expression control, modulation of the neurotransmitter system, and activation of signaling pathways [36]. Progesterone activates various pathways in the nervous system that can perform different tasks. Progesterone can affect the proliferation, survival, and death of the cells using MAPK [6].

Progesterone can also activate the ERK pathway to protect nerve cells with estradiol help [29]. Progesterone exerts its neuroprotective effects by activating the MAPK and Akt signaling pathways. Activation of these signaling pathways by progesterone increases the expression of Bcl-2. This protein prevents neurons from entering apoptosis [32].

The neuroprotective effects of progesterone are associated with the expression of brain-derived neurotrophic factor (BDNF). BDNF is a neurotrophin that is abundantly expressed in different CNS regions and is very important for strengthening specific learning and memory processes[50]. Preliminary studies suggest the existence of coordination between BDNF and steroid hormones. In brain ischemia, progesterone acts as a suppressor of the inflammatory response and expression of nitric oxide synthase 2(NOS2) [22]. In addition to its direct effects on nerve cells, progesterone may exert its indirect effects by regulating glial activity and increasing myelination.

The effect of progesterone in modulation in Alzheimer's diseases showed in figure 3.

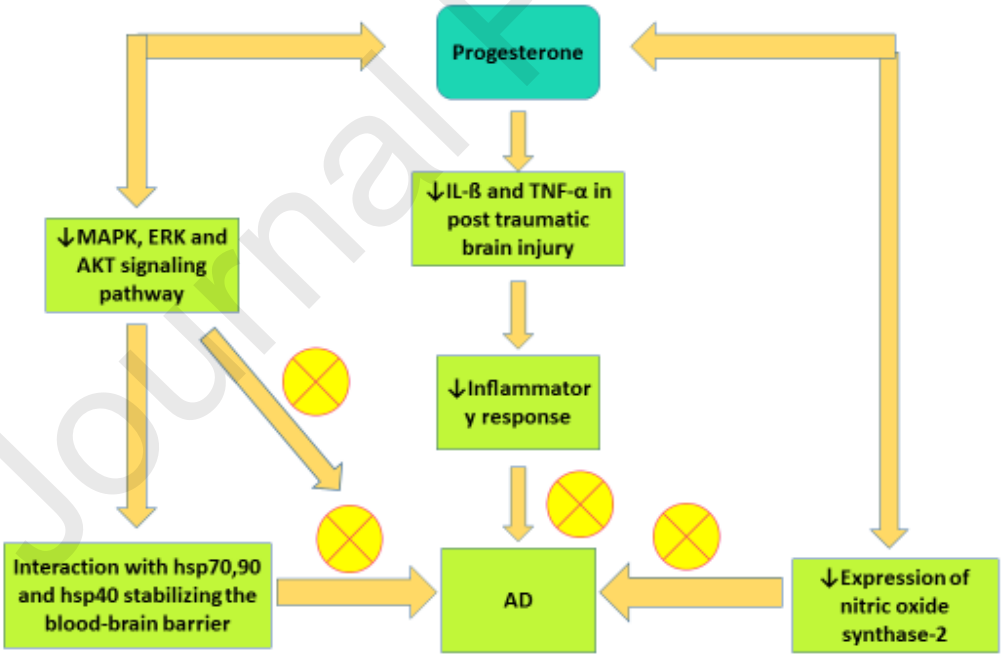

Fig3. Effects of progesterone in the modulation of Alzheimer diseases

Conclusion

. Neurodevelopmental aspects of AD vary between men and women. Also, risk factors such as genetics and the environment are gender-specific for AD. The current knowledge provides valuable opportunities to understand the disease and make effective interventions. In general, sexual hormones and their metabolites can play an essential role in the survival of nerve cells, glial cells' function. Sexual steroid hormones can exert effects in learning by inducing the mitosis of the nerve cells. In adults, sexual steroid hormones have a broad range of neuroprotective effects; postmenopausal women are also at risk of neurological diseases such as AD. Due to steroid hormones and their metabolite's significant effects on re-myelination, steroid hormones could be one of the essential factors for the treatment of AD. Also, accurate knowledge of signaling pathways in therapeutic strategies can be beneficial.

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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Author's contributions

AN and VK were involved in the study design. SR and BS Participate in the manuscript writing.AN ,MN and FKH contributed to manuscript figures design and draw. VK, FKH and AN contributed to the revision of the manuscript content, and AN gave consent for the final version of the manuscript.

- Sexual hormones and their metabolites can play an essential role in the survival of nerves.
- Sexual steroid hormones exert effects in learning by inducing mitosis of the nerve cells.

- In adults, sexual steroid hormones have a broad range of neuroprotective effects.