Chapter 7

Sex Hormones and Alzheimer's Disease

Wafik Said Bahnasy, Yasser A. El-Heneedy and Ehab A. El-Seidy

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.72561

Abstract

Alzheimer's disease (AD) is the most common type of dementia and the most common neurodegenerative disorder of elderly. It is not an accelerated form of aging but it is characterized by distinct temporospatial brain pathological changes, including amyloid plaques accumulation, neurofibrillary tangles deposition, synaptic loss and neuronal death with gross brain atrophy. These changes result in persistent progressive memory and cognitive decline interfering with the usual daily activities. AD is a multifactorial disorder results from the interaction of genetic, epigenetic, environmental and lifestyle factors. Estrogen, progesterone and androgen effects are important building stones in AD pathogenesis, and their effect in brain modulation and development results in different gender susceptibility to the disease. These sex hormones whether gonadal or neurosteroids (synthesized locally in the brain) play important neuroprotective roles influencing the individual's vulnerability to AD development, rate of mild cognitive impairment (MCI)/AD conversion and speed of AD progression. Despite the little therapeutic implications of hormonal replacement therapy in AD treatment, yet this topic still represents a challenging hopeful way to construct a strategy for the development of personalized, gender-specific AD management.

Keywords: Alzheimer's disease, sex hormones, neurosteroids, estrogens, progesterone, androgens

1. Introduction

Alzheimer's disease (AD) is the most common type of dementia and a key determinant of healthcare costs. It is an age-related neurodegenerative disorder, and due to increased people life expectancy, AD becomes one of the most burdensome threats to public health and a

grand international research challenges. It is a system-specific brain disease affecting discrete neurons in a nearly consistent temporospatial pattern and is characterized by progressive memory decline and persistent cognitive impairment enough to interfere with the person's performance of the usual daily activities.

1.1. History

The gender difference in the cognitive and neurobehavioral performance had been noticed since ancient time which may be the origin of the popular legend (men are from Mars, women are from Venus and had met here in Earth) [1]. The concept of age-related cognitive decline was well known since antiquity, which progressed through the ages till reached the term dementia. The link between female sex and dementia had also noticed since a very long period and this made Jean Etienne Esquirol put menstrual disorders and sequelae of delivery as direct causes of dementia in his book Des Maladies Mentales [2, 3]. In 25 November 1901, the German neurologist, Dr. Alois Alzheimer admitted a patient presented by recent cognitive decline to the public mental asylum in Frankfurt. Surprisingly, this first description was on a 51-year-old lady named Auguste Deter, who experienced marked memory decline, fear of people and became jealous of her husband in the last year preceded her admission in Frankfurt asylum by Dr. Alois Alzheimer and Dr. Hermann P. Nitsche. Later, the patient developed severe behavioral abnormalities, delusions, disorientation of time and place, hallucinations and severe language difficulties. In 1906, Auguste died and her autopsy revealed gross brain atrophy and microscopically increased silver staining by using Bielschowsky method, which later named amyloid plaques and neurofibrillary tangles (NFTs) [4].

1.2. Epidemiology

Dementia affects about 47 million people worldwide, and this number is expected to double every 20 years due to increased life expectancy. AD is the leading cause of dementia accounting for about 30% of early onset cases before the age of 50 years and 60–80% of late onset ones either as pure or mixed form [5]. It is one of the commonest causes of prolonged disability in old age, the sixth cause of death in USA globally and the fifth cause for seniors above the age of 65. Old age is the most important AD risk with estimated prevalence of 3% in people aged 65–74 years, 17% between 75 and 84 years and 32% in those >85 years [6, 7].

AD disproportionately affects both sexes, with females have 2–3 times higher incidence of AD than males of the same age. The age-specific risk of developing AD is almost twofold greater in women than men, 17.2% vs. 9.1% at 65 years and 28.5% vs. 10.2% at 75 years. The incidence of amnestic mild cognitive impairment (MCI) is equal both in male and female, denoting that females take shorter MCI/AD transitional state with rapid conversion to manifest AD [5, 8, 9].

1.3. Pathology

AD is not an accelerated form of aging but it is characterized by distinct cellular and molecular pathological changes, including amyloid plaque deposition, NFTs accumulations, synaptic loss and neuronal death with gross brain atrophy.

1.3.1. The amyloid hypothesis

The amyloid cascade theory with the resultant extracellular amyloid plaque aggregation is the leading one for AD pathogenesis. Amyloid plaques are aggregates of amyloid beta (Aβ) peptide derived mainly from the cleavage of a transmembrane protein named amyloid precursor protein (APP) by the sequential action of two aspartyl protease enzymes, β- and γ-secretases (amyloidogenic pathway) in which the APP is firstly cleaved by β-secretase to soluble APP and residual C-terminal segment that is further digested by the γ-secretase to Aβ-40/42 segments. The insoluble Aβ aggregates start to appear 15–25 years prior to the onset of cognitive decline or tau pathology, and their formation is triggered by enhancement of the amyloidogenic pathway with increasing the pool of soluble Aβ production, which in turn aggregate to form monomeric, oligomeric, protofibrils and finally mature insoluble Aβ [10]. Under normal circumstances, the ratio of Aβ-42: Aβ-40 is 1:9 and increase in this ratio due to either aberrant production (increased γ-secretase activity) or clearance (abnormal microglial activities) is the cause of Aβ accumulation as the former has a high tendency to aggregate. The amyloid aggregates spark a sequence of events that lead to AD development including neuronal injury and synaptic loss. It is generally accepted that brain β-amyloid deposition is relatively diffuse, and there is non-linear correlation between the density of mature Aβ aggregate and severity of AD, which denotes that soluble Aβ oligomers per se are neurotoxic and cause synaptic dysfunction even in the absence of insoluble aggregate [11, 12].

1.3.2. Neurofibrillary tangles

Tau pathology, including NFTs, neuritic plaques and neuropil threads intraneural deposition is assumed to be the consequence of amyloid accumulation. NFTs are intraneural misfolded twisted paired helical filaments, which accumulate to form intracellular deposits composed of hyperphosphorylated tau protein that concentrates in the inner side of the cell membrane, but when the neurons die, NFT may migrate to other healthy or less affected neurons or may be found extracellular. Tau is essential for NMDA-dependent long-term potentiation and AMPA-dependent long-term depression and acts as autophagy regulator by inhibiting histone deacetylase-6 enzyme. Thus, tauopathies result in marked synaptic disturbances and impaired selective autophagic clearance. Tau has more than 25 serine, threonine and tyrosine residue sites, which can be phosphorylated by specific protein kinases and phosphatases [13]. Genetic or acquired

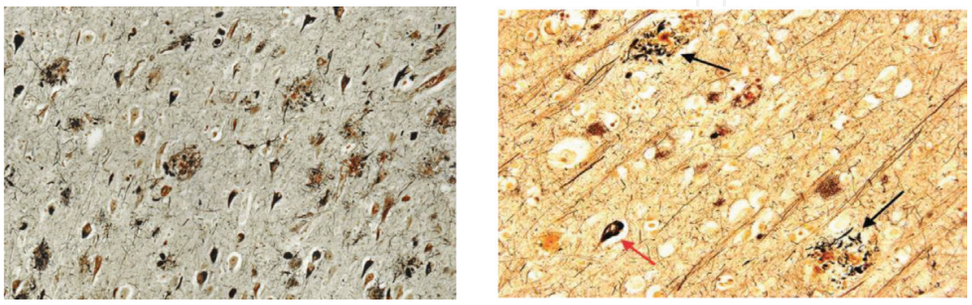

Figure 1. Photomicrography of Alzheimer's disease pathology using Bielschowsky stain demonstrating neurofibrillary tangles and amyloid plaques.

induced dysfunctions result in tau hyperphosphorylation, misfolding and fibrillar formation ending in NFTs deposition. On the other hand, tau dephosphorylation is regulated by protein phosphatase 2A enzyme, which activity is impaired in AD. NFTs accumulation starts several years after Aβ deposition but still before AD clinical manifestations and its accumulation dense and distribution is directly proportional with the severity of AD cognitive decline. NFTs deposition usually follows a stepwise progression typically starting in the transentorhinal cortex, the entorhinal cortex, hippocampus, medial temporal cortex and lastly other areas of the neocortex [14, 15] (**Figure 1**).

1.3.3. Microglia and neuroinflammation

It is well known that the density of β-amyloid deposition is not proportional with the severity of AD cognitive decline making the amyloid hypothesis alone is not sufficient to explain the whole AD pathological cascade and in turn the possible role of additional pathogenetic factors, including neuroinflammation and vascular amyloidosis. The neuroinflammatory theory was supposed after identification of activated microglia within the vicinity of the amyloid plaques, which number was proportional with the size of the plaques. At the same time, several microglial expressed genes were associated with AD predisposition, including TREM2, CD33, CR1, CLU, CD2AP, EPHA1, ABCA7 and INPP5D. Under normal circumstances, microglial activities are modulated by several neuroimmune regulatory proteins, including insulin-like growth factor-1, brain-derived neurotrophic factor, transforming growth factor-b and nerve growth factor, which help in slowdown and resolving the inflammatory process [16].

Microglia have no role in Aβ production; however, they act as Aβ scavengers as they play major roles in its clearance either directly through phagocytosis or indirectly via the secretion of several enzymes, including insulin degrading enzyme, neprilysin, matrix metalloproteinase-9 and plasminogen. At the same time, microglia regulate synaptic network remodeling (synaptic pruning) and neural circuit maintenance [17].

In AD, chronic reactivation and excessive proliferation of microglia result in the production of inflammatory mediators, including reactive oxygen species, interleukin-1, interferon-γ and tumor necrosis factor-alpha. This imbalanced microglial function results in aberrant synaptic pruning, pathological synaptic stripping, neuronal loss, enhancing the endothelial response to hypoxia with impaired blood-brain barrier (BBB) stability, disturbed Aβ clearance, increased levels of phosphorylated tau protein, promoting NFTs accumulation and, consequently, cognitive decline. Microglia also transport amyloid and tau from one brain area to another; thus, they play a major role in spatial AD progression. Microglia are candidate for the action of sex hormones, and they express abundant sex hormone receptors. These receptors modulate microglial activities producing potent anti-inflammatory actions that resist AD development and progression [18, 19].

1.3.4. Vascular theory

Diabetes, hypertension, smoking and heart diseases are associated with increased risk of AD. This concept resulted in the emergence of the AD vascular theory, which can explain why aging is the major risk of AD as vascular dysfunction is considered as a universal feature

of aging and why AD progression increases after cerebral ischemic events like stroke and transient ischemic attacks. Cerebral amyloid angiopathy (CAA) is present in more than 75% of autopsy confirmed AD brains especially in mixed AD/vascular dementia where the vascular risk factors predominate. Cerebral microvascular compromise is more common among subjects having the APOE4 allele making them at increased risk of AD development. CAA represents imbalanced Aβ production and clearance with consequent deposition within the basement membrane of the leptomeningeal vessels, intracerebral arteries and arterioles, and less frequently in capillaries and veins [20].

Amyloid deposition in and around the blood vessel wall impairs its endothelial integrity and disturbs the BBB leading to Aβ trapping in the CSF and its diminished clearance to the venous circulation. At the same time, CAA disrupts the microvascular homeostasis leading to chronic cerebral parenchymal hypoperfusion with focal ischemia, microinfarcts, release of inflammatory mediators, oxygen-free radicals, loss of nitric oxide bioavailability and mitochondrial dysfunction. The net result is neurotoxicity, reduced neural plasticity, neural apoptosis and synaptic loss [21]. Sex hormone receptors are heavily expressed in the cerebral blood vessels and exert very important actions to keep the vascular integrity and prevent chronic ischemic hypoperfusion through promoting endothelial relaxation by increasing the production/activity of nitric oxide and prostacyclin and at the same time prevent vascular smooth muscle contraction by inhibiting intracellular Ca^{2+} influx and antagonize the actions of protein kinases [22].

1.3.5. Monoaminergic and cholinergic abnormalities

Synaptic failure is an important factor in the cognitive manifestations of AD before manifest neuronal loss takes place. The neurochemical changes in AD include extensive serotonergic denervation in the hippocampus and neocortex, depletion of the cholinergic neurons in the basal forebrain, loss of >70% of noradrenergic locus coeruleus neurons, reduction of dopamine, dopamine metabolites and dopamine receptors, histaminergic tuberomammillary nucleus degeneration and impaired melatonin secretion and action in the pineal body and suprachiasmatic hypothalamic nucleus, respectively [23].

Glutamate is a non-essential amino acid but it is one of the most important excitatory synaptic neurotransmitter as most of the CNS myelinated axons are glutamatergic. AD patients show aberrant increase in extracellular glutamate, which enhances tau pathology and enhances glutamate receptors expressed oligodendroglia to transport tau from one brain area to another leading to AD spatial progression. At the same time, there is a reciprocal relationship between glutamate and Aβ as soluble amyloid oligomers as well as insoluble Aβ deposits increases the extracellular glutamate concentration resulting in AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate) and NMDA (N-methyl-ᴅ-aspartate) receptors dysfunction, disturbed synaptic pruning and impaired synaptic plasticity with promotion of long-term synaptic depression and inhibition of long-term synaptic potentiation leading to cognitive decline especially memory domain. At the same time, NMDA receptor inhibition promotes amyloidogenic γ-secretase activities and inhibits non-amyloidogenic α-secretase with the resultant increase in Aβ production and accumulation and vice versa. Many studies revealed protective effects of sex hormones against glutamate-induced neurotoxicity through inhibition of glutamate

release by reducing the activities of lactate dehydrogenase, inhibiting intracellular Ca^{2+} influx, exerting antioxidant action and enhancing mitogen-activated protein kinase action [24, 25].

1.4. Genetics and epigenetics of AD

Genetic predisposition to AD is very complex although positive family history is a common patients' finding. The rare early onset AD constitutes less than 1% of cases and often transmitted as autosomal dominant and fully penetrant inheritance. Common affected genes include APP (genes encoding γ-secretase complex), presenelin-1 (PSNL1) and presenelin-2 (PSNL2) gene mutation in chromosomes 21, 14 and 1, respectively. Overexpression of these genes results in increased production of the highly hydrophobic fibrillogenic longer Aβ-42 and on the expense of the relatively shorter Aβ-40 [23].

In late onset AD, apolipoprotein E series, especially APOE4, is the major genetic risk as >60% of AD patients harbor at least one APOE4 allele. APOE is a lipid-binding cholesterol transporter protein essential for maintenance of myelin and neuronal membranes, synaptogenesis and dendritic reorganization. Three APOE isoforms exist in humans: APOE2, APOE3 and APOE4. Heterozygous and homozygous APOE4 are at increased risk of significantly lower age of AD onset and higher rate of AD development by about 4 and 15 folds than other allele types. At the same time, males with APOE4 are more liable to develop MCI than others. APOE4 allele expression interacts with the sex hormones leading to increased risk of AD in women than men of the same age. APOE4 expression results in decreased soluble APPα/Aβ ratio, reduced Sirtuin T1 expression (NAD+-dependent deacetylases that attenuate amyloidogenic), triggered tau phosphorylation and induced neuronal apoptosis [26].

Many studies revealed that people with a rare missense mutation (rs75932628-T) in the gene encoding TREM2 (Triggering Receptor Expressed on Myeloid Cells 2) are at increased risk of developing AD 2–3 folds than others possibly due to reduced clearing abilities of their microglia to Aβ and apoptotic cells [10]. At the same time, other studies suggested a possible role of epigenetic changes and aberrantly expressed micro-RNAs (miRNAs) in the pathogenesis of AD through disturbing neurogenesis, synaptic plasticity, synaptogenesis and neuronal network preservation as well as enhancing Aβ production and neuroinflammation [27]. Both epigenetics and miRNAs are influenced by sex hormone receptor activation, and they are potentially versatile and adaptive, which gives a challenging hope for novel therapeutic approaches in AD management. The epigenetics represents alterations in genetic functions without changing DNA sequence and constitutes an interface of genetic/environmental factors interplay, e.g. DNA methylation, histone modifications, non-coding RNAs regulation and higher order chromatin remodeling [28]. MiRNAs are 18–22 nucleotide long, non-coding RNAs that are involved in post-transcriptional suppression of gene expression [29].

1.5. Clinical signs and symptoms

Dementia of Alzheimer's type typically presents by episodic memory impairment, which gradually progresses to interfere with the activities of daily living. Memory impairment is

usually followed by other cognitive domains declines which vary according to the pattern of cortical progression, including apathy, loss of interest in hobbies, sleep disturbances, impaired spatial and temporal navigations, inability to solve problems due to executive dysfunction, behavioral changes, difficulty in using common instruments due to apraxia, language difficulties, incontinence and high dependency on others [7, 11].

The AD cognitive decline is usually preceded by a period of mild cognitive impairment (MCI) in which the individual retains his usual daily activities but has subnormal performance in cognitive neuropsychological testing. Many researchers reported a prodromal stage of subjective cognitive decline in which the person experiences worsening in his memory and/or cognitive performance despite the normal objective performance in standardized cognitive neuropsychological tests [30]. Atypical AD types start by non-amnestic manifestations but have the same pathological hallmarks include logopenic aphasia type, dysexecutive type, parietal dominant and frontal dominant atrophy subtypes [31, 32].

1.6. Investigations and biomarkers

It is generally accepted that AD pathological changes begin decades before the appearance of dementia symptoms and this leads to the introduction of the term preclinical AD, which is defined as biomarker evidences of AD pathological changes in a cognitively healthy individual. The current challenge is to develop reliable biomarkers for early pre-dementia AD diagnosis to maintain longer patients' independence and prepare the floor for the discovery of disease modifying agents including hormonal replacement therapy before irreversible neural damage takes place [11].

The ADNI-2 (Alzheimer Disease Neuroimaging Initiative-2) established CSF biomarkers include reduced CSF Aβ-42 and elevated total and phosphorylated tau-181, which are very accurate in prediction of MCI/AD conversion with 85% sensitivity and 90% specificity. Novel but still non-approved CSF biomarkers include high Aβ oligomers and neurogranin levels [33].

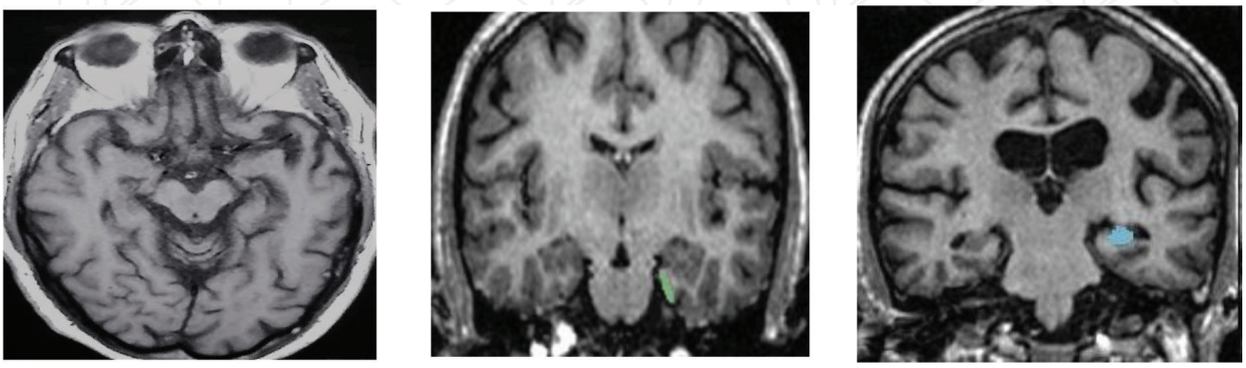

Figure 2. Brain MRI of a 56 years old female with early Alzheimer Disease showing medial temporal atrophy in T1 axial section (left), decreased right entorhinal cortex volume (middle) and right hippocampus volume (right) in coronal 3D spoiled gradient magnetic resonance images.

Blood biomarkers include high plasma homocysteine, high serum angiotensin converting enzyme activities and low plasma levels of the obesity-related hormone leptin [20]. Other ongoing research biomarkers include prostate-specific antigen complexed to α1-antichymotrypsin, pancreatic prohormone, clusterin and fetuin B [34].

The imaging biomarkers that can predict MCI/AD conversion are usually directed to measure the neural and synaptic densities in the commonly affected cortical areas. In volumetric MRI, manual and/or automated techniques can detect hippocampus and entorhinal cortex atrophy with concomitant dilatation of the temporal horns of the lateral ventricle. Other early neuroimaging biomarkers include task-free functional MRI (measures network failure quotient), diffusion tensor imaging (DTI) MRI, SPECT, FDG-PET, amyloid PET and tau PET [35] (**Figure 2**).

2. Sex hormones in normal cognition

Better keep progestogen as it is a wider term than progesterone and this is clarified in the section of progesterone are synthesized from cholesterol by the action of aromatase enzyme, and they play important roles in shaping the neural functions and behavior throughout all stages of human life. The sex steroid hormones are potent regulators of neuronal survival and function in multiple CNS regions during normal development, aging and in some neurodegenerative disorders including AD. In aging individuals, low levels of gonadal sex hormones are associated with decline in neurogenesis especially in the hippocampus with the resultant age-dependent memory decline and executive function difficulties [36].

2.1. Gender cognitive variability

Over a long time, obvious sexual dimorphism in adult human brain was observed with females harbor larger frontal and medial paralimbic cortices, while males exhibit bigger medial frontal cortex, amygdala and hypothalamic volumes. This gender difference is mainly due to variability in sex chromosome and sex hormone neuronal action. Genetic studies revealed that X-chromosome carry genes which expressions enhance visuospatial, executive and/or social cognitive tasks, whereas genes on Y-chromosome are more responsible for behavioral sexual differentiation [37].

At the same time, there is different gender cognitive performance starting during the early neonatal period and persists throughout human survival. This sex difference may be the base of the striking variable susceptibilities to various cognitive disorders in men and women [38]. Under normal circumstances, there is non-significant sex difference in global cognitive performance, but generally, males are better in mathematics and 3D spatial tests, while females are superior in autobiographic, episodic memory and verbal tests. Regarding spatial navigation, males perform better in allocentric strategy (world-centered object-to-object spatial relations) but females excel in egocentric navigation (self-centered subject-to-object spatial relations). This different cognitive performance is universal and evident in humans and animals which weaken the suggestion that environmental factors or gendered socialization are the causes of these gender variations [39, 40].

2.2. Estrogen actions in normal cognition

Estrogen is the primary female sex hormone, which regulates fundamental physiological processes in both reproductive and nonreproductive organs, including the CNS. The brain can synthesize estrogens (neuroestrogens) either by the aromatization of androgens or via a series of enzymatic steps from the precursor of all steroids, cholesterol. This neuroestrogen plays major roles in sexual differentiation of brain in both male and female. Four natural types of estrogens exist: estrone (E1; a weak estrogen and the main postmenopausal type), estradiol (E2; the most potent endogenous estrogen and the main type during the reproductive age), estriol (E3; very weak estrogen and hardly detected in non-pregnant females) and estetrol (E4; secreted only during pregnancy) [41].

Estrogens can cross the cell membrane lipid bilayer to bind to the estrogen receptors (ER), which are of two types: nuclear and membrane ER. The nuclear ER are either ERα or ERβ, which are responsible for the estrogen genomic action through regulation of various transcriptional gene expression mechanisms. The brain contains both types of nuclear ER, which are abundant in the hippocampus, pyramidal cells and glial tissue [42]. The membrane estrogen receptors (mERs) are G protein-coupled and ligand-gated ion channels, including GPER1 (previously known as GPR30), ER-X and Gq-mER, which are responsible for the rapid non-genomic actions of estrogen that is initiated within minutes after estrogen administration (estrogen neurotransmitter actions) due to recruitment and activation of kinase-dependent signaling pathways. Membrane ER are abundant in the neocortex and their activation results in increased activity of nitric oxide synthase and Ca^{2+} influx to the cells through N-methyl-D-aspartate (NMDA) receptor-mediated mechanism [43, 44].

The cellular mechanisms underlying estrogen CNS actions are still uncertain due to the different estrogen expression in both sexes and in different brain areas, but it is generally accepted that estrogens usually promote neurogenesis, exert neuroprotective actions and support neuronal survival by antiapoptotic action, stimulating nerve growth factor and brain-derived neurotrophic factor [45]. Estrogens also improve neuronal plasticity especially in the hippocampus, increase cerebral blood flow by enhancing endothelial derived nitric oxide and prostacyclin pathways, regulate neural mitochondrial functions (both types of ER are expressed in the mitochondria) especially in stressful conditions by stimulating anti-apoptotic proteins and decrease free radical production. At the same time, estrogen exerts anti-inflammatory actions by reducing the expression of astrocyte to chemokines, promoting the maturation of oligodendrocyte precursor cells and improve their ability for CNS repair, which enhances the growth and differentiation of axons and dendrites and prevents axonal loss and demyelination [46].

Estrogens also have well-documented direct cognitive and behavioral actions, and their postmenopausal depletion been associated with cognitive decline and increased risk of AD. The rapid estrogen non-genomic actions are important for hippocampal memory consolidation and hippocampal-dependent spatial navigation memory and improve learning performance, novel objects recognition and object placement tasks when administered before the cognitive tests. At the same time, estrogens improve choline acetyltransferase activity, promote serotonergic neuronal function and stimulate dopamine release in the caudate, prefrontal cortex, nucleus accumbens and dorsal raphe nucleus, which in turn enhance age-related learning and memory declines [36, 47].

2.3. Progesterone actions in normal cognition

Progesterone is a steroid hormone and it is most active natural progestogen, synthesized in the gonads, placenta, adrenal glands and CNS (neurosteroids). It has many reproductive and non-reproductive functions, including regulation of a wide range of brain functions [48]. Progesterone has a lipophilic structure, which can cross the cell membrane to interact with its specific intracellular progesterone receptors (PRs) expressed throughout the brain without sex difference with special higher expression in the hypothalamus, hippocampus, frontal cortex, medial amygdaloid nucleus, norepinephrine neurons of the nucleus tractus solitaries and cerebellum. Progesterone exerts its CNS actions through regulation of gene expression, modulation of neurotransmitter systems and epigenetic actions as well as enhancing estrogen actions [49].

PRs are either nuclear type (PR-A and PR-B), transmembrane PR (7TMPRβ) or membrane-associated 25-Dx PR (PGRMC1). Nuclear PRs are ligand inducible transcription factors that regulate target genes expression and play important roles in sexual brain differentiation, reproductive behavior, neuroprotection, neurogenesis, Schwan cell activities and their myelination programs, proliferation of neural progenitor cells and the release of the brain-derived neurotrophic factor important for cell differentiation and survival. Progesterone also has anti-inflammatory actions through regulation of the activities of astrocytes, microglia and oligodendrocytes [50, 51].

Transmembrane PRs are G protein-coupled receptors responsible for the rapid action of progesterone, and when activated, they block the activity of adenylyl cyclase, including enhancement of mitochondrial functions and regulation of cell viability. At the same time, progesterone alters dopaminergic and GABAergic system activities in many brain regions mainly the hippocampus, amygdala and fusiform gyrus enhancing the memory and learning performances [52, 53].

2.4. Androgen actions in normal cognition

Androgens are very important sex steroids that exert cognitive functions in both males and females as they not only regulate the CNS development but also help to maintain its proper function from infancy to adulthood [54]. It is generally accepted that androgens play a pivotal role in cognitive performance and their depletion or signaling inhibition (in normal aging or anti-androgen hormonal therapy in cancer prostate) results in dysfunction in androgen-responsive tissues, including the brain and consequently deleterious cognitive impairment. At the same time, discontinuation of anti-androgen in cancer therapy restores cognitive performance especially verbal memory [55].

The CNS action of androgens is mediated either directly through stimulation of androgen receptors (ARs) (nuclear receptors regulating target genes expression at transcriptional level) or indirectly after conversion to estrogen by the action of aromatase enzyme. ARs are highly expressed in the septum pellucidum, stria terminalis, preoptic area, ventromedial hypothalamus and cerebellum where they regulate the sexual reproductive behaviors [56, 57]. Neuroandrogens production had detected in the hippocampus where they modulate the hippocampal structure specifically CA1 and CA3 areas. In the medial amygdala and prefrontal cortex, androgens exert

important roles in cognitive function regulation through promoting neuroprotection (anti-glutamate action) and neurogenesis, improving neuronal survival and anti-apoptotic effect (regulating mitochondrial genome activities and suppressing reactive oxygen species), modulating hippocampal synaptic plasticity, enhancing remyelination and exerting anti-inflammatory action by regulating astrocytic and oligodendrocytic activities [58]. Beside the delayed genomic effects of androgens, non-genomic rapid actions are mediated by trans-membrane G-protein-coupled ARs, which stimulations increase the intracellular Ca^{2+} influx and result in improved inhibitory avoidance task, spatial learning and memory performance [59, 60].

Androgens especially anabolic androgen steroids (AAS) are not always neurobehaviorally beneficial, and their short-term use results in aggressive and manic behaviors, whereas their long-term use is associated with impairment of decision making, behavioral flexibility, cognitive control and spatial memory [61, 62].

3. Brain responses variability to sex hormones

The neurocognitive actions of sex hormones are not simple but several factors may interact to control their beneficial effects including the inter-balance between their levels as well as the age and sex of the individual. In pregnancy, simultaneous increase in progesterone and estrogens results in impaired mood and decreased memory [63]. At the same time, sex hormones seem to play their major neuromodulatory action in early person's prepubertal life with subsequent decrease in the neuronal sensitivity to their actions with advancement of age. Some studies revealed that prepubertal sex hormones have permanent effects in individual's behaviors and cognition including spatial abilities. Early pubertal testosterone administration to gonadectomized male Syrian hamsters resulted in their attaining adult mating behaviors while administration in late puberty did not give the same results denoting that neurons are highly sensitive to the organizational effect of sex hormones at certain age with decreased sensitivity later after passage of this time [64–66]. On the other hand, brain estrogen expression was reduced in adult female mice previously exposed to stress in adolescence but not in early adulthood which concludes that adolescent stresses suppress estrogen activities and interfere with its organizational actions to attain adult mating behavior. From these results, we can conclude that the individual's susceptibility to many neurodegenerative disorders including AD may be attained since early life and we may not be able to reverse it easily later [67, 68].

4. Sex hormones in MCI and Alzheimer's disease

Alzheimer's disease is a heterogenous disorder with multiple variants and wide variety of manifestations, which result from the interactions between multiple etiological factors, including genetic, epigenetic, environmental and lifestyle factors. Neuronal action of sex hormones represents one of the well-defined AD pathogenetic factors and may represent a hope to understand the biology of sex-dependent variability in AD predisposition and in turn leads to the development of personalized, gender-specific AD management.

4.1. Sex hormones and MCI

The concept of MCI had received much attention nowadays for early detection of those candidates to AD conversion which open a gate for future disease modifying agents including hormonal therapy before irreversible neuronal damages take place. MCI is a clinical condition lies between normal aging and dementia in which the cognitive dysfunctions are greater than expected for age but is not severe enough to significantly interfere with the daily life or warrant the diagnosis of dementia [8, 69]. MCI is classified to amnestic (am-MCI) and non-amnestic (nam-MCI) types. In the former, memory impairment is the dominating manifestation, and in the latter, non-memory cognitive domain is the affected one (language, attention, executive function, visual-spatial). Amnestic MCI is termed multiple domain if another cognitive domain is affected, whereas nam-MCI becomes multiple domain if more than one cognitive non-memory domain is affected. People with am-MCI are more liable to develop AD [11, 70].

The prevalence of am-MCI is about 8.5–25.9 per 1000 of general population and 10–20% of those above the age of 60 years; 10–15% of am-MCI persons will develop AD compared to 1–2% of nam-MCI people. Several clinical and biochemical markers had been studied to be used as predictors of MCI/AD progression. In general, women have a higher prevalence of nam-MCI but most metanalytic studies showed non-significant gender difference in the prevalence of am-MCI, which means that women take shorter time to convert from am-MCI to manifest AD [71, 72].

4.2. Sex hormones and Alzheimer's disease

One of the most common observations associated with AD onset is decreased levels of sex hormones, including estrogens, progesterone and androgens, pointing the potential role of these hormones in AD pathogenesis and the possible benefits of their targeting in AD management strategies.

4.2.1. Estrogens and Alzheimer's disease

Estrogen neuroprotective actions in AD are well documented by decades of researches showing that women used estrogen supplements or those with late menopause are at significantly decreased risk of AD development. On the other hand, early menopause because of increased sex hormone-binding globulin is associated with higher risk of AD in later life [73]. Estrogens exert anti-AD actions through different mechanisms including inhibition of tau deposition and Aβ accumulation. The former action is exerted through inhibition of tau hyperphosphorylation and promotion of tau dephosphorylation in an estrogen receptor-dependent mode through inhibition of protein kinases and promotion of protein phosphatase 2A enzyme activities, respectively [13, 74]. Estrogens inhibit Aβ accumulation by several mechanisms, one of which is decreasing Aβ production by enhancement of non-amyloidogenic APP pathway through activation of α-secretase enzyme that cleaves APP to soluble APP-α peptides and shorter membrane-attached C-terminal segment. The latter is further digested by γ-secretase to non-toxic P3 and C59 segments. Other estrogen actions include inhibition of β-secretase (amyloidogenic pathway) and stimulation of APP-containing vesicle budding by trans-Golgi

network [75]. Estrogens also promote Aβ clearance by stimulation of microglial Aβ phagocytosis and enzymes involved in Aβ degradation, including metalloproteases-2 and -9, insulin-degrading enzyme and neprilysin [76].

At the same time, estrogens exert anti-AD actions by increasing dendritic spine densities, promoting synaptogenesis, inhibiting the neurotoxic effects of oxidized low-density lipoproteins and glutamate, improving mitochondrial functions and enhancing the hippocampal cholinergic neurotransmitter system. Estrogens also regulate the epigenetic DNA methylation and miRNAs biogenesis especially in the hippocampus and thus master the genes expressions both transcriptionally and post-transcriptionally, which in turn play pivotal roles in enhancement of neuroprotection and prevention of neurodegeneration. Estrogen actions seem to be age dependent with obvious dysregulation in old-aged people. At the same time, estrogens have neuroprotective actions through increasing the expression of antiapoptotic Bcl-xL and Bcl-w and suppressing the expression of proapoptotic Bim, which lead to prevention of neuronal loss from Aβ toxicity [77–80].

Women are at increased risk of AD due to age-related sharp decline in sex steroid hormones and spending a large proportion of their life in the postmenopausal period because of increased their life longevity with the resultant prolonged hypoestrogenic state and its negative neurological consequences. Studies showed that postmenopausal women with AD had lower estradiol (E2) and estrone (E1) levels in both blood and CSF compared to normal controls. Moreover, female CSF-E2 level is positively correlated with CSF-Aβ level and cerebral glucose metabolism in the left hippocampus PET scan, which denotes that they are at increased risk to develop AD. In short-term studies, transdermal estrogen administration is associated with increased attention, verbal and visual memories; however, long-term studies failed to slow down AD progression or adding benefits to rivastigmine therapy in postmenopausal women [47, 81].

The neuroprotective effect of estrogen is not the same in both sexes as brain E1 and E2 levels have no relations with Aβ accumulation in males pointing to different gender expression of sex steroid hormones. At the same time, estrogen administration in male to female cross sex subjects results in significant decreases in the hippocampal volume despite producing neurogenesis, which means that the estrogen AD risk prevention in males is negligible [82, 83] (**Figure 3**).

4.2.2. Progesterone and Alzheimer's disease

Studies in progesterone neuroprotective actions against AD predisposition are not so plenty like those on estrogens but despite this, it is generally accepted that progesterone has a direct neuroprotective action while its indirect actions against AD development by regulating the neuroestrogen effects are matter of controversy as in some studies, progesterone enhances estradiol neuroprotective actions and in others antagonizes them beside reducing the cerebral blood flow [84].

The direct progesterone protecting actions against AD development and/or progression include regulation of β-amyloid metabolism by reducing Aβ production and decreasing the pool of soluble Aβ by enhancement of the non-amyloidogenic α-secretase pathway, decreasing Aβ accumulation through modulation of γ-secretases activities and increasing Aβ

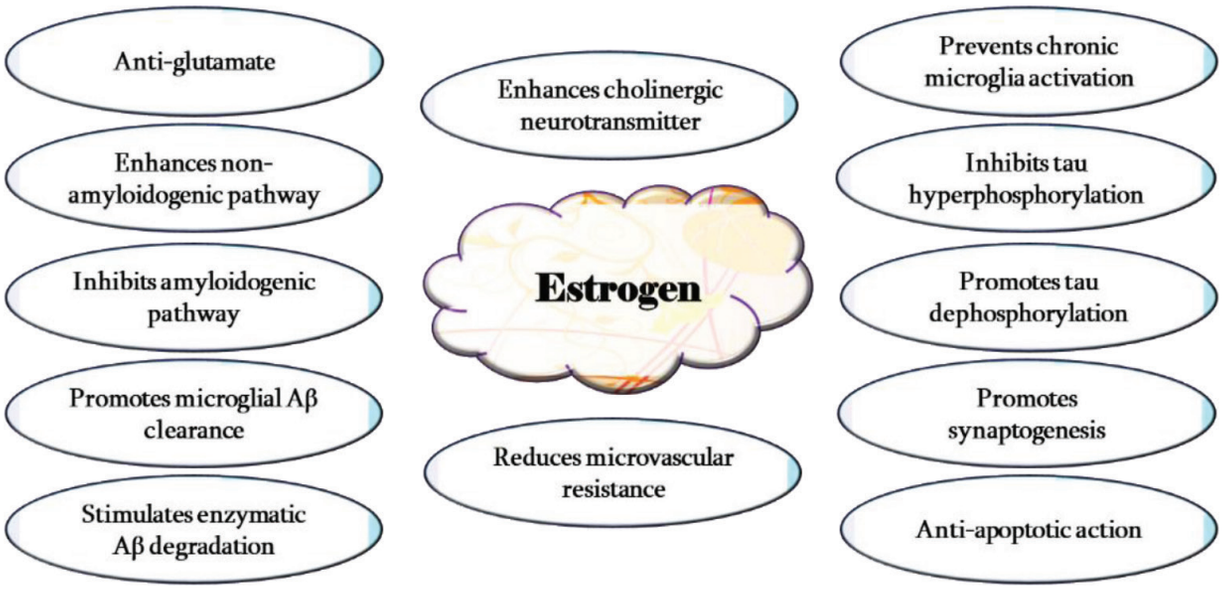

Figure 3. Estrogen anti-Alzheimer's neuroprotective actions.

clearance by enhancing insulin-degrading enzyme expression and downregulation of β-secretase gene expression [85, 86]. At the same time, progesterone reduces tau hyperphosphorylation and the serum level of endogenous progesterone is inversely correlated with tau accumulation, and at the same time, progesterone administration in transgenic AD mice improved cognitive performance in object recognition and T-maze task [87].

4.2.3. Androgens and Alzheimer's disease

Androgens have neuroprotective effects against AD in both males and females. Many studies had detected lower testosterone level in men with AD relative to normal age-matched control both in the blood and CSF. At the same time, APOE4 allele, which is a major risk of late onset AD, is associated with significantly lower level of circulating testosterone [88]. In accordance with these results, the Baltimore Longitudinal Study on Aging had detected significantly lower testosterone level 5–10 years in healthy men prior to their development of clinically manifest AD compared to those who did not develop AD [89].

Short-term testosterone administration improves cognitive functions in MCI and AD patients possibly through non-genomic transmembrane ARs activation [90, 91]. The long-term direct genomic action of androgens results in reduction of Aβ accumulation through enhancement of non-amyloidogenic APP pathway and promoting Aβ clearance by stimulation of Aβ-degrading enzyme action. Postmortem studies had shown that brain levels of testosterone were inversely correlated with cerebral soluble Aβ, which precedes insoluble fibrillar Aβ accumulation. These androgenic anti-amyloid actions are exerted in both sexes [92, 93]. Androgens can also indirectly reduce Aβ accumulation either through enhancing the estrogen pathway or through hypothalamo-hypophyseal-gonadal axis where they inhibit the release of gonadotropin luteinizing hormone secretion by the negative feedback, and it is well known that the latter hormone increases Aβ production by enhancement of APP/β-secretase initiated amyloidogenic pathway [94].

Males are subjected to andropause due to age-dependent high level of sex hormone-binding globulin with subsequent decrease in androgen levels and effects. Sex hormone-binding globulin is significantly higher in AD patients than age- and sex-matched control resulting in functional impairments of androgen-responsive tissues including the brain with consequent increase in AD risk [73]. Male andropause occurs very slowly over a long period of time where total androgen level starts to decline in thirties in a rate of 0.2–1% per year, while free testosterone decreases in a higher rate (2–3% yearly). This slowly gradual andropause relative to the rapid menopause may be one of the explanations of decreased male gender AD risk, delayed male MCI/AD conversion and slower AD cognitive deterioration [78, 95].

5. Sex hormone therapy trials for Alzheimer's disease

Based on the abundant data supporting the numerous neuroprotective actions of sex hormones in ameliorating many pathological processes occurring in AD, hormonal replacement therapy (HRT) seems to be theoretically beneficial but the translation of this hypothesis to practice met a lot of difficulties which made the use of HRT in AD management still a matter of skepticism [36, 94]. The values of female estrogens and progesterone replacement therapies carry controversial results, which are mainly dependent on the timing, dose and duration of their application to the AD predisposed individual. Promising results were only attained on early HRT initiation at a close menopause temporal proximity and any delayed administration may even give counterproductive bad consequence. This time limit of proper HRT initiation resulted in introduction of the term the critical window of intervention or the window of opportunity which describes the time after which HRT become worthless. HRT has not the same effect in all genotypes but it is found to be more beneficial in people with APOE2 and APOE3 genotypes than APOE4 [96–100]. At the same time, some studies revealed that the protective effect of HRT against AD is only achieved in long-term users (>10 years), while short-term therapy had no AD preventive actions pointing to the need of long-term HRT use to gain significantly beneficial AD protection [101, 102]. The need for long-term use of conventional HRT opens a new obstacle due to the high cardiovascular risks which in some instances may overwhelm the anti-AD cognitive benefits. This makes AD patients in ultimate need for future introduction of new hormonal drugs with little side effects [103, 104]. At the androgenic level and despite their numerous anti-AD neuroprotective actions, the long-term androgens use carries many neurological and extra-neurological risks including decreased dendritic reorganization and spine density in the limbic regions after initial increase due to increased glutamate turnover and neurotoxicity in amygdala structures with functional impaired connectivity with areas involved in cognitive functions [105, 106].

6. Conclusions and future prospect

Alzheimer's disease is a complex multifactorial neurodegenerative disorder resulted from dysregulation of many biological processes at multiple levels in a specific neuronal temporospatial pattern. Sex hormones, including estrogens, progesterone and androgens, play crucial

CNS modulatory functions and their disturbances result in impairment of neuroprotection, neurogenesis, synaptogenesis, synaptic plasticity and myelination as well as abnormal glial cell activities. The sharp decrease of neurosteroids influences in menopause relative to the slow andropause makes females sex at increased risk of AD development, rapid MCI/AD conversion and rapid course of cognitive deterioration. Trials used sex hormones as a disease modifying neuroprotective anti-AD agents revealed that their possible beneficial effect can be achieved only by early HRT before the beginning of critical window of intervention and the therapy must continue for long time which may put the treated individuals at increased risk of cardiovascular complications.

So, what is nowadays considered normal menopausal or andropausal sex hormones' declines may be sufficient triggers irreversible neuropathological changes which latter on progress to AD in susceptible individuals, and it is the time to use these changes as early AD biomarkers in high risk persons and in turn correct them before the onset of the window of opportunity by safe and effective HRT for long-term use and sufficient to produce significant AD prophylaxis.

Disclosure of interest

No conflict of interest was reported.

Author details

Wafik Said Bahnasy*, Yasser A. El-Heneedy and Ehab A. El-Seidy

*Address all correspondence to: wafikbahnasy@gmail.com

Department of Neurology, Faculty of Medicine, Tanta University, Tanta, Egypt

References

[1] Li R, Singh M. Sex differences in cognitive impairment and Alzheimer's disease. Frontiers in Neuroendocrinology. 2014;**35**:385-403. DOI: 10.1016/j.yfrne.2014.01.002

[2] Esquirol J. Des maladies mentales. Paris: Baillie're; 1838

[3] Boller F, Forbes MM. History of dementia and dementia in history: An overview. Journal of the Neurological Sciences. 1998;**158**:125-133

[4] Cipriani G, Dolciotti C, Picchi L, Bonuccelli U. Alzheimer and his disease: A brief history. Neurological Sciences. 2011;**32**:275-279. DOI: 10.1007/s10072-010-0454-7

[5] Alzheimer's Association. Alzheimer's Association Report 2017 Alzheimer's disease facts and figures. Alzheimer's & Dementia. 2017;**13**:325-373. DOI: 10.1016/j.jalz.2017.02.001

[6] Scheltens P, Blennow K, Breteler MB, de Strooper B, Frisoni GB, Salloway S, Van der Flier WM. Alzheimer's disease. Lancet. 2016;**388**:505-517. DOI: 10.1016/S0140-6736(15)01124-1

[7] Ulrich JD, Ulland TK, Colonna M, Holtzman DM. Elucidating the role of TREM2 in Alzheimer's disease. Neuron. 2017;**94**:237-248. DOI: 10.1016/j.neuron.2017.02.042

[8] Au B, Dale-McGrath S, Tierney MC. Sex differences in the prevalence and incidence of mild cognitive impairment: A meta-analysis. Ageing Research Reviews. 2017;**35**:176-199. DOI: 10.1016/j.arr.2016.09.005

[9] Phung KTT, Chaaya M, Prince M, Atweh S, El Asmar K, Karam G, Khoury RM, Ghandour L, Nielsen TR, Waldemar G. Dementia prevalence, care arrangement, and access to care in Lebanon: A pilot study. Alzheimer's & Dementia. 2017;**13**(12):1317-1326. DOI: 10.1016/j.jalz.2017.04.007

[10] Roher AE, Kokjohn TA, Clarke SG, Sierks MR, Maarouf CL, Serrano GE, Sabbagh MS, Beach TG. APP/Aβ structural diversity and Alzheimer's disease pathogenesis. Neurochemistry International. 2017;**110**:1-13. DOI: https://doi.org/10.1016/j.neuint.2017.08.007

[11] Peterson R, Graff-Radford J. Alzheimer disease and other dementias. In: Daroff RB, Jankovic J, Mazziotta JC, Pomeroy SL, editors. Bradley's Neurology in Clinical Practice. 7th ed. Vol. 95. Elsevier; 2016. pp. 1380-1421

[12] Mohamed T, Shaker A, Rao PPN. Amyloid cascade in Alzheimer's disease: Recent advances in medicinal chemistry. European Journal of Medicinal Chemistry. 2016;**113**:258-272. DOI: 10.1016/ j.ejmech.2016.02.049

[13] Arendt T, Stieler JT, Holzer M. Tau and tauopathies. Brain Research Bulletin. 2016;**126**:238-292. DOI: 10.1016/j.brainresbull.2016.08.018

[14] Mishra S, Gordon BA, Su Y, Christensen J, Friedrichsen K, Jackson K, Hornbeck R, Balota DA, Cairns NJ, Morris JC, Ances BM, Benzinger TLS. AV-1451 PET imaging of tau pathology in preclinical Alzheimer disease: Defining a summary measure. NeuroImage. 2017;**161**:171-178. DOI: 10.1016/j.neuroimage.2017.07.050

[15] Theendakara V, Bredesen DE, Rao RV. Downregulation of protein phosphatase 2A by apolipoprotein E: Implications for Alzheimer's disease. Molecular and Cellular Neuroscience. 2017;**83**:83-91. DOI: 10.1016/j.mcn.2017.07.002

[16] Carlsen EM, Rasmussen R. Protein networks in Alzheimer's disease. Cell Systems. 2017;**4**:153-155. DOI: 10.1016/j.cels.2017.02.006

[17] El Ali A, Rivest S. Microglia in Alzheimer's disease: A multifaceted relationship. Brain, Behavior, and Immunity. 2016;**55**:138-150. DOI: 10.1016/j.bbi.2015.07.021

[18] Piirainen S, Youssef A, Song C, Kalueff AV, Landreth GE, Malm T, Tian L. Psychosocial stress on neuroinflammation and cognitive dysfunctions in Alzheimer's disease: The emerging role for microglia? Neuroscience and Biobehavioral Reviews. 2017;**77**:148-164. DOI: 10.1016/j.neubiorev.2017.01.046

[19] Spangenberg EE, Green KN. Inflammation in Alzheimer's disease: Lessons learned from microglia-depletion models. Brain, Behavior, and Immunity. 2017;**61**:1-11. DOI: 10.1016/j.bbi.2016.07.003

[20] Chakraborty A, de Wit NM, van der Flier WM, de Vries HE. The blood brain barrier in Alzheimer's disease. Vascular Pharmacology. 2017;**89**:12-18. DOI: 10.1016 /j.vph.2016.11.008

[21] Kapasi A, Schneider JA. Vascular contributions to cognitive impairment, clinical Alzheimer's disease, and dementia in older persons. Biochimica et Biophysica Acta. 2016; **1862**:878-886. DOI: 10.1016/j.bbadis.2015.12.023

[22] do Nascimento GRA, Barros YVR, Wells AK, Khalil RA. Research into specific modulators of vascular sex hormone receptors in the management of postmenopausal cardiovascular disease. Current Hypertension Reviews. 2009;**5**(4):283-306. DOI: 10.2174/157340209789587717

[23] Šimic G, Leko MB, Wray S, Harrington CR, Delalle I, Jovanov-Miloševic N, Bažadona D, Buée L, de Silva R, Giovanni GD, Wischik CM, Hof PR. Monoaminergic neuropathology in Alzheimer's disease. Progress in Neurobiology. 2017;**151**:101-138. DOI: 10.1016/j.pneurobio.2016.04.001

[24] Hu NW, Ondrejcak T, Rowan MJ. Glutamate receptors in preclinical research on Alzheimer's disease: Update on recent advances. Pharmacology, Biochemistry and Behavior. 2012;**100**:855-862. DOI: 10.1016/j.pbb.2011.04.013

[25] Kilian JG, Hsu HW, Mata K, Wolf FW, Kitazawa M. Astrocyte transport of glutamate and neuronal activity reciprocally modulate tau pathology in drosophila. Neuroscience. 2017;**348**:191-200. DOI: 10.1016/j.neuroscience.2017.02.011

[26] Theendakara V, Peters-Libeu CA, Spilman P, Poksay KS, Bredesen DE, Rao RV. Direct transcriptional effects of apolipoprotein E. Journal of Neuroscience. 2016;**36**(3):685-700. DOI: 10.1523/JNEUROSCI.3562-15.2016

[27] Wang J, JT Y, Tan MS, Jiang T, Tan L. Epigenetic mechanisms in Alzheimer's disease: Implications for pathogenesis and therapy. Ageing Research Reviews. 2013;**12**:1024-1041. DOI: 10.1016/j.arr.2013.05.003

[28] Shamsi MB, Firoz AS, Imam SN, Alzaman N, Samman MA. Epigenetics of human diseases and scope in future therapeutics. Journal of Taibah University Medical Sciences. 2017;**12**(3):205-211. DOI: 10.1016/j.jtumed.2017.04.003

[29] Van den Hove DL, Kompotis K, Lardenoije R, Kenis G, Mill J, Steinbusch HW, Lesch KP, Fitzsimons CP, De Strooper B, Rutten BPF. Epigenetically regulated microRNAs in Alzheimer's disease. Neurobiology of Aging. 2014;**35**:731-745. DOI: 10.1016/j.neurobiolaging.2013.10.082

[30] Buckley RF, Maruff P, Ames D, Bourgeat P, Martins RN, Masters CL, et al. Subjective memory decline predicts greater rates of clinical progression in preclinical Alzheimer's disease. Alzheimer's & Dementia. 2016;**12**(7):796-804. DOI: 10.1016/j.jalz.2015.12.013

[31] Kenawy WS, Bahnasy WS, Aboelsafa AA, Ramadan ES. Sleep disorders in Alzheimer's and vascular dementia [master thesis]. Tanta (Egypt): Tanta University; 2016. 108-120 p 10.13140/RG.2.2.23574.24649

[32] Leyton CE, Hodges JR, Piguet O, Ballard KJ. Common and divergent neural correlates of anomia in amnestic and logopenic presentations of Alzheimer's disease. Cortex. 2017; **86**:45-54. DOI: 10.1016/j.cortex.2016.10.019

[33] Mattsson N, Lönneborg A, Boccardi M, Blennow K, Hansson O. Clinical validity of cerebrospinal fluid Aß-42, tau, and phospho-tau as biomarkers for Alzheimer's disease in the context of a structured 5-phase development framework. Neurobiology of Aging. 2017;**52**:196-213. DOI: 10.1016/j.neurobiolaging.2016.02.034

[34] Sattlecker M, Kiddle SJ, Newhouse S, Proitsi P, Nelson S, Williams S, Johnston C, Killick R, Simmons A, Westman E, Hodges A, Soininen H, Kłoszewska I, Mecocci P, Tsolaki M, Vellas B, Lovestone S. Alzheimer's disease biomarker discovery using SOMA scan multiplexed protein technology. Alzheimer's & Dementia. 2014;**10**(6):724-734. DOI: 10.1016/j.jalz.2013.09.016

[35] Beheshti I, Demirel H, Matsuda H. Classification of Alzheimer's disease and prediction of mild cognitive impairment-to-Alzheimer's conversion from structural magnetic resource imaging using feature ranking and a genetic algorithm. Computers in Biology and Medicine. 2017;**83**:109-119. DOI: 10.1016/j.compbiomed.2017.02.011

[36] Engler-Chiurazzi EB, Brown CM, Povroznik JM, Simpkins JW. Estrogens as neuroprotectants: Estrogenic actions in the context of cognitive aging and brain injury. Progress in Neurobiology. 2017;**157**:188-211. DOI: 10.1016/j.pneurobio. 2015.12.008

[37] Hong DS, Reiss AL. Cognitive and neurological aspects of sex chromosome aneuploidies. Lancet Neurology. 2014;**13**:306-318. DOI: 10.1016/S1474-4422(13)70302-8

[38] Hyde JS. Sex and cognition: Gender and cognitive functions. Current Opinion in Neurobiology. 2016;**38**:53-56. DOI: 10.1016/j.conb.2016.02.007

[39] Shah DS, Prados J, Gamble J, De Lillo C, Gibson CL. Sex differences in spatial memory using serial and search tasks. Behavioural Brain Research. 2013;**257**:90-99. DOI: 10.1016/j.bbr.2013.09.027

[40] Sommer W, Hildebrandt A, Kunina-Habenicht O, Schacht A, Wilhelm O. Sex differences in face cognition. Acta Psychologica. 2013;**142**:62-73. DOI: 10.1016/j.actpsy. 2012.11.001

[41] Cornil CA, Ball GF, Balthazart J. The dual action of estrogen hypothesis. Trends in Neurosciences. 2015;**38**(7):408-416. DOI: 10.1016/j.tins.2015.05.004

[42] Alexander A, Irving AJ, Harvey J. Emerging roles for the novel estrogen-sensing receptor GPER1 in the CNS. Neuropharmacology. 2017;**113**:652-660. DOI: 10.1016/j.neuropharm.2016.07.003

[43] Hamilton KJ, Hewitt SC, Arao Y, Korach KS. Estrogen Hormone Biology. In: Wassarman PM, editor. Current Topics in Developmental Biology. 1st ed. Elsevier; 2017;**125**(4); 110-146. DOI: http://dx.doi.org/10.1016/bs.ctdb.2016.12.005

[44] Warner M, Huang B, Gustafsson J. Estrogen receptor β as a pharmaceutical target. Trends in Pharmacological Sciences. 2017;**38**(1):92-99. DOI: 10.1016/j.tips.2016.10.006

[45] Mennenga SE, Baxter LC, Grunfeld IS, Brewer GA, Aiken LS, Engler-Chiurazzi EB, Camp BW, Acosta JI, Braden BB, Schaefer KR, Gerson JE, Lavery CN, Tsang CW, Hewitt LT, Kingston ML, Koebele SV, Patten KJ, Ball BH, McBeath MK, Bimonte-Nelson HA. Navigating to new frontiers in behavioral neuroscience: Traditional neuropsychological tests predict human performance on a rodent-inspired radial-arm maze. Frontiers in Behavioral Neuroscience. 2014;**8**:294. DOI: 10.3389/fnbeh.2014.00294

[46] Koebele SV, Bimonte-Nelson HA. The endocrine-brain-aging triad where many paths meet: Female reproductive hormone changes at midlife and their influence on circuits important for learning and memory. Experimental Gerontology. 2017;**94**:14-23. DOI: 10.1016/j.exger.2016.12.011

[47] Kim J, Frick KM. Distinct effects of estrogen receptor antagonism on object recognition and spatial memory consolidation in ovariectomized mice. Psychoneuroendocrinology. 2017;**85**:110-114. DOI: 10.1016/j.psyneuen.2017.08.013

[48] Mani SK, Blaustein JD. Neural progestin receptors and female sexual behavior. Neuroendocrinology. 2012;**96**(2):152-161. DOI: 10.1159/000338668

[49] Camacho-Arroyo I, Hansberg-Pastor V, Vázquez-Martínez ER, Cerbón, M. Mechanism of Progesterone Action in the Brain. In: Pfaff DW, Joëls M, editors. Hormones, Brain, and Behavior. 3rd ed. Oxford: Academic Press; 2017;**3**:181-214. DOI: 10.1016/B978-0-12-803592-4.00053-5

[50] Gagnidze K, Weil ZM, Faustino LC, Schaafsma SM, Pfaff DW. Early histone modifications in the ventromedial hypothalamus and preoptic area following estradiol administration. Journal of Neuroendocrinology. 2013;**25**(10):939-955. DOI: 10.1111/jne.12085

[51] Guennoun R, Labombarda F, Gonzalez Deniselle MC, Liere P, De Nicola AF, Schumacher M. Progesterone and allopregnanolone in the central nervous system: Response to injury and implication for neuroprotection. Journal of Steroid Biochemistry and Molecular Biology. 2015;**146**:48-61. DOI: 10.1016/j.jsbmb.2014.09.001

[52] Su C, Cunningham RL, Rybalchenko N, Singh M. Progesterone increases the release of brain-derived neurotrophic factor from glia via progesterone receptor membrane component 1 (Pgrmc1)-dependent ERK5 signaling. Endocrinology. 2012;**153**(9):4389-4400. DOI: 10.1210/en.2011-2177

[53] Berent-Spillson A, Briceno E, Pinsky A, Simmen A, Persad CC, Zubieta JK, Smith YR. Distinct cognitive effects of estrogen and progesterone in menopausal women. Psychoneuroendocrinology. 2015;**59**:25-36. DOI: 10.1016/j.psyneuen.2015.04.020

[54] Moghadami S, Jahanshahi M, Sepehri H, Amini H. Gonadectomy reduces the density of androgen receptor-immunoreactive neurons in male rat's hippocampus: testosterone replacement compensates it. Behavioral and Brain Functions. 2016;**12**:5-14. DOI: https://doi.org/10.1186/ s12993-016-0089-9

[55] Carcaillon L, Brailly-Tabard S, Ancelin ML, Tzourio C, Foubert-Samier A, Dartigues JF, Guiochon-Mantel A, Scarabin PY. Low testosterone and the risk of dementia in elderly men: Impact of age and education. Alzheimer's & Dementia. 2014;**10**:S306-S314. DOI: 10.1016/j.jalz.2013.06.006

[56] Zup SL, Edwards NS, Mccarthy MM. Sex- and age-dependent effects of androgens on glutamate-induced cell death and intracellular calcium regulation in the developing hippocampus. Neuroscience. 2014;**281**:77-87. DOI: http://dx.doi.org/10.1016/j.neuroscience.2014.09.040

[57] Perez-Pouchoulen M, Toledo R, Garcia LI, Perez-Estudillo CA, Coria-Avila GA, Hernandez ME, Carrillo P, Manzo J. Androgen receptors in Purkinje neurons are modulated by systemic testosterone and sexual training in a region-specific manner in the male rat. Physiology & Behavior. 2016;**156**:191-198. DOI: 10.1016/j.physbeh.2016.01.027

[58] Bielecki B, Mattern C, Abdel G, Javaid S, Smietanka K, Abi Ghanem C, Mhaouty-Kodja S, Ghandour MS, Baulieu EE, Franklin RJ, Schumacher M, Traiffort E. The spontaneous regeneration of myelin: an unexpected central role of the androgen receptor. Proceedings of the National Academy of Sciences of the United States of America. 2016;**113**:14,829-14,834. DOI: 10.1073/pnas.1614826113

[59] Christou MA, Christou PA, Markozannes G, Tsatsoulis A, Mastorakos G, Tigas S. Effects of anabolic androgenic steroids on the reproductive system of athletes and recreational users: A systematic review and meta-analysis. Sports Med. 2017;**47**(9):1869-1883. DOI: 10.1007/s40279-017-0709-z

[60] Klores M, Moon JT, Duncan KA. Expression of glial CBP in steroid mediated neuroprotection in male and female zebra finches. Journal of Chemical Neuroanatomy. 2017;**79**:32-37. DOI: 10.1016/j.jchemneu.2016.11.002

[61] Westlye LT, Kaufmann T, Alnæs D, Hullstein IR, Bjørnebekk A. Brain connectivity aberrations in anabolic-androgenic steroid users. NeuroImage: Clinical. 2017;**13**:62-69. DOI: 10.1016/j.nicl.2016.11.014

[62] Bjørnebekk A, Walhovd KB, Jørstad ML, Due-Tønnessen P, Hullstein IR, Fjell AM. Structural brain imaging of long-term anabolic-androgenic steroid users and non-using weightlifters. Biological Psychiatry. 2017;**82**:294-302. DOI: 10.1016/j.biopsych.2016.06.017

[63] Keiser AA, Tronson NC. Molecular mechanisms of memory in males and females. In: Shansky RM, editor. Sex Differences in the Central Nervous System. Elsevier; 2016;**2**:27-51. DOI: 10.1016/B978-0-12-802114-9.00002-0

[64] Berenbaum SA, Bryk KLK, Beltz AM. Early androgen effects on spatial and mechanical abilities: Evidence from congenital adrenal hyperplasia. Behavioral Neuroscience. 2012;**126**:86-96. DOI: 10.1037/a0026652

[65] Beltz AM, Berenbaum SA. Cognitive effects of variations in pubertal timing: Is puberty a period of brain organization for human sex-typed cognition? Hormones and Behavior. 2013;**63**:823-828. DOI: 10.1016/j.yhbeh.2013.04.002

[66] Nelson LH, Warden S, Lenz KM. Sex differences in microglial phagocytosis in the neonatal hippocampus. Brain, Behavior, and Immunity. 2017;**64**:11-22. DOI: 10.1016/j.bbi.2017.03.010

[67] Mahmoud R, Wainwright SR, Galea LAM. Sex hormones and adult hippocampal neurogenesis: Regulation, implications, and potential mechanisms. Frontiers in Neuroendocrinology. 2016;**41**:129-152. DOI: 10.1016/j.yfrne.2016.03.002

[68] Heberden C. Sex steroids and neurogenesis. Biochemical Pharmacology. 2017;**141**:56-62. DOI: 10.1016/j.bcp.2017.05.019

[69] Petersen RC, Roberts RO, Knopman DS, Boeve BF, Geda YE, Ivnik RJ, Smith GE, Jack CR. Mild cognitive impairment: Ten years later. Archives of neurology. 2009;**66**(12):1447-1455. DOI: 10.1001/archneurol. 2009.266

[70] Lee LK, Shahar S, Chin AV, Yusoff NAM, Rajab NF, Abdul Aziz S. Prevalence of gender disparities and predictors affecting the occurrence of mild cognitive impairment. Archives of Gerontology and Geriatrics. 2012;**54**:185-191. DOI: 10.1016/j.archger.2011.03.015

[71] Ward A, Arrighi HM, Michels S, Cedarbaum JM. Mild cognitive impairment: Disparity of incidence and prevalence estimates. Alzheimer's & Dementia. 2012;**8**:14-21. DOI: 10.1016/j.jalz.2011.01.002

[72] Roberts RO, Knopman DS, Mielke MM, Cha RH, Pankratz VS, Christianson TJ, Geda YE, Boeve BF, Ivnik RJ, Tangalos EG, Rocca WA, Petersen RC. Higher risk of progression to dementia in mild cognitive impairment cases who revert to normal. Neurology. 2014;**82**(4):317-325. DOI: 10.1212/WNL.0000000000000055

[73] Muller M, Schupf N, Manly JJ, Mayeux R, Luchsinger JA. Sex hormone binding globulin and incident Alzheimer's disease in elderly men and women. Neurobiology of Aging. 2010;**31**:1758-1765. DOI: 10.1016/j.neurobiolaging.2008.10.001

[74] Zhang HZ, Simpkins JW. Okadaic acid induces tau phosphorylation in SH-SY5Y cells in an estrogen-preventable manner. Brain Research. 2010;**1345**:176-181. DOI: 10.1016/j.brainres. 2010.04.074

[75] Merlo S, Spampinato SF, Sortino MA. Estrogen and Alzheimer's disease: Still an attractive topic despite disappointment from early clinical results. European Journal of Pharmacology. 2017;**817**:51-58. DOI: 10.1016/j.ejphar.2017.05.059

[76] Barratt HE, Budnick HC, Parra R, Lolley RJ, Perry CN, Nesic O. Tamoxifen promotes differentiation of oligodendrocyte progenitors in vitro. Neuroscience. 2016;**319**:146-154. DOI: 10.1016/j.neuroscience.2016.01.026

[77] Jung JI, Ladd TB, Kukar T, Price AR, Moore BD, Koo EH, Golde TE, Felsenstein KM. Steroids as γ-secretase modulators. FASEB Journal. 2013;**27**(9):3775-3785. DOI: 10.1096/fj.12-225,649

[78] Vest RS, Pike CJ. Gender, sex steroid hormones, and Alzheimer's disease. Hormones and Behavior. 2013;**63**:301-307. DOI: 10.1016/j.yhbeh.2012.04.006

[79] Fortress AM, Frick KM. Epigenetic regulation of estrogen-dependent memory. Frontiers in Neuroendocrinology. 2014;**35**(4):530-549. DOI: 10.1016/j.yfrne.2014.05.001

[80] Rao YS, Shult CL, Pinceti E, Pak TR. Prolonged ovarian hormone deprivation alters the effects of 17beta-estradiol on microRNA expression in the aged female rat hypothalamus. Oncotarget. 2015;**6**:36965-36983. DOI: 10.18632/oncotarget.5433

[81] Tschiffely AE, Schuh RA, Prokai-Tatrai K, Prokai L, Ottinger MA. A comparative evaluation of treatments with 17β-estradiol and its brain-selective prodrug in a double-transgenic mouse model of Alzheimer's disease. Hormones and Behavior. 2016;**83**:39-44. DOI: 10.1016 /j.yhbeh.2016.05.009

[82] Rosario ER, Chang L, Head EH, Stanczyk FZ, Pike CJ. Brain levels of sex steroid hormones in men and women during normal aging and in Alzheimer's disease. Neurobiology of Aging. 2011;**32**(4):604-613. DOI: 10.1016/j.neurobiolaging.2009.04.008

[83] Seiger R, Hahn A, Hummer A, Kranz GS, Ganger S, Woletz M, Kraus C, Sladky R, Kautzky A, Kasper S, Windischberger C, Lanzenberger R. Subcortical gray matter changes in transgender subjects after long-term cross-sex hormone administration. Psychoneuroendocrinology. 2016;**74**:371-379. DOI: 10.1016/j.psyneuen.2016.09.028

[84] Garcia-Segura LM, Jacques Balthazart J. Steroids and neuroprotection: New advances. Frontiers in Neuroendocrinology. 2009;**30**:v-ix. DOI: 10.1016/j.yfrne.2009.04.006

[85] Carroll JC, Rosario ER, Villamagna A, Pike CJ. Continuous and cyclic progesterone differentially interact with estradiol in the regulation of Alzheimer-like pathology in female 3xTransgenic-Alzheimer's disease mice. Endocrinology. 2010;**151**:2713-2722. DOI: 10.1210/en.2009-1487

[86] Jayaraman A, Carroll JC, Morgan TE, Lin S, Zhao L, Arimoto JM, Murphy MP, Murphy MP, Beckett TL, Finch CE, Brinton RD, Pike CJ. 17 beta-estradiol and progesterone regulate expression of beta-amyloid clearance factors in primary neuron cultures and female rat brain. Endocrinology. 2012;**153**:5467-5479. DOI: 10.1210/en.2012-1464

[87] Zhao L, Morgan TE, Mao Z, Lin S, Cadenas E, Finch CE, Pike CJ, Mack WJ, Brinton RD. Continuous versus cyclic progesterone exposure differentially regulates hippocampal gene expression and functional profiles. PLoS ONE. 2012;**7**:e31267. DOI: 10.1371/journal.pone.0031267

[88] Raber J. AR, apoE, and cognitive function. Hormones and Behavior. 2008;**53**:706-715. DOI: 10.1016/j.yhbeh.2008.02.012

[89] Moffat SD, Zonderman AB, Metter EJ, Kawas C, Blackman MR, Harman SM, Resnick SM. Free testosterone and risk for Alzheimer disease in older men. Neurology. 2004; **62**:188-193 PMID: 14745052

[90] Cherrier MM, Matsumoto AM, Amory JK, Asthana S, Bremner W, Peskind ER, Raskind MA, Craft S. Testosterone improves spatial memory in men with Alzheimer disease and mild cognitive impairment. Neurology. 2005;**64**:2063-2068. DOI. DOI: 10.1212/01.WNL.0000165995.98986.F1

[91] Filová B, Ostatníková D, Celec P, Hodosy J. The effect of testosterone on the formation of brain structures. Cells Tissues Organs. 2013;**197**(3):169-177. DOI: 10.1159/000345567

[92] Butchart J, Birch B, Bassily R, Wolfe L, Holmes C. Male sex hormones and systemic inflammation in Alzheimer disease. Alzheimer Disease and Associated Disorders. 2013; **27**:153-156. DOI: 10.1097/WAD.0b013e 318,258 cd63

[93] Lee JH, Byun MS, Yi D, Choe MC, Choi HJ, Baek H, Sohn BK, Lee JY, Kim HJ, Kim JW, Lee Y, Kim YK, Sohn CH, Woo JI, Lee DY. Sex-specific association of sex hormones and gonadotropins, with brain amyloid and hippocampal neurodegeneration. Neurobiology of Aging. 2017;**58**:34-40. DOI: 10.1016/j.neurobiolaging.2017.06.005

[94] Burnham VL, Thornton JE. Luteinizing hormone as a key player in the cognitive decline of Alzheimer's disease. Hormones and Behavior. 2015;**76**:48-56. DOI: 10.1016/j.yhbeh.2015.05.010

[95] Wang S, Wang R, Chen L, Bennett DA, Dickson DW, Wang DS. Expression and functional profiling of neprilysin, insulin-degrading enzyme, and endothelin-converting enzyme in prospectively studied elderly and Alzheimer's brain. J Neurochem. 2010;**115**(1):47-57. DOI: 10.1111/j.1471-4159.2010. 06899.x

[96] Maki PM, Henderson VW. Hormone therapy, dementia, and cognition: The women's health initiative 10 years on. Climacteric. 2012;**15**(3):256-262. DOI: 10.3109/13697137.2012.660613

[97] Maki P. Is timing everything? New insights into why the effect of estrogen therapy on memory might be age dependent. Endocrinology. 2013;**154**(8):2570-2572. DOI: 10.1210/en.2013-1598

[98] Xu L, Freeman G, Cowling BJ, Schooling CM. Testosterone therapy and cardiovascular events among men: A systematic review and meta-analysis of placebo-controlled randomized trials. BMC Medicine. 2013;**11**(1):108. DOI: 10.1186/1741-7015-11-108

[99] Riedel BC, Thompson PM, Brinton RD. Age, APOE and sex: Triad of risk of Alzheimer's disease. Journal of Steroid Biochemistry & Molecular Biology. 2016;**160**:134-147. DOI: 10.1016/j.jsbmb.2016.03.012

[100] Wroolie TE, Kenna HA, Williams KE, Rasgon NL. Cognitive effects of hormone therapy continuation or discontinuation in a sample of women at risk for Alzheimer disease. American Journal of Geriatric Psychiatry. 2015;**23**(11):1117-1126. DOI: 10.1016/j.jagp.2015.05.009

[101] Shao H, Breitner JC, Whitmer RA, Wang Hayden K, Wengreen H, Corcoran C, Tschanz J, Norton M, Munger R, Welsh-Bohmer K, Zandi PP. Cache county investigators, hormone therapy and Alzheimer disease dementia: New findings from the cache county study. Neurology. 2012;**79**:1846-1852. DOI: 10.1212/WNL.0b013e318271f823

[102] Imtiaz B, Taipale H, Tanskanen A, Tiihonen M, Kivipelto M, Heikkinen AM, Tolppanen AM. Risk of Alzheimer's disease among users of postmenopausal hormone therapy: A nationwide case–control study. Maturitas. 2017;**98**:7-13. DOI: 10.1016/j.maturitas.2017.01.002

[103] O'Brien J, Jackson JW, Grodstein F, Blacker D, Weuve J. Postmenopausal hormone therapy is not associated with risk of all-cause dementia and Alzheimer's disease. Epidemiologic Reviews. 2014;**36**(1):83-103. DOI: 10.1093/epirev/mxt008

[104] Depypere H, Vierin A, Weyers S, Sieben A. Alzheimer's disease, apolipoprotein E and hormone replacement therapy. Maturitas. 2016;**94**:98-105. DOI: 10.1016/j.maturitas.2016.09.009

[105] Maggio M, DeVita F, Fisichella A, Colizzi E, Provenzano S, Lauretani F, Luci M, Ceresini G, Dall'Aglio E, Caffarra P, Valenti G, Ceda GP. DHEA and cognitive function in the elderly. Journal of Steroid Biochemistry & Molecular Biology. 2015;**145**:281-292. DOI: 10.1016/j.jsbmb.2014.03.014

[106] Seitz J, Lyall AE, Kanayama G, Makris N, Hudson JI, Kubicki M, Pope HG, Kaufman MJ. White matter abnormalities in long-term anabolic-androgenic steroid users: A pilot study. Psychiatry Research: Neuroimaging. 2017;**260**:1-5. DOI: 10.1016/j.pscychresns.2016.12.003

IntechOpen