Review

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Relationship between androgen deficiency and memory impairment in aging and Alzheimer's disease

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Aging and Alzheimer's disease (AD) are associated with a declination of cognition and memory, whose severity increases in AD. Recent investigations point to a greater participation of neurofibrillary tangles (NFTs) than that of senile plaques, as responsible for cognitive impairment in AD and normal aging. On the other hand, aging is related with reduced levels of dehydroepiandrosterone (DHEA) and its sulfate (DHEA-S) as well as testosterone (T). Basic and clinical studies give evidence that hypoandrogenism is associated with memory impairment. Accordingly, some animal studies show that the administration of these hormones improves the performance of cognitive tasks. However, effects of DHEA, DHEA-S, and T in the clinical setting, are not clear in part because of the balance between the benefits and risks of hormone therapy in aging subjects and because the cellular mechanism underlying its effects on memory in old age and related pathologies are unknown. The objective of this review is to analyze the role of DHEA, DHEA-S, and T, on memory in normal aging and in AD, and to determine whether these hormones modulate the hyperphosphorylation of tau protein, a molecular marker in AD pathology. The method used in the review included articles from the PubMed database, using the following search terms: DHEA, DHEA-S, T, memory, androgen deprivation therapy, tau protein, aging, and AD. Finally, we analyze the use of these steroids as an adjunct in the treatment of memory deficits in aging subjects and AD patients.

Keywords: Memory, Testosterone, Dehydroepiandrosterone, Androgen deprivation therapy, Tau protein, Aging, Alzheimer's disease

Actas Esp Psiquiatr 2017;45(5):227-47

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La deficiencia de andrógenos y su relación con el deterioro en la memoria en el envejecimiento y en la enfermedad de Alzheimer

El envejecimiento y la enfermedad de Alzheimer (EA) se asocian con una declinación de la cognición y la memoria, cuya gravedad aumenta en la EA. Varias investigaciones apuntan a una mayor participación de los ovillos neurofibrilares respecto a las placas seniles, como responsables del deterioro cognitivo en la EA y en el envejecimiento normal. Por otro lado, el envejecimiento se relaciona con una reducción en los niveles de dehidroepiandrosterona (DHEA) y su sulfato (DHEA-S), así como de testosterona (T); algunas evidencias básicas y clínicas indican que esta condición se asocia con deterioro en la memoria. Varios estudios en animales revelan que la administración de DHEA, DHEA-S y T mejoran la ejecución de tareas cognitivas. Sin embargo, el efecto de estas hormonas en el ámbito clínico no es claro, en parte por el balance entre los beneficios y los riesgos de una terapia hormonal en pacientes ancianos, así como por el desconocimiento de los mecanismos celulares que subyacen a sus efectos sobre la memoria en la vejez y en patologías relacionadas. El objetivo de esta revisión narrativa es analizar el papel de los esteroides DHEA, DHEA-S y T en la memoria en el envejecimiento normal y en la EA, así como la modulación en la hiperfosforilación de la proteína tau, un marcador molecular de la patología de la EA, por estas hormonas. El método empleado en esta revisión fue una búsqueda en la base de datos de Pubmed con los siguientes términos: DHEA, DHEA-S, T, memoria, terapia de privación de andrógenos, proteína tau, envejecimiento y EA. Finalmente, se analizará el empleo de estos esteroides como un coadyuvante en el tratamiento de las alteraciones de memoria en sujetos envejecidos y en pacientes con EA.

Palabras clave: Memoria, Testosterona, Dehidroepiandrosterona, Terapia de privación de andrógenos, Proteína tau, Envejecimiento, Enfermedad de Alzheimer

INTRODUCTION

Elderly population has sharply increased in the past 100 years due to advances in medicine and public health[1]. The percentage of people over 60 years of age has increased around the world from 9.2% in 1990 to 11.7% in 2013 and it is estimated to reach 21.1% by 2050. The increase in the number of elderly people will lead to the rise of demands in public health and social and medical services. Therefore, creating preventive alternatives and treatments is of great importance to reduce the impact of aging on health and improve the quality of life among the geriatric population.

Aging is associated to gradual memory impairment. Experts estimate that the prevalence rate of dementia -mainly Alzheimer's type- is considerably increased in subjects older than 65 years of age. Among the risk factors leading to dementia in old age are: unhealthy lifestyle, depression through life, and cardiovascular diseases. Some authors propose that the reduction of steroid hormones during aging might play an important role in the onset and progression of neurodegenerative diseases[2]. Research in men and male animal models suggests the existence of a relationship between the decrease of androgens and memory alterations during aging[3-8]. Consequently, studies consider the possibility that androgen restitution prevent or delay some aspects of cognitive impairment and its molecular correlates in normal aging and AD dementia.

In this review, we describe the relationship between the decrease in testosterone (T) and dehydroepiandrosterone (DHEA) and the deficit in memory associated to aging. We reviewed studies regarding the effect of antiandrogen therapies on memory and other cognitive functions of aging men. We include basic and clinical studies regarding the effect that the androgen restitution treatments have on memory. Additionally, we propose an association between an improvement in memory, the effect of androgens, and the decrease of phosphorylation of tau protein, a neuropathological marker present in AD.

METHODS

The articles analyzed in this narrative review were found in the PubMed database. The search was done on November 11, 2016 and covers a period from 10 to 28 years and a number of search paths, using MeSH terms. The articles were selected considering their titles and abstract as well as the inclusion and exclusion criteria. Then, we evaluated the full texts and chose 60 articles from the total 188 (see table 1).

AGE-DEPENDENT ANDROGEN REDUCTION

Androgens and their metabolites are steroids derived from cholesterol (Figure 1). In humans, DHEA and DHEA-S represent the main androgens released by the adrenal gland. The levels of DHEA and DHEA-S increase during childhood and puberty, reaching their peak at age 20 and their lowest point between ages 60 and 70[9,10]. Because of their action in the central nervous system (CNS), DHEA and DHEA-S (along with T) have been classified as neuroactive steroids since they are released by glands and are able to regulate neuronal activity[11]. They are also considered neurosteroids because they can be synthetized *de novo* in nervous tissue, independently from adrenal glands and gonads[12]. Both DHEA and DHEA-S act through a number of mechanisms to produce biological effects on the hypothalamic-pituitary-adrenal axis and the immune and the cardiovascular systems. In the CNS, these androgens promote neuroprotection, neurite growth, neurogenesis, neuronal survival, and catecholamine synthesis and release. In addition, they produce antioxidant, anti-inflammatory, and antiglucocorticoid effects. Both androgens modulate physiological functions, such as: sexual behavior, diet, emotion, and cognition[13-18].

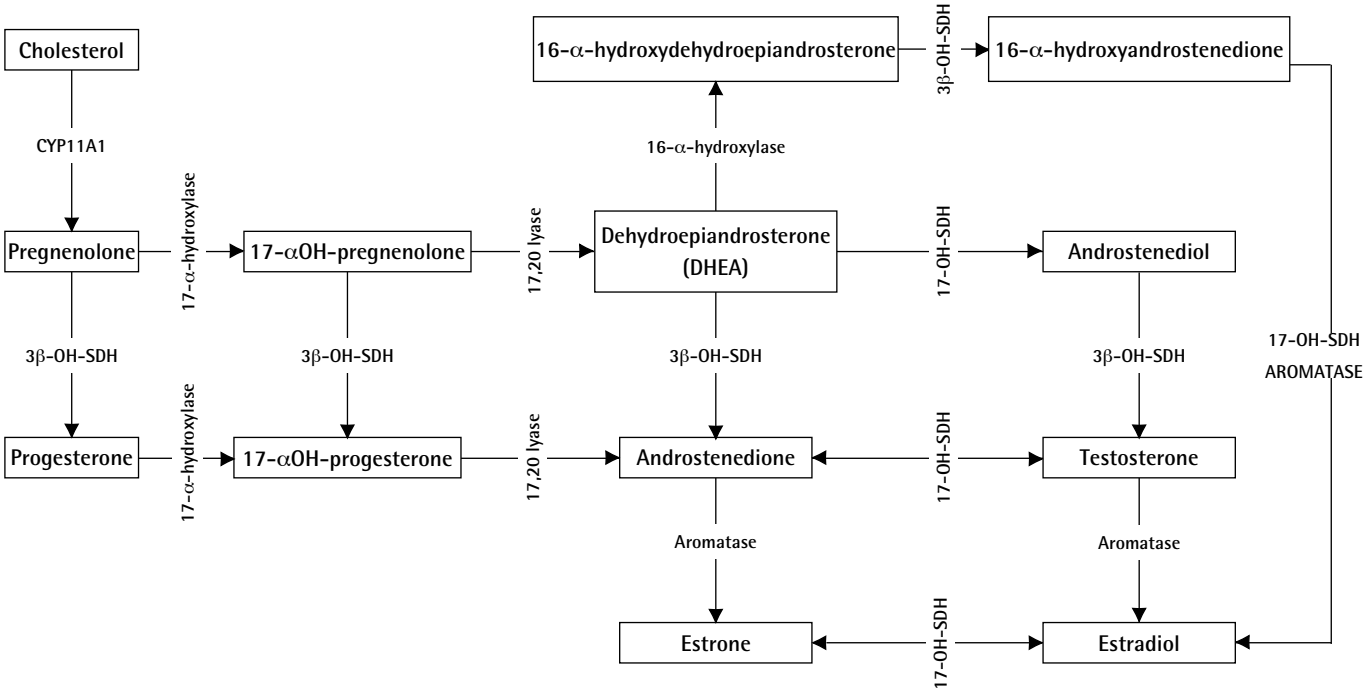
DHEA is a T precursor, considered to be the predominant androgen and, biologically, the most important one in men. Most of the circulating T in men originates in the testes, which release the hormone in a circadian rhythm. Then, the highest levels of this hormone are present in the morning while the lowest occur at night[19]. Longitudinal studies have confirmed that the highest levels of T occur during the second and third decades of life; in the years after, the levels decrease at a rate of 1-1.5% per year[20]. This decline is observed in both the free fraction (available fraction, unbound to proteins) and the total T serum levels (defined as the sum of T bound to proteins in blood and free T)[21]. The decline is caused by the decrease in the secretory capacity of the testes and pulse disruptions in neurons that synthesize and release the gonadotropin-releasing hormone (GnRH)[21]. As a result, over 60% of the healthy elderly men have around 50% of the free T levels of a man between 30 and 35 years of age (0.25 vs 0.55 ng/ml)[22]. This effect is known as partial androgen deficiency.

Partial androgen deficiency causes physical, emotional, and behavioral alterations, such as: fatigue, decreased muscle mass, weight gain, irritability, depression, and cognitive impairment. These alterations are caused by the decreased effect of T on the activity of brain structures as the medial preoptic area, the nucleus of the *stria terminalis*, medial amygdala, hypothalamic nuclei, lateral septum, and the hippocampal pyramidal cell layer[23,24]. Within these neurons, T produces its effects through genomic and non-genomic mechanisms[25]. Most of the biological effects produced by androgens are mediated by genomic mechanisms through the androgen receptor (AR) that can act as an activator of signaling pathways and as a transcription factor activated by its ligand, regulating the expression of androgen target genes[26]. Additionally, androgens can act

Table 1 Methodology used to select the articles from the PubMed database included in the review

Title / Name	Search period	MeSH terms	Articles found	Articles included	Inclusion and exclusion criteria
DHEA and DHEA-S participation in memory of elderly subjects and Alzheimer's disease patients	1988-2016	(("Aging"[Mesh]) and "Dehydroepiandrosterone" [Mesh]) and "Memory"[Mesh]	26	6	**Inclusion:** elderly men; Alzheimer's disease patients; spatial memory or working memory evaluation; DHEA, DHEA-S administration or level measurement **Exclusion:** review articles, women and animal studies
Testosterone effects on memory of elderly subjects and Alzheimer's disease patients	1990-2016	(("Aging"[Mesh]) and "Testosterone" [Mesh]) and "Memory" [Mesh]	33	11	**Inclusion:** elderly men, Alzheimer's disease patients, spatial memory or working memory evaluation, testosterone administration or level measurement **Exclusion:** review articles, women and animal studies
DHEA and DHEA-S evaluation in memory animal models	1987-2016	(("Dehydroepiandrosterone" [Mesh]) and "Memory"[Mesh]) not "Humans"[Mesh]	35	12 1 related article was included	**Inclusion:** young and elderly rats; spatial memory, working memory or reference memory evaluation; DHEA or DHEA-S administration **Exclusion:** review articles, female rat studies, tests in which spatial memory is not evaluated
Study of testosterone effect in memory animal models	1983-2016	((("Testosterone"[Mesh]) and "rats"[Mesh]) and "Memory"[Mesh]) not "humans"[Mesh]	40	13 1 related article was included	**Inclusion:** young and elderly rats; spatial memory, working memory or reference memory evaluation; dementia animal models; testosterone administration. **Exclusion:** review articles, female rat studies, tests in which spatial memory is not evaluated
Evaluation of the effect of DHEA, DHEA-S in tau protein	2002-2016	(("Alzheimer disease"[Mesh]) and "Dehydroepiandrosterone" [Mesh]) and "tau proteins"[Mesh]	3	2	**Inclusion:** elderly subjects, Alzheimer's disease patients, Alzheimer's animal model studies, DHEA or DHEA-S administration or level measurement, tau protein determination **Exclusion:** review articles
Effect of androgen deprivation therapy on memory	2006-2016	Androgen deprivation therapy and cognition (PubMed)	43	8 2 related articles were included	**Inclusion:** cases and controls design; longitudinal and retrospective studies. **Exclusion:** review articles and qualitative studies
Study of the effect of testosterone on tau protein	1997-2016	(("Alzheimer Disease"[Mesh]) AND "Testosterone"[Mesh]) AND "tau Proteins"[Mesh]	4	2 2 related articles were included	**Inclusion:** elderly subjects, Alzheimer's disease patients, studies using Alzheimer's animal model, testosterone administration or level measurement, determination of tau protein. **Exclusion:** evaluation in cell cultures

PubMed: Public Medline; MeSH: Medical Subject Headings; DHEA: dehydroepiandrosterone; DHEA-S: dehydroepiandrosterone sulfate.



CYP11A1: cholesterol side-chain cleavage enzyme.
3β-OH-SDH: 3β-hydroxysteroid dehydrogenase.
17-OH-SDH: 17-hydroxysteroid dehydrogenase.

Figura 1 | *Biosynthesis pathways of DHEA and Testosterone.*

by non-genomic mechanisms involving the formation of second messengers, the activation of signaling pathways such as the protein kinase A and C (PKA and PKC, respectively), and mitogen-activated protein kinase (MAPK) and intracellular calcium concentration increase[27]. Considering the location of the AR and these mechanisms, restitution treatments with T have been demonstrated to improve the mood and some aspects of cognition[28,29], although the balance between the risks and the benefits casts doubts on the use of T as a treatment during old age[30].

On the other hand, the action mechanism of DHEA and DHEA-S is complex. Its low affinity for AR seems to point that its effects on neuronal plasticity are not mediated by these receptors. Regardless, studies have described a wide variety of action mechanisms this androgen has, which involve several neurotransmission systems[31-39] (Table 2). Among these systems there is an interaction with the sigma opioid and N-methyl-D-aspartate (NMDA) receptors; therefore, they can modify neuronal excitability. Studies suggest that the interaction with these systems underlies the long-term changes as the increase in neurogenesis and neuroprotection.

AGING PRODUCES MEMORY IMPAIRMENT

Aging is a process of functional decline involving a deficit in cognitive abilities[40]. Two common events in aging are deficiencies in working memory, which depends on the prefrontal cortex[41,42] (see table 3), and declarative memory, depending on the hippocampus and other regions of the medial temporal lobe (perirhinal, entorhinal, and parahippocampal cortices adjacent to the hippocampus)[43]. Working memory involves processing and temporary storage of information during the performance of a cognitive task[44]. Declarative memory is a long-term memory that can be either episodic or semantic. It involves information consciously accessible regarding facts and events; it contextualizes subjects in space, time, and a determined situation[43].

Table 2 Action mechanisms of DHEA and DHEA-S

Reference	Action mechanism	Biological response
Kurata et al.[31]	Inhibits NMDA-induced nitric oxide production and activity of Ca(+2)-sensitive nitric oxide synthase σ1 receptor	Neuroprotection. It protects against NMDA-induced neurotoxicity
Hajszan et al.[32]	Effects are mediated through aromatization to estradiol	Neurite growth. Increases spine synapse density in CA1 area of hippocampus
Compagnone y Mellon[33]	NMDA receptor participation	Neurite growth.Produces morphological changes in neocortical neurons, increasing axonal length, presence of varicosities and formation of basket-shaped processes around cell bodies
Suzuki et al.[34]	NMDA receptor signaling after σ1 receptor activation	Neurogenesis. Increases proliferation and number of neural stem cells
Zhang et al.[35]	Serine-threonine protein kinase Akt signaling pathway	Apoptosis. Increases Akt kinase activity in neural precursor cultures and decreases apoptosis
Charalampopoulos et al.[36]	Stimulates actin depolymerization and disassembly of actin filaments	Catecholamine synthesis and release. Increases norepinephrine and dopamine release (DHEA-S slower than DHEA) and stimulates catecholamine production (DHEA-S)
Aragno et al.[37]	Inhibits NF-κB activation	Antioxidant. Decreases hydrogen peroxide and 4-hydroxynonenal, increases glutathione, catalase, and glutathione peroxidase; decreases NF-κB activation in hippocampus of diabetic rats
Iwasaki et al.[38]	Inhibits NF-κB activation	Anti-inflammatory. Inhibits TNFα-stimulated NF-κB activation
Cardounel et al.[39]	Decreases nuclear localization of glucocorticoid receptor	Antiglucocorticoid. Protects against glutamate-induced neuronal death

DHEA: dehydroepiandrosterone; DHEA-S: dehydroepiandrosterone sulfate; NMDA: N-methyl-D-aspartate; NF-κB: nuclear factor kappa B; TNFα: tumor necrosis factor alpha

Episodic memory is that of personal events that occur in a particular place and time. This is the most affected memory in elderly people who express recent events less precisely or less specifically. For instance, although they may know a particular event took place, it is unlikely they remember where and when it happened[45]. In elderly subjects, problems in episodic memory involve deficiencies in the processes of coding, storing, and retrieving information[45,46] (see table 3). Still, they do not show a significant impairment of semantic memory, which is the general knowledge about the world, words, and concepts. Even though access to information can be slower -particularly for words and names-, the organization of knowledge does not change with age[47].

Other cognitive functions that deteriorate in aging are attention and executive control. Elderly subjects show a significant damage in tasks demanding divided attention or a change of attention between multiple tasks[48]. As for cognitive impairment related to age, it is partly caused by a deficit in executive control; that is, a deficit in the processes involved in planning, organizing, coordinating, implementing, and evaluating activities[49].

Formation of memory mostly depends on the hippocampus, a structure that loses part of its integrity and functionality in aging. This is evident from studies that show a deficient performance of elderly subjects in tasks of formation and use of cognitive maps[50]. Several studies using rodents report that the execution of learning and memory tasks by old subjects is lower than that of younger rodents[51–54]. According to this idea, experiments in which spatial memory was evaluated using Barnes' maze and T maze showed that old rats have a lower performance during the tests[55–57]. Additionally, Small et al.[58,59] and Moreno et al.[60]

Table 3 Deficits in working memory, episodic memory and semantic memory in elderly people and Alzheimer's disease patients

Reference	Participants	Test performed	Result
Gick et al.[42]	18 young subjects (aged 22 years) and 18 elderly subjects (aged 68 years)	Working memory tasks	Elderly subjects showed a decrease of execution in working memory
Jennings y Jacoby[46]	24 young subject (aged 18–21 years) and 24 elderly subjects (aged 63–80 years)	Episodic memory. Interval-repetition paradigm	Compared with young subjects, elderly subjects showed a deficit in data recollection, which demands recovery of episodic details
Baddeley et al.[90]	28 Alzheimer's disease patients (aged 65 years; 12 men and 16 women). 18 elderly control subjects (aged 64 years; 8 men and 10 women)	Working memory. Tasks: tracking (subjects track a square in movement), articulatory suppression (subjects pronounce numbers 1 to 5 repeatedly); reaction time to tones; memory span (subjects memorize a series of numbers and repeat them back)	Alzheimer's disease patients show a deficit in central executive component of working memory since they have trouble coordinating two tasks at the same time
Rémy et al.[81]	11 healthy control subjects (aged 65.9 years; 5 men-6 women) and 8 Alzheimer's disease patients (aged 72.2 years; 1 man-7 women)	Verbal episodic memory. Coding and recognition tasks	Alzheimer's disease patients showed deficits in verbal episodic memory
Hodges et al.[83]	52 controls (aged 68.7 years; 30 men, 22 women), 52 Alzheimer's disease patients (aged 71.7 years; 34 men-18 women)	Semantic memory (object naming). Boston naming test	Alzheimer's disease patients show alterations in semantic knowledge since they make more mistakes naming objects when compared to normal elderly subjects
Aronoff et al.[85]	25 young subjects (aged 20.2 years); 24 elderly subjects (aged 78 years) and 15 Alzheimer's disease patients (aged 83.5 years)	Memory and semantic knowledge. Tasks involving naming photographs and classifying concepts on a board	Alzheimer's disease patients showed a deficit in the naming photographs task. Additionally, they showed less knowledge on concepts of a determined category
Chen et al.[87]	483 controls (aged 73 years; 63% women); 68 Alzheimer's disease subjects(aged 77 years; 57% women)	Memory tasks (recall and recognition of a word list); story recall Verbal fluency; Boston naming test; praxias Executive function: trail making test	Alzheimer's disease patients showed cognitive impairment in memory tasks and in executive function task

showed a reduction in the metabolism of the dentate gyrus in the hippocampus of aged humans, monkeys and mice; this reduction is correlated to memory impairment. Similarly, Shing et al.[61] reported that the reduction in the volume of the dentate gyrus and CA3 in elderly adults is correlated to memory impairment.

The neuropathological events that characterize aging and that take part in the impairment of the functions of the prefrontal and frontal cortex as well as the medial temporal lobe include: damage in the electrophysiological processes[62], alterations in synapsis[63], neurogenesis decline[64], white matter atrophy (particularly in the frontal lobes)[65], increase of the amyloid-β protein (Aβ)[66] and hyperphosphorylation of tau protein[67]; these last two are also alterations present in AD.

AD is a disorder associated to the deficit of memory dependent on aging; its prevalence increases exponentially after the sixth decade of life[68].

COGNITIVE IMPAIRMENT IN ALZHEIMER'S DISEASE

AD is characterized by a progressive cognitive impairment and represents between 50% and 80% of all types of dementia[69]. This disease is diagnosed *post mortem* quantifying senile plaques and neurofibrillary tangles (NFTs) in the medial temporal lobe and brain cortical areas. Senile plaques consist of extracellular Aβ deposits while NFTs are constituted by abnormally phosphorylated tau protein and are locat-

ed in the cytoplasm of neurons[70]. Tau protein belongs to the family of proteins associated to the microtubules; its function is to stabilize them during axonal transport and participate in neurite growth[71]. When tau protein is abnormally phosphorylated, it tends to aggregate in filaments, inducing therefore the break of microtubule pathways leading to neuronal death[72].

AD initially affects limbic regions involved in episodic memory[70,73-75], progressing to neocortical regions[76-79]. At this point, an additional cognitive deficit arises in the language area, the executive function, and the abstract reasoning; it also affects decision making[80] while dementia syndrome is also present.

AD patients carry out episodic memory tasks (free recall, recognition, paired-associate learning) deficiently in the auditory, visual, and olfactory modalities[81,82] (see table 3). Evidence shows that this deficit is mostly due to the ineffective consolidation or storage of new information. Besides, patients show language and semantic knowledge impairment and have difficulties performing tasks in which they name objects[83], show verbal fluency[84], and perform semantic categorizing[85] (see table 3).

At AD onset, patients have difficulties in executive functions, responsible for mental manipulation of information, concept formation, problem solving, and objective-directed behavior[86,87] (Table 3). These alterations are associated to the increase of NFTs in the prefrontal cortex[88,89]. A deficit in working memory (immediate memory) is commonly found[90,91] (Table 3). In addition, AD patients with moderate dementia show a decline in dual-processing task, tasks that require the disengagement and shifting of attention[86,92]. In contrast, the ability to focus and sustain attention is only affected during the last stages of the disease. Additionally, patients show a deficit in the visuospatial abilities: ability to perceive space and guide and direct movement across it[93].

It has been established that AD biological markers appear years before cognitive and behavioral symptoms. Therefore, recognizing the pre-clinical phase of AD in elderly people is a priority of public health.

PATHOLOGICAL MARKERS IN AGING AND ALZHEIMER'S DISEASE

There are reports that the NFTs and Aβ plaques are present in the brains of aged individuals, even without AD medical diagnosis[94-96]; this suggests the existence of a preclinical stage of AD[97]. In aged brains without dementia, the formation pattern of NFTs is considerably different from that of the plaques. Price and Morris[97] observed that subjects over 60 years of age without dementia or cognitive change had NFTs in vulnerable areas (entorhinal or perirhinal cortex). The age-related increase of NFTs in cases without dementia is exponential; this is particularly evident after 70 years of age. Contrastingly, the plaques were only found in a fraction of the cases without dementia and were absent in some brains of subjects older than 80 years. The presence of NFTs preferentially occurred in hippocampus, perirhinal and entorhinal cortex and CA1, while the plaques were found in neocortical areas. The authors also demonstrated that NFT distribution was similar in the cases of groups with young subjects and those with older subjects with mild or severe dementia. However, they observed that NFTs increased in number in older subjects and those with severe dementia. Finally, Prince and Morris concluded that NFTs appear before amyloid plaque deposits; however, the development and increase of NFTs is slow.

Braak and Braak[77] described the progression of AD pathology in 6 stages. Stages I and II are characterized by the emergence of NFTs in the transentorhinal region while in stages III and IV, NFTs are confined in the entorhinal and transentorhinal regions. In stages V and VI, there is a severe destruction of the isocortical association areas, a macroscopically detectable atrophy of the cortex and an acute loss of brain weight. The high density of the neurofibrillary changes virtually occurs in all the subdivisions of the brain cortex. States V and VI correspond to the conventional criterion for neuropathological confirmation of AD clinical diagnosis.

Knopman et al.[98] evaluated the brain of elderly subjects between 74 and 95 years of age who were cognitively normal. They observed that 56% of them showed Braak stages I or II while 28% presented Braak stage III. In 13% of the subjects, NFTs were observed in hippocampus, isocortex, association cortex and primary sensory cortex (Braak stage IV or higher).

Studies have described that hippocampal lesions are the *sine qua non* of AD[99]; patients with these lesions lose pyramidal cells in the CA1 area of the hippocampus[10]. Additionally, AD has been reported to induce the emergence of NFTs and senile plaques in specific hippocampal formation areas (CA1 and entorhinal cortex, among others). These changes hamper communication between hippocampal formation and cortex and/or specific subcortical structures, which might explain memory impairment in AD[100].

It has been proposed that the acuteness of dementia is better related to the density of the NFTs than to the density of senile plaques[77,101]. Berg et al.[102] found a significant relationship between the severity of dementia and the density of NFTs in the cortex and the hippocampus, although hippocampal NFTs have a greater density. Regardless, senile plaques have a higher prevalence in neocortical regions

when compared to other locations as the hippocampus and the entorhinal cortex. Additionally, the authors observed that senile plaques are substantially increased in severe stages of AD.

THE ROLE OF ANDROGENS IN MEMORY

There is a hypothesis that the decline of DHEA and DHEA-S concentrations may accelerate the aging process in physical and cognitive terms[103]. However, studies in humans regarding this relationship have provided contradictory results (see table 4). In a longitudinal study, Kalmijn et al.[104] demonstrated an inverse, yet not significant, relationship between DHEA-S levels and cognitive impairment of healthy men and women who averaged 67 years of age. Contrastingly, Carlson and Sherwin[105] observed that the decrease of DHEA-S levels in the plasma of men and women older than 60 years were not associated with the subjects' cognitive execution. According to this, DHEA treatment (50 mg for 13 weeks) in healthy subjects between ages 60 and 80 did not improve cognitive execution; however, the authors observed that the quotient cortisol/high DHEA was associated to a lower execution in visuospatial memory[106].

Among AD patients, those with higher plasmatic DHEA-S levels showed a better cognitive execution[107] while DHEA treatment for 6 months did not improve cognition in these patients with respect to the placebo[108]. Discrepancies in these studies might be associated to methodological differences as scales to evaluate cognitive function, age of the subjects, acuteness of the disease, gender, and steroid levels reached with treatment.

Sorwell and Urbanski[109] have proposed that a decline related to age in the conversion of DHEA to estradiol in brain regions associated to memory explains the lack of efficacy DHEA-S has on memory. Supporting this idea, a study proved that old male macaques have a reduced expression of enzyme 3β-hydroxysteroid dehydrogenase in the hippocampus[110]. In consequence, they are less capable of centrally converting DHEA to T, which is a precursor of estradiol. Therefore, the authors suggest that DHEA and T supplementation in elderly subjects would improve the memory deficits of aging[111].

Unlike clinical research, studies carried out using young and aged rodents have established that DHEA and T improve memory in different tasks (see tables 5 and 6). Rats administered with DHEA and DHEA-S have been proven to reduce the deficits in working, reference, and spatial memory, induced by dizocilpine (NMDA receptor antagonist)[112–114], scopolamine[115], ethanol[116], and aging[117]. These effects were also found in several animal models: senescence induced by D-galactose[103], vascular dementia[118], mice with olfactory bulbectomy-induced cognitive impairment[119], hippocampal degeneration[120], and Aβ administration in the brain[121]. Unlike in these studies, Bodensteiner et al.[122] did not observe changes in the spatial memory of young or old mice treated with DHEA-S while Bazin et al.[123] found that DHEA and its analogous could not reverse the deficit in working memory produced by scopolamine. In general, the studies reveal that memory dependent on hippocampus is favored by DHEA treatment in models producing neurotoxicity or blocking of diverse neurotransmission systems involved in memory. They also support the therapeutic potential of DHEA in normal and pathological aging.

The role T plays in cognition has been researched in both humans and rodents. Studies suggest that men have an advantage over women when executing spatial tasks involving mental rotation and spatial perception and visualization[124–126]. When evaluating the cognitive function in elderly subjects, studies have found that T levels have a negative correlation with reaction time, while the correlation is positive regarding execution of spatial, semantic, working, and verbal episodic memory[3,4,127–129]. Besides, T administration reduces deficits in working, spatial, and verbal memory, associated to aging[29,130,131]. On the contrary, some studies report that T levels are not related to either spatial or semantic memory[132] and that there is a negative correlation between T levels and spatial memory[133] or between speed of processing, executive function, and perceptual discrimination[134] (see table 7). The differences in these studies might be explained by the diversity of the cognitive evaluations applied to the subjects, some of whom can be more sensitive to the effects of hormonal changes, study design, hormonal analysis conducted, and the methodological differences used in each of the studies.

In old age, men can suffer cognitive deficits after interventions as androgen-dependent pharmacotherapy for prostate cancer. Androgen deprivation therapy (ADT) consists of inactivating the interaction of these hormones with target tissue or reducing their levels. As a result, there is a marked decrease of the effects that T and its derivatives have in organs and tissue. The analysis of these studies may provide valuable evidence about the causes of memory alterations in middle-aged and old subjects and androgen suppression. The first systematic review published in 2009 by Nelson et al.[135] refers 9 longitudinal studies (published between 2002 and 2006) with prostate cancer patients under ADT treatment for periods ranging from six months to one year. The results of the cognitive evaluation of the patients were compared with those from patients under medical supervision but without ADT (controls). According to Nelson et al.[135], the decrease in the levels of androgens after ADT produced a mild impairment in visuospatial memory and executive functions in 47%–69% of men. The authors suggest a cautious interpretation of the results due

Table 4 Effect of DHEA and DHEA-S on memory of elderly subjects or Alzheimer's disease patients

Reference	Subjects	Hormone	Test	Result
Carlson y Sherwin[105]	31 men, 14 and 41 women with and without estrogen treatment, respectively. Age >60 years	Determination of DHEA-S levels in plasma (on two occasions separated by 18 months)	Evaluation of declarative memory, language fluency and concentration/attention	No correlation was observed between decrease of DHEA-S levels in plasma and cognitive execution
Kalmijn et al.[104]	189 healthy men and women. Age: 55–80 years	Follow-up study (1.9 years). Determination of DHEA-S in serum	Global cognitive function	Inverse, yet not significant, relationship between DHEA-S levels and cognitive damage
Valenti et al.[168]	755 subjects (345 women, 410 men). Age: >65 years	Transversal and longitudinal study (3 years). Determination of DHEA-S, total testosterone and estradiol	Cognitive function evaluated with MMSE	Low DHEA-S levels are associated to a poor cognitive state and accelerated decline in MMSE scores 3 years after
Van Niekerk et al.[106]	46 healthy men. Age: 60–80 years	Double-blind, randomized, cross-over study. Administration of 50 mg DHEA for 13 weeks, followed by 13 weeks with placebo	Cognitive evaluation. Word list memory and object location memory	Inverse relationship between DHEA levels and age. No significant correlation was observed between DHEA levels and cognitive function
Wolkowitz et al.[108]	58 subjects (men and women) diagnosed with Alzheimer's disease. Age: >55 years	6-month treatment with 50 mg DHEA twice per day.	ADAS-Cog and CIBIC-plus. MMSE and ADAS-non Cog were additionally applied	In DHEA group there was no significant improvement in ADAS-Cog scores at month 6. However, at month 3 a tendency to improvement was observed in DHEA group
Carlson et al.[107]	52 Alzheimer's disease patients (26 men and 26 women). Average age: 76.2 years	Determination of DHEA levels in plasma	Rivermead behavioral memory test (remembering a name, remembering a belonging, remembering an appointment, photograph recognition, face recognition, recalling a story immediately and with delay, remembering to send a message, orientation, and date)	Alzheimer's disease patients with high DHEA-S levels obtained better score in subtest "remembering a name associated to a photo", digit recall task, and MMSE

DHEA: dehydroepiandrosterone; DHEA-S: dehydroepiandrosterone sulfate; MMSE: mini-mental state examination; ADAS-Cog: Alzheimer's disease assessment scale cognitive; CIBIC-plus: clinician's interview-based impression of change plus caregiver input; ADAS-non Cog: Alzheimer's disease assessment scale – non-cognitive

to opposing findings reported in two studies (visuospatial memory improved in a subgroup of patients under treatment). They also advise to consider the heterogeneity of the studies, the low number of subjects, and the differences in the neuropsychological instruments.

The aim of the present review was to update the existing review on the topic during the period from 2006 to April 2016 (Table 8). The results suggest that ADT produces impairment in visuospatial, immediate, and working memory as well as in attention, information processing, and executive functions, in elderly or middle-aged men[136–145]. It must be pointed out that two studies enrichen the neuropsychological information through the analysis of brain images taken from patients while they were carrying out a specific task. Thus, neural correlates for cognitive impairment were obtained. The studies found a decrease of the gray matter in

Table 5 Effect of DHEA, DHEA-S on memory of rodents evaluated in different behavioral tasks

Reference	Animals	Hormone	Task	Result
Markowski et al.[117]	Male and female mice (aged 18–20 months)	DHEA-S orally (1.5 mg/day for 5 days)	Y maze	↑ Working memory
Zou et al.[112]	Young male rats treated with dizocilpine	DHEA-S i.p. (25 mg/kg); dizocilpine (0.15 mg/kg)	8 arm radial maze	↓ Dizocilpine-induced deficits in working and reference memory
Chen et al.[103]	D-galactose-induced senescent rat model (both genders)	DHEA i.p. (final percentage 3%, for 8 weeks)	Morris water maze	↑ Spatial memory
Maurice et al.[121]	Male mice administered beta amyloid protein in brain	DHEA and DHEA-S (20 mg/kg) s.c.	Y maze Stepdown passive avoidance	↓ Deficits in spontaneous alternation and retention session
Sakr et al.[118]	Vascular dementia model in young male rats	DHEA (250 mg/kg/day) orally for 7 days	Holeboard memory test	↓ Deficits in working and reference memory
Moriguchi et al.[119]	Young male mice with olfactory bulbectomy	DHEA (30 or 60 mg/kg; orally) 7–12 days	Y maze	↑ Spatial reference memory
Bazin et al.[123]	Young male mice treated with scopolamine	DHEA and analogous (0.300–1.350–6.075 µmol/kg) s.c. Scopolamine (1 mg/kg) i.p.	Y maze. DHEA, analogous and scopolamine were administered 30 min before task	DHEA or its analogous caused no change in scopolamine-induced deficit in working memory
Bodensteiner et al.[122]	Young (aged 2–4 months) and old (aged 14–16 months) mice	DHEA-S (20 mg/kg) s.c.	Morris water maze. DHEA-S was administered 30 min before each session	DHEA-S produces no changes in spatial memory
Maurice et al.[113]	Young male mice treated with dizocilpine	DHEA-S (20 mg/kg) s.c.; dizocilpine (0.15 mg/kg) i.p.	Y maze. DHEA-S was administered 10 min before task. Dizocilpine was administered 20 min before task	DHEA-S ↓ Dizocilpine-induced deficits in spatial working memory
Maurice et al.[120]	Young male mice exposed to CO (hippocampal neurodegeneration model)	DHEA (20 mg/kg) s.c.	Y maze. DHEA was administered 20 min before each CO exposure	DHEA ↓ Deficits in spatial working memory produced by CO exposure
Shi et al.[115]	Young (aged 1–2 months) and old (aged 22–23 months) mice treated with scopolamine	7-oxo-DHEA acetate (24 mg/kg) and DHEA (20 mg/kg). s.c. Scopolamine (1 mg/kg) s.c.	Morris water maze. Treatments were administered 2 and 45 min after last learning trial	7-oxo-DHEA acetate and DHEA ↓ Scopolamine-induced deficits in spatial memory
Reddy y Kulkarni[114]	Young (aged 3 months) and old (aged 16 months) mice treated with dizocilpine	DHEA-S (1, 5, 10, and 20 mg/kg) s.c.; dizocilpine (0.1 mg/kg) i.p.	Elevated plus maze. DHEA-S was administered 45 min and dizocilpine 30 min after first learning trial	DHEA-S ↓ Dizocilpine-induced deficits in long-term spatial memory
Melchior y Ritzmann[116]	Young mice administered with ethanol	DHEA and DHEA-S (0.05 mg/kg) i.p. Ethanol (0.5 mg/kg)	T maze. DHEA and DHEA-S were administered 30 min before task. Ethanol was administered 10 min before task	DHEA y DHEA-S ↓ Ethanol-induced deficits in spatial working memory

↑ = improves, increases or promotes. ↓ = Decreases.

DHEA: dehydroepiandrosterone; DHEA-S: dehydroepiandrosterone sulfate; CO: carbon monoxide; i.p.: intraperitoneal; s.c.: subcutaneous

Table 6 Effect of testosterone on memory of rodents evaluated in different behavioral tasks

Reference	Animals	Hormone	Task	Result
Spritzer et al.[146]	Orchidectomized young rats (aged 2 months)	Testosterone (0.5 mg/rat/30 days) subcutaneous	8 arm radial maze	↑ Working memory
Spritzer et al.[146]	Orchidectomized young rats (aged 2 months)	Testosterone (0.06–1 mg/rat/14 days) subcutaneous	Morris water maze	↑ Spatial learning
Hawley et al.[7]	Orchidectomized young rats (aged 2 months)	Testosterone (implant)	Y maze. Test performed 1 month after surgery and/or implant placement	↑ Spatial memory
McConnell et al.[6]	Orchidectomized young rats (aged 1 month)	Testosterone (implant; hormone concentrations of 6.05 ± 0.67 ng/ml are obtained)	Object location. Task was performed 3–5 days after implant placement	↑ Spatial memory
Bimonte-Nelson et al.[5]	Old male rats (aged 22 months)	Testosterone (implant; 50 mg released in 60 days)	8 arm radial water maze. Task was performed 1 month after implant placement	↑ Reference memory
Locklear y Kritzer[8]	Orchidectomized young rats	Testosterone propionate (implant; 3–4 ng/ml blood/day) 17β-estradiol (implant; 25 pg/ml blood/day)	Barnes maze. Task was performed 28 days after surgery/implant placement	↑ Spatial memory
Jacome et al.[147]	Orchidectomized young male rats (aged 2 months)	Testosterone (750 µg/kg), or estradiol (20 µg/kg), 1 subcutaneous administration (immediately after learning trial)	Object location task	↑ Spatial memory
Moghadami et al.[148]	Orchidectomized young male rats	Intracerebroventricular administration of testosterone (10, 40, or 120 µg/0.5 µl) 30 min before task for 5 days	Morris water maze	↑ Spatial memory
Narenji et al.[150]	Young male rats	Microinjection 3α-diol (testosterone metabolite) (0.2, 1, 3 or 6 µg/0.5 µl/ CA1 area of hippocampus) 25–35 min before task for 4 consecutive days	Morris water maze	↓ Spatial memory acquisition
Gibbs y Johnson[155]	Orchidectomized young male rats	Testosterone (implant; 2.9–4.9 ng/ml hormonal levels were reached)	12 arm radial maze. Task was performed 2 weeks after surgery/implant placement	↓ Working memory in orchidectomized rats. Testosterone did not reestablished deficit. ↓ Reference memory in orchidectomized rats treated with testosterone
Sandstrom et al.[149]	Orchidectomized young male rats	Testosterone (implant; 4.69 ± 0.42 ng/ml hormonal levels were reached)	Morris water maze. Task was performed 1 week after castration. Implant was placed at day 4 of task	↑ Working memory

Table 6 Continuation

Reference	Animals	Hormone	Task	Result
Naghdi et al.[151]	Young male rats	Intracerebral injections (CA1 area of hippocampus) testosterone enanthate (80 µg/0.5 µl; 30 min before task)	Morris water maze	↓ Spatial memory
Naghdi et al.[152]	Young male rats	Intracerebral injections (basolateral nucleus of amygdala) testosterone enanthate (0, 20, 40, 80, and 120 µg/0.5 µl 30 min before task) or flutamide -androgen receptor antagonist- (0, 2, 5, 10, 20 and 40 µg/0.5 µl; 30 min before task)	Morris water maze	↓ Spatial memory and learning (120 µg/0.5 µl testosterone). Flutamide produced no changes in memory
Smith et al.[154]	Young male rats	17α-methyltestosterone (7.5 mg/kg); methandrostenolone (3.75 mg/kg); testosterone cypionate (7.5 mg/kg). Subcutaneous administration for 30 days	8 arm radial maze	Treatments did not modify spatial working memory
Goudsmit et al.[153]	Young male rats (aged 3 months), middle-aged rats (aged 18 months) and old rats (aged 30 months)	Testosterone (implant)	Morris water maze (task started 1 month after implant placement)	↓ Spatial memory

↑ = improves, increases or promotes. ↓ = Decreases

the primary motor cortex, which correlated with poor working memory[140], or reduced activity in the dorsolateral prefrontal cortex when the patients under treatment carried out a cognitive control task, and poor execution of the task with respect to healthy controls[139]. On the other hand, we must consider the retrospective report by Shahinian et al.[145] in which over 50,000 patients with at least 5 years of survival to prostate cancer participated. The study describes that 31% of the patients with ADT were diagnosed with cognitive alterations with respect to 23% of the healthy controls paired for age. However, when the results were adjusted per age, ethnicity, and tumor degree, the differences were cancelled. The main limitation of the study was the assertiveness of the diagnosis of cognition, which was taken from files of the health system/ministry. Therefore, it should be considered that, although the alterations were present in some patients, many of them might not be clinical. The age of the patients and the acuteness of the pathology—which, in itself, might be an influence on the outcome—must also be considered. In conclusion, ADT might impair the memory and the cognition, in general, of subgroups of patients who are especially sensitive to changes in the levels of androgens.

The relationship between androgens and cognition may be complex, a fact that is added to the diversity of experimental designs in research with humans and the methodological differences used to evaluate this relation. Some studies using animal models show that old and young castrated rodents present a deficit in spatial, reference, and working memory in a number of tasks. These alterations were reverted with T restitution[5–8,146–149] (see table 6), indicating a positive relationship between this androgen and cognition. Unlike this idea, other works have reported that intracerebral T injections in the CA1 hippocampal area[150,151] or the basolateral nucleus of the amygdala[152] of young intact rats produce a deficit in spatial memory using Morris water maze. The same results were obtained placing a T implant in young and middle-aged rats[153]. Additionally, the administration of T in young intact[154] or orchidectomized[155] rats does not modify the spatial working memory in the 8 arm radial maze (see table 6). The results obtained in these studies may be contradictory because of the different tasks evaluated, the ages of the animals, the dosage used, the length of the treatments, and the routes of administration. Finally, it should also be considered whether the evaluation was done using intact or orchidectomized animals.

Table 7 Effect of testosterone on memory of elderly subjects or Alzheimer's disease patients

Reference	Subjects	Hormone	Test	Result
Janowsky y Chavez[130]	18 young men (aged 29 years), 19 elderly men (aged 68 years), 30 young women (aged 30 years), 13 post-menopausal women (aged 69 years)	Estrogen: 0.625 mg/day, orally in elderly women. Testosterone: 150 mg testosterone enanthate/ week in elderly men	Working memory. Task was performed before and after supplementing sex steroids: twice (1-month period between tasks) in young men, and in luteal phase of menstrual cycle in women (6–10 days before menstruation)	Sexual steroids increased execution in elderly men, but not in elderly women. Working memory in men is positively associated to testosterone levels and negatively to age and estradiol levels
Wolf y Kirschbaum[132]	38 post-menopausal women (aged 68 years) and 30 healthy elderly men (aged 69 years)	Determination of testosterone and estradiol levels in blood	Cognitive tasks: semantic memory, spatial memory, executive control, verbal fluency, mental rotation	Estradiol and testosterone levels in elderly women are associated to better execution in verbal memory. In elderly men no association between sexual steroid levels and cognitive function was found
Fontani et al.[127]	68 healthy volunteers (aged 18–77 years)	Testosterone levels were determined (total, free, bound to albumin and sex hormone binding globulin)	Attention tasks: alertness, go/no-go, divided attention, working memory	Negative association between time of reaction and levels of testosterone, FT and unbound testosterone; hence, reduction in testosterone levels in elderly subjects negatively affects attention activities
Cherrier et al.[131]	61 healthy subjects (aged 50–90 years)	6-week treatment: 1) 100 mg testosterone enanthate/week. 2) 100 mg testosterone + 1 mg anastrozole (aromatase inhibitor)/week	Tasks involving: spatial memory, verbal memory, working memory, language and selective attention. They were performed in baseline, during weeks 3 and 6 of treatment and 6 weeks after wash-out	Testosterone improved verbal and spatial memory. Testosterone + anastrozole improved spatial memory. Testosterone aromatization to estradiol participates in verbal memory but not in spatial memory
Cherrier et al.[29]	Alzheimer's disease patients and subjects with mild cognitive impairment (aged 63–85 years)	100 mg/week Testosterone enanthate for 6 weeks (followed by 6 weeks of wash-out)	Measurements of verbal and spatial memory, working memory, language, and selective attention. Cognitive evaluation was performed in baseline, after 3 and 6 weeks of treatment and 6 weeks after wash-out	Testosterone improved execution in verbal and spatial memory
Thilers et al.[3]	1107 men and 1276 women (aged 35–90 years)	Determination of testosterone in serum	Visuospatial ability, episodic memory, semantic memory, and verbal fluency	In men, testosterone was positively related to visuospatial ability, semantic memory and episodic memory. In women, FT was negatively associated to verbal fluency
Yorker et al.[133]	450 men (aged 35–80 years)	Determination of FT	Spatial visualization, problem solving, verbal fluency, and episodic and semantic memory	Reduction in cognitive tasks related to age is independent from FT levels. Negative relation between FT and execution in spatial visualization tasks and MMSE "draw a figure" task

Table 7 Continuation

Reference	Subjects	Hormone	Test	Result
Martin et al.[134]	1195 men (aged 35–80 years)	Determination of plasma total testosterone, sex hormone binding globulin and FT	Tridimensional mental rotation (Vandenberg and Kuse), executive function, processing speed, time of reaction, working memory, and visualization speed/ perceptual decision tasks	FT levels are not associated to execution in mental rotation task in middle-aged or elderly subjects; low FT levels are associated to a higher speed of processing, better executive function and perceptual discrimination
Matousek y Sherwin[4]	54 healthy men (aged 61–77 years)	Determination of total testosterone and estradiol	MMSE; evaluation of spatial ability: mental rotation test, water level test, paper folding test, block design. Verbal ability: paragraph recall/ verbal memory, verbal paired-associates, visuomotor scanning. Working memory: letter-number sequencing	Positive association between function in working memory and bioavailable testosterone levels
Hyde et al.[128]	585 men (aged≥ 65 years)	Total testosterone levels in serum were determined (samples were obtained at 8:00 and 10:30 hrs)	MMSE: evaluates orientation in time and place, visuospatial ability, recall and ability to understand and follow instructions; California verbal learning test	Levels of FT are associated to global cognitive function (MMSE)
Panizzon et al.[129]	1237 men (average age 55.4 years)	Measurement of testosterone in saliva upon waking up, 30 min after waking up and at night	Neurocognitive battery. Verbal episodic memory (California verbal learning test); logical memory test (story recall—Wechsler memory scale); visuospatial episodic memory (visual reproduction test, figure recall—Wechsler memory scale)	Positive association between FT levels and execution in episodic verbal memory

FT: free testosterone; MMSE: mini-mental state examination.

It has been suggested that the risk of showing AD and the onset/progression of its biological markers is negatively associated to the androgen levels in old age[156–161].

ANDROGENS MODULATE EXPRESSION OF TAU PROTEIN

There is little information concerning the effect of DHEA or DHEA-S in memory and in relation with hyperphosphorylation of tau protein. Weill-Engerer et al.[162] found that AD patients showed lower DHEA-S levels in striatum, cerebellum, and hypothalamus, when compared to age-matched control subjects. They also observed a negative correlation between DHEA-S and phospho-tau protein levels in hypothalamus and Aβ peptide levels in striatum and cerebellum.

Furthermore, Dudas et al.[163] proved that a 10-day treatment of 7β-Hydroxy-epiandrosterone (7β-OH-EpiA), a derivative credited with providing DHEA with its neuroprotective effect, prevents the Aβ25–35-induced increase of Tau-2 protein (total tau) immunoreactivity in rat hippocampus. Also, treatment using steroids for 10 days reduced cholinotoxin AF64A-induced glial and cholinergic lesions in the septum.

On the other hand, Papasozomenos[164] and Papasozomenos & Shanavas[165] observed that T (but not its aromatized metabolite 17β-estradiol) reduces heat shock-induced hy-

Table 8 Studies of the effects of androgen deprivation therapy (ADT) on cognition in prostate cancer (PC) survivors

Reference	Study	Subjects	Result
Yang et al.[136]	Cases and controls	PC and ADT patients (n=43), without ADT (n=35) and healthy subjects (n=40); evaluation of EBPM and TBPM	ADT patients suffer EBPM impairment
Yang et al.[137]	Cases and controls	PC and ADT patients (n=33), without ADT (n=32) and healthy subjects (n=35); different cognitive tasks	ADT patients suffer attention and information processing impairment
Wu et al.[138]	Pilot study	11 subjects with ADT with semi-structured telephone interview	8/11 participants reported impairment in: concentration, verbal fluency, executive functions, information processing
Chao et al.[140]	Cases and controls	15 goserelin subjects and 15 controls MRI evaluation, gray matter and working memory (baseline, 3 and 6 months)	↓Gray matter in PMC, DLPFC and FPC; ↓ PMC correlates to ↑RT in a working memory task
Chao et al.[139]	Prospective goserelin	30 patients, 15 with ADT and 15 without ADT. fMRI evaluation while executing a cognitive control task ("Go-Stop" paradigm). N-Back task for working memory	↓ MPFC activity in cognitive control task
Alibhai et al.[141]	Prospective clinical trial	Men with PC and ADT (n=77) with PC and without ADT (n=82) and healthy (n=82); evaluation in baseline, 6, and 12 months	↓ Visuospatial memory, immediate memory, and working memory
Mohile et al.[142]	Prospective	21 subjects aged 71 years (average with beginning of ADT), evaluation in baseline and at 6 months	ADT did not impair cognitive function. Detection of impairment in baseline
Jim et al.[143]	Cases and controls	48 subjects with ADT and 48 healthy controls; patients with 6-month treatments	↓ Ability to execute several cognitive tasks vs controls
Cherrier et al.[144]	Prospective	20 subjects with high prostatic antigen, beginning of ADT vs healthy controls; evaluation in baseline, and at 3 and 6 months.	↓ Working memory, spatial reasoning, and spatial memory at 3 months vs baseline
Shahinian et al.[145]	Retrospective and observational	50613 men with ADT, with 5 years of survival, and healthy men	Occurrence of cognitive alteration (1 dominion) was higher in subjects with ADT (31 % vs controls 23 %). Matching age, comorbidity, and tumor characteristics, cancelled differences

MRI: magnetic resonance imaging; fMRI: functional magnetic resonance imaging; PMC: primary motor cortex; DLPFC: dorsolateral prefrontal cortex; FPC: frontopolar cortex; MPFC: medial prefrontal cortex; RT: reaction time; EBPM: event-based prospective memory; TBPM: time-based prospective memory

perphosphorylation of tau protein, a model that reproduces the most important biochemical abnormalities in AD. Other evidence suggests that androgens regulate the proteolytic cleavage of tau protein[166]; specifically, T blocks calpain activation, thus decreasing the generation of toxic tau fragments. The *in vivo* evidence was generated in a 3xTgAD mice strain, a triple-transgenic mouse model that expresses mutations in the amyloid precursor protein, presenilin-1, and tau. This model revealed that long term treatment with T or 17β-estradiol lowered hyperphosphorylation of tau in the CA1 area of the hippocampus while dihydrotestosterone yielded no changes[167]. The results suggest that the conversion to estrogens is an essential step for T neuroprotection in the expression of pathology in AD that involves a decrease of phospho-tau protein levels. The evidence also suggests that the changes in estrogen levels (mainly in the CNS) may play a role in the etiology of the disease and, possibly, in neuroprotection for cognitive deficits related to normal and pathological aging. However, the relation between changes in androgen levels in the brain, cognition impairment, and phospho-tau levels in healthy elderly subjects and patients with AD, has yet to be established by a single study.

CONCLUSIONS

Studies have proposed that the decrease in T levels might be associated with the progression of AD and that the decline in DHEA, DHEA-S, and T levels may be related to cognitive function and dementia.

The evidence shown in this review suggests a causal role between the decrease in androgen levels and the cognitive impairment related to age. Particularly, maintaining normal concentrations of androgens has been proposed to prevent or reverse age-related decline in memory and cognitive function and delay AD progression. However, the benefits of androgen administration to such ends are still under consideration since a positive effect of some androgens (like DHEA) in memory have been found when using degeneration animal models, but not in animal under normal aging process. Views thereon consider that androgen neuroprotective action might require a process or pathological event to demonstrate its benefits on cognition, which could explain the differences in these results. The neuroprotective effect may also be observed after long-term treatments since the negative results obtained by studies in humans match short periods of treatment, whose justification is the possible increase of androgen adverse effects. In this regard, even though several multicenter studies report the increase of urinary retention in patients under T supplement therapy, other reports suggest there is no significant clinical risk of prostatic adenocarcinoma. Therefore, ongoing randomized clinical assays must report all the adverse occurrences in androgen treatment to know the correct balance between risks and benefits. Another aspect to consider in clinical studies is the small size of samples that yield results with low statistical power.

Comparing the effect of T on animal and human cognition is a difficult task. Animal experiments have been conducted under complete androgen deprivation (neutered males) while studies in humans use elderly subjects with low T levels. Additionally, most of the hormone replacement studies in animals use young or middle-aged subjects. Regardless, these studies allow suggesting that T may play a subtle neuromodulatory role in adulthood and a neuroprotective role in aging when T levels and cognition decline. The neuroprotective role of T might also be reflected in the neuropathological markers present in aging and AD, mainly in NFTs. Even though there is a lack of studies that examine the relationship between androgens and hyperphosphorylation of tau, evidence shows that androgens are protectors of tau pathology present in AD.

Finally, gonadectomy has been proven to reduce the release of acetylcholine (a neurotransmitter that plays a relevant role in memory and cognitive functions) in some brain regions. Therefore, it is suggested to conduct prospective and long-term studies to prove if this relationship affects cognition and whether the combination of hormone therapy and acetylcholinesterase inhibitors improves it. This might raise the possibility of using hormone therapy as an alternative for treating deficits in cognition in elderly subjects and AD patients.

ACKNOWLEDGMENTS

This work was supported by INPRFM, project number 17062.0.

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