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Mini-Review

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Androgen Therapy in Neurodegenerative Diseases

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Abbreviations: Aβ, amyloid-β; AD, Alzheimer disease; ALS, amyotrophic lateral sclerosis; APP, amyloid precursor protein; AR, androgen receptor; BBB, blood-brain barrier; BDNF, brain-derived neurotrophic factor; CAG, cytosine-adenine-guanine; CNS, central nervous system; DHEA, dehydroepiandrosterone; DHEAS, dehydroepiandrosterone sulfate; DHT, dihydrotestosterone; DNA, deoxyribonucleic acid; ER, estrogen receptor; ERK, extracellular signal-regulated kinase; GABA, gamma-aminobutyric acid; GH, growth hormone; HD, Huntington disease; IGF, insulin-like growth factor; MAPK, mitogen-activated protein kinase; mAR, membrane AR; mRNA, messenger ribonucleic acid; MS, multiple sclerosis; NMDA, N-methyl-D-aspartic acid; OPC, oligodendrocyte precursor cell; PD, Parkinson disease; polyQ, polyglutamine; RRMS, relapsing-remitting MS; SBMA, spinal and bulbar muscle atrophy; T, testosterone; VEGF, vascular endothelial growth factor.

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Abstract

Neurodegenerative diseases, including Alzheimer disease (AD), Parkinson disease (PD), multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), and Huntington disease, are characterized by the loss of neurons as well as neuronal function in multiple regions of the central and peripheral nervous systems. Several studies in animal models have shown that androgens have neuroprotective effects in the brain and stimulate axonal regeneration. The presence of neuronal androgen receptors in the peripheral and central nervous system suggests that androgen therapy might be useful in the treatment of neurodegenerative diseases. To illustrate, androgen therapy reduced inflammation, amyloid-β deposition, and cognitive impairment in patients with AD. As well, improvements in remyelination in MS have been reported; by comparison, only variable results are observed in androgen treatment of PD. In ALS, androgen administration stimulated motoneuron recovery from progressive damage and regenerated both axons and dendrites. Only a few clinical studies are available in human individuals despite the safety and low cost of androgen therapy. Clinical evaluations of the effects of androgen therapy on these devastating diseases using large populations of patients are strongly needed.

Key Words: androgens, testosterone, Alzheimer's disease, Parkinson's disease, Multiple sclerosis, neuroregeneration, remyelination

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Neurodegenerative diseases including Alzheimer disease (AD), Parkinson disease (PD), multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), and Huntington disease (HD) are characterized by progressive alterations of neuronal function in the brain and spinal cord. Progression of these diseases causes the loss of cognitive and motor functions and the consequent death of patients. The pathogenesis of neurodegenerative diseases is multifactorial and not completely understood. The most intensively investigated contributing factor is that of epigenetic factors, which showed the potential role of deoxyribonucleic acid (DNA) and histone modifications in the etiology of these disorders [1]. The incidence of neurodegenerative diseases and dementia is high, affecting more than 47.4 million people worldwide in 2015, with projected patient numbers of 75.63 million in 2030 and 135.46 million in 2050 [2]. Although there is a significant gender difference in the incidence of neurological disorders, the specific contributing substrates remain unknown [3]. AD and MS are more prevalent in women [4] when compared with the disproportionate incidence of PD and ALS in men [5]. Circulating levels of androgens and estrogens could have a role in determining gender differences in some neurodegenerative diseases.

It has been calculated that an intervention that reduces risk factors by 10% to 25% could potentially decrease the incidence of AD cases by 184 000 to 492 000 cases in the United States alone and up to 1.1 million to 3.0 million cases worldwide [6]. Emerging clinical evidence shows that androgens are essential not only in maintaining sexual function, mood, and cognition [7] but also in brain efficiency and reducing the incidence of dementia [8]. However, the pleiotypic effects of androgens on brain function are complex and not fully elucidated. This article aims to consider potential preventive and therapeutic effects of androgens on neurodegenerative diseases.

1. Androgens and Brain Function

The classical androgens, testosterone (T), dihydrotestosterone (DHT), and dehydroepiandrosterone (DHEA) act on cells through 2 independent genomic and nongenomic pathways. The classical genomic pathway is activated by androgen receptor (AR) binding to specific DNA response elements in target gene promoters, and subsequent regulation of messenger ribonucleic acid (mRNA) transcription and protein synthesis. The nongenomic pathway can give rise to a response within seconds to minutes, and the mechanism of action is independent of DNA binding because the AR does not need to translocate into the nucleus [9]. The nongenomic effects of androgens are mediated not only by interactions with classical nuclear ARs, but also by putative membrane androgen receptors (mARs). Despite the limited demonstration of the nongenomic effects of androgens, the most evident one is a rapid rise in intracellular calcium [10]. GPRC6A is a pertussis toxin-sensitive G-protein–coupled receptor that allows extracellular T to activate a rapid, nongenomic signal to cells lacking ARs [11]. Among mARs, GPRC6A is a membrane protein involved in physiological responses to hormones and environmental stimuli regulating the effect of androgens in various tissues [12]. However, androgens interact also with other different mARs that are unrelated to nuclear receptors (extensively reviewed by Thomas, [13]). Androgens regulate neuronal growth, differentiation, survival, or death through both genomic and nongenomic signaling pathways [14].

T activates several intracellular signal transduction pathways, including the growth hormone/insulin-like growth factor (GH/IGF)-1 axis [15], the phosphatidylinositol 3-kinase/protein kinase B pathway [16], the Wnt/b-catenin signaling pathway [17], and Notch signaling [18].

In aging men, plasma total T levels decline progressively [19] at an average rate of 110 ng/dL per decade [20]; by comparison, free T levels decrease at a higher rate (2%-3% per year) than total T [20]. The decrease in plasma T levels is correlated with functional alterations in the brain [21] and cognitive dysfunction in aging [22], classical symptoms of androgen deficiency syndrome [23]. Rosario et al [24], during a postmortem neuropathological investigation on patients more than 80 years old, found that decreased levels of brain T were correlated with advancing age; in comparison, no changes in brain 17β-estradiol levels were observed. The brain is greatly influenced by changes in circulating T levels; however, its actions are integrated with those of other essential hormones, such as 17β-estradiol, progesterone, and IGF-1 [15]. T protects neurons from different types of insults, increasing the level of neuroglobin [25] secreted by astrocytes and microglia in critical conditions, that is, after injury [26], glucose deprivation [27], and kainic acid toxicity [28]. T also stimulates neuronal differentiation, thereby maintaining neuronal plasticity [29], promoting synaptic density [30], increasing connectivity of hypothalamic neurons [31], as well as stimulating neurite outgrowth [32]. It reduces the reactivity of astrocytes following brain injury, gliosis reactivity [33], and retards the aging process [34]. T improves the survival of human neurons and astrocytes, acting directly on the mitochondrial membrane, inhibiting the generation of reactive oxygen [35, 36] and nitrogen species [27], as well as sirtuin-1 expression [37]. Conversely, the absence of T may contribute to the neurodegenerative process [38] as observed in animal models of PD [39] and AD [40] and may decrease the density of spinal

synapses in the hippocampus [30]. These pathological effects were reversed following treatment with T or DHT; 17β-estradiol, likely, partially mediates these effects.

In light of these observations, it is not surprising that the protective effect of T is dose dependent. Dosages of T that induced physiological plasma concentrations (10 nM) exerted significant neuroprotective influences; by contrast, dosages 10-fold greater were ineffective [41]. This neuroprotective effect is due to T inhibition of caspase-3, an effector of the apoptotic cascade [27]. T also exerted a neuroprotective effect in experimental autoimmune encephalomyelitis, a disease model used to study the inflammatory process in MS [42]. The disease was correlated with altered immunoregulation [43] including activation of $CD8^+$ T cells [44], and $CD4^+$ T lymphocytes [45].

In order to exert its effects on the brain, plasma T must cross the blood-brain barrier (BBB). It is generally believed that steroid hormones freely diffuse from plasma into the brain by passing through the BBB [46]. However, this concept has been challenged recently by the demonstration that in *Drosophila*, a membrane transporter expressed on the surface of glial cells, the Ecdysone Importer, is necessary to allow steroid hormones to cross the BBB and permit T entry into the brain [47]. The Ecdysone Importer belongs to the family of organic anion transporting polypeptides that could have potential functions in transmembrane transport of mammalian steroid hormones [48]. Another transporter, the MDR1-type P-gp is involved in transporting these hormones out of the brain, providing a kinetic barrier. The intracerebral concentrations of sex hormones are at least in part regulated by the activity of MDR1-type P-gp [49].

2. The Neuroactive Steroids

A group of steroids, including T, deoxycorticosterone, progesterone, the bound sulfate form of DHEA, (DHEAS), and their metabolites, are also called neurosteroids because they can regulate neuronal excitability and function [50]. Neurosteroids are synthesized within the brain or derived from peripheral precursors. They act on neurons by a rapid nongenomic pathway, primarily interacting with a diversity of receptors, including glutamate and gamma-aminobutyric acid (GABA)-A receptors [51], N-methyl-D-aspartic acid (NMDA), and 5-hydroxytryptamine type 3 receptors [52, 53]. The various types of neurotransmitter receptors in the brain are responsible for different clinical effects such as potent anxiolytic [54], antidepressant [55, 56], and antiepileptic activities [57]. Furthermore, neurosteroids modulate learning and memory processes in the young and elderly [58] and are also involved in the pathophysiology of schizophrenia [59].

The principal neurosteroids are progesterone and deoxycorticosterone, which are precursors for the endogenous allopregnanolone (5α-pregnane-3α-ol-20-one) and THDOC (5α-pregnane-3α, 21-diol-20-one), respectively [58], and both hormones stimulate GABA-A receptors. Neurosteroids modulating GABA-A activity present significant anxiolytic, antidepressant [55], and antiepileptic effects [60].

T acts indirectly after its aromatization to 17β-estradiol and to DHT as a consequence of 5α-reductase activity. DHT can be metabolized by 3alpha-hydroxysteroid oxide reductase and 3beta-hydroxysteroid oxide reductase, to 5α-androstan-3α,17β-diol (3α-Diol) and 5α-androstane-3β,17β-diol (3β-Diol), respectively [61]. Both steroids, 3α-Diol and 3β-Diol, have little activity on the AR, while 3β-Diol exerts a moderate activation of estrogen receptor (ER)β [62]. 3α-Diol exerts a positive allosteric action on GABA-A receptors [63], while 17β-estradiol stimulates mitochondrial activity and neuroprotection [64] (Fig. 1).

DHEA and DHEAS are both partially converted to either T, DHT, or estradiol. DHEA has a neuroprotective effect on the brain [65] and is involved in the regulation of depression and seizures [66] through the activation of GABA-A [67] and NMDA receptors [53] (Fig. 1). The activation of NMDA receptors stimulates brain development, working memory [68, 69], and learning performance and regulates psychoses [70]. The modulation of NMDA receptors in the prefrontal cortex plays a fundamental part of the neurobiology of cognition and is positively correlated with sex hormone levels [71].

Although DHEAS levels showed a positive correlation with cognitive function, randomized clinical trials did not provide clear evidence for the usefulness of DHEA treatment in improving cognitive function in elderly participants with dementia [72, 73]. Neurosteroids are likely to be more effective in prophylactic roles, and endogenous hormones are more effective than exogenous.

3. ARs and Neurodegenerative Diseases

An early study demonstrated the expression of ARs and ERs in the brain [74], and a detailed distribution map of ARs [75] and ERs [76] was generated. Simerly et al [77] found widespread AR and ER mRNA in neurons of the rat brain. ARs are mostly expressed in the hypothalamus [78], telencephalon, and amygdala and also in the majority of the brainstem and spinal cord areas associated with sensory functions [77], as well as in Purkinje cells of the cerebellar cortex. At the cellular level, ARs were found on axons and dendrites, suggesting that androgens may have an essential and novel extranuclear role in neuronal function [79]. ARs are distributed in

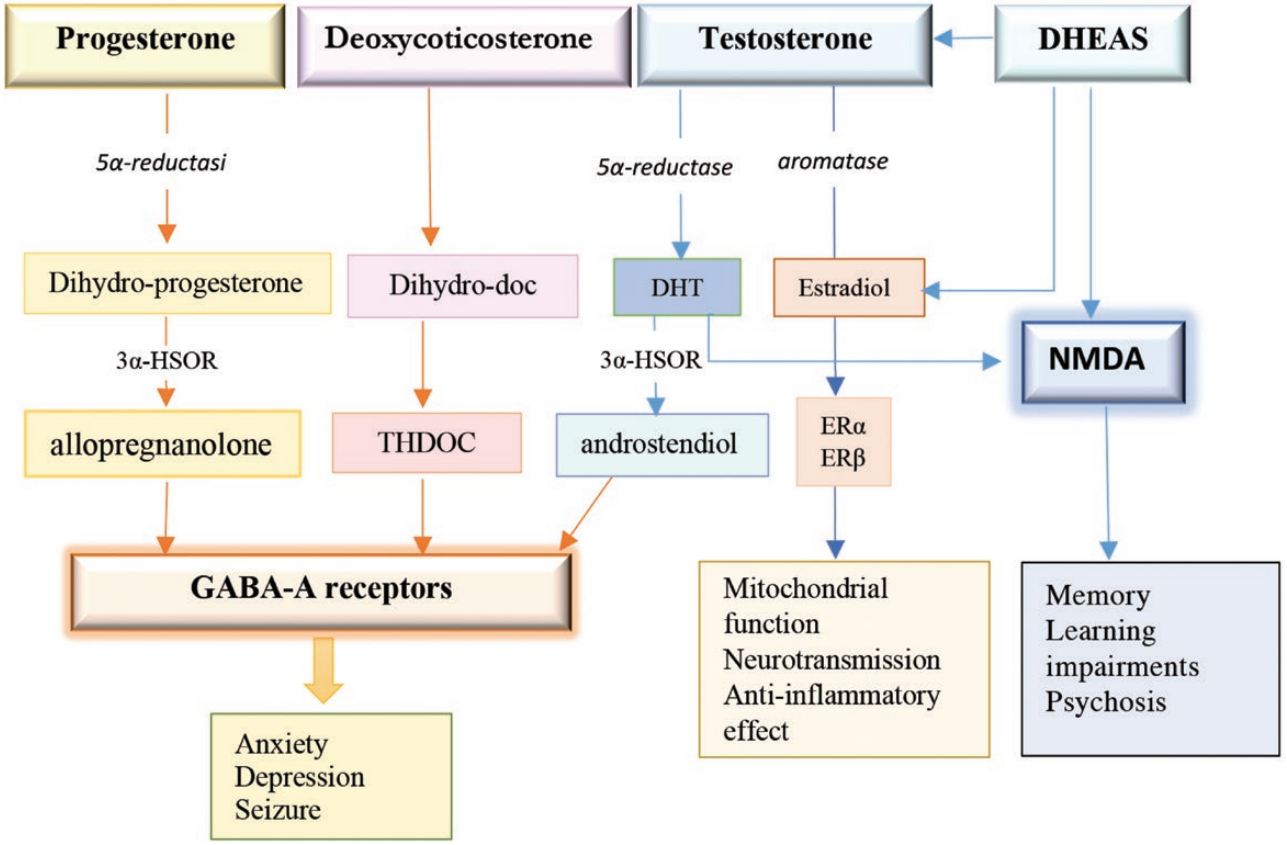

Figure 1. Neurosteroids: biosynthesis in the human brain and their function. Progesterone, testosterone, and deoxycorticosterone are converted by 5α-reductase into 5-dihydro-reduced steroids, which are then reduced further to 3α-hydroxylated neurosteroids by 3-HSOR in allopregnenolone, THDOC, and androstendiol. All these metabolites activate GABA-A receptors that regulate anxiety, depression, and seizure.Testosterone is converted by aromatase into 17β-estradiol that activates ERα and ERβ improving mitochondrial function, anti-inflammatory effect, and neurotransmission. DHEAS and testosterone activate NMDA and can converted in testosterone and estradiol. NMDA activation is involved in memory, learning impairments, and psychosis. DHEAS, dehydroepiandrosterone sulfate; DHT, dihydrotestosterone; ER, estrogen receptor; GABA, gamma-aminobutyric acid; HSOR, 3alpha-hydroxysteroid oxide reductase; NMDA, N-methyl-D-aspartate;THDOC, 5α-pregnane-3α, 21-diol-20-one.

many brain areas, especially in those regions involved in learning and memory such as the hippocampus and amygdala [78].

The loss of AR function could contribute to motor neuron degeneration [80, 81]. During spinal cord motor neuron growth in vitro, ARs facilitated the growth of cell bodies and elongation of neurites [32, 82]. An AR signal plays an essential role in the development and trophism of motor neurons as well as in the maintenance of their morphology and survival [83]. Motor neuron vulnerability increases when AR expression is reduced [84] (Fig. 2).

The activation of ARs exerts direct trophic effects on motor neurons of the spinal cord anterior horn as manifested in larger cell bodies, broader dendritic processes, extended life spans [82, 85], and increased synaptic densities in the cervical ganglion [86]. Effects of T on the hippocampus in maintaining spine synaptic density is direct and not mediated by 17β-estradiol [29]. AR signaling has a neuroprotective effect in neuroblastoma cells [87], as shown in vitro by the administration of T, which stimulated the secretion of the non-amyloidogenic amyloid-β (Aβ) precursor protein and decreased the secretion of Aβ peptides from neuronal cells and rat primary cerebrocortical neurons [88, 89].

AR signaling is associated with various trophic factors acting on motor neuron biology. AR activation increases the expression of vascular endothelial growth factor (VEGF), brain-derived neurotrophic factor (BDNF), and neurogenesis in the brain [90] and promotes IGF-1 secretion in various tissues [91]. Androgens stimulate BDNF expression, which activates brain neurogenesis [92], dendritic spine maturation [93], and motor neuron morphology [94]. On the other hand, BDNF has an autocrine effect, stimulating steroidogenesis in Leydig cells [95]. Neuronal health and survival are associated with the number of ARs in the motor neuron. Nguyen et al [96] demonstrated an AR-dependent androgen activation of mitogen-activated protein kinase/extracellular signal-regulated

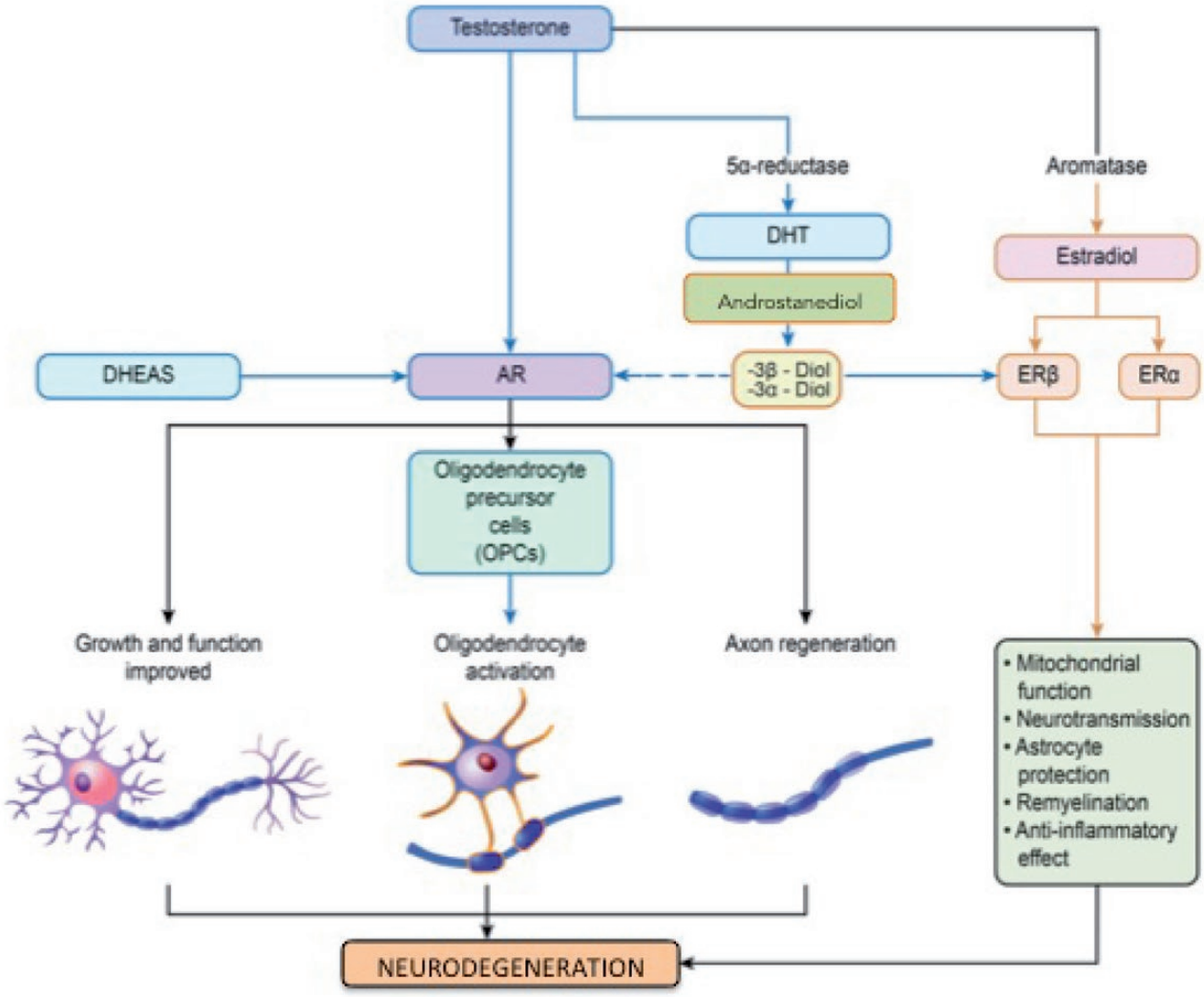

Figure 2. Effect of androgens on neuron and myelin regeneration. Androgens (testosterone, DHT, and DHEAS) activate ARs, which are located on the membrane of neurons and mitochondria. The activation of ARs promotes the trophism and growth of neurons and the formation of new myelin following the OPCs activation and axonal regeneration. Testosterone, after its aromatization in 17β-estradiol, activates the ERα and Erβ, improving mitochondrial function, anti-inflammatory and neurotransmission effects and protecting astrocytes. Testosterone is converted in DHT by 5α-reductase and then in androstendiol for which the metabolites 3α and 3β-diol then have a weak effect on ARs but are more active on ERβ. AR, androgen receptor; DHEAS, dehydroepiandrosterone sulfate; DHT, dihydrotestosterone; ER, estrogen receptor; OPC, oligodendrocyte precursor cell.

kinase (MAPK/ERK) signaling that activates a specific neuroprotective pathway in neurons.

Alterations in AR function may produce various pathologies as observed in spinal and bulbar muscle atrophy (SBMA), a degenerative disease of lower motor neurons with consequent atrophy of muscle limbs [97]. SBMA is comparable with ALS but differs in that only lower motor neurons are affected in ALS, whereas both upper and lower motor neurons degenerate in SBMA. SBMA is characterized by the expansion of a polymorphic trinucleotide (cytosine-adenine-guanine, CAG) that encodes a polyglutamine (polyQ) tract in the AR gene altering the normal protein function [98]. The expansion of the polyQ tract to a length of 36 to 40 glutamines favors modifications in folding and structure of the amino terminal domain of the receptor that is responsible of AR aggregation and has been reported in 9 neurodegenerative disorders, including HD and other types of spinocerebellar ataxia [99]. Changes involving interaction amino-N-terminal FXXLF motif and carboxyl-C- terminal AF-2 domain interaction are a determinant of the mutant AR aggregation and toxicity [100]. An AR mutation is also a determinant in SBMA pathogenesis; however, although patients present clinical signs of androgen insensitivity (eg, gynecomastia and infertility), loss of AR function is not the primary mechanism of the disease [101]. Neuronal loss is due to binding of the polyQ-AR to T or DHT, which induces toxicity, while T reduction prevents the phenotypic expression of SBMA [102, 103]. Although the reduction of T levels by leuprorelin showed

a significant reduction in polyQ-AR, no beneficial effects on the swallowing reflex in patients with SBMA were observed [104]. In patients with SBMA, the endocrine alterations of the polyQ expansion contributes only partially to the pathogenesis of the disease by increasing misfolded protein toxicity and the loss of normal protein function [80].

Interdomain interactions of AR transcription factors involve a variety of nuclear receptors [100]. In SBMA animal models, a downregulation of genes that regulate the expression of VEGF, IGF-1, glial cell line-derived neurotrophic factor [105], and transforming growth factor-beta type II receptor [106] has been reported. Importantly, IGF-1 mediates the inactivation of mutant AR, reducing muscle and spinal cord pathology in SBMA. The activation of IGF-1/Akt signaling reduced histopathological abnormalities and extended life span in SBMA mice [107]. These data suggest that therapy to improve skeletal muscle tropism is a helpful strategy in SBMA intervention. However, the pathogenesis that leads to AR toxicity remains unknown [101]. An enhanced understanding of AR signaling in neurons may provide the conceptual basis for therapeutic strategies to mitigate, or perhaps inhibit, the progress of neurodegenerative diseases [84].

4. Androgens and Neurodegenerative Diseases

A. Alzheimer Disease

Alzheimer disease (AD) is responsible for about 70% of the global incidence of dementia, which involves 24 million people and has been predicted to increase 4-fold by the year 2050 [108]. The etiology of AD is complex but is allegedly the consequence of an interaction between genetic and environmental factors. Aging is the preponderant factor: the incidence of AD at 80 years of age is 4-fold greater than that at age 70 years and 9-fold greater than that at age 65 years [109, 110]. The influence of genetic [108, 111] nutritional [112, 113], and hormonal components; low serum T levels in men [112]; and low 17β-estradiol in females [114] are involved. Furthermore, high serum levels of free T in males and females have a protective effect against AD incidence and its progression [115].

The neuropathology of AD is characterized by the formation of extracellular amyloid plaques in the brain, and the accumulation of cellular neurofibrillary tangles [108]. In neuron cell cultures with genetic induction of AD, T administration significantly reduced Aβ neurotoxicity [116], and the anti-Aβ effect was potentiated in association with high estrogen levels [89]. Aβ is derived from amyloid precursor protein (APP), which is a glycoprotein found ubiquitously in the cells. APP may be metabolized in 2 metabolic pathways: the amyloidogenic and non-amyloidogenic [117]. The amyloidogenic pathway produces Aβ by the activity of the secretases β and γ. The β-secretase, also called BACE1, is a type-1 membrane protein essential for the generation of Aβ and AD. In BACE1 knockout mice, neither the production of Aβ nor development of AD was observed [118]. Therefore, inhibition of BACE1 represents an exciting area of research for the treatment of AD [119]. Recently, it has been suggested that BACE1 levels in plasma may serve a useful biomarker of latent AD [120]. Aβ deposition originates from APP [121, 122] after a proteolytic catalyzation by β- and γ-secretase [123] as observed in the brain cortex of patients with AD [124]. In the non-amyloidogenic pathway, APP is cleaved by secretase-α and removed from the brain [125]. Physiologic androgen levels decrease the incidence of AD related to Aβ by a classic genomic pathway activating AR and neprilysin gene expression, as well as by a nongenomic activation of MAPK/ERK that can represent a therapeutic strategy against AD and other age-related neurodegenerative diseases [126]. Low serum T levels in men have been associated with increased Aβ deposition in brain tissue, favoring the progression of AD [8, 114, 127-130], while high T levels reduced the onset and development of AD [131]. T administration increased the amount of APP secretion of the non-amyloidogenic pathway; this effect is due to the 17β-estradiol derived from T aromatization [132]. 17β-estradiol plays a significant role in reducing amyloid formation in the brain by downregulating BACE1 mRNA [133] and consequent levels of the APP mRNA isoform [134] by activation of the MAPK signaling pathway, independently of the ER [135]. It is conceivable that T could interfere in APP metabolism through an estrogen-dependent pathway. Non-aromatizable androgens, such as DHT, did not show any effect on α-APP levels but reduced Aβ deposition in the brain [136]. However, T has a direct beneficial effect by increasing Aβ degradation and downregulating BACE1 expression; these activities are independent of T conversion into estradiol [137] and are consistent with the effects of DHT (a non-aromatizable androgen). The deposition of Aβ seems to be synergistically regulated by the activation of both ARs and ERs [138].

DHEAS also presents neuroprotective effects in a variety of experimental models by antagonizing NMDA-induced excitotoxicity [139], Aβ peptide toxicity [140], and oxygen-glucose deprivation [141].

Although there is evidence for positive effects of T in the treatment of AD in experimental models, clinical studies conducted on aging male patients with AD present conflicting results. To illustrate, T administration improved cognition [142], and visual-spatial skills [143] in some cases, whereas other studies showed no positive effects

on memory or mental impairment [144-147]. In a recent meta-analysis, Buskbjerg et al [147] showed that T therapy in men with normal plasma T levels had no significant clinical effect on cognitive function; T effects on men with hypogonadism remain to be evaluated.

These contradictory findings may be a consequence of different methodologies of investigation; to illustrate, some studies administered T via a subcutaneous gel (5 mg/day) [146, 148] whereas other studies administered T by intramuscular injection (100/200 mg weekly or biweekly). Furthermore, if androgens are considered primary regulators in the maintenance of cognition, other important hormones are implicated as well, including insulin and IGF-1 [149]. High serum cortisol levels favor a low sex steroid production and may play a critical indirect action in the pathogenesis of AD [150].

Moreover, in patients with AD, high plasma levels of luteinizing hormone had functional consequences on vulnerable neurons, and in women with AD not taking estrogens, these levels might be involved in the pathogenesis of Aβ plaque formations [151]. Another essential aspect may be related to the stage of the disease at which therapy starts. If the neuroanatomical condition of neurons is severely compromised, the probability of reversing disease progression is inconsistent. Nonetheless, the potential utility of androgen and estrogen therapy for AD is significant, although the mechanisms are not clearly understood [152].

B. Parkinson Disease

Parkinson disease (PD) is the second most common neurodegenerative disease after AD and is mainly characterized by a progressive and selective depletion of dopamine neurons in the substantia nigra [153]. The selective degeneration of the dopamine neurons in the pars compacta of the substantia nigra and the progressive buildup of intracellular alpha-synuclein protein deposits and Lewy bodies [154-156] are recognized as the crucial features of the pathology [157]. The classical motor signs including rest tremors, bradykinesia, rigidity, and postural instability are accompanied by a variety of nonmotor symptoms such as cognitive decline and neuropsychiatric deficits, sleep, autonomic and sensory problems that deeply affect the quality of life [157, 158]. Only in few familial events PD is accounted for by sporadic genetic mutations [159]; however, in most cases, the underlying causes are currently unknown, and a combination of genetic, epigenetic, and environmental risk factors have been proposed as triggers of PD onset [160]. Over the past years, considerable data have come to light concerning the susceptibility to the disease development, the age at onset, and the phenotype of the symptoms that support the existence of a sex difference. Indeed, PD affects males and females differently [161, 162]. Numerous reports have proposed a lower incidence and more benign phenotype in women, which appear to be mediated by neuroprotective effects of estrogens and genetic factors [161-164].

In PD, neuropathology is characterized by the reduction of dopaminergic, cholinergic, and other nondopaminergic neurotransmitters, with consequent neuron atrophy in the hippocampus and brain cortex [165]. In patients with PD, dementia is particularly prevalent with advancing age and is responsible for higher morbidity and mortality. The pathogenesis of PD is not clearly explained, but recently, the role of insulin resistance has been proposed [166, 167], suggesting a correlation between the alteration of glucose metabolism and neurodegeneration. The mechanisms of steroid hormone actions are complex and multifaceted.

PD is substantially an idiopathic, multifactorial disease caused by the interplay between genetic and environmental factors. Genetic studies have identified increasing numbers of risk polymorphisms. Heinzel et al recently highlighted the sex-related differences in prodromal PD. They concluded that women and men show distinctive prodromal markers of PD (subthreshold parkinsonism, constipation, olfactory loss, depression, probable rapid eye movement sleep behavior disorder, nonsmoking, abstinence from caffeine, nigral hyperechogenicity), suggesting that these differences should be taken into account in order to guarantee the diagnostic accuracy of PD [168]. Sex hormones (estrogens, androgens) can influence oxidative stress generation, and it is known that estrogens are protective against oxidative stress insults [169]. While the neuroprotective role of estrogens has been studied in many models, potential roles of progesterone have received less attention. This steroid exerts functions in the brain other than reproduction, including neuroprotection, enhanced cognitive function, and stimulation of neurogenesis [170].

In male patients with PD, lower plasma T levels were observed compared with age-matched control individuals [171]. Sex hormones are active in the basal ganglia and dopaminergic neurons and may be involved with different mechanisms in the pathogenesis of PD [172]. In a case report study, it was found that T therapy improved motor symptoms, handwriting, and general well-being [173]. For these reasons, some studies have focused on the therapeutic potential of T and its metabolite DHT, which have been shown, in preclinical settings, to improve cognitive performance [174].

T replacement therapy significantly improved motor and nonmotor symptoms [173, 175]. The impact of androgen deficits in increasing PD risk onset or exacerbating the incidence and/or severity of nonmotor and extrapyramidal symptoms was also observed in men affected by

prostate cancer and subjected to androgen deprivation therapy [176, 177]. In these patients, the withdrawal of anticancer therapy reversed the cognitive and motor deficits [178]. However, the androgen protective role in neurodegenerative conditions is still a matter of debate as other studies did not detect a clear association between androgen deprivation therapy and PD [179].

Although the etiology of PD remains elusive, oxidative stress has been linked to PD development and progression [180]. Diminished neurotransmitter level, oxidative stress, mitochondrial dysfunction, and perturbed protein homeostasis over time worsen the disease manifestations in elderly people.

At the moment, no pharmacological breakthrough has been made to protect dopaminergic neurons and associated motor circuitry components, and current management strategies aim to provide symptomatic relief and to retard disease progression.

C. Multiple Sclerosis

Multiple sclerosis (MS) is an autoimmune inflammatory disease of the CNS that causes neuronal demyelination with subsequent loss of axonal function and paralysis. MS manifests itself with varied symptoms ranging from loss of vision, to neuromuscular disorders. Sex hormones influence the incidence and progression of MS, and for relapsing-remitting multiple sclerosis (RRMS), a clear predominance of women (ratio 3:1 women to men) has been reported [181].

The neurologic decline in patients with MS is associated with an irreversible degeneration of axons and neurons that have lost their capacity for remyelination [182]. There are 2 clinical variants of MS: the RRMS in 85% of cases and the primary progressive MS [183]. MS starts as a severe immune disease mediated by the $CD4^+$ T-helper 1 cell. However, other cells, such as $CD8^+$ T cells, B cells, macrophages, dendritic cells, astrocytes, and oligodendrocytes [184], are all variously involved in the progression of the disease. The pathogenesis of MS is manifold, and genetic susceptibility cannot in itself explain this autoimmune disease [185]. Although significant advances in immunotherapy have been made, the actual therapy for MS shows few benefits to remediating the pathology [186], and many needs remain unresolved [187].

The brain has the endogenous capability to repair myelin damage, a process depending at least in part on AR activation [188]. In animal models of MS, it has been demonstrated that T exerts a strong stimulation on remyelination (even in cases where spontaneous remyelination would not have been possible [189] with a protective role against the progression of the disease [190]. Furthermore, there is evidence for androgen protective effects in experimental autoimmune encephalomyelitis [190, 191], with immunomodulatory actions mediated by ARs on $CD4^+$ T lymphocytes [42, 45, 192].

Without functional AR, T fails to stimulate remyelination and recruitment of new oligodendrocytes in the chronically demyelinated corpus callosum [193]. Low plasma androgen levels (T, DHEA, or DHEAS) were found both in men and women affected by MS [194-196]. In men with MS at different ages, low plasma levels of T were found in about 40% of patients and correlated with the worst progression of the disease [197]. Also, low T levels in women with MS were associated with tissue damage revealed by magnetic resonance imaging and accompanied by clinical disability [196]. The demyelination process is also a consequence of aging, but myelin regeneration can be restored by neurosteroids [198]. Only a few studies on the effect of androgen therapy in neurodegenerative diseases in humans have been conducted. T therapy for 12 months in patients with MS increased gray matter volume [199], improved cognitive performance [200], and increased the production of BDNF and platelet-derived growth factor BB [201].

Even though some positive effects of T on myelin regeneration have been demonstrated, only a few clinical studies have investigated the impact of androgen therapy in patients with MS, and no definitive conclusions can be drawn from these data.

Myelin regeneration represents the primary therapeutic goal in demyelinating diseases [202]. Although the remyelination process exists naturally in the brain, it is often inadequate in conditions such as MS [202]. The remyelination process is mediated by the oligodendrocyte precursor cells (OPCs), which are widely distributed throughout the adult CNS. Myelin regeneration depends on the efficiency of oligodendrocytes and OPC differentiation [202, 203] that remyelinate the axon. Oligodendrocytes are responsible for the maintenance of healthy axons [204] and neuron survival [205]. In MS, demyelination plays a primary role, but in recent years, it has become increasingly apparent that in the pathology there is also substantial axonal and neuronal loss [202] (Fig. 2). Findings in postmortem brains of patients with MS showed that oligodendrocyte activity never stops, even during the illness, and the presence of new active oligodendrocytes and OPCs in the cortex, compared with controls, was found to be more evident in gray matter than white matter in patients with primary progressive than in those with RRMS [206, 207]. In the early stage of MS, neurons can repair myelin loss, but with the progression of the disease, this ability decreases. Sicotte et al [200] showed that in male patients with RRMS presenting chronically demyelinated brain lesions, T therapy induced a significant improvement in cognitive

performance and reduced brain atrophy. Kurth et al [199], in a pilot clinical trial in 10 men with RRMS, demonstrated a neurotrophic effect of T on cerebral gray matter and reduced brain atrophy associated with increased gray matter in the right frontal cortex. These data are of significant importance because cortical lesions and brain atrophy are correlated with mental disorders in RRMS [208]. Both aromatizable and non-aromatizable androgens [209], such as 7-methyl-19-nortestosterone [209] and oxandrolone, effectively stimulated myelin repair [210].

Estrogens contribute substantially to the remyelination process [211], leading to axon repair [212]. The mechanism of neuroprotection is sustained by the activation of ERα and ERβ, which are also implicated in significantly decreasing inflammation in the CNS [213]. Estriol showed a protective action as an immunomodulator in patients with MS [214] and pregnant patients with MS. Estrogen and androgen therapy should be further investigated in future clinical trials as possible adjunctive therapy in MS, given the encouraging results that have been provided [38]. In conclusion, in patients with MS, AR and ER activation may represent important therapeutic strategies for myelin recovery and a viable strategy in future clinical trials.

D. Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS) is characterized by the degeneration of the motor neurons of the corticospinal tract, brainstem, and spinal cord causing progressive muscle atrophy and paralysis [215]. Death results from progressive respiratory failure; the average survival time is 2 to 4 years, and only 10% to 20% of patients survive longer than 10 years [216]. ALS has an incidence of approximately 3.9 to 8 per 100 000 individuals in the United States, and an increase of 69% is expected mainly in developing nations [217]. ALS is a multifactorial interacting disease, but a genetic cause has been identified in approximately 30% of familial ALS cases [218]. Genes and environmental factors may interact in the genesis of ALS [219], but also a viral etiology is gaining increasing credence [220]. Family history, age, and sex are the main risk factors, with a male to female ratio of 1:3 [221]. In the pathogenesis of ALS, the toxicity of mutant SOD1 may be involved in reducing the nuclear protection from the active enzymes [222]. In ALS, motor neurons have metabolic alterations in the mitochondria with a change in lipid oxidation, leading to increased glycolysis, which suggests that metabolic intervention may represent a viable therapeutic strategy [223]. There is increasing interest in the impact of nutrition on the pathogenesis and development of ALS [224, 225]. Lower body mass index is correlated with an increased risk of ALS [226], whereas patients who are overweight and obese have a more prolonged survival [227]. Weight loss in patients with ALS has an adverse prognostic index that may be evident even when patients eat regularly [228]. In ALS, the most suspected risk factors are sports activity, exposure to chemicals, smoking, and nutrition [229, 230]. In patients with ALS, the anabolic condition is reduced and is associated with a low level of free T [231]. Spinal motor neurons degenerate when the production of muscle trophic factors is decreased [232-234]. Alterations in muscle tissue can contribute to increasing axonal vulnerability as trophic muscle factors such as IGF-1 [235] and androgen levels are supportive of muscle maintenance [236]. Interestingly, interactions between androgens and IGF-1 have been described in animal models and in humans [237]. Elevated levels of IGF-1 delay disease progression [238], extend survival time, and decrease disease progression in the ALS mouse model [239]. Muscle atrophy and strength loss are responsible for physical disability in ALS, and androgen therapy should be considered for the treatment of ALS with the aim to stimulate motor neuron recovery from regressive damage and restore normal neuromuscular function [240, 241]. In a murine model of familial ALS, the administration of nandrolone improved the structural preservation of mitochondria in the neuromuscular junction and modestly increased the innervation of diaphragm muscle fibers [242]. However, Galbiati et al [243], in a mouse model of ALS expressing mutant human SOD1, found that nandrolone altered the muscle gene expression and exacerbated the alterations induced by SOD1. Nandrolone administration induced muscle fiber hypertrophy but caused motor neuron death. The activation of endogenous AR protein aggregation revealed the involvement of AR dysfunction in the pathogenesis of ALS [244]. However, in this study, the dose of nandrolone administered was extremely high (10 mg/kg body weight/week), and there was no comparison with the effects of physiologic doses (1 mg/kg body weight/week). Consequently, it is difficult to discern if, in this study, motor neuron death was an artifact of the excessive pharmacologic dose of nandrolone.

The effect of androgens on motor neuron regeneration results from interactions with other hormones. AR has the ability to "crosstalk" with other growth factors, such as IGF-1, as observed in prostate cancer [245]. Therefore, both the evaluation of plasma androgens and IGF-1 levels should be taken into account. In patients with ALS, an appropriate anabolic program including nutrition, exercise, and hormonal therapy may provide positive results [232].

E. Huntington Disease

Huntington disease (HD) is a dominant inherited neurodegenerative disease with a brain pathology

located in the basal ganglia with hypothalamic involvement [246]. The neuropathology of HD arises from the expansion of a polymorphic trinucleotide repeat (CAG) in the huntingtin gene [247]. HD is characterized by severe motor dysfunction, chorea, psychosis, and dementia, which have an insidious progression, with a fatal outcome in about 15 to 20 years following onset [248]. Furthermore, it was found that the dysfunction and death of neocortical and basal ganglia neurons responsible for severe motor symptoms, psychosis, and dementia [249] worsened with disease progression and were manifested by progressive cognitive impairment [250]. Various clinical studies have shown that in patients with HD [251-254], symptoms were associated with a progressive alteration of the hypothalamic-pituitary-gonadal axis and changes in neuroendocrine systems [255]. Hypothalamic neurons are reduced in number accompanied by a reduction in gonadotropin-releasing hormone production [256]. Saleh et al [254], evaluated the 5 hypothalamic-pituitary axes in 219 patients with genetically documented HD and found that GH, IGF-1, and cortisol levels were significantly higher than in controls. In contrast, thyroid-stimulating hormone, free triiodothyronine, and T were lower compared with healthy individuals. Endocrine alterations were correlated with the severity of the disease. Markianos et al [250] demonstrated that in male patients with HD, hypothalamic dysfunction caused hypogonadism and low T levels. Interestingly, it was demonstrated that patients with HD had a specific testicular pathology with reduced numbers of germ cells and abnormal seminiferous tubule morphology [257]. This testicular atrophy, characterized by low plasma T levels and reduced spermatogenesis, is negatively correlated with the CAG expansion tract, a direct toxic effect of mutant AR [257]. In R6/HD mice, T administration rescued AR density and functionality in the dentate gyrus [249] and in testes improved testicular function and spermatogenesis [258]. Considering that in patients with HD, therapies are symptomatic and limited to antidopaminergic neuroleptics and antidepressant drugs to regulate motor dysfunctions and mood disorders [259, 260], androgen therapy may represent a valuable tool not yet explored. At this time, there is no documented evidence arising from human clinical trials of T treatment of patients with HD. In light of the emerging evidence of neuroendocrine compromise in males affected with HD, the potential benefits associated with T replacement therapy suggest a novel and promising therapeutic paradigm [249]. Recently, the effects of gene therapy for HD has been evaluated in vitro using primary fibroblasts from patients with HD; it consisted of excision of the excessive CAG repeat tract in the huntingtin gene and its repair using the CRISPR-Cas9n method with insertion of a correct DNA sequence [261]. If this gene therapy is successful, it will open the horizon for new therapeutic approaches to HD in humans.

Conclusions

In animal models and in humans, the potent neuroprotective and trophic effects exerted by androgens have been demonstrated. Low serum T levels represent a predisposing risk factor involved in various neurodegenerative diseases. Androgens could play an essential role in the prevention and treatment of neurodegenerative diseases because of their anti-inflammatory effects, which include the inhibition of proinflammatory cytokines production [262], protection from oxidative stress (thereby increasing Cu-Zn SOD activity in adipocytes [263], and modulation of Aβ formation). However, clinical studies conducted in patients with AD have provided conflicting results.

Better prospective long-term studies are necessary to assess the correlation between androgen deprivation and dementia; confounding factors, such as chronic pain or other treatments such as chemotherapy, may interfere with the selection of appropriate candidates.

In preclinical models of the neurodegenerative diseases considered above, androgens have been shown to exert an essential role in remyelination and axon regeneration; consequently, future clinical studies should better investigate androgen therapy as a promising avenue of treatment for demyelinating diseases and the aging process, both in male and female patients [198]. In women, androgen therapy at low doses is well tolerated and appears to be safe in the short term [264], but long-term treatment should be carefully monitored [265, 266]. Considering the limited number of clinical trials published, no definitive conclusion can be drawn on the effect of androgens on neurodegenerative diseases. Accordingly, new clinical trials will require (a) large numbers of patients, (b) prolonged therapeutic durations, (c) appropriate and comprehensive brain imaging, coupled with (d) accurate and cumulative assessment of cognitive function.

Additional Information

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