Chapter 1

Cellular and Molecular Mechanisms of the Effects of Sex Hormones on the Nervous System

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Additional information is available at the end of the chapter

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Abstract

The mechanisms of the action of sex steroid hormones on the nervous system are related to both classical, intracellularly mediated effects and non-classical membrane effects due to binding to membrane receptors. Some steroids are capable of inducing rapid neurotransmitter-like effects, similar to those of dopamine or glutamate that alter the activity of neuronal systems via different types of receptors. The neuroactive steroids are endogenous neuromodulators synthesized in the brain and rapidly affecting neuronal excitability. Sex steroids exert many pleiotropic effects in the nervous system: they modulate main neurotransmitter systems, promote the viability of neurons, play an important role in myelination, and influence cognitive processes. Estradiol protects neurons from excitotoxic damage and increases neuronal survival. Progesterone stimulates neurological and functional recovery. Androgens also exhibit a wide array of neuroprotective effects in motoneurons, including supporting cell survival, axonal regeneration, and dendritic maintenance. Despite the considerable increase of sex hormones and neurosteroids research in recent years and the ongoing discovery of biochemical mechanisms of action, their role in neurodegenerative processes remains not well determined.

Keywords: sex hormones, neurosteroids, genomic effects, non-genomic effects, neuroprotection, neurodegenerative diseases

1. Introduction

Sex hormones are synthesized from cholesterol mainly in the gonads and adrenal cortex. In the brain, different sex steroids can also be further metabolized to different neurosteroids or be produced anew in neurons and glial cells, with an even more potent effect on the nervous system. The mechanisms of action of the sex steroid hormones on the brain are related to both classical, intracellularly mediated effects and non-classical (non-genomic) membrane effects

due to their binding to membrane receptors. Some steroids are capable of inducing rapid neurotransmitter-like effects. Sex steroids exert diverse pleiotropic effects on the nervous system: they modulate major neurotransmitter systems, promote the viability of neurons, play an important role in myelination, and influence cognitive processes. Estradiol increases neuronal survival and recovery. It protects neurons from excitotoxic damage, amyloid β (Aβ) toxicity, oxidative stress, and glucose deprivation. The defense induced by estrogens is mediated by complex mechanisms. Progestins have also been found to exert neuroprotective effects similar to those of estrogens. Androgens exhibit a wide range of neuroprotective effects in motoneurons, including supporting cell survival, axonal regeneration, and dendritic maintenance. The relationship between sex steroids and the brain-derived neurotrophic factor (BDNF) has garnered a growing interest due to the role BDNF plays in the pathogenesis of neurodegenerative diseases.

2. Steroidogenesis

Sex hormones are steroid compounds synthesized from cholesterol mainly in the testes, ovaries, and adrenal cortex. The male sex hormones (androgens) and female sex hormones (estrogens and gestagens) have a common biosynthetic pathway (**Figure 1**).

The final product of the steroidogenesis of sex hormones depends on whether or not specific metabolizing enzymes are available in the respective cell [1]. The sex steroids in human blood include androgens (testosterone, dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEAS), androstenedione, and dihydrotestosterone), estrogens (estradiol, estriol, and estrone), and gestagens (progesterone and 17α-hydroxyprogesterone). The major male hormone, testosterone, is produced by the Leydig cells in the testes. Dihydrotestosterone (DHT) is a potent androgen, derived from testosterone by the enzyme 5α-reductase (type 1 and type 2) in some peripheral tissues, mediating some testosterone-induced effects. This enzyme is expressed in the skin, scalp, prostate, epididymis, liver, and nervous system (neocortex, subcortical white matter, and hippocampal tissues) [2]. DHEA, DHEAS, and androstenedione are secreted mainly by the adrenal cortex in the same amounts in both sexes. DHEA and androstenedione are steroids involved in the sex hormones' biosynthesis pathway; both are primary endogenous precursors of testosterone and estrogens. Although they are weak androgens, they are circulating steroids that can be converted into active androgens and estrogens in the peripheral tissues [1, 3].

Estrogens are produced by aromatization of androgens, including those derived from adrenal steroidogenesis. Although the ovaries produce large amounts of androgens, they secrete little of these into the blood, while the rest are aromatized to estradiol, which is the major estrogen. The theca cells in the ovaries synthesize testosterone and androstenedione, which then diffuse into the granulosa cells of the follicles. There androstenedione is converted into testosterone, which in turn is aromatized to estradiol that enters the blood stream. A portion of the androstenedione is aromatized to estrone, which in turn is converted into estradiol. Androgen aromatization is realized under the influence of the enzyme aromatase, which is

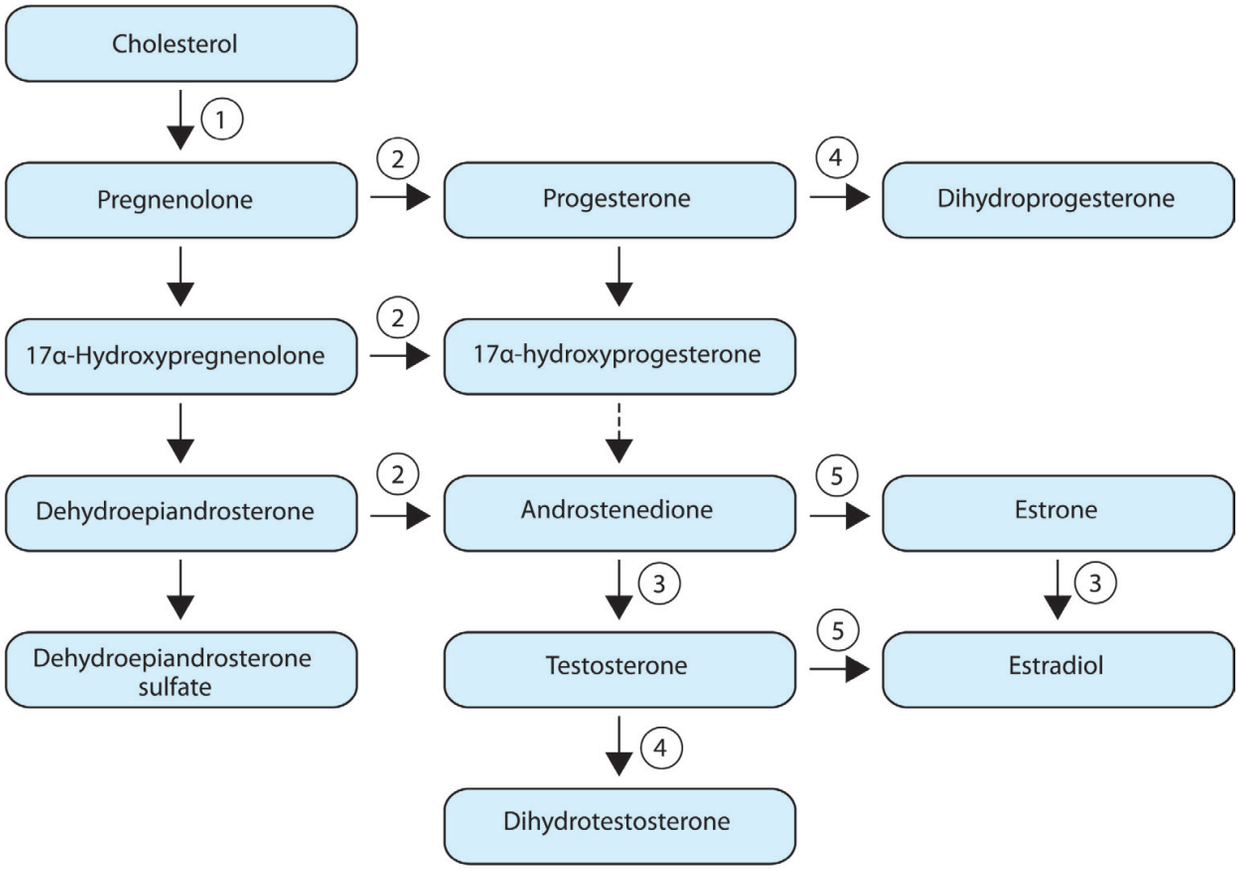

Figure 1. Sex steroid biosynthesis pathway. Enzymes are shown as follows: (1) P450 side-chain cleavage enzyme; (2) 3β-hydroxysteroid dehydrogenase; (3) 17β-hydroxysteroid dehydrogenase; (4) 5α-reductase; (5) aromatase. The dashed arrow indicates poor flux. Not all intermediate steroids, pathways, and enzymes are included (modified from Refs. [1, 55]).

expressed in steroidogenic tissues, the brain, and nonsteroidogenic tissues, especially fat and bone. Progesterone is the major progestogen and is produced in both theca and granulosa cells, the adrenal gland, and testes [1, 3].

The neuroactive steroids are brain-synthesized endogenous neuromodulators that rapidly alter neuronal excitability. Some of them reach the brain from adrenals and gonads and are further metabolized locally just like the aromatization of testosterone into estradiol [4]. They have been referred to as neurosteroids as they can be derived anew from cholesterol in neurons and the glial cells [5]. The synthesis of neuroactive steroids requires the translocation of cholesterol across the mitochondrial membrane [6]. This process occurs through a molecular complex formed by the translocator protein 18 kDa (TSPO), the steroidogenic acute regulatory protein (StAR), the voltage-dependent anion channel protein (VDAC), and the adenine nucleotide transporter protein (ANT).

In the mitochondria, cholesterol is converted into pregnenolone by the P450 side-chain cleavage enzyme (P450scc). Soluble pregnenolone diffuses into the cytosol (the endoplasmic reticulum) where it is further metabolized into various neuroactive steroids such as progesterone,

5α-dihydroprogesterone, DHEA, androstenedione, etc. The enzyme 3β-hydroxysteroid dehydrogenase, required for further conversion of pregnenolone into progesterone, has been found in the brain [7]. The enzyme 17β-hydroxysteroid dehydrogenase type 10 catalyzes the oxidation of neuroactive steroids in mitochondria with NAD^+ as the coenzyme. This enzyme catalyzes most effectively the oxidation of allopregnanolone and allotetrahydrodeoxycorticosterone, which is essential for the homeostasis of these neuroactive steroids [8].

Although TSPO is highly expressed in microglia and astrocytes and is less abundant in neurons, neurosteroidogenesis occurs primarily in principal neurons of several brain areas that have the necessary set of enzymes to convert cholesterol into neuroactive steroids [9].

3. Mechanisms of action

The first thing a hormone does is to bind to specific receptors on the target cell. Cells without receptors for the hormone do not respond to the action. The receptors for certain hormones are localized on the cell membrane, while others are located in the cytoplasm or nucleus. After binding to the specific receptor, the hormone triggers a cascade of cellular responses that become increasingly potent with each successive stage. Thus even small concentrations of the hormone can produce a significant effect [3].

3.1. Genomic action via steroid receptors

According to the classic genomic theory of action, sex hormones as steroid hormones bind preferentially to specific protein receptors within the cell rather than to receptors located on the cell membrane. These hormones are fat-soluble and can easily pass through the cell membrane and bind to specific receptors in the cytoplasm. Depending on the steroid and tissue, however, unbound steroid receptors may be located in the nucleus as well. The particular distribution of the receptor between the cytoplasm and nucleus varies. When the cytoplasmic receptors bind to their specific steroid hormone ligands, they translocate to the nucleus. Depending on their mechanism of action and subcellular distribution, nuclear receptors may be classified into at least two groups [10]. Nuclear receptors that bind to steroid hormones are all classified as type I receptors. Only type I receptors have a heat shock protein (HSP) associated with the inactive receptor that will be released when the receptor interacts with the ligand. Type II nuclear receptors have no HSP and in contrast to the classical type I receptor are located in the cell nucleus. The activated hormone-receptor protein complexes then bind to a specific regulatory section of DNA, called hormone response element, by activating or inhibiting the transcription of specific genes and the formation of messenger RNA. Later on, after an extended period of time (usually from a few hours to a few days) counted from the entry of the hormone into the cell, new proteins develop in the cell and alter the cell functions.

The complexity of the steroid action can be accounted for by the abundance of identified steroid receptors and their affinity for the hormone. The excess/deficiency of the respective sex steroid regulates the number of the active receptors (downregulation/upregulation) in the target cells. Testosterone and DHT exert their functions via binding to the androgen receptor

(AR), resulting in conformational change of the receptor and translocation of the androgen/AR complex from the cytosol to the nucleus. Various AR coregulators can further modulate the transcriptional regulation of target genes [11]. AR receptors are expressed in neurons and glial cells and their expression can be regulated by injury and by circulating testosterone concentration [12–14]. AR mRNA is downregulated post-orchidectomy and after axotomy [12]. AR levels also decrease with aging, especially in the nucleus basalis of Meynert (which degenerates in Alzheimer's disease (AD)) and the diagonal band of Broca [15].

The estrogen receptor-α (ERα) was characterized as an intracellular, ligand-regulated transcription factor located primarily in the nucleus [16]. Once bound to estradiol, ERα dimers were shown to regulate gene expression via interaction with estrogen response elements. Following a series of discoveries, a structurally related estrogen receptor-β (ERβ) was identified [17]. Sites of estrogen receptor expression identified in the brain comprised the hypothalamus, pituitary, and preoptic area, among others, which, based on a series of lesion and stimulation studies, were known to affect physiology and behavior related to endocrine function [18]. Apart from the great number of various isoforms, the classic intracellular receptors have also many splice variants that have been studied and characterized. For example, for estrogens besides the ERα and ERβ isoforms, multiple splice variants (e.g., ER$\alpha\Delta$4) can initiate signaling from the membrane [19]. Experiments demonstrated that the same protein is capable of mediating both intracellular and membrane actions of estradiol. For progesterone, a whole new class of progesterone receptors (PRs) has been identified—the membrane PRs localized on the membrane and involved in the reproductive actions of progesterone [20].

3.2. Non-genomic action

The classic genomic mechanism of the action of steroid hormones alone cannot account for all subsequent changes in the target cells; hence, it has been updated to include an additional (non-classic) explanation of the rapid, non-genomic, membrane-initiated action. For decades, steroid hormones have been known to induce acute changes (within minutes) in the physiological functions [21], neuronal activity [22], and behavior [23].

Recent research demonstrated that steroids can function in a "neurotransmitter-like" way, being synthesized at precise spatial locations within neural circuits in the brain and acting within minutes as local neuromodulators that rapidly regulate cognitive functions and behavior [24–27].

Some steroids, such as progesterone, are capable of inducing rapid neurotransmitter-like effects, similar to those of dopamine or glutamate, which alter the activity of neuronal systems via multiple types of receptors [19, 25, 28]. Some of these steroid receptors have been classified as extranuclear or membrane receptors, which signal through G-proteins or other second messenger systems [29, 30]. There is recent evidence of these classical steroid receptors binding to response elements on DNA to regulate gene expression, showing that they contain palmitoylation sequences allowing them to be trafficked to the plasma membrane to quickly alter cellular activity [19, 31]. After being trafficked, these nuclear transcription factors interact with other proteins to initiate their signaling at the level of the plasma membrane. From here, intracellular signaling cascades involving effectors (e.g., the mitogen-activated protein kinase (MAPK) and cAMP response element binding protein (CREB)) are initiated via

the transactivation of cell surface–bound receptors, most notably the metabotropic glutamate receptors (mGluRs). Subsequently, estrogen membrane–initiated signaling can in turn activate the regulatory section of DNA and trigger transcription processes.

The modern understanding of a cell response to a steroid action is that it occurs within the same time frame as that of the G protein–coupled receptors influencing a variety of cellular functions such as gating membrane channels, increasing the intracellular calcium release, activating tyrosine-protein kinase (Src), MAPK, and others [27]. Many studies support a model of integrated signaling that couples signal transduction cascades to transcription in the nucleus, providing an integrated view of hormone signaling in the brain [32].

Recently, extensive research focused on the rapid, non-genomic action of estrogens has raised the question of how rapidly the increase of these steroids can occur in the brain. Of course, estrogens, just like any other steroids, cannot be stored in synaptic vesicles prior to their rapid release, due to their lipophilic nature [4]. It has been suggested, therefore, that the rapid effects of estrogens require a corresponding rapid change of local steroid concentration via rapid changes in their rate of synthesis by androgen conversion [24, 33], which implies changes in aromatase activity. Changes of aromatase activity reflect changes in aromatase protein concentrations. For instance, sex steroids control the hypothalamic aromatase expression in most vertebrates: weak aromatase expression is detected in castrated male animals, while testosterone replacement increases significantly aromatase protein and enzyme activity [34, 35]. There is strong evidence suggesting that aromatase activity can be rapidly modulated via translational modifications, most notably via phosphorylation. The rapid modulation of aromatase activity by phosphorylation is a widespread mechanism present in certain tissues of various species, including humans [4]. The enzymatic changes lead to a rapid local modulation of estrogen availability and consequently to a modification of cellular estrogen-dependent processes that are not mediated by the genomic actions of these steroids. The phosphorylation/dephosphorylation processes provide a new widespread mechanism by which estrogen concentration could be rapidly altered in the brain and other tissues.

Although most of the research on neurotransmitter-like actions of steroid hormones is focused on sex hormones and reproduction, other steroids also induce effects through non-classic mechanisms. As with estrogens and progestins, glucocorticoids can act on the membrane to alter physiology, functioning more like neurotransmitters than classical steroid hormones.

Neurosteroids are also capable of interacting with cell surface neurotransmitter receptors to modulate neural cell physiology. Two of the endogenous neurosteroids, pregnenolone sulfate and pregnanolone sulfate, can potentiate or inhibit N-methyl-D-aspartate (NMDA) receptor responses [36]. $GABA_A$ receptors represent one of the most elaborate neurotransmitter receptor structures, harboring multiple binding sites for allosteric modulators, neuroactive compounds, and neuroactive steroids [37]. Allopregnanolone has been shown to promote neurogenesis in both rodent and human neuroprogenitor cells, most likely through binding to the $GABA_A$ receptor [38]. The modulation of the activity of receptors by neurochemicals such as allopregnanolone has been extensively studied in the context of neurodegenerative disorders [39].

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Another mechanism of steroid action takes effect at the level of the microtubules via a proposed receptor microtubule-associated protein of type 2 (MAP2) [40]. Neuronal microtubules play an important role in the growth and maintenance of neurites during neuronal differentiation. They are composed of tubulin and microtubule-associated proteins (MAPs). MAPs determine neuronal shape and control the balance between rigidity and plasticity in neuronal processes. Neurosteroids may be involved in the formation and stabilization of microtubules and thus neuronal plasticity and function [40]. Experimental data demonstrate that progesterone treatment attenuated the injury-induced loss of MAP2 [41].

4. Biological effects of sex hormones on the nervous system

Testosterone and its metabolite estradiol induce numerous effects during critical periods of pre- and perinatal brain developments (organizational effects) that are necessary for brain sexual differentiation. Testosterone exposure is an essential requirement for masculinization of the brain. Nuclear volume, neuronal morphology, and astrocyte complexity are examples of the wide range of effects by which testosterone and estradiol can induce permanent changes in the function of neurons [42]. In the developing male rat, testosterone secreted from the testes is not bound by α-fetoprotein and freely enters the brain where it is locally converted into estradiol in specific nuclei. Consequently, neonatal males have more than double the levels of estradiol than females in brain regions subject to sexual differentiation [43]. High levels of the ER are concentrated in the same brain regions and ER is essential for transducing the steroid signal [44]. The gain or loss of function upon developmental estradiol exposure corresponds to the specific cellular morphological changes observed during the critical period, and the dendritic spines and astrocytes seen in each brain region retain that "memory" of early steroid exposure [42].

4.1. Effects of female sex steroids

It is generally accepted that estrogen acts as a conditional neuroprotectant with a complex pattern of biological actions, which are modulated by several interacting factors [45]. It has been found that administration of estradiol increases neuronal survival and recovery in adult animals and different lesion models [46, 47]. Estradiol protects neurons from excitotoxic damage due to seizures and stroke, as well as in AD [48]. One of the suggested mechanisms of this effect is the ability of estrogens to enhance neuropeptide Y (NPY) expression and release, as NPY has antiexcitatory effects [49]. In vitro estradiol was found to protect neurons from glutamate toxicity and Aβ peptide toxicity, oxidative stress, and glucose deprivation [50–53]. The defense state induced by estrogen is mediated by complex mechanisms that converge upon regulation of mitochondrial function. Estrogen preserves ATP levels via increased oxidative phosphorylation and reduced ATPase activity, thereby increasing mitochondrial respiration efficiency. Estrogen increases antiapoptotic proteins, Bcl-2 and Bcl-xL, which prevent formation of the permeability transition pores protecting against estrogen-induced increase in mitochondrial Ca^{2+} sequestration and triggering of apoptotic processes [54]. Therefore, the

decreased levels of estrogen could most likely contribute to the increased risk of developing neurodegenerative diseases, especially in postmenopausal women [52, 55].

It is suggested that in addition to having a direct effect on neurons, estrogens may affect the astrocytes by stimulating them to release protective growth factors and regulate the astrocytes genes and proteins associated with the glutamate level control. Other mechanisms implicated here may include the anti-inflammatory effect associated with suppression of microglia, inflammatory cytokines, and free radicals production, which cause inflammatory damage to the neurons, effects on endothelial cells realized by increasing the mitochondrial efficiency and stimulating angiogenesis, genomic influence on anti-apoptotic protein genes of Bcl family and reduction of apoptotic trends and effect of free radical scavenging. These are the hypothetical models of estrogen neuroprotection in cerebral ischemia and in other neurodegenerative disorders such as Parkinson's disease (PD) and AD [52, 56].

There is growing evidence that estrogen may have a neuroprotective role in PD. Experimental studies have demonstrated that estrogen is neuroprotective in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced nigrostriatal lesions, an animal model of idiopathic PD [57, 58]. In these and other studies, 17β-estradiol was used and its effect was shown to be stereospecific. An isomer with weak estrogenic activity, 17α-estradiol, was ineffective with regard to the prevention of MPTP-induced dopamine loss [52]. What is worthy of note is that the receptors ERα and ERβ are sparsely localized in the striatum and substantia nigra of mice, and treatment with MPTP or estrogen does not change the distribution and density of the estrogen receptor. Despite the low availability of ER in these parts of the brain, estrogen has managed to induce a protective effect on the striatum against MPTP-induced loss of dopaminergic neurons [59].

Studies in humans showed that short-term estrogen treatment in postmenopausal women increased dopamine transporter availability in the caudate putamen [60] and that women who had taken postmenopausal estrogen replacement therapy were less likely to develop PD than those who had not [61].

There is evidence of inducing differentiation of human neural stem cells, which develop in the tyrosine hydroxylase (dopaminergic) neurons, and the effect was blocked by application of an estrogen receptor antagonist [62, 63].

As it is supposed that oxidative stress plays an important role in the processes of neuronal degeneration in the PD, it is interesting that estrogens suppress free radical production and protect striatal neurons against oxidative stress, providing another mechanism of estrogen neuroprotection in PD [64, 65].

Recent studies in both animals and humans have provided additional evidence supporting a potentially beneficial protective role for estrogen in AD. The mechanisms of estrogen protection in AD are not clear. At the molecular level, estrogen has been shown to enhance activation of the survival factors, protein kinase B, BDNF [66, 67], while inducing phosphorylation and deactivation of glycogen synthase kinase (GSK3B) and Bcl-2 associated agonist of cell death (BAD), involved in death signaling pathways in neurons [67, 68].

Progestins have also been found to exert neuroprotective effects similar to those of estrogens. Progesterone stimulates the neurological and functional recovery after spinal and brain traumas [56, 69] and exerts neuroprotection in cerebral ischemia [70, 71].

4.2. Effects of androgens

The effects of androgens on the nervous system have been far less characterized than those produced by estrogens and progestins. Androgens also exhibit a wide array of neuroprotective effects in motoneurons, including supporting cell survival, axonal regeneration, and dendritic maintenance [72]. Testosterone influences neuroplastic changes in nuclei of the limbic system, particularly in the amygdala, bed nucleus of the stria terminalis, and the hippocampus [73, 74]; it exerts neuroprotective effects by stimulating neuron survival and regeneration after a nerve injury by actions mediated via the androgen receptor [75, 76]. It has been observed to have a protective effect on apoptosis in cell cultures of human neurons. This effect is mediated directly by androgen receptors, without testosterone aromatization to estradiol [77]. Testosterone replacement in gonadectomized male adult mice reverses the pathological changes in the spine morphology of hippocampal CA1 pyramidal neurons. The dendritic spines are specialized to receive synaptic inputs, and a change in spine morphology is correlated with the strength and maturity of each synapse [78]. Similar data were obtained in experimental motoneuron damage, with the use of DHT reducing the atrophy of adjacent dendrites [79]. Recent findings suggest that one of the mechanisms of the neuroprotective effects of physical training is the increased DHT production in the hippocampus providing evidence for androgenic mediation of neurogenesis by androgen receptors [80].

Androgens may regulate the production and the levels of Aβ, by a classic genomic mechanism and rapid non-genomic signaling or via aromatization to estradiol and activation of estrogen pathways [81, 82]. Testosterone can attenuate the toxicity of Aβ in cultured hippocampal neurons via a rapid, estrogen-independent mechanism [83]. DHT increases Aβ-catabolizing enzyme neprilysin in cultured neurons by an AR-dependent mechanism, which promotes Aβ degradation, thereby decreasing Aβ levels in AD [84].

4.3. Effects of steroid precursors

Precursors of estrogens, progestins, and androgens (pregnenolone and DHEA) also affect neuronal functions. When administered in vivo, pregnenolone reduces histopathological changes, protects neural tissues from secondary lesions, and promotes the recovery of motor functions after spinal cord injury [85, 86]. DHEA is one of the first neurosteroids identified in rat brains. Neuroprotective effects induced by DHEA and its sulfate DHEAS, defined as primary in their biological action, have been documented [87]. Both steroids contribute to the differentiation and survival of neurons in cell cultures [88]; have a protective effect on hippocampal neurons against the toxic effects of glutamate [89]; stimulate the growth of neuritis of the cortical neurons of embryonic rat brains [90]; affect apoptosis, catecholamine synthesis, and secretion; and have exhibited anti-oxidant, anti-inflammatory, and anti-glucocorticoid effects [87].

Studies suggest that these are different mechanisms for DHEA and DHEAS effects. It is assumed that DHEAS mediates its effects via $GABA_A$ receptors, probably by metabolizing DHEAS into a $GABA_A$ receptor agonist, such as androsterone or androstanediol [91]. The neuroprotective effect of DHEAS to NMDA receptor-induced cytotoxicity is probably mediated by the σ1 receptor, while DHEA inhibits NMDA-induced nitric oxide (NO) production and NO synthase activity by NMDA receptor, modulating calcium/NO signaling pathway [92]. Concentrations of DHEA and of its sulfate are also important with respect to the final effect. Low concentrations of these steroids may be neuroprotective, while high concentrations of DHEA are ineffective or neurotoxic and lead to the inhibition of complex I of the mitochondrial respiratory chain [93].

4.4. Interaction between steroids and neurotrophins

Recently, researchers have studied the relationship between the gonadal steroids, adrenal steroids, and BDNF focusing on intersexual differences and incidence of mental diseases [94]. BDNF belongs to the neurotrophin family and plays an important role in the survival, differentiation, and outgrowth of select peripheral and central neurons during development. BDNF impacts significantly on neuronal survival, acting in the adult brain through a variety of cell types, which include neurons, astrocytes, oligodendrocytes, microglia, and endothelial cells. It is essential for the process of learning and improvement of cognitive function via activation of the TrkB receptor [95]. Our previous data demonstrated that the negative effect of the anticonvulsant lacosamide on the processes of learning and memory is related to suppressed expression of BDNF/TrkB ligand receptor system in the hippocampus of rats [96]. Sex steroid hormones and neurotrophic factors are involved in the neuroendocrine control of reproduction as well as in brain adaptation during reproductive aging. There is a great body of evidence showing the role BDNF plays in the pathogenesis of neurodegenerative diseases. Low post-mortem parietal cortex BDNF levels have been found in patients with mild cognitive impairment [97] and AD [97, 98].

Research shows that BDNF mRNA and protein expression levels in the brain cognitive regions are affected in a region-specific manner when hormone replacement therapy is administered. BDNF mRNA levels have been reported to be significantly reduced in almost all hippocampal layers and the cortex in 28-week ovariectomized rats [99]. Estradiol replacement therapy reverses this effect in the hippocampus, suggesting a regional divergence in ovarian steroid requirements for BDNF expression. After gonadectomy, BDNF mRNA levels are significantly reduced at postnatal day 7 in male rat pups, but after treatment with estradiol benzoate, the levels were similar to those in intact animals. The authors demonstrated that ERα and BDNF were localized in the same cells (pyramidal cells of the CA3 sub-region and to a lesser extent in CA1) within the developing hippocampus [100].

Estrogens have been implicated in the increase of hippocampal BDNF mRNA and protein levels in exercising animals. The exercise effect on BDNF upregulation was reduced after 7 weeks of estrogen deprivation. Exercise in combination with long-term estrogen replacement increased the BDNF protein above the effects of estrogen replacement alone [101].

Androgens also have a bearing on the BDNF expression; some of their effects on the nervous system are most likely to be realized through influencing the production of this neurotrophin.

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Testosterone administration was shown to increase BDNF protein levels in motoneurons of spinal nucleus of the bulbocavernosus of castrated male rats [102]. Gonadectomy induces a significant decrease in the protein levels of BDNF and its downstream target post-synaptic density protein 95 (PSD-95) in the hippocampal CA1 area, which is reversed by testosterone replacement [78]. Knowledge of the interactions between BDNF and sex steroids could be essential for the understanding of the BDNF role in brain development, adaptation during aging, and the pathogenesis of neurodegenerative diseases.

5. Conclusion

The functions of the sex hormones exceed the limits of reproduction in that they regulate vital neuronal and glial features. The chronic effects of neurosteroids are due to both genomic (classical intracellular steroid receptors) and non-genomic rapid effects (ion channels and membrane receptors) in the brain.

Some of the hypothetical models of estrogen neuroprotection include complex mechanisms, which converge upon regulation of mitochondria function–preserved ATP levels via increased oxidative phosphorylation and increased antiapoptotic proteins of Bcl family. Estrogen stimulates the astrocytes to release protective growth factors and has an anti-inflammatory effect associated with suppression of microglia and inflammatory cytokines. It suppresses free radical production and protects striatal neurons against oxidative stress, providing another mechanism for neuroprotection in PD. The female sex steroids promote cell survival via protein kinase B activation and BDNF upregulation; they inactivate GSK3B and BAD, involved in neuronal death signaling pathways in AD. The androgens also have neuroprotective effects in motoneurons, including supporting neuron survival, axonal regeneration, and dendritic maintenance. Testosterone can attenuate the toxicity of Aβ and decreases Aβ levels in AD.

Despite the growing amount of research on sex hormones and neurosteroids in recent years and the ongoing discovery of biochemical mechanisms of action, their role in neurodegenerative processes remains uncertain. Further elucidation of the cellular and molecular mechanisms responsible for the effects of neurosteroids on the normal function of neuronal and glial cells would provide important insights related to the development of new therapeutic strategies aimed at delaying the onset and slowing the progression of cognitive dysfunctions and neurodegenerative diseases.

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