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Chapter 9

Sex Hormones: Role in Neurodegenerative Diseases and Addiction

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.71380

Abstract

The brain is a complex organ in charge of regulating the homeostasis of our body and behaviors such as motivation, reward, memory, and movement control, between others. These behaviors are regulated by dopaminergic neurons, which can be modulated by several stimuli throughout the life of an individual. For example, early exposure to sex hormones or endocrine disruptors during critical period of neuronal development affects dopaminergic pathways permanently, producing some disorders such as drug addiction. On the other hand, current knowledge regarding neurodegeneration in Parkinson and Alzheimer diseases pointed out the neuroprotection that estradiol can exert, but contradictory information can also be found in the literature. To know the underlying mechanisms that are related to the above mentioned diseases will help to improve health policies and treatments development.

Keywords: sex hormones, neonatal programming, dopaminergic circuit, neuroprotection, drug addiction, Alzheimer, Parkinson disease

1. Introduction

In the current world, humans are exposed to different compounds that can exert deleterious modifications in their bodies, taking special attention of the short- and long-term effects of endocrine disruptor chemicals, which mimic or block hormonal activity. Endocrine disruptor chemicals are natural or synthetic molecules that can alter the endocrine homeostasis, especially if exposure to these molecules is during critical developmental windows [1]. These compounds are used in plastic industries, chemical, and pharmaceutical industries, and for different events that are bioavailable in the environment affecting animals and humans. Endocrine disruptors exert their action through different pathways that converge on the molecular targets such as hormone receptors, enzymatic pathways involved in biosynthesis and metabolism of endobiotics

in endocrine, reproductive, and nervous system. In this sense, different brain areas are sensible to the action of endocrine disruptors and sex hormones due to the presence of its receptors that can modulate the synaptic transmission and neuronal survival. In this regard, nuclear receptors for sex hormones are ligand-activated transcriptional factors that regulate different neural process such as neurodevelopment and behaviors. Alterations in hormonal homeostasis (e.g., aging) or signaling (e.g., exposure to agonists or antagonists of sex hormone receptors) may induce the onset of diseases before mentioned, affecting lifespan, quality of life, and high medical costs.

Worldwide, drug abuse has increased dramatically, especially in susceptible populations such as youth. However, human and animal studies show that not all drug consumers become addicts. In addition, it has determined sex differences in behaviors related to motivation, reward, and cognition, among others. Clinical observation has shown that children who have developed precocious puberty show an increase in risky behaviors such as drugs abuse, sexual risk, and anti-social behaviors in adolescence.

Also, when Parkinson (PD) and Alzheimer disease (AD) is analyzed, it observed a sex difference in terms of prevalence, which draws the attention to the possible role of sex hormones in the onset of these pathologies. In this term, meta-analysis has shown that males have augmented prevalence of PD than women, overall in the age range of 50–59 years (134 per 100,000) compared to women (41 per 100,000) [2]. However, the prevalence of AD is greater in women compared to men, considering different age range and ethnicity [3, 4].

In this chapter, we will discuss about the exposure to abnormal levels of sex hormones, due to metabolic alterations or endocrine disruptor chemicals, during critical period of neurodevelopment; and based on clinical evidence and current scientific knowledge, we will discuss the mechanisms involved in the development of drug addiction, Alzheimer and Parkinson disease, and the sex differences observed between patients.

2. Programming: early exposure to sex hormones

Programming concept was defined by Lucas as the physiological redirection of a tissue or organ by a deleterious stimulus in a sensitive period of development produces adverse functional changes in adulthood [5]. Currently, research in programming has been focused in the study of stimuli that affects sensitive periods of development such as prenatal and neonatal stages.

In that sense, experiments are carried out in female rats, where precocious puberty is induced by neonatal exposure to estradiol valerate, is accompanied by increased catecholamine content in the adrenal gland, noradrenaline content in the ovary and reproductive alterations in the adulthood [6]. Using the same model of neonatal administration of estradiol valerate [7], it observed an increase in dopamine (DA) and noradrenaline content in dopaminergic neurons of tuberoinfundibular [8], nigrostriatal, and mesolimbic pathways [9] of the adult. Indeed, neonatal administration of estradiol valerate and testosterone propionate increases DA content and tyrosine hydroxylase (TH), (rate limiting enzyme of dopamine synthesis) expression in substantia nigra (SN), and ventral tegmental area (VTA) of adult male rats [10]. Others works

have shown that neonatal administration of testosterone reduces spatial memory and TH positive terminals in prefrontal cortex in an animal model of attention deficit disorder with hyperactivity [11].

In recent years, it has been shown that environmental pollutants (being most of them chemical disruptors) produce a myriad of effects in the brain [12]. For example, in rats, neonatal and postnatal administration of bisphenol A produce an increase of spontaneous locomotion behavior associated with the decreased immunoreactivity for TH in SN and decreased expression of dopamine transporter (DAT) in midbrain nuclei [13].

Sex hormone levels affect cortical and subcortical brain areas, especially in sensitive periods of development in childhood and adolescence [14]. In this regard, dopaminergic brain areas such as SN, VTA, and hypothalamus are sensitive to the effects of sex hormones because they express estrogens and androgens receptors [7, 15, 16].

It has been demonstrated that exposure to a single dose of sex hormones during the neonatal period can change the profile expression of DA [8]; in fact, when female rats are exposed to a single dose of estradiol during the neonatal period, DA levels are increased in the ventromedial hypothalamus–arcuate nucleus, but not the exposure to testosterone, during adult life [8]. In addition, when male rats are exposed to estradiol or testosterone, DA levels and TH expression are increased in substantia nigra-ventral tegmental in addition to increased dopamine release in nucleus accumbens. This effect is not seen when rats are exposed to a nonaromatizable androgen, dihydrotestosterone, suggesting an estrogenic mechanism involving increased TH expression, either by direct estrogenic action or by aromatization of testosterone to estradiol in substantia nigra-ventral tegmental area [10].

2.1. Long-term epigenetic programming of the dopaminergic circuit

The programming is exerted through epigenetic modifications, which comprised DNA methylation and post-translational histone modifications, interacting with regulatory proteins and noncoding RNA to reorganize the chromatin in active or inactive domains (euchromatin or heterochromatin), being possible to be inherited from one generation to another without subsequent exposure to the endocrine disruptor [17]. The normal development of mammals involves the activity of DNA methyl transferase (DNMTs) to determine the *de novo* methylation, where DNMT3A and DNMT3B are involved, and to maintain the methylation pattern in the genome, where DNMT1 is involved. The expression levels of these enzymes are highly regulated during specific stages of life [18], and therefore, the impact of the exposure to endocrine disruptors and the consequences over the offspring are alarming.

In this view, in humans the social alcohol drinking during periconceptional or pregnancy period may induce changes in the promoter methylation of DAT in mothers and their babies. Specifically, using peripheral blood from mothers or cord blood from newborns, they found that alcohol intake decreases the methylation level of the locus-specific DAT promoter region of the parents and newborns [19]. However, these findings are controversial, since also found a decrease of DAT mRNA expression in drug addicts (to opioid drugs) compared to control subjects, but not in the methylation pattern of DAT promoter [20]. One of the methodological

factors that could determine this difference is from where the samples are obtained, in the case of the peripheral blood, it is not a direct measurement of DAT expression in brain.

3. Sex hormones, dopaminergic neurotransmission, and addiction

Worldwide, drugs of abuse have increased dramatically, especially in susceptible populations such as youth. However, human and animal studies show that not all drug consumers become addicts [21, 22]. Lately, it has been determined differences in behaviors related to motivation reward and cognition between women and men (for review see 23). Accordingly, sex hormone levels affect cortical and subcortical brain areas, especially in sensitive periods of development in childhood and adolescence [14]. In this regard, dopaminergic brain areas such as SN, VTA, and hypothalamus are sensitive to the effects of sex hormones because they express estrogens and androgens receptors [7, 15, 16]. Interestingly, sex hormones induce opposite effects between female and males. While estrogens increase the expression of tyrosine hydroxylase in SN and VTA of adult female rats [24], androgens such as testosterone and dihydrotestosterone reduce TH expression in the same brain areas in adult male rats [25]. However, in adolescent male rats, androgens increase TH expression in SN [26].

In humans, it has been observed that an excess of testosterone levels during prenatal stage is related with the development and maintenance of alcohol dependence during adolescence and adulthood [27, 28]. Children who have developed precocious puberty (an early activation of the reproductive axis leading to the onset of puberty closer to 8, 9 years in girls and boys, respectively) shows an increase in risky behaviors such as drugs abuse, sexual risk, and anti-social behaviors in adolescence [29]. Many of these behaviors and the neuroendocrine pathways that regulate them are sexually dimorphic. These sex dimorphisms reflect adaptive differences for behavioral strategies in coping as a result of sexual selection. Disruptions in these behaviors may lead to reduced social adaptation and impaired responsiveness to environmental demands [30]. On the other hand, the exposure to several environmental pollutants, with neuroendocrine activity, has been associated with behavioral effects. For example, genistein (a phytoestrogen produced by legumes and present in soy bean-based food) increases locomotor activity in males, ethinylestradiol (a synthetic estrogen used as contraceptive) affects response to reward in females and bisphenol A, an endocrine disruptor, increases anxiety and sexual behavior in males (for review see [12]). In summary, our brain is modulated by sex hormones (or exogenous compounds) and depending on the stage of development, this interaction could affect the organization and activation of neural systems (for review see [31–33]). The alteration of sexually-dimorphic behaviors may be relevant for concerns regarding the increased developmental, cognitive, and⁄or emotional disabilities reported over the past 30 years [34].

Some studies of enrichment and deprivation of sensory inputs to the brain have provided information regarding the role of experience on the development of the brain. These studies suggest widespread effects of experience on the complexity and function of the developing system, while the deprivation studies document the capacity for neural reorganization within particular sensory systems [35]. These studies suggest that plasticity in developing neural systems can modulate the capacity to develop fundamentally different patterns of organization

http://dx.doi.org/10.5772/intechopen.71380

and function in response to injury. Therefore, the neurochemical interaction and environmental aspects can modulate the pathophysiological processes that determine the development of neurodegenerative events [36] (**Figure 1**).

The mesocorticolimbic system comprises the midbrain dopaminergic projection from the VTA to the nucleus accumbens (NAcc) [23, 37] and prefrontal and orbitofrontal cortexes [38]. One of the most important neurotransmitters in mesocorticolimbic system is DA, which is released in response to natural rewarding stimuli as food [39] or sex [40]. Drugs of abuse produce an increase in DA release in NAcc and striatum [41]; however, the magnitude and duration of this effect are much greater than with natural reinforces [42]. This acute supraphysiological DA release induced by drugs of abuse in the NAcc exherte its actions through the activation of the DA receptor type 1 (D_1 receptor), leading to early gene products induction (e.g., cFos) [43]. *In situ* hybridization studies have demonstrated the expression of estrogen receptors (ESR1, ESR2) and androgen receptors in SN-VTA [16, 44]. Using immunohistochemistry, it has been shown that ESR2 is expressed in high proportion in TH positive neurons of the VTA, whereas

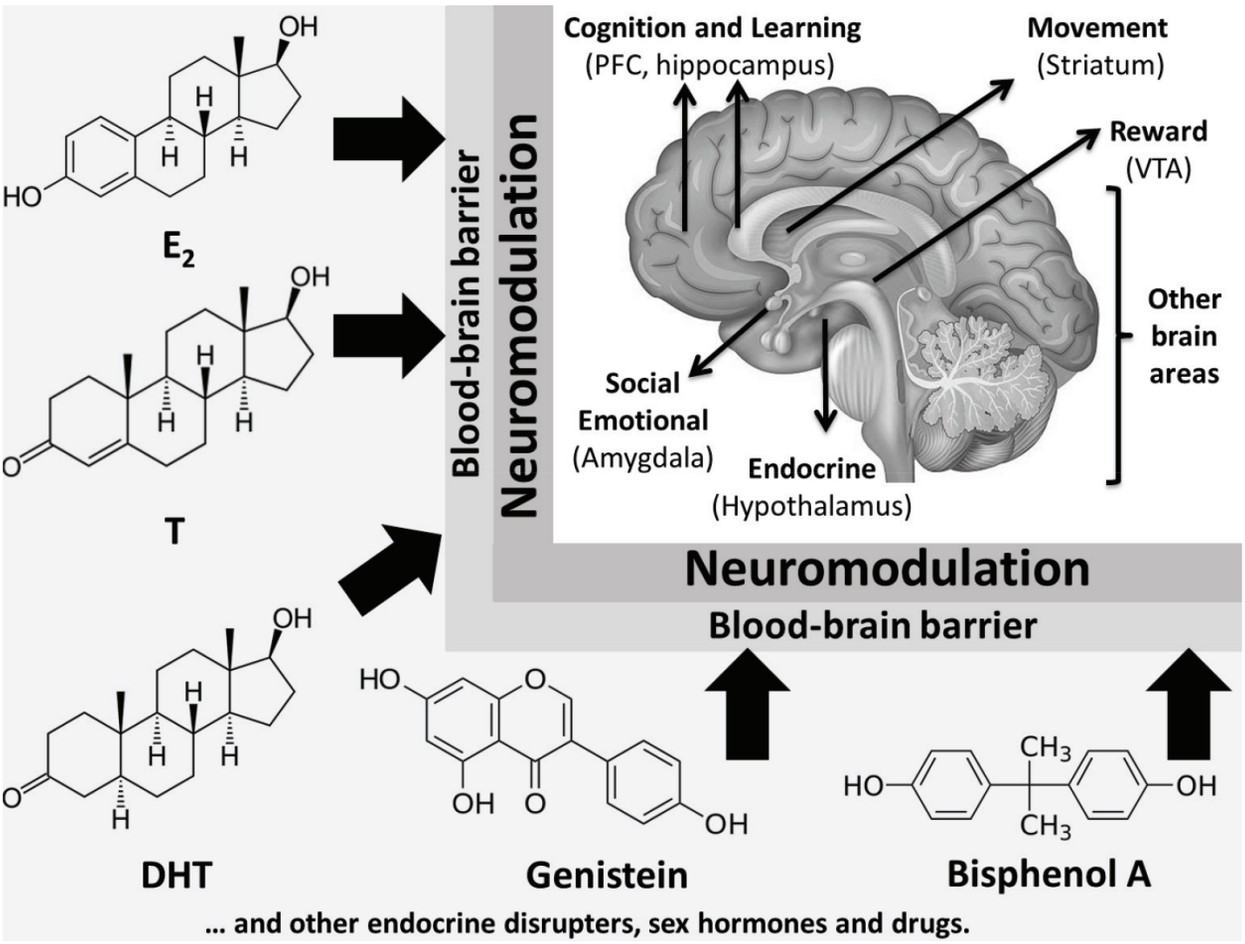

Figure 1. Schematic representation of the influence of neuroactive compounds like estradiol, testosterone, DHT, genistein, and bisphenol A on brain areas. These compounds can cross the blood–brain barrier, reaching brain areas that are related to cognition and learning (prefrontal cortex and hippocampus), movement (striatum), reward (VTA), social emotional (amygdala), the endocrine system (hypothalamus). Abbreviations: E_2, estradiol; T, testosterone; DHT, dihydrotestosterone; PFC, prefrontal cortex; VTA, ventral tegmental area.

androgen receptor is expressed in high proportion in TH positive neurons of NAcc [15]. Thus, sex hormones can regulate the expression of Tyrosine hydroxylase; specifically, estrogens can increase the expression of TH in SN and VTA of adult female rats [24], while androgens reduce TH expression in the same brain areas in adult male rats [25]. Noteworthy, in adolescent male rats, androgens increase TH expression in SN [26], suggesting a mechanism that depends on the physiological/hormonal context. The effects of sex hormones are mediated by the activation of specific receptors expressed in cell bodies of midbrain dopaminergic neurons and its limbic projections. The dopamine transporter, DAT, is a protein that mediates the active reuptake of dopamine from the synapse and is a principal regulator of dopaminergic neurotransmission, dopamine receptor 1 and 2 (D_1 and D_2, respectively) are modulated by 17β-estradiol and testosterone. Experiments using ovariectomized adult rats have shown a significant reduction of DAT levels in the NAcc and Striatum, which is restored to normal levels after E_2 replacement or the use of diarylpropionitrile (a selective ERβ agonist) and tamoxifen (selective estrogen receptor modulator) [45–48]. In the same model, levels of D_1 in mPOA are decreased after E_2 replacement [49]. Noteworthy, immunoreaction to D_2 is not affected by E_2 replacement, when is measured using immunohistochemistry. However, when western blot is used, levels of D_2 are apparently increased in mPOA and PLC [49]. In NAcc, D_2 levels are significantly increased in the NAcc and striatum of ovariectomized rats and E_2 replacement reduced D_2 receptors to lower levels than in controls rats [48].

It has been shown that circulating levels of female and male sex hormones modulate the mesocorticolimbic system, regulating the addictive behavior. Women in reproductive age who are users of drugs of abuse show greater rate of escalation of drug use than men [50], leading to the establishment of the addictive behavior quickly [51]. On the other hand, depending on circulating levels of sex hormones in menstrual cycle, the reward effects of psychostimulant drugs such as amphetamine are more potent in follicular phase when estradiol levels are higher than luteal phase, when progesterone levels are higher [52, 53].

Exposure to hormone disruptors has shown to produce effects on the behavior of animals. Thus, the prenatal administration of bisphenol A to pregnant mice and postnatal administration to offspring until postnatal day 15 produces anxiolytic behavior in elevated plus-maze and open field tests [54]. Interestingly, this behavior has been related to a significant decrease of DAT in striatum and NMDA receptor in frontal cortex [54]. Silverman and Koenig [55] showed the involvement of ESR2 in the reinforcement induced by low doses of amphetamine in female rats. In this work, ovariectomized female rats do not show conditional place preference to amphetamine compared with intact female rats. The replacement with estradiol or estradiol plus progesterone reestablishes the conditioned place preference induced by amphetamine in ovariectomized rats [55]. Interestingly, the authors found that conditioning with amphetamine was significant in the ovariectomized groups that were administered with estradiol or the ESR2-specific ligand DPN. These results provide new evidence of the specific requirement of ESR2 in response to drugs of abuse [55].

3.1. Attention-deficit/hyperactivity disorder (ADHD)

Regarding the behavioral effects produced by the administration of androgens, it has been observed that the neonatal administration of testosterone in spontaneously hypertensive rats

(SHR) (an animal model of attention-deficit hyperactivity disorder [ADHD]) decreases cognitive function and TH immunoreactivity in prefrontal cortex [11]. In this work, the authors implanted at postnatal day 1 pellets of testosterone in SHR rats, observing at postnatal day 45, through the Morris water maze test, an increased latency to find the platform. The authors conclude that the administration of androgens in neonatal period may predispose to ADHD-like behaviors in the adulthood.

With regard to pharmacological therapies of ADHD, animal studies and case reports have suggested that methylphenidate exerts adverse effects on gonadal hormones. In this case, methylphenidate could be altering testosterone levels in children with attention-deficit/hyperactivity disorder through the comparison of those with or without methylphenidate treatment [56].

Recently, prospective study conducted in Taiwan that included 203 ADHD patients with a mean age of 8.7 years (boys: 75.8%). After the initial recruitment, 137 received daily methylphenidate treatment and 66 were assessed through naturalistic observation (nonmedicated group). During the study period, salivary testosterone levels did not significantly change in the treated group ($P = 0.389$) or in the nontreated group ($P = 0.488$). After the correction for potential confounding effects of age and sex, salivary testosterone levels still remained unchanged in the treated and nontreated groups during the 4-week follow-up [57]. Findings suggest that the short-term treatment with methylphenidate at usual doses does not significantly alter salivary testosterone levels in attention-deficit/hyperactivity disorder patients. Future studies should clarify whether long-term methylphenidate treatment disrupts testosterone production as well as the function of the reproductive system.

In summary, these evidences indicate that sex hormones play an important role modulating the mesocorticolimbic system and behavioral, neurochemical, and neuroplastic effects of drugs of abuse.

4. Sex hormones and Alzheimer disease

During the menopause in women or andropause in men, there is a normal decrease in sexual hormones, due to the loss of ovarian sex hormones (estrone, estradiol, and progesterone) or to a decrease in testosterone levels, correspondingly. Noteworthy, postmortem analysis has shown lower brain levels of estrogens in women with AD, and lower levels of androgens in men with AD compared to nonAD patients. Specifically, studies performed in caucasic female subjects with neuropathological diagnosis of AD, according to Braak stages V–VI, with the absence of other neuropathologies (ranging in age from 61 to 90 years old) show a decrease of two times in estrone levels (midfrontal gyrus samples) when compared to controls, but not in estradiol, testosterone, or dihydrotestosterone (DHT) levels [58]. However, when male subjects with neuropathological diagnosis of AD, according to Braak stages V–VI, are analyzed (ranging in age from 50 to 97 years old) estradiol or estrone levels are not different between AD subjects and controls, but there is a decrease in androgen levels in AD patients, compared to controls [58]. Thus, it is proposed that the sex hormone decrease observed in brain samples from AD patients is not just related to the normal decrease in gonadal synthesis, but also to a decrease in local brain steroidogenesis [58, 59].

Supporting that, the premenopausal bilateral oophorectomy (surgical menopause), which induces early menopause through an abrupt decrease in circulating estrogen levels in young women, has shown lights about the role of sex hormones, its decline during the menopause and correct timing of hormonal replace therapy [60, 61]. Thus, in a study where 1884 women were followed longitudinally for upto 18 years (natural menopause n = 1277, surgical menopause n = 607) relating the onset of menopause (natural or surgical) to cognitive decline and AD. According to the study, surgical menopause at earlier age was associated with the decline in cognition (decline in episodic and semantic memory) as well as a greater level of Alzheimer disease in women who survived free of dementia to a mean age of 78 years [61]. Noteworthy, when the use of hormone therapy was considered in the study, a protective role was found when the treatment was administrated within 5-year perimenopausal period for at least 10 years: less decline in visuospatial ability, episodic, and semantic memory, but no influence over the onset of AD [61].

In women, it has been determined that the hormonal treatment with estradiol has more protective effects than the treatment with conjugated equine estrogen. Noteworthy, many studies have pointed out that the hormonal treatment needs to start during what is called a "window of opportunity", since the protective effects of estradiol treatment depend on when hormonal treatment is started. In particular, hormonal treatment needs to start during the perimenopause period (i.e., under age of 65 years). During this period is necessary to maintain a constant treatment (not withdraw), since doing so could decrease the memory improvement obtained by the hormonal treatment [62]. Verbal memory is enhanced with the treatment with E_2. Although there are many studies supporting the benefits of hormonal treatment, there are other studies that are against this statement. The window of efficient therapy depends on the capacity of the brain to respond to sexual hormones, and the presence of receptors in brain areas related to memory. This decrease is related to the normal decrease in sexual hormones due to aging, in man and woman. In that term, HT is focused on to keep the hormonal levels constant, so the brain cannot lose its responsiveness to hormones. Basic studies have shown that the role of estrogens or molecules like tamoxifen, a selective estrogen receptor modulator used as hormone therapy, may induce/modulate the dopamine system, inducing neuroprotection. In that term, the use of tamoxifen in murine AD model has shown an increment in dopamine content in striatum, and an improvement in memory tasks [63].

Recently, seven prospective cohort studies with a total of 5251 elderly men and 240 cases of Alzheimer's disease were included into the meta-analysis of AD follow-up. Meta-analysis using random effect model showed that low plasma testosterone level was significantly associated with an increased risk of Alzheimer's disease in elderly men (RR = 1.48, 95% CI 1.12-1.96, P = 0.006) [64]. This decrease is in direct relation with appearance of Aβ plaques in the brain, since androgen and estrogens can regulate the amount of Aβ through the modulation of signal transduction or enzymes related to the clearance of Aβ, like insulin-degrading enzyme, neprilysin, endothelin-converting enzymes 1 and 2, and angiotensin-converting enzyme. In that term, animal models of gonadectomy, to reduce the sexual hormones, have shown a direct relationship between the hormonal decrease and the increased amount of Aβ in the brain [65–67]. Also, in this type of models, the hormone therapy reduces the levels of Aβ and improves the memory. Thus, the

formation of Aβ plaques can be induced by a reduction in sensitivity to estrogens or androgens due to long periods of low steroid hormones synthesis from gonads, modifying the mechanism of amyloid precursor protein elimination that is regulated by estradiol.

Clinical approach involved the estradiol and its role in maintaining brain architecture and metabolism, and chronically low levels of estradiol associated to anovulation may impair brain health. In women with functional hypothalamic amenorrhea, alterations in the thyroid axis impair neurogenesis and synaptic connectivity [68].

5. Sex hormones and Parkinson disease

Parkinson disease is a progressive neurodegenerative, multisystemic disorder characterized by a combination of motor symptoms like resting tremors, rigidity, bradykinesia, and postural abnormalities [69]. In addition, there are cognitive, neuropsychiatric, sleep, autonomic, and sensory disturbances associated to PD, which are related to the degeneration of serotoninergic neurons of the raphe nucleus, noradrenergic neurons of the locus coeruleus or cholinergic neurons of the nucleus basalis of Meynert [70]. PD is associated to degeneration of dopamine neurons in substantia nigra pars compacta, being PD the most common disease of dopamine dysfunction [71].

It has been reported that higher incidence rates of PD in men are compared to women [72, 73], and special interest has been put on sex hormones, due to its role on the regulation of dopamine synthesis, being estradiol the main regulator of this synthesis. In addition, studies performed to oophorectomized women, have revealed a higher risk of PD in this patients, suggesting that the abnormal decrease in estradiol prior to the menopause can be related to the onset of PD condition [74]. On other hand, increased exposure to endogenous estrogen can be associated with a late onset of PD and less sever motor impairment according to a study where 579 female patients were analyzed according to menarche age, menopause age, and PD onset age; also, delayed exposure to estrogens, through an increased age at menarche, is associated with older age at PD onset [75].

The synthesis of estrogen differs between reproductive and nonreproductive women, being the extragonadal tissues, like kidney, adipose tissue, skin, and brain, the main source of estrogen in nonreproductive women. In reproductive women, the main sources are ovaries, corpus luteum, and placenta. In men, the main source of testosterone is the testis.

As was mentioned for Alzheimer, sex hormones levels are crucial to maintain the proper functioning of brain circuits. Regarding to that, the normal decrease of estrogen levels in women, or testosterone in men, has been related to the onset of Parkinson. Many studies have shown that hormonal replacement therapy can reduce the risk of PD is applied during what is called a "window of opportunity", which is immediately after menopause. Using the same treatment after that period, the beneficial effects could be lost, due to a long-term hormone deprivation reviewed by [76] (**Figure 2**).

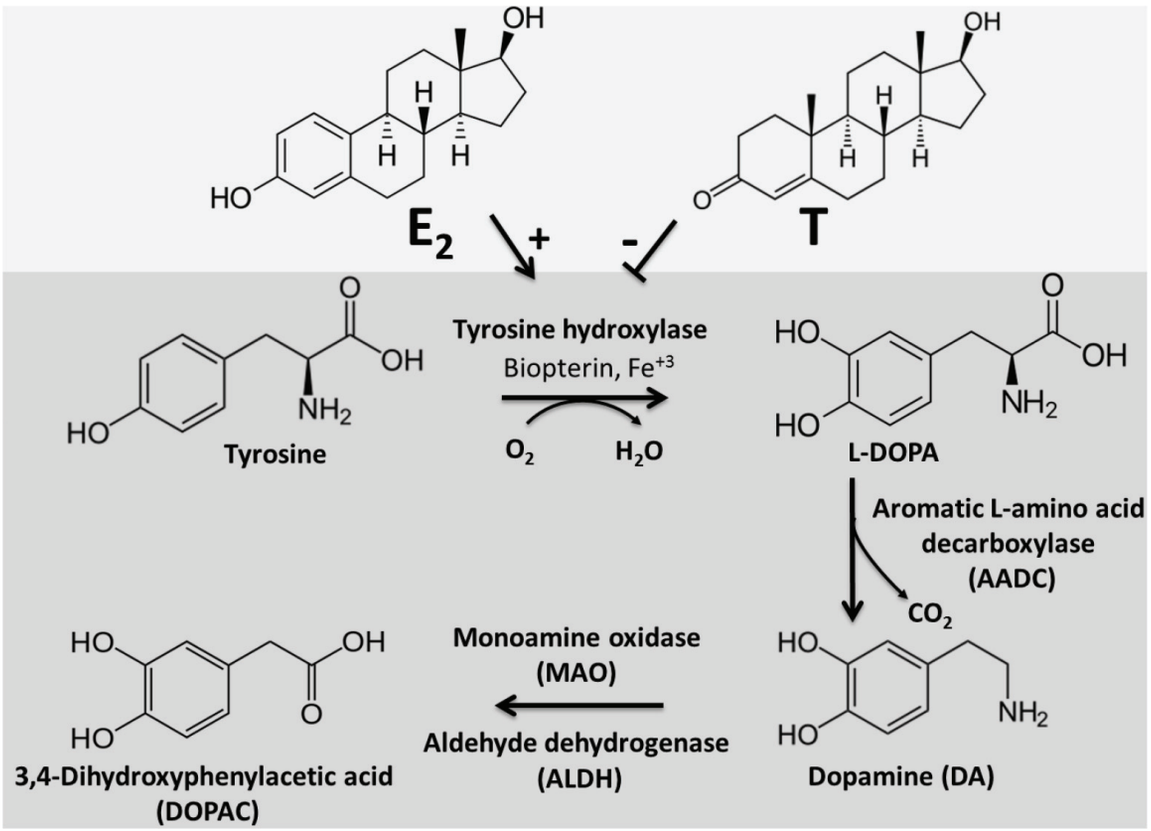

Figure 2. Effects of estradiol and testosterone on dopamine synthesis. Neonatal exposure to estradiol or testosterone increases TH expression in midbrain dopaminergic neurons. Abbreviations: E_2, estradiol; T, testosterone.

5.1. Clinical aspects in Parkinson disease

Male patients with Parkinson disease have less testosterone and estradiol than healthy males. In a recent study, it was determined if dopaminergic therapy using levodopa and dopamine agonist influenced testosterone levels. In this study, a cohort of 32 consecutive male patients from the INSPECT trial were used. INSPECT is a multi-center, prospective study that primarily examined the effects of short-term treatment with pramipexole or levodopa on cohort of PD patients [77]. There were statistically significant differences in the change in free testosterone level, increased in both the levodopa group and pramipexole group but decreased in the untreated group at 12-weeks post-treatment. These preliminary data support the premise that dopaminergic medications do not reduce testosterone levels in early PD patients. In a clinical study, where male subjects were analyzed (36 PD patients and 69 age-matched controls): prolactin levels were higher in PD subjects, compared to healthy ones. Also, concentrations of estradiol and testosterone in the control group were higher than those found in patients. In addition, the level of sex hormones was positively correlated with better mood and quality of life in patients affected with PD; prolactin levels correlated negatively with sex steroid concentrations [78, 79]. Therefore, it is extremely necessary to determine the level of hormones that may influence patients' cognition, mood, and quality of life of PD patients. The more important clinical trials that show the relationship between sex hormones and neurodegenerative disorders are shown in **Table 1**.

Pathology	Trial (N)	Primary end point	Treatment/Results (R)	Reference
ADHD	Phase III trial (n = 203)	Salivary testosterone levels	137 received daily methylphenidate treatment and 66 were assessed through naturalistic observation	[57]
Alzheimer disease	Phase II trial (n = 240)	Plasma testosterone	Meta-analysis using random effect model showed that low plasma testosterone level was significantly associated with an increased risk of Alzheimer's disease in elderly men	[64]
	Prospective brain imaging study (n = 54)	2-year prospective brain imaging study and randomized trial of HT continuation or discontinuation in a sample of middle-aged postmenopausal women (aged 49-69 years).	Continuation of HT use appears to protect cognition in women with heightened risk for AD when initiated close to menopause onset	[62]
Parkinson Disease	INSPECT trial–A multi-center Phase III trial (n = 32)	Testosterone levels and motor scores	There were statistically significant differences in the change in free testosterone level, increased in both the levodopa group and pramipexole group but decreased in the untreated group at 12-weeks post-treatment	[77]
	Phase II trial (n = 36)	The plasma levels of oestradiol, testosterone, prolactin and sex hormone-binding protein were examined in 36 patients affected with Parkinson's disease and in 69 age-matched control subjects, using chemiluminescent reactions.	The level of sex hormones was positively correlated with better mood and quality of life in patients affected with Parkinson's disease; prolactin levels correlated negatively with sex steroid concentrations.	[78]
Hormone decrease	Cognitive Impairment in postmenopausal women (n = 4532)		Participants received either one daily tablet of 0.625 mg of conjugated equine estrogen plus 2.5 mg of medroxyprogesterone acetate or a matching placebo. Results demonstrate that estrogen plus progestin therapy increases older women's risk for probable dementia, including Alzheimer	[80]
	Phase II trial Functional hypothalamic amenorrhea (n = 60)	Ovarian function (ovulating)	Randomized to Cognitive behavioral therapy or observation for 20 weeks	[68]

Table 1. More important clinical trials that show the relationship between sex hormones and neurodegenerative disorders.

6. Concluding remarks

Here, we review how sex hormones (i.e., neuroactive modulators) can differentially modulate neuronal neurodegeneration in animal and clinical models. Specifically, we provide an overview of the effects of sex hormones, stress hormones, and metabolic hormones on structural

plasticity and some pharmacological targets. In addition, we also discuss how sex hormones such as estrogen and testosterone can be affected by variables such as duration and intensity of motor and cognitive impairment. Understanding the neurobiological mechanisms underlying the modulation of neuronal structural plasticity by intrinsic and extrinsic factors will impact the design of new therapeutic approaches aimed at restoring physiological state and determine some pharmacological therapies. This approach is very important for the design of phase III clinical trial (randomized clinical trial) in the clinical practical conditions.

Acknowledgements

This work was supported by FONDECYT Grant N° 116-0398 and DIUV-CI Grant 01/2006 to Ramón Sotomayor-Zárate.

Conflict of interest

The authors of this work declare that they have no conflicts of interest.

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