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Chapter 12

New Insights for Hormone Therapy in Perimenopausal Women Neuroprotection

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Additional information is available at the end of the chapter

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Abstract

Perimenopause is a mandatory period in women's life, when the medical staff may initiate hormone therapy with sex steroids for the delay of brain aging and neurodegenerative diseases, during the so-called "window of opportunity." Animals' models are helpful to sustain the still controversial results of human clinical observational and/or randomized controlled studies. Estrogens, progesterone, and androgens, with their nuclear and membrane receptors, genes, and epigenetics, with their connections to cholinergic, GABAergic, serotoninergic, and glutamatergic systems are involved in women's normal brain or in brain's pathology. The sex steroids are active through direct and/or indirect mechanisms to modulate and/or to protect brain plasticity, and vessels network, fuel metabolism—glucose, ketones, ATP, to reduce insulin resistance, and inflammation of the aging brain through blood-brain barrier disruption, microglial aberrant activation, and neural cell survival/loss.

Keywords: perimenopause, "window" of opportunity, neuroprotection, sex steroid hormones

1. Introduction

The months/years of perimenopause represent an important moment during women's aging, when sex steroids and their receptors decline are evident in the hippocampal and cortical neurons, after estrogen exposure during the reproductive years. The sex steroid hormones decline is associated/acts synergic to other factors as hypertension, diabetes, hypoxia/obstructive sleep apnea, obesity, vitamin B12/folate deficiency, depression, and traumatic brain injury to promote diverse pathological mechanisms involved in brain aging, memory impairment, and AD.

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2. Sex steroid hormones involvement in aging brain. The perimenopausal "window" of opportunity for neuroprotection

Perimenopause represents the critical period during women's brain aging when it is possible to use the "window" of opportunity to delay/postpone the proved deleterious effects of sex steroids decline. The complex/complicated feedback loops between non-reproductive brain regions—prefrontal neocortex, hippocampus, amigdala, and brainstem, thalamus and hypothalamus, and the ovaries are made by sex steroid hormones, their network receptors through the entire brain, enzymes involved in their metabolism, their metabolites, neurotransmitters, cytokines, chemokines, and many other proteins/peptides. A multitude of studies are demonstrating the effects of estrogens (estradiol-E2, estetrol-E4, and in a less measure estrone-E1), progesterone, and androgens in brain during reproductive years, and have preventive functions to cognitive and memory performances, being involved in brain bioenergetic control by regulation of glucose transport, aerobic glycolysis coupled to the citric acid cycle, and mitochondrial respiration to generate ATP [1], and also in anti-inflammatory actions in the biology of neuroaging and neurodegenerative diseases. These effects of sex steroids are covering the two hypothesis of neurodegeneration discussed in the previous chapter.

Beside involvement in reproduction, sex steroids exert regulatory actions on the receptors in non-reproductive brain regions, including (but not limited to) prefrontal cortex and hippocampus, amigdala, thalamus, and brainstem, which occur *via* neural circuitry linking the hypothalamus to other CNS systems.

The steroid hormones are acting by indirect mechanisms on coagulation, metabolisms to prevent atherosclerosis, and to vasodilation of cerebral vessels, increasing the blood flow to the hippocampus and left superior temporal gyrus [2], and through direct cellular mechanisms on different types of neurons, microglia, and astroglia, on their synapses particularly in the brain regions that show preclinical abnormalities in individuals who are at risk for AD (**Table 1**).

Starting from basic science, preclinical and clinical studies, experimental, observational, and controlled trials are linked to estrogen-inducible neuroprotective, neurotrophic, and neurogenic actions. There are animal (rats, mice, non-human primates) and human evidences on cellular mechanisms of estrogen-regulated functions/systems, which are presented in **Table 2**.

2.1. Estrogens' involvement in brain aging

All types of studies have demonstrated that the neuroprotective effects of estrogens—mainly 17 β—and 17α-estradiol, progesterone, and androgens (DHEA mainly) are on the vessels, neurons, microglia, and astroglia. The vast majority of gynecological, endocrinological, and/or neurological research studies are about the thrombotic and ischemic stroke risks after the age of 50 years (median age of menopause).

Observational studies on large numbers of cases from North America as the Baltimore Longitudinal Study of Aging [3], the Manhattan Study of Aging [4] have associated HT/ET to significant prevention or delay onset of AD, or reduction risk of AD (9/156 [5.8%] estrogen

Author(s)/year	Type of study	Steroid	Action/Effect
Tang et al. [138]	Prospective observational (1–5 yrs. follow-up)	E2	Estrogen promotes the growth and survival of cholinergic neurons, and could decrease cerebral Aβ deposition, both of which may delay the onset or prevent AD.
Maki and Resnick [2]	Prospective (2 yrs. follow-up)	E2	Increasing the blood flow to the hippocampus and left superior temporal gyrus
McEwen et al. [79] Adams et al. [37]	Experimental Experimental	E2 E2	Estrogen synapses formation in the CA1 region of the dorsal hippocampus during the estrous cycle of the female rat E2 did not induced the increased synapses number in aged rats
Zhang et al., [34]	Experimental	17β E2, testosterone or methyl-testosterone	Estrogen & Androgen Protection of Human Neurons against Intracellular Amyloid Toxicity through Heat Shock Protein 70
Xu et al. [139]	Basic study	E2	Provides protection against β-amyloid-induced damage and tau-related changes
Norbury et al. [140]	RCT	E2	Maintenance of the cholinergic system in the hippocampus and frontal cortex
Persad et al. [141]	RCT	Ethinyl-E2 and progestin	Increased activation in brain regions associated with the left middle/superior frontal cortex, and left inferior parietal cortex during verbal memory encoding tasks on functional magnetic resonance imaging
Harburger et al. [64]	Experimental	E2 + progesterone	E2 alone and combined E2 + P4 may influence ERK activation in different time frames or enhance memory of objects recognition in young ovariectomized mice
Silverman et al. [142]	RCT	E2	Higher metabolism in language processing and auditory association areas compared to other HRT regimens (CEE or CEE + MPA)
Yao et al. [143]	Experimental	17β-E2	Early correction of bioenergetics deficits, and mitochondrial β-amyloid deposition when ovarian hormones decline
Zhao et al. [52]	Experimental	E2 + CyP4 vs. E2 + CoP4	Differential regulation of hippocampal gene expression according to P4 supplementation to E2
Tskitishvili et al. [46]	Experimental	E4	Antioxidative actions, neurogenesis and possibly promyelinating activities

Legend: E2: estradiol; Ethinyl-E2: ethinylestradiol; MPA: medroxyprogesterone acetate; CEE: conjugated equine estrogens; RCT: randomized control trial; CyP4: progesterone cylic; CoP4: progesterone continuous

Table 1. Actions/effects of sex steroid hormones on brain aging.

users vs. 158/968 [16.3%] nonusers; 0.40 [95% Cl 0.22–0.85], $p < 0.01$), and for a longer duration than 1 year, with no effect observed for the age of menopause. At that moment, the researchers considered the necessity of prospective studies for the establishment of the dose and duration of ET to provide this benefit and to assess the safety in elderly postmenopausal women.

The "healthy-cell bias" hypothesis demonstrated the E2 neural different effects at different ages, and at different stages of Aβ presence, making the explanations of different results

Estrogen-regulated functions/systems	Reference(s)
• Estrogens prevent apoptotic death cascades and neuronal death	Lebesgue et al. [40] Etgen et al. [144] Inagaki et al. [42]; Etgen and Inagaki [41]
• Estradiol rapidly stimulates signaling cascades: as the mitogen-activated protein (MAP) kinase family and the phosphatidylinositol 3-kinase (PI3K), pathway leading to the phosphorylation of Akt (a key signaling molecule), and Akt can promote local protein synthesis related to the formation of new spines through a non-genomic mechanism • Estradiol increases phosphorylated Akt (pAkt) present in CA1 dendrites, spines, and synapses	Cordey et al. [145] Znamensky et al. [90] Zhao et al. [146]; Mannella and Brinton [86];
• Estrogens increase the dendritic spine and synaptic density by 30% on CA1 pyramidal cells in the hippocampus • Estrogens provide potential to protect or have the capacity to alter synaptic and postsynaptic circuitry in hypothalamus, hippocampus, and neocortex	Gould et al. [36]; Adams et al. [147] Choi et al. [148].
• Estrogen- induced mitochondrial functions in brain bioenergetics • Estradiol promotes mitochondrial respiration and hence ATP generation and antioxidant enzymes that offset the increase in free radical generation induced by increased respiration • Estradiol significantly reduces mitochondrial lipid peroxidation	Nilsen and Brinton [149]. Nilsen et al. [150]. Simpkins et al. [151]
• Estrogen-induced calcium signaling pathways both promote neuronal function and can exacerbate neuronal demise in neurodegenerative disease states.	Brewer et al. [152]
• Estrogens augment the glutamatergic impact on hippocampal function	Zhao et al. [153];
• Estrogens exerts on the GABAergic and cholinergic systems in the hippocampus and frontal cortex	Rudick et al. [154] Tinkler et al. [155].

Table 2. Evidences on cellular mechanisms of estrogen-regulated functions/systems.

between experimental, observational studies and large RCT, that E2 is beneficial on rats' healthy hippocampal neurons before Aβ exposure [4–6]. More than this hypothesis on "healthy-cell bias," there are discussions and comments about the discrepancies between basic science and/or observational studies supporting estrogen neuroprotective effects and RCT results, focusing the attention to age, stage of reproductive aging, duration of hypogonadism, and the presence of symptoms of cognition or memory impairment, in the efforts for reconciliations [7] between HT and risk for AD [17]. If neurons are healthy at the time of estrogen exposure, their response to estrogen is beneficial for both neuronal survival and neurological function. In contrast, if neurological health is compromised, estrogen exposure over time exacerbates neurological demise. These last two statements represent the opinion of Brinton [8] from the Department of Pharmacology and Pharmaceutical Sciences of California University (USA). In concordance to these facts, the North American and Chinese researchers had elaborated, and tried to confirm the "hypothesis of critical period of estrogen neuroprotection," which appreciates the risk of duration of estrogen deprivation [9]. It was suggested as a "critical period" or a "critical window of opportunity" for the beneficial protective effect of E2 on the human brain [10, 11], and that estrogens have to be administered at perimenopause or earlier to observe a beneficial effect on the neural system [12, 13], as it is for the cardiovascular system.

A consensus began to emerge (although not without controversies) that HT/ET at the time of the menopause transition and afterward could have beneficial effects on several neurological

symptoms [7, 14]. The actions of sex steroid hormones are bidirectional to the body periphery and to the brain, and today, there are current evidences that estrogen and progesterone may have beneficial, neutral, or detrimental effects on the brain, depending on age at therapy initiation, type of menopause (natural vs. induced), or stage of menopause, specificity of administered medication, mainly the association of E2 to progesterone (P4) (exogenous), active on cognition through its 5α-reduced metabolite, allopregnanolone [15].

There are characteristics that contribute to several discrepancies in the results: age, stage of reproductive aging, duration of hypogonadism, and symptoms presence. A better understanding of the nature of these discrepancies will be base for future studies of clinical relevance of ovarian steroids and hormone therapies in women.

The Canadian gynecologists [16] were the first who described neurological and psychological disturbances after oophorectomy, than the Italian gynecologists [17]. One may consider that these surgical circumstances are an abrupt, deep decline/withdrawal of steroids, different from the gradual decline in natural menopause, and the cognitive decline in surgical/chemical menopause is more severe [18]. In natural menopause, either premature or early or at the median age of 51 years, the hormonal decline is on a slow slope for E2 and E1, and the androgens (testosterone, androstenedione, and dehydroepiandrosterone) [19] are still present up to the age of 65 [20].

Professional organizations including the British Menopause Society [21], the International Menopause Society [22], and North American Menopause Society [23] recommend estrogen replacement therapy for women with premature menopause or premature ovarian failure. There are evidences, although not from RCT that restoring pathologically low estrogen levels will reduce the later development of cardiovascular disease, osteoporosis, and possibly dementia. This leads to the general recommendation that estrogen be continued in women who experience premature menopause or early menopause until at least around the median age of natural menopause (approximate age 51 years), effects which are evident up to 60 years for women in natural menopause treated for menopausal symptoms [10]. Different to this category of age, the initiation of ET alone or in combination with a progestin in the late postmenopausal stage (ages 65–79 years) induced an increased risk of dementia and cognitive decline regardless of the type of menopause ([10], citing WHIMS), as the "continuum of neurological health progresses from healthy to unhealthy so to do the benefits of ET/HT" [4].

2.1.1. Animal models

Experimental evidences support the favorable estrogen effect in neurons, on spinogenesis and synaptogenesis, and the rationale option for the prevention/reduction of the risk or the delay of the onset of AD in postmenopausal women. The North American experiments of McEwen at the Laboratory of Neuroendocrinology from The Rockefeller University, New York, on rats' brain in the years of 1990s' were a surprising discovery on the modulation of hippocampal structural plasticity done by estrogens, and it was considered as a "whole new field in the science" [24]. In the animal models, there are differences between species, regarding reproductive and brain aging scenarios, both changes precede natural reproductive failure [7]. There are some similarities between humans and rodents, and differences between rats and mice.

Estrogens influence the process of adult neurogenesis. E2 promotes the migration of newly generated neurons toward the damaged brain regions, facilitating brain remodeling, and repair after ischemic stroke injury [25].

E2 induces neuronal plasticity underlying cognitive function. Acute E2 treatment promotes hippocampal neurogenesis in the female rat [26], which has been linked to hippocampal-dependent learning and memory [27]. It was revealed on rats experiments [28] that different forms of estrogens modulate neuroplasticity and cognition in complex and intriguing ways. Estrogens specifically up-regulate adult hippocampal neurogenesis (*via* cell proliferation) and synaptic protein levels in the hippocampus in a time- and dose-dependent manner [29]. Low levels of E2 facilitate spatial working memory and contextual fear conditioning, while high levels of estradiol impair spatial working, spatial reference memory and contextual fear conditioning, and estrone (E1) impairs contextual fear conditioning. The rats' experiments show that only 17β-E2 and not E1 is increasing the survival and activation of new neurons in the hippocampus in response to spatial memory compared to controls [30].

The Chinese experiments on menopausal mice had identified morphological changes in the hippocampus mitochondrial damage, lipofuscin deposition and microtubule degradation, which were possible to be partially restored: mitochondrial damage and lipofuscin increase, not the microtubules degradation, and only in early postmenopausal stages [31].

Regarding the first hypothesis on bioenergetics failure in females' brain aging, animal models demonstrated estrogens effects on mitochondria energetic metabolism. E2 is regulating mitochondrial proteome, being a key metabolic control of enzymes including pyruvate dehydrogenase, aconitase, and ATP-synthetase, and so it is a high respiratory control ratio, elevated cytochrome-c oxidase activity and expression, and it is reduced brain free radical generation [32], according to the knowledge that in aging brain is a high lactate level [30].

E2 is able to mitigate negative effects of glucocorticoids, as animal and human researches indicate: E2-related mitigation of glucocorticoid damage and interference is one benefit of E2 supplementation during perimenopause or soon after menopause. The evidence for E2-related protection against glucocorticoids suggests that maintaining E2 levels in postmenopausal women could protect them from stress-induced declines in neural and cognitive integrity [33].

Physiological doses of 17β-E2, testosterone or methyl-testosterone reduce induced cell death by 50% in neurons treated after the injection and by 80–90% in neurons treated 1 h before the injection [34]. The effect is mediated by genomic mechanisms proved by the blockage of ERs and ARs, and by a proteomic mechanism—the increasing levels of heat shock protein 70 (Hsp70), and the hormones role is to protect from the development and toxicity of the intracellular Aβ (iA1–42), which induces neuronal apoptosis and death, being known that AD starts with intraneuronal iA1–42 accumulation in human brain [35].

The "estrogen action hypothesis" known as "healthy-cell bias" elaborated in the North American Laboratories for Neuroscience Research [4, 5, 8] tries to explain the differences between the effects of estrogens on normal/healthy neurons and aged/damaged neurons. It was demonstrated with different doses (low dose of 10 ng/ml and large dose of 200 ng/ml) and on different schedules (acute vs. continuous vs. intermittent) in experiments on rats' hippocampal neurons

exposed to Aβ, that is possible to prevent neurodegeneration when E2 is administered before or during Aβ exposure, the strongest effect being on continuous administration, and the effects are worsened up to neuronal death when are large doses or when Aβ is already present. These results were obtained after previous studies regarding estrogen critical different effects on synaptic system at different rats' ages. Whereas, young rats displayed a 30% increase in axospinous synapse density in CA1 [36], fact which is absent in aged rats [37], as is mentioned in **Table 2**.

There are findings in rodents and monkeys providing evidences that the hippocampus (in rats) and the frontal cortex (in monkeys) remain responsive to E2 administered either *in vivo* or *in vitro* even after prolonged periods of hormone withdrawal [38, 39]. The physiological concentrations of E2 exert profound neuroprotective action on apoptotic death cascades and neuronal death from focal and global ischemia causing selective, delayed death of hippocampal CA1 neurons and associated cognitive deficits after a single injection in acute ischemia [40]. E2 administered at physiological levels for 2 weeks before ischemia rescues neurons destined to die in the hippocampal CA1, and ameliorates ischemia-induced cognitive deficits in ovariectomized female rats [41]. An acute post-ischemic infusion of E2 into the brain ventricles is neuroprotective in aged rats after 6 months of hormone deprivation, and E2 enhances synaptic transmission in CA1 pyramidal neurons of aged long-term hormone deprived females [42].

There are evidences about distinct estrogens effects on different cognitive aspects, anxiety-like, and depressive-like behaviors. There are comparisons regarding the subregion-specific effects on tryptophan hydroxylase-2 (TpH2, the brain-specific, rate-limiting enzyme for 5-HT biosynthesis, a serotonin precursor). The comparison of CEE and E2 treatments on behavior and TpH2 mRNA on female ovariectomized Sprague Dawley rats [43]. Both CEE and E2 exert beneficial behavioral effects, although efficacy depended on the distinct behavior and for cognition, on the task difficulty. Compared to CEE, E2 generally had more robust anxiolytic and antidepressant effects. E2 increased TpH2 mRNA in the caudal and mid dorsal raphe nucleus. The recent Chinese study on adult male Sprague Dawley rats [44] demonstrated that low dose E2 administered for the first 3-months after bilateral common carotid artery occlusion (BCCAO) exerted long-lasting beneficial effects, including significant neuroprotection of hippocampal CA1 neurons and preservation of hippocampal-dependent cognitive function when examined at 6 months after BCCAO.

Recent evidences demonstrate a *de novo* estradiol synthesis within the hippocampus and other brain regions, which seems highly likely that activity-dependent estradiol signaling can play an essential role in the modulation of discrete signaling units within individual cells, affording "fine- tuned" control of neuronal excitability [45].

Animals and *in vitro* studies are demonstrating the role of estetrol (E4) on nervous system. The antioxidative actions of E4 mostly depend on ER-α and ER-β, whereas neurogenesis and possibly promyelinating activities might be realized through ER-β, and the membrane GRP30 receptor for estrogens and progesterone is less important for LDH activity and cell survival in E4 actions [46].

The animal experiments reconcile the discordance between studies showing favorable steroids/estrogen effects in neurons to the results from former randomized trials, as the largest randomized clinical trial of HT ever conducted—Women's Health Initiative Memory Study

(WHIMS), which showed that women who initiated estrogen therapy alone or in combination with the progestin MPA after the age of 60 years had a twofold greater risk to develop dementia [47] or are affected regarding mean cognitive performance over periods of time ranging up to 5 years [10], or estrogen-containing hormone therapy initiated in the late postmenopausal stage (ages 65–79 years) is followed by an increased risk of dementia and cognitive decline regardless the type of menopause—naturally, medically, or surgically induced [48].

2.1.2. Human studies

The Mayo Clinic Cohort Studies of Oophorectomy and Aging—unilateral or bilateral oophorectomy [48–50] and estrogens, before the age of menopause. The risk of cognitive impairment/dementia is increased after either unilateral or bilateral oophorectomy compared to referent women (Hazard ratio [HR] of 1.46; 95% CI 1.13 to 1.90; adjusted for education, type of interview, and history of depression). These associations were similar regardless of oophorectomy indication, and for women who underwent unilateral or bilateral oophorectomy were considered separately. The risk increased with younger age at oophorectomy (test for linear trend; adjusted $p < 0.0001$). The same study group from the Mayo Clinic showed that women who underwent bilateral oophorectomy before menopause were at increased risk of Parkinsonism, and the risk increased with younger age at time of oophorectomy [49, 50]. Their conclusion was a sizeable neuroprotective effect of estrogen before the age of 50 years.

Some studies are sustaining that estrogen neuroprotective actions are modulated by progesterone/progestogens. Specifically, continuous progestogen exposure is associated with inhibition of estrogen actions, whereas cyclic delivery of progestogens may enhance neural benefits of estrogen [51]. In the next subchapter, more evidences on these findings are discussed. The North American study [52] provides evidence at the molecular level that different regimens of HT can induce disparate gene expression profiles in brain. From a translational perspective, confirmation of these results in a model of natural menopause would imply that the common regimen of continuous combined HT may have adverse consequences, whereas a cyclic combined regimen, which is more physiological, could be an effective strategy to maintain neurological health and function. It has to be remembered that different factors may determine the efficacy of ER/HT as age, menopausal status, route of administration and dose, the starting cognitive function, and the presence of pre-existing risk factors (smoking, apolipoprotein E genotype) [53].

2.2. Progesterone neuroprotective role in women's aging

During menopausal transition on assists at lowering progesterone (P4) values by luteal defect, and afterward in perimenopause P4 which is absent, and at the beginning of the history of HT recommendations, P4 administration was mandatory for women with intact uterus, fact that continues to be actual. There were intensive efforts to develop progesterone neurobiology in the hippocampus and cortex, and current discoveries are sustaining P4 administration for more than uterine protection from endometrial hyperplasia and cancer, but for brain aging protection, besides the much analyzed "therapeutic window" of progesterone in brain trauma. P4 is active

on cognition through its 5α-reduced metabolite, allopregnanolone [15, 54], a fact that differentiates P4 from the progestin MPA, which proved as a jeopardizing drug for elder postmenopausal women. P4 has neuroprotective effects mediated by various mechanisms such as reduction of neuronal vulnerability to neurotoxic molecules, reduction of cell loss, inhibition of lipid peroxidation, and expression of pro-inflammatory genes [55–57]. P4 can exert protective effects through its metabolites—allopregnanolone or 3α, 5α-tetrahydroprogesterone, the best known, which can interact with membrane-associated receptors coupled to ion-channels, such as the $GABA_A$ receptor system. P4 and allopregnanolone, exert various effects on both cognitive and non-mnemonic functions in females. Allopregnanolone may also elicit its protective effects through its actions on the mitochondria [58]. Allopregnanolone is enhancing cognitive performances and placement memory in mice, by inducing higher levels of brain-derived neurotrophic factor (BDNF) in the prefrontal cortex and hippocampus, an effect that is contrary to the lowest levels among mice administered MPA [15]. MPA—the progestin used to balance CEE in WHIMS—was proved by *in vitro* studies to be the best antagonist to neurotrophic and neuroprotective estrogen actions in neurons, fact that makes it completely different to P4 which alone is neuroprotective [59], and acts synergistic with estradiol [60]. MPA (Provera®) metabolic involvement is also divergent from P4, regarding the action on nuclear mitogen-activated protein kinase signaling [61], and on the exacerbation of neuroexcitotoxicity of glutamate [62]. The well-known object recognition task is a valuable experimental paradigm that can be used to determine the effects and mechanisms of progestogens for mnemonic effects across the lifespan. Improvements in object recognition performance of rodents are often associated with higher hormone levels in the hippocampus and prefrontal cortex during natural cycles, with progesterone replacement following ovariectomy in young animals, or with aging [54].

The estrogens neuroprotective actions are modulated by progesterone. It was demonstrated [63] in young ovariectomized mice that E2 enhances object memory consolidation, which depends on dorsal hippocampal activation of the extracellular signal-regulated kinase/mitogen-activated protein kinase (ERK/MAPK) signaling pathway, and the questions were if the E2 actions need progesterone adding, which was latter demonstrated, and more than this the effect is E2 dose-dependent [64]. It was suggested that E2 alone, and combined with P4, may influence ERK activation in different time frames or enhance memory through different mechanisms. E2 alone significantly increased phospho-p42 ERK protein levels in the dorsal hippocampus relative to vehicle controls. In contrast, no combination of E2 and P4 affected dorsal hippocampal phospho-ERK levels.

2.3. Androgens neuroprotective role in women's aging

Recent studies on normal age-related testosterone and its androgen metabolite dihydrotestosterone (DHT) loss in plasma and brain in men are emerging AD risk, and the protective role of endogenous testosterone/DHT is not only to increase the neuronal resilience against AD-related insults, but also to reduce intracellular Aβ accumulation [34, 36, 52], testosterone actions are similar, but also cumulative to those of estrogens in perimenopausal women. In perimenopause, estrogens and androgens are still in physiological levels in plasma and brain, and their presence is considered to prevent the accumulation of intracellular amyloid 1-42

(iA1-42) in the hippocampus and the entorhinal cortex neurons, preceding amyloid plaque formation, and further induction of neuronal death [65]. Proteomic analyses are demonstrating increased levels of Hsp70 in testosterone- and estrogen-treated human neurons [15], which is a sign of Aβ toxicity inhibition.

Cell cultures are bringing strong evidences that both androgens and estrogens are neuroprotective, and many studies analyzed the different pathways for neural cells protection from Aβ toxicity. Testosterone is involved in regulation of spine synapse density in the CA1 region of hippocampus [66].

A special analysis is to be made on DHEA(S)—the "youth" hormone—for which human body does not have receptors, but it is a source of intracrinology, with different enzymes for steroid-forming and/or for steroid-inactivating, permitting each cell/tissue to synthesize a small amount of androgens and/or estrogens in order to meet the local physiological needs without affecting the other tissues of the organism [67]. Blood concentrations are not different from those observed in normal postmenopausal women having high serum DHEA concentrations, when DHES is supplemented to maintain serum estrogen level at sub-threshold or biologically inactive concentrations.

On the other hand, all androgens are made intracellularly from DHEA by the mechanisms of intracrinology, and are always maintained at very low levels in the blood in pre- and postmenopausal women [67]. According to this conceptus, it was proposed a short-term DHEA supplementation (5 mg/day × 7 days) in perimenopausal female rhesus macaques [68]. The comparison of serum and hippocampal levels in treated and controls of the same age revealed that despite lower concentrations of the estrogens in the serum of elder animals, their concentrations in the hippocampus did not show any obvious differences due to age or to DHEA supplementation. The results suggest that *de novo* estrogen synthesis in the brain may compensate for the perimenopausal loss of estrogens in the circulation even without supplemental DHEA.

3. Receptors mediators of sex steroid hormone signaling mechanisms of action in neuroprotection

The sex steroids can protect through the activation of transcriptional activity in the genomic mechanism or *via* signaling of neurons survival pathways [69–71] or *via* non-genomic mechanism through membrane receptors.

More and more studies/trials are presenting new insights of sex steroids involvement in hypothalamic, hippocampal, and other brain neurons, their actions being partially common to other organs/tissues effects, but with important peculiarities. The well-known mediation *via* intracellular receptor/transcription factors that interact with steroid response elements on target genes, regarding the genomic mechanism, is doubled or tripled in the speed of alterations of the neuronal activity within seconds, indicating that some cellular effects can occur *via* membrane delimited events. Sex steroid hormone ligands bind to membrane-associated G protein-coupled receptor (GPR 30) [72], and caveolin proteins have an essential role for

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membrane receptors [73]. In addition, estrogens can affect metabotropic glutamate receptors, and the second messenger systems, including calcium mobilization, and a plethora of kinases to alter cell signaling. This subchapter considers the current knowledge of rapid membrane-initiated and intracellular signaling by steroids in the brain, the nature of receptors involved, and how they contribute to homeostatic functions.

3.1. Estrogen receptors (ERs). Genetic polymorphism and epigenetics of ERs

The protective role of estrogens in the brain is sure, and the missing preventive effects revealed by RCT is connected to the age-related changes of ERs, as it is in the endometrium/uterus [74], suggesting that several key players in the local synaptic response to E2 are compromised in aging females. The brain has one of the most complex and complicated ERs network of the body, which is changing life-long. In addition to its well-documented hormonal action, E2 is considered as a neurotransmitter in the brain [75].

In the last 10 years, molecular and biochemical animal studies are demonstrating that the mechanisms used by estrogens are greatly influenced by brain cell type, ER type, and metabotropic glutamate receptors (mGluRs) independent of glutamate, and/or region of the brain-cortex and/or hippocampus, all these leading to differential regulation of neuronal circuitry in each area [45, 76]. The hippocampus cognitive performance is directly connected to ER-α, other ERs such as ER-β and GPR30 [8]. The ERs have similar distribution in female and male brains, but may differ in relative expression [77]. ER-α and ER-β expression patterns generally overlap, where ER-α is associated with reproductive behavior, whereas ER-β is associated with non-reproductive behaviors such as learning and memory [78] and anxiety-related behaviors. In hippocampus and cortical neurons, the estrogens—mainly E2 and other estrogenic ligands bind to membrane—associated and mitochondrial-associated G protein-coupled receptor (GPR 30), and activates the classical/canonical nuclear and extranuclear or intra-cytoplasmatic ER isoforms—α and β—functioning as transcription factors [79–81], and a new type of nuclear ER, the orphan estrogen-related receptor γ (ERR γ), which regulates dopaminergic neuronal phenotype [82], and IGF-1 receptor, which was recently recognized as a receptor for estrogens.

The nongenomic or alternative signaling pathways mechanism involving extranuclear ERs respond to physiological concentration of estrogens to elicit neuroprotection, resulting in the "fine tuning" of neuronal circuitry [45]. Often, rapid activation of intracellular signalers such as mitogen-activated protein kinase (MAPK) or phosphatidylinositol-3-kinase (PI3K) underlie alternative estrogen-induced neuroprotection upon activation of specific binding sites at the plasma membrane. The plasma membrane ER (mER) originates from, or is related to canonical nuclear ERs, and GPR30 mimics short latency E2 facilitation of synaptic transmission in the hippocampus, to enhance memory and cognition [83]. The activation of GPR30 by G-1 (its specific ligand) is associated with a mobilization of calcium in dissociated and cultured rat hypothalamic neurons [80, 84, 85]. There were elaborated cellular models of Aβ toxicity where classical and alternative pathways activated by estrogens seem to coexist to orchestrate neuroprotection, fact that is a unique signaling profile of estrogen neuroprotection, dependent upon activation of the MAPK signaling [86].

ER-α and ER-β mediate the effects of E2 on both intracellular signaling and gene transcription, sharing similar domain organization, and using almost identical DNA-binding elements, co-regulators, and transcription machinery. There are differences between ER-labeled regarding each female, species (rats, non-human primates, human), age (young, old), estrogen levels, brain reference area, vulnerability of spines/synapses based on size (large or small), or presynaptic/postsynaptic location of ER. Both, ER-α and ER-β are located predominantly at extranuclear sites; ER-α are found in dendritic spines, many originating from pyramidal cells, axons, terminals, astrocytes, and microglia [81], in symmetric and asymmetric synapses. ER-β is detected on or near the plasma membrane of somata and dendritic shafts and spines in hippocampal neurons [81], in axons and axon terminals and both in the cytoplasm and on endomembranes near mitochondria *in vivo* [81], and within mitochondria *in vitro*, in pyramidal cells, in newly generated cells in a few interneurons and in glia [81]. Changes in ER-β expression occur in the presynaptic membrane, cleft, and postsynaptic membranes, where neurotransmitter release and postsynaptic receptor binding occurs. Conversely, ER-α changes are detected presynaptically in synaptic vesicles and postsynaptically in plasmalemmal and cytoplasmic regions of spine heads where protein translation occurs. In aged animals, it was demonstrated for the first time [78] that the window for E2-mediated benefits on cognition and hippocampal E2 responsiveness can be reinstated by increased expression of ER-α.

Studies have determined that membrane-localized ER-α and ER-β are capable of activating multiple metabotropic glutamate receptors (mGluRs) independent of glutamate, leading to downstream second messenger signaling [73, 76]. The expression of ER-α and ER-β mRNA in the hippocampus is limited [87], and GPR30 may be the major receptor subtype by which estrogen produces its enhancing effects. The physiological consequence of activation of GPR30 can regulate local synthesis pathways in a novel direction of our understanding of rapid estrogen signaling within the brain and its ability to induce the "fine-tuning" of neuronal circuits [45]. E2 works as a neuroprotector by membrane receptors coupled to E2 induction of intracellular $Ca^{(2+)}$ influx *via* the L-type channels, connected to memory mechanisms, and through Src/ERK/cyclic AMP response element-binding protein activation in single hippocampal neurons [88]. The presence of the L-type Ca (2+) channel inhibitor, nifedipine (10 microM), partially inhibits 17 β E2 [89].

It was discovered an aging decrease of about 50% of ER-α-labeled synapses [37, 45], with alteration in the ratio of ER-β to ER-α, fact that contributes to age-related decreases in the capacity to form additional spines and synapses in response to E2 in rats. In addition, synaptic pAkt thought is activated by ER-α [90], which is also decreased dramatically in aged CA1 axospinous synapses [91], as is ER-β [92], suggesting that several key players in the local synaptic response to E2 are compromised with age in female rats.

It was reported for the first time in Mont Sinai University (New-York, USA) [93] that in the monkey's neocortex 46, approximately 50% of the axospinous synapses contains ER-α, with axon terminals more likely to have ER-α than spines, and that presynaptic ER-α was often associated with vesicles, whereas postsynaptic ER-α was widely distributed in the PSD, adjacent to the PSD, and in the spine core.

The duration of brain's estrogen deprivation is connected to C terminus of heat shock cognate protein (Hsc) 70-interacting protein (CHIP)-mediated proteasomal degradation of hippocampal

estrogen receptor-α in conditions of rats' global ischemia, or of aging hippocampal CA1 region [9]. Natural aging is associated with increased ER-α and ER-β CHIP binding and ubiquitination, and with decreased ER-α and ER-β levels in the hippocampal CA1 region, fact that is different from the aging uterus in the rat model of long-term E2 deprivation (LTED) or after ovariectomy, where the level of ER *via* the ubiquitin-proteasome degradation pathway is increasing after estrogen exposure [9].

The studies on rats and monkeys [39] from Mount Sinai School of Medicine (New York, USA) have emerged three key findings: (1) synaptic ER-α is present in axospinous synapses in monkeys dorsolateral prefrontal cortex, in area 46; (2) it is stable across treatment and age groups (which is not the case in rat hippocampus); and (3) the abundance and distribution of synaptic ER-α is a key correlate of individual variation in cognitive performance in certain age and treatment groups.

Another interesting and important findings about rats cortex are that ER-α can modulate synaptic function and behavior even in the absence of circulating gonadal E2, in response to E2 synthesized within neurons [94], and that ER-α may initiates the non-genomic signaling mechanisms modulating synaptic plasticity in the hippocampus in response to either circulating or locally synthesized E2 [39, 93]. These findings are considered of great importance for the design of HT strategies for both surgically and naturally menopausal women.

The detected levels of ERs in postmortem brain tissue of AD patients is related to the severity of cognitive impairment assessed proximate to death, and only the reduction of ER-α from frontal cortex is correlated to Mini-Mental State Examination score, not the ER-β [95]. The spectrometry, immunohistochemistry, and quantitative real-time PCR of the autopsied Japanese AD patients compared to controls [96] have revealed a glial nuclear ER-β expression significantly lower in white matter in the AD group vs. controls, without any significant differences in estrogen concentrations, and the conclusion was that estrogens have effects on glias and neurons in the etiology of AD, and the correlation between BMI and estrogen concentrations in the frontal lobe suggests the importance of non-brain sources of estrogens particularly in controls.

Long-term E2 treatment initiated 14 days prior to global ischemia in ovariectomized female rats demonstrated that E2 at near physiological concentrations acts *via* the IGF-1 receptor to protect the functional integrity of hippocampal CA1 neurons and synapses in conditions of global ischemia, but not the classical ER-α or β. [97]. The transactivation of IGF-1 receptors and stimulation of ERK/MAPK signaling pathway maintains CREB activity in the ischemic CA1.

All three types of ERs cooperate in neuroprotection against AD [98], in association to intracellular calcium signaling cascade, which is very important, and the ER-α is the central key, for maintaining channel inactivation and may be relevant in neuronal preservation against Aβ injury. It was demonstrated that combination of ERm and caveolin in caveolae, and ER-α-mediated inhibition of Death domain-associated protein translocation may protect neurons against Aβ injury. ER-α and IGF-IR co-activation may mediate neuroprotection, and many other growth factors and intracellular signaling responses triggered by ER-α may play important roles in the process [98].These data are crucial for contemporary societies, with high risks for diabetes mellitus, in all populations. A very recent study from the University of Missouri,

St. Louis (USA) [99] demonstrated the neuroprotection of the coupling of IGF1 to estrogens and/androgens. It is considered that both steroids are involved in many neuroprotective processes that operate on similar signaling cascades [100].

Another tested hypothesis is upon GPR30 that act together with intracellular estrogen receptors to activate cell signaling pathways to promote hippocampal neuron survival after global ischemia [101]. E2 at physiological concentrations intervenes in apoptotic death cascades and ameliorates neuronal death, increasing BCL-2 expression in rat hippocampal neurons [88] (in experimental models of focal and global ischemia), but the proper mechanism is still unclear.

Regarding ERs, there are new details about the genes, and mRNA variants of ER-α expressed in different parts of the human brain, and there are specific ER-α mRNA splice variants or isoforms of ER-α in the medial mammillary nucleus (MMN) in AD [102] or in the frontal cortex in AD patients [95], and their relationship to cognitive impairment.

There are some therapeutic indications for cognition and memory support, which are partially controversial. The first is regarding the benefits from the upregulation of the expression of ER-α, but not of ER-β, in the hippocampus of aged animals, in order to restore the potential of E2 treatments and rejuvenate E2-induced hippocampal plasticity [78]. The second are from the results of a multinational study [103] sustaining the beneficial effects of long-term treatment with diarylpropionitrile (DPN, 0.05 mg/kg/day, sc.), a selective ER-β agonist, on the hippocampal transcriptome in ovariectomized, middle-aged (13 months) rats. The results reveal the contribution of ER-β-mediated processes to the regulation of transcription, translation, neurogenesis, neuromodulation, and neuroprotection in the hippocampal formation, and the authors concluded that the findings are supporting the notion that selective activation of ER-β may be a viable approach for treating the neural symptoms of E2 deficiency in menopause. There are studies suggesting that DPN—a selective ER-β agonist—mimics many basic effects of E2 in the hippocampus and enhance mice's hippocampus-dependent spatial memory [104, 105].

Recent studies are involving the genetic polymorphism of ERs, especially of ER-β in cognitive impairment and increased risk for AD predominantly in women [106]. It was examined that the role of single nucleotide polymorphisms (SNP) in the ERs genes: rs9340799, rs2234693, rs2228480 (in the ESR1 gene), and rs4986938 (in the ESR2 gene) as a risk factor for amnesic mild cognitive impairment (MCI) and AD. The less represented alleles of SNPs studied are associated with MCI and AD in women APOEε4 allele carriers [107, 108]. Some studies are focusing the association of Eε4 allele of apolipoprotein E gene to obesity, inflammation, and the risk of AD. Although, the pathways underlying this relationship are unclear the sex steroid hormones may be the connection [109, 110].

The epigenetic processes are associated to brain aging. The post-translational histone changes and DNA methylation are modulating the hippocampal memory-enhancing effects of E2 [111, 112].

3.2. Progesterone receptors

P4 has neuroprotective effects mediated by various mechanisms P4 or its metabolites-regulated neural responses are mediated by an array of progesterone receptors (PRs) which

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are broadly expressed throughout the brain, inclusive the hippocampus, and can be detected in every neural cell type [113]. There are known the classic nuclear PR-A (the N-terminally truncated form of PR-B) and PR-B receptors, and splice variants of each, explaining the P4 genomic mechanism of action through specific progesterone response elements (PRE) within the promoter region of target genes to regulate transcription of the genes [114], and the two types of cell surface-associated proteins [membrane PRs (mPRs) and the progesterone membrane receptor component (PGMRC)].These PRs induce classic regulation of gene expression while also transducing signaling cascades that originate at the cell membrane and ultimately activate transcription factors. As for estrogens the genomic and non-genomic mechanisms of P4 are coupled, so the distinctions are not as clear-cut as was first thought [115]. The nuclear PRs are up-regulated by E2 in glial and neural cells, but more in the glial cells, implicating crucial progenitor cells, as preferential targets of P4 [116] (**Figures 1** and **2**).

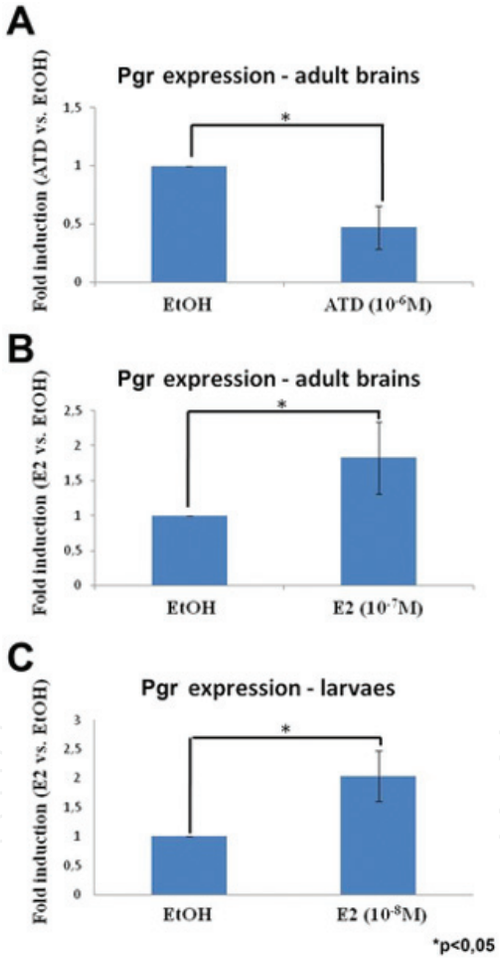


Figure 1. Progesterone nuclear receptor (pgr) is upregulated by estrogen. Experiments on developing and adult brain of zebrafish, and larvae. Legend: Fold induction of P4 expression after treatment of adult zebrafish with an aromatase inhibitor (A, 10^{-6} M of ATD) or estradiol (B, 10^{-7} M of 17β-estradiol), and larvae with E2 (C, 10^{-8} M of 17β-estradiol). The graphs present the mean value +/− the standard deviation. Asterisk (*) indicates significant differences ($p < 0.05$, Student's t test). **Panel A:** the aromatase inhibitor (ATD) leads to a significant decrease of *pgr* expression in individual brains of adult zebrafish (n = 4). **Panel B**, the estrogenic treatment leads to a significant increase of *pgr* expression in pools of 5 brains of adult zebrafish (n = 3). **Panel C**: the estrogenic treatment leads to a significant increase of *pgr* expression in pool of 20 larvae (n = 2).

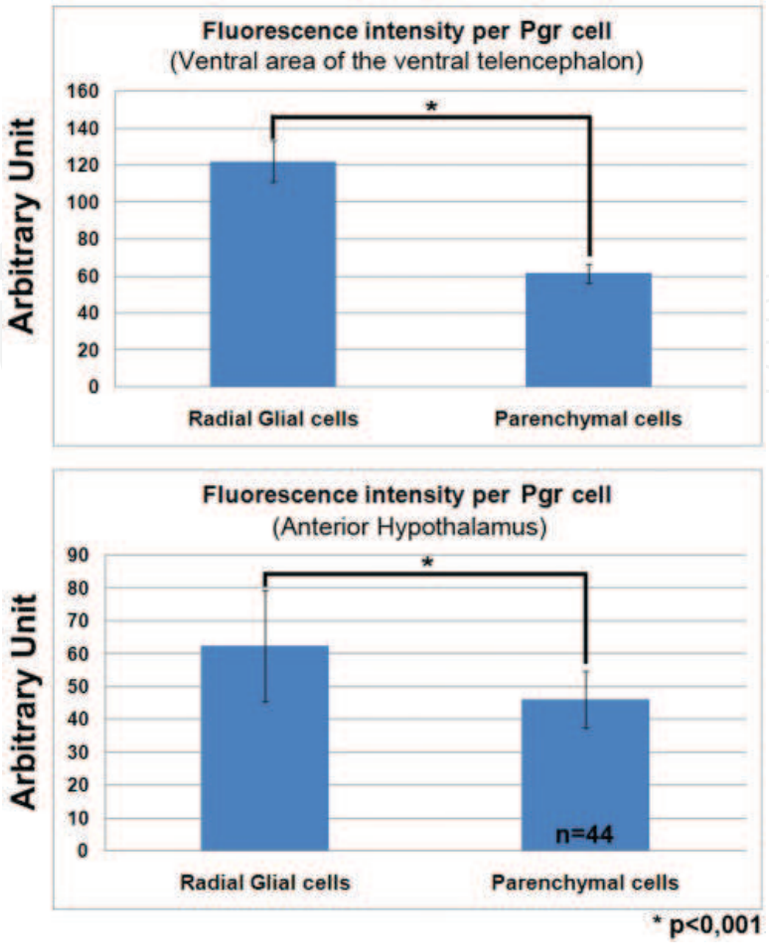


Figure 2. Experiments on Zebrafish hypothalamicP4 receptors. *Legend*: Analysis of the P4 staining intensity in the ventral subpallium and in the anterior hypothalamus revealing a stronger intensity (mean value +/− the standard deviation).in the radial cells than neural cells ($p < 0.001$ Student's t test). **Figures 1** and **2** are adapted from [116].

PR-A is exerting a negative control on PR-B-mediated transcription, and the mediated transcription of the ER and glucocorticoid receptors [117], fact that may underlie, at least in part, the mechanism by which progesterone functionally antagonize the effects of estrogen. PRA and PRB can interact as dimers with DNA progesterone responsive element, and with signaling proteins of the Src/Ras/Erk pathway outside the nucleus [118]. The "non-genomic" mechanisms explains the non-reproductive P4 actions, the rapid activation of cytoplasmic kinase signaling that can result in both transcription-independent and transcription-dependent effects. These "non-genomic" actions can be partially explained by membrane transport *via* nuclear receptor [119]. The mPRs (molecular mass of approximately 40 kDa) had thought to be comprised of three subtypes, mPR α, β, and γ, which belong to the seven-transmembrane domain adiponectin Q receptor (PAQR) family, plus two newly discovered subtypes (mPRδ, and mPRε) [120]. It was shown that cDNAs for the mPRα subtypes of spotted seatrout (st-mPRalpha) and humans (hu-mPRα-) encode progesterone/progestin receptors that display many functional characteristics of G protein-coupled receptors [121], and that mPRβ promotes progesterone-dependent neurite

outgrowth in PC12 neuronal cells *via* non-G protein-coupled receptor (GPCR) signaling [122]. Progesterone receptor membrane component-1 (PGRMC-1) and PGRMC-2, with a single-transmembrane domain protein, are mediating the rapid non-genomic effects of E2 and P4, such as the activation of MAPK signaling and intracellular Ca^{2+} increase [123, 124] mPRβ activates also MAPK cascade, without GPCR signaling, and progesterone-stimulated mPRβ activation did not exhibit the elevation of [Ca^{2+}] [121]. In comparison to the mPRs, the single-transmembrane protein Pgrmc1 (molecular mass 25–28 kDa) and the related Pgrmc2 are a part of a multi-protein complex that binds to P4, other steroids, and to pharmaceutical compounds [123]. Besides the location to membrane surface, Pgrmc1 was reported to have subcellular localization: in endoplasmic reticulum, Golgi apparatus, and nuclei [125].

PRs are differentially expressed in neurons, in oligodendrocytes, astrocytes, and reactive microglia, the mPRα expression is observed in oligodendrocytes, astrocytes, and reactive microglia. The increase in mPR expression was proposed to mediate the anti-inflammatory effects of progesterone under conditions of injury [126].

The classical PR and mPRs have overlapping regional expression (e.g., both are expressed in the hippocampus, cortex, hypothalamus, and cerebellum), but their profile of ligand specificity is not identical [126]. The "non-classical/non-genomic" effects of P4 can be initiated rapidly at the cell surface to activate intracellular signaling pathways, through modulation of putative cell surface receptors, ion channels, and cytoplasmic second messenger cascades, the rapid activation of cytoplasmic kinase signaling can result in both transcription-independent and transcription-dependent effects.

Among the rapid non-genomic signaling pathways activated by P4 are the extracellular signal-related kinase (ERK) pathways [127], cAMP/protein kinase A (PKA) signaling [128], PKG signaling [129], Ca^{2+} influx/PKC activation [130], phosphatidylinositol 3-kinases (PI3 K)/Akt pathway [124], and other signal transduction cascades. P4 or its metabolites can act directly and rapidly on neurotransmitter receptors as the GABA-A receptor [131] and Sigma-1/2 receptors [132] to regulate cellular function.

The consequences of activation of these signaling pathways are numerous and include influences on neurotrophin release [125], neural progenitor proliferation, regulation of intracellular Ca^{2+} levels, and regulation of cell viability [57, 127, 131] all of which can contribute to the overall health and function of the brain.

3.3. Androgens mechanisms in neuroprotection

Androgen neuroprotective effects are mediated both directly by activation of androgen receptors (ARs) pathways, and indirectly by aromatization to estradiol and initiation of protective estrogen signaling mechanisms, but this last action is not totally accepted [133–135]. The knowledge on the effects of testosterone on women cognitive capacities are few.

Testosterone protects primary human neurons against serum deprivation [134], cultured rat hippocampal neurons against extracellular Aβ toxicity [136], rat neurons against heat shock-mediated

hyperphosphorylation of tau by modulating glycogen synthase kinase 3 activation [85], cerebellar granule neurons against oxidative stress [133], and rat hippocampal neurons against kainic acid-induced toxicity [135] transiently activate mitogen-activated protein kinase (MAPK) in cultured hippocampal neurons, as evidenced by phosphorylation of extracellular signal-regulated kinase (ERK)-1 and ERK-2 and by this effect subsequently drives neuroprotection [137].

4. Perspectives

Brain aging and neurodegenerative diseases have a multifactorial nature, metabolic and inflammatory changes from the moment of transition to menopause, blood-brain barrier disruption, and aberrant microglial activation can be modulated or prevented in a moment prior to their onset in the "critical period of opportunity," if the clinicians and the patients are both interested and have a good understanding of very early perimenopausal symptoms. The differences between estrogen types, between progesterone and progestins, between the classes of steroid receptors agonists—NeuroSERMs (novel neuro-selective estrogen receptor modulator) and PhytoSERMs (phyto-selective estrogen receptor modulator), and the new molecules tested in high-tech laboratories, will help the clinicians to recommend the best neurotrophic, neuroprotective molecule without any breast or uterine harmful action.

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