Neuroendocrinology

At the Cutting Edge

Neuroendocrinology
DOI: 10.1159/000525677

Received: December 13, 2021
Accepted: June 17, 2022
Published online: June 27, 2022

Progestogen-Mediated Neuroprotection in Central Nervous System Disorders

Taysa Bervian Bassani[a, b] Cynthia Silva Bartolomeo[c] Rafaela Brito Oliveira[a, b] Rodrigo Portes Ureshino[a, b]

[a]Department of Biological Sciences, Universidade Federal de São Paulo, Diadema, Brazil; [b]Laboratory of Molecular and Translational Endocrinology, Escola Paulista de Medicina, Universidade Federal de São Paulo, São Paulo, Brazil; [c]Department of Biosciences, Universidade Federal de São Paulo, Santos, Brazil

Keywords
Progesterone · Allopregnanolone · Neurodegenerative disease · Neuroprotection

Abstract
Neuroactive steroids can be synthetic or endogenous molecules produced by neuronal and glial cells and peripheral glands. Examples include estrogens, testosterone, progesterone and its reduced metabolites such as 5α-dihydroprogesterone and allopregnanolone. Steroids produced by neurons and glia target the nervous system and are called neurosteroids. Progesterone and analog molecules, known as progestogens, have been shown to exhibit neurotrophic, neuroprotective, antioxidant, anti-inflammatory, glial modulatory, promyelinating, and remyelinating effects in several experimental models of neurodegenerative and injury conditions. Pleiotropic mechanisms of progestogens may act synergistically to prevent neuron degeneration, astrocyte and microglial reactivity, reducing morbidity and mortality. The aim of this review is to summarize the significant findings related to the actions of progesterone and other progestogens in experimental models and epidemiological and clinical trials of some of the most prevalent and debilitating chronic neurodegenerative disorders, namely, Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and multiple sclerosis. We evaluated progestogen alterations under pathological conditions, how pathology modifies their levels, as well as the intracellular mechanisms and glial interactions underlying their neuroprotective effects. Furthermore, an analysis of the potential of natural progestogens and synthetic progestins as neuroprotective and regenerative agents, when administered as hormone replacement therapy in menopause, is also discussed.

Introduction

Sex steroid hormones play fundamental roles in reproductive biology and participate in other modulatory functions such as nervous system homeostasis. The gonads, adrenal glands, and placenta mainly produce sex steroids. However, steroids are also synthesized de novo in the central nervous system (CNS) and peripheral nervous system (PNS) from cholesterol molecules by glia (oligodendrocytes and astrocytes in the CNS and Schwann cells in the PNS) and neurons (Fig. 1). When produced in the CNS and PNS, they are called neurosteroids [1].

In the CNS, neurosteroids exert diverse functions, such as regulation of γ-aminobutyric acid (GABA) and

Karger@karger.com
www.karger.com/nen

Correspondence to:
Rodrigo Portes Ureshino, rpureshino@gmail.com

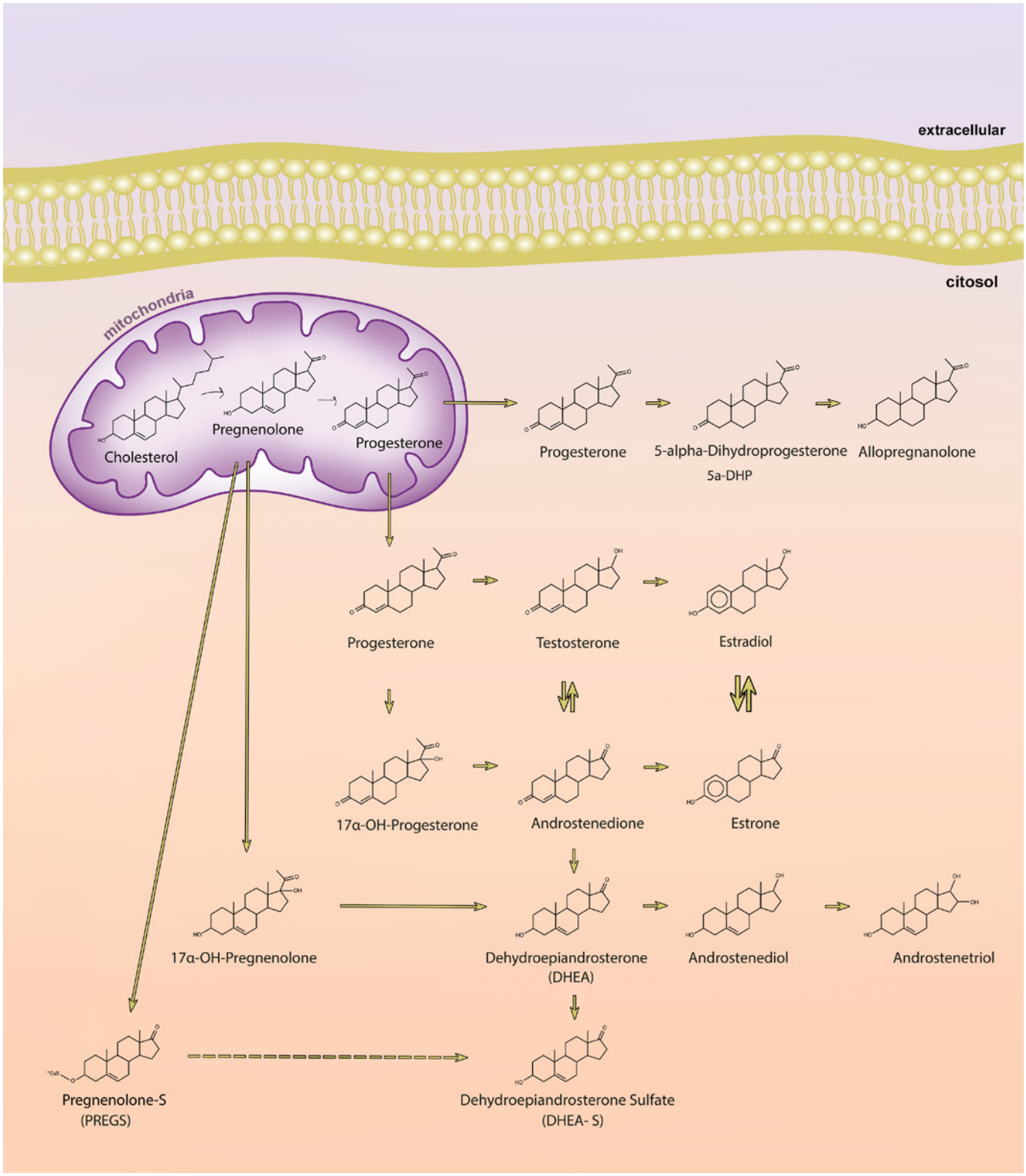

Fig. 1. Steroid metabolism in the CNS. Neurosteroids are biosynthesized in the central nervous system (CNS) and peripheral nervous system (PNS) by neuronal and glial cells from cholesterol. Neuroactive steroids can also be synthesized peripherally by adrenal and gonadal glands, cross the blood-brain barrier, and act on steroid receptors in the CNS. The first limiting step in steroid synthesis is the conversion of cholesterol to pregnenolone.

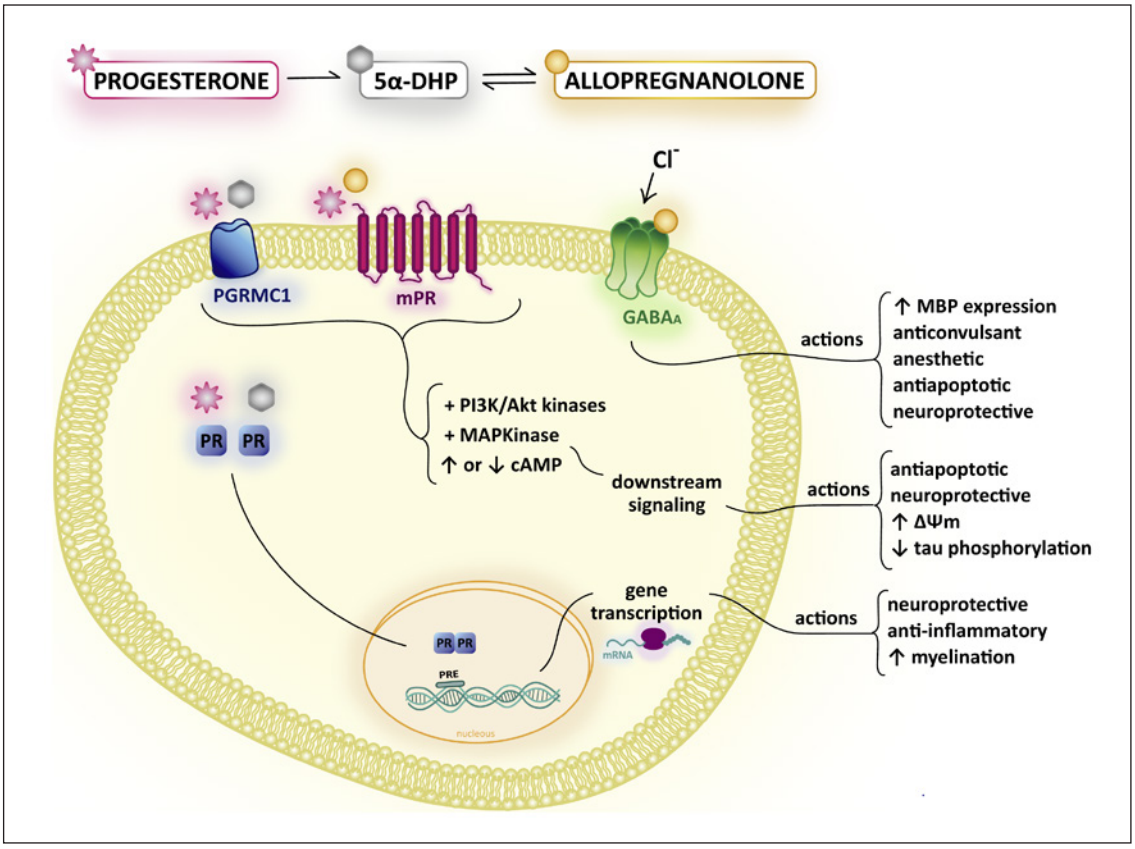

Fig. 2. Mechanisms of action of progesterone and allopregnanolone on the CNS. Two main pathways mediate the effects of progesterone on target cells: the classical (canonic pathway) and nonclassical (noncanonic pathway). In the classical signaling pathway, both progesterone and 5α-dihydroprogesterone (5α-DHP) bind to intracellular progesterone receptors (PR), which dimerize and translocate to the nucleus, thus interacting with the regulatory progesterone response elements (PRE) in the DNA, which regulates the expression of specific genes. While in the nonclassical pathway, there is activation of G protein-coupled membrane progesterone receptors (mPRs) and progesterone receptor membrane component 1 (PGRMC1), leading to activation of MAPK, protein kinase C (PKC), and PI3K/Akt pathways. 5α-Dihydroprogesterone is converted to allopregnanolone. The latter has no affinity for PR but is a positive modulator of type A γ-aminobutyric acid receptors ($GABA_A$) and is also a ligand for mPRs. MBP: myelin basic protein, ΔΨm: mitochondrial membrane potential.

glutamate transmission, neuronal growth, brain development, synapse formation, myelination, cognition, neurogenesis, emotion, mood, dendritic growth, neuronal survival, reproductive and social behavior [1, 2]. Neurosteroids correspond to a range of estrogens, androgens, and progestogens, including 17β-estradiol (E2), testosterone, dihydrotestosterone, androstanediol, progesterone, allopregnanolone, and dehydroepiandrosterone (DHEA) [2, 3]. This review focuses on the role of specific neuroactive progestogens in neurodegenerative disorders.

Progesterone is the key regulator of the female cyclic reproductive tract. Changes in the levels of this hormone maintain pregnancy in all mammals. Interestingly, the physiological effects of progestogens on target cells are mediated by the classical (slow actions) and the nonclassical (fast actions) pathways (Fig. 2). The progesterone classical pathway is triggered by association in the cytoplasm and subsequent nuclear translocation of the classical progesterone receptors (PR): PR-A and PR-B, which are members of the nuclear receptor superfamily, that act as ligand-activated transcription factors [4, 5]. The complex progesterone-PR binds to progesterone responsive elements in the DNA, allowing the transcription of a specific set of genes [6]. The PR gene in humans is localized on chromosome 18, and it consists of 8 exons. The PR-A and PR-B isoforms are produced from the same gene transcript but are controlled by different promoters. Both isoforms have been identified in diverse tissues, including gonads, uterus, mammary glands, pancreas, bones, urinary tract, and brain. PR-B acts as a transcription activa-

tor of progesterone responsive genes, while PR-A inhibits or counteracts PR-B activity, functioning as a modulator [7].

Concerning the nonclassical pathway, it is triggered by membrane progesterone receptors (mPR) and progesterone receptor membrane components 1 and 2 (PGRMC1 and PGRMC2), which initiate rapid intracellular signaling cascades. The mPRs are metabotropic receptors composed of seven transmembrane domains which have been shown to activate G proteins. They belong to the progestin and adipoQ receptor (PAQR) family, and there are five known isoforms (mPRα, mPRβ, mPRγ, mPRδ, and mPRε). Interestingly, mPRα is expressed in neurons and, following an insult, it has its expression increased in glial cells, suggesting a role in neuroinflammation [4]. Nonetheless, the functions and intracellular pathways activated by PGRMC1 and 2 have not been fully elucidated. Recent evidence suggests that PGRMC1 acts as an adaptor molecule for mPR, facilitating its translocation to the plasma membrane. In this sense, nonclassical progesterone actions are proposed to be initiated by the PGRMC1-mPR complex and not the result of receptor action alone [8, 9]. Stimulation of mPR triggers many quick gene transcription-independent responses accompanied by increased intracellular Ca^{2+} concentrations and second messenger activation [10]. Indeed, cAMP and mitogen-activated protein kinase (MAPK) activation has been shown to promote CREB phosphorylation and regulate SRC2 coactivator activity [11]. Notably, these intracellular signaling cascades can trigger specific nongenomic responses or modulate genomic pathways [7]. For example, progesterone-mediated mPR activation leads to MAPK and protein kinase C (PKC) activation via cAMP, and mPRs also activate PI3K/Akt intracellular pathways. Simultaneously, phospholipase C (PLC) is activated, leading to intracellular Ca^{2+} store mobilization and increased cytosolic concentration of this cation [7, 12].

It is relevant to point out that the hormonal activity of the neurosteroid allopregnanolone, an active metabolite of progesterone, was for a long time considered insignificant due to the lack of activity on classic PR. However, antiseizure activity, mediated by positive $GABA_A$ receptor modulation, has been reported for this steroid (for a review on allopregnanolone synthesis, mechanisms, and effects, see Diviccaro et al. [13]). Moreover, there is evidence that allopregnanolone and its analog ganaxolone act by binding to the neuronal cell mPRs and inhibit apoptosis [14]. Therefore, the combined $GABA_A$ modulation and the antiapoptotic effect by mPRs stimulation respond to the complexity of allopregnanolone effects in the brain and will be discussed later in this review.

Regarding the regulation of production and release mechanisms, evidence supports that both progesterone and allopregnanolone increase during stress condition in healthy humans, with positive correlation between cortisol and progesterone levels. Progesterone has been especially linked to the willingness for social interaction, which supports the concept that allopregnanolone and progesterone release can ultimately lead to a decrease in anxiety and stress [15]. Moreover, the levels of the neurosteroids DHEA, DHEA sulfate (DHEAS), and allopregnanolone decrease during aging, increasing neuron vulnerability to toxic agents, which is associated with neuronal apoptosis and degeneration [16]. Therefore, the production and release of these neuroactive steroids could provide protection against neuron dysfunction and apoptosis, whereas its gradual reduction would contribute to the aging process.

Progestogens in Neurodegenerative Disorders

Levels of neuroactive steroids, including progestogens, were shown to be altered under various experimental neurodegenerative conditions [17]. A variety of PRs are also expressed in both neurons and glia [12]. Interestingly, there is growing evidence that progesterone and other neurosteroids provide neuroprotection to the CNS and PNS through several mechanisms.

Moreover, neurosteroids are reported to have neuroinflammation modulatory properties [18] that may be attributed at least in part to suppression of microglial cell activation [19]. A previous study showed that allopregnanolone and progesterone reduce injury-induced expression of interleukin-1 beta (IL-1β) and tumor necrosis factor-alpha (TNF-α) at the mRNA and protein levels [20]. A recent study reported the allopregnanolone immunomodulatory effects at supraphysiologic levels (10 μM) in murine microglial cells. Allopregnanolone reduced microglial cell migration and phagocytic function [21]. These reports suggest that progestogens exert anti-inflammatory actions, at least in part, via downregulation of glial proinflammatory cytokine gene expression. Besides the effects on glial cells, progesterone was also reported to protect hippocampal neurons in vitro and additionally enhance the cognitive function of rats subjected to glutamate-mediated excitotoxicity [22].

Alzheimer's Disease

Alzheimer's disease (AD) is a neurodegenerative condition characterized by a progressive cognitive decline. The onset and progression of this disease are associated with extracellular deposits of amyloid-beta (Aβ) protein and intracellular deposits of hyperphosphorylated tau protein. Lower neurosteroid levels were observed in several brain regions of AD patients than in nondemented patients. For example, DHEAS levels were found to be reduced in the striatum, cerebellum, and hypothalamus and pregnenolone sulfate levels were reduced in the striatum and cerebellum. The levels of cortical Aβ peptides and pregnenolone sulfate in the striatum and cerebellum, and the levels of phosphorylated tau and DHEAS in the hypothalamus, were negatively correlated, suggesting that these neurosteroids may affect metabolism of AD-related proteins and present neuroprotective properties [23].

Additionally, the expression of enzymes involved in the biosynthetic neurosteroid pathway was found to be upregulated in the prefrontal cortex (PFC) of AD patients. Aromatase (an enzyme that converts testosterone into estrogen) and 17β-hydroxysteroid dehydrogenase type 1 (HSD17B1, an enzyme of the estradiol biosynthetic pathway) gene expression was upregulated in later stages of the disease. Notably, aldo-keto reductase 1C2 (AKR1C2, an enzyme of the allopregnanolone biosynthesis) gene expression was upregulated in early or mild cognitive impairment (MCI) stages of AD brains, and many $GABA_A$ subunits were downregulated. The increased estradiol and allopregnanolone bioavailability may represent a compensatory neuroprotective mechanism in the PFC [24, 25]. Conversely, in other study when gender was taken into consideration, allopregnanolone was found to be reduced in the PFC of male AD patients compared with age-matched controls. The authors observed an inverse correlation between allopregnanolone levels and the Braak stage, suggesting the decrease in this neurosteroid may worsen AD neuropathology [26].

Evidence of Progestogens Modulation of Cognition and AD-Related Proteins in Preclinical Studies

AD-related proteins can modify neurosteroid production by nerve cells and vice versa. Wild-type tau (hTau40) increased progesterone production in SH-SY5Y-transfected cells, but mutant tau (P301L) did not elicit the same effect. Conversely, wild-type amyloid precursor protein (APPwt) inhibited progesterone production [27], suggesting that there are mutual and complex regulations which can affect both the neuroendocrine systems and AD pathology. Table 1 summarizes the main preclinical findings discussed here.

Progesterone and its reduced metabolites (dihydroprogesterone and allopregnanolone) have complex effects on phosphorylation of several tau epitopes, which have been related to the modulation of kinases and phosphatases of tau protein. For example, Guerra-Araiza et al. [28] showed that administration of progesterone and its metabolites to ovariectomized rats increased Tau-1 (dephosphorylated tau) and PHF-1 (phosphorylated tau) epitopes in the cerebellum but not in the hypothalamus. In addition, progesterone decreased GSK3β serine 9 (S9) phosphorylation, which is associated with an increase in kinase activity, suggesting that progesterone's effect on tau phosphorylation is mediated by GSK3β activation [28]. Additionally, tibolone, a synthetic steroid with progestogenic, estrogenic, and androgenic activities used to treat menopausal symptoms, has been shown to reduce tau phosphorylation (PHF-1) and increase tau dephosphorylation (Tau-1) associated with GSK3β inhibition in ovariectomized rats [29].

Regarding the intracellular signaling, progesterone activity on phosphoinositide-3 kinase (PI3K)/Akt/GSK3β and mitogen-activated protein kinase (MAPK) pathways influences tau phosphorylation status and could be explored as therapeutic targets. For example, progesterone enhanced the phosphorylation of extracellular signal-regulated kinase (ERK) and Akt and increased the expression of PI3K in the cerebellar, hypothalamic, and hippocampal tissues of ovariectomized rats [30]. Additionally, progesterone has been shown to stimulate the activation of tau phosphatases such as protein phosphatase 2A (PP2A) and phosphatase and tensin homolog deleted on chromosome 10 (PTEN) in the brain, which can contribute to tau dephosphorylation [31], suggesting progesterone effects on tau phosphorylation are the result of a complex regulation of kinases and phosphatases activities.

Progesterone also displayed neuroprotective properties through several mechanisms in studies using Aβ peptides as a cellular insult. The Aβ peptide-induced neuroinflammatory response was attenuated by progesterone in cultured astrocytes through suppressing cytokine production and decreasing endoplasmic reticulum stress activation by attenuating PERK/eIF2α activity [32]. Moreover, this hormone reduced Aβ-induced cytokine production and inflammasome activation by stimulating mTOR-dependent autophagy in cultured astrocytes [33, 34]. Besides inflammation, progesterone treatment attenuated Aβ-induced apoptotic mitochondrial pathway and

Table 1. Evidence of progestogens effects in preclinical models of neurodegenerative diseases

Hormones	Model	Main outcomes	Reference
Progesterone	SH-SY5Y transfected cells	Wild-type tau (hTau40) increased progesterone production, but not mutant tau (P301L); wild-type amyloid precursor protein (APPwt) inhibited progesterone production	[27]
Progesterone and its reduced metabolites	Ovariectomized rats	Increased Tau-1 (dephosphorylated tau) and PHF-1 (phosphorylated tau) epitopes in the cerebellum, but not in the hypothalamus; increased GSK3β activation	[28]
Tibolone	Ovariectomized rats	Increased tau dephosphorylation (Tau-1) and reduced tau phosphorylation (PHF-1) associated with GSK3β inhibition	[29]
Progesterone	Ovariectomized rats	Enhanced phosphorylation of ERK and Akt and increased expression of PI3K in the cerebellar, hypothalamic, and hippocampal tissues	[30]
Progesterone	Ovariectomized rats	Increased activation of the tau phosphatases such as PP2A and PTEN in the brain	[31]
Progesterone	Astrocytes cell culture	Attenuated Aβ peptide-induced neuroinflammation; suppressed cytokine production and decreased endoplasmic reticulum stress activation by attenuating PERK/eIF2α	[32]
Progesterone	Astrocytes cell culture	Attenuated Aβ-induced cytokine production and inflammasome activation by stimulating mTOR-dependent autophagy	[33, 34]
Progesterone	Cortical neurons culture	Reduced Aβ-induced apoptotic mitochondrial pathway and neuronal toxicity by inactivating JNK and activating PGRMC1	[35]
Progesterone	Rat primary cortical neurons challenged with $A\beta_{25-35}$	Antiapoptotic effects mediated by PGRMC1 activation of Ras signaling	[36]
Progesterone	Ovariectomized 3×Tg-AD	Diminished tau hyperphosphorylation alone and combined with estrogen, but blocked estrogen-mediated Aβ reduction	[37]
Progesterone	Female 3×Tg-AD mice	Decreases phosphorylated abnormal tau (AT8 site) in continuous or cyclic administration, but Aβ was decreased only with cyclic progesterone	[38]
Progesterone	Ovariectomized $A\beta_{1-40}$-injected rats	Improved spatial learning and memory; reduced neuronal apoptosis; cholinergic and serotonergic protection; decreased GFAP expression in the hippocampus; effects were potentiated by a combination of estrogen and progesterone	[39]
Progesterone	Ovariectomized middle-aged rats	Reversion of estradiol-induced spatial memory improvements, but attenuation of the estradiol increased mortality	[40]
Progesterone	Rat hippocampal slices challenged with NMDA	Inhibition of E2 neuroprotective effect; reversion in the estradiol-induced increase in BDNF protein levels and TrkB receptor activation	[41]
Allopregnanolone	Human NT2 neurons	Prevention of NMDA-mediated excitotoxicity	[44]
Allopregnanolone	Organotypic slices culture of rat medial PFC	Reduced evoked presynaptic glutamate release dependent on inhibition of L-type Ca^{2+} channels and PKA activation	[45]
Allopregnanolone	Rat cortical terminal nerves (synaptosomes)	Decreased glutamate release and Ca^{2+} influx by activation of $GABA_A$ receptors	[46]
Allopregnanolone	Male 3x transgenic mouse model of AD (3×TgAD)	Restored hippocampal-dependent learning and memory associated with increased hippocampal neurogenesis	[47, 48]
Allopregnanolone	Rat and human neural progenitor cells	Induced neural progenitor cells proliferation	[49]

Table 1 (continued)

Hormones	Model	Main outcomes	Reference
Allopregnanolone	3×Tg-AD model	Improved survival of newly generated neurons; reduced Aβ generation and activated microglia; increased oligodendrogenesis	[50]
Allopregnanolone	Adult mouse neural stem cells and 3×Tg-AD model	Enhanced oligodendrocyte and neuronal differentiation	[51]
Allopregnanolone	Young 3×TgAD and aged nontransgenic mice	Increased hippocampal neurogenesis	[52]
Levonorgestrel	Rat model of transitional menopause	Improvement in cognition, anxiety- and depressive-like behaviors, especially when combined with estrogen	[53]
Levonorgestrel	Middle-aged ovariectomized rats	Impaired spatial working memory with estrogen combination, but improved cognitive performance if administered separately	[54]
Norethindrone acetate, MPA, Levonorgestrel	Middle-aged ovariectomized rats	Norethindrone acetate and medroxyprogesterone impaired working and reference memories; levonorgestrel improved the learning process	[55]
Progesterone, 19-norpro-gesterone and MPA	Rat hippocampal neurons challenged with glutamate	Progesterone and 19-norprogesterone promoted neuronal protection, but not MPA, and it reduced the estrogen-mediated benefits when administered together; MPA increased glutamate excitotoxicity	[56, 58]
Progesterone and MPA	Cortical organotypic explants	Progesterone increased BDNF gene expression and protein levels, but not MPA	[59]
MPA	Rat glial cells	Impaired Aβ proteolytic degradation by reducing metalloproteinase 9 expression	[60]
Progesterone	Cerebral cortex of APP/PS1 mice and primary cortical neuron cultures	Improved learning and memory, upregulated GLUT3, GLUT4, CREB, PPARγ, and increased neuronal glucose uptake through PGRMC1 activation	[61]
Progesterone and E2	APP/Aβ and tau P301L cells	Improved mitochondrial membrane potential and ATP production	[62]
Progesterone and E2	Brain mitochondria	Improved respiratory function through the upregulation of complex IV (cytochrome *c* oxidase) expression and attenuated oxidative stress	[63]
Allopregnanolone	Female 3×TgAD model	Improved mitochondrial respiration, biogenesis, and enzymes activity; decreased lipid peroxidation and expression of AD-related genes	[64]
Allopregnanolone	$A\beta_{25-35}$-challenged PC12 cells	Attenuated neuronal death and oxidative stress markers	[65]
Progesterone and E2	Toxin-challenged hippocampal neurons	Estrogen or progesterone alone improved mitochondrial respiratory capacity; coadministration decreased mitochondrial respiration; estrogen prevented cell death, and progesterone did not	[66]
Progesterone and estrogen	Ovariectomized Rhesus macaques; female AD patients and controls	Genes related to mitochondrial function were upregulated by estrogen and downregulated by progesterone in macaques brains; the genes upregulated by estrogen in macaques were downregulated in postmortem brains of AD patients	[67]
Progesterone and E2	MPTP-injected mice	Prevented striatal depletion of dopamine and its metabolites, and prevented dopamine transporter (DAT) downregulation in the striatum and substantia nigra	[89, 90]
Progesterone	MPTP-injected mice	Increased striatal dopamine, DAT, vesicular monoamine transporter 2 (VMAT2), and BDNF levels and reduced GFAP expression in the striatum	[91, 92]
Progesterone	MPTP-injected mice	Prevented the decrease in dopamine neurons and BDNF levels and the increase in GFAP and proinflammatory gut macrophages, protecting myenteric plexus	[93]

Table 1 (continued)

Hormones	Model	Main outcomes	Reference
Progesterone	6-OHDA unilaterally injected rats	Neuroprotective and neuromodulatory effects on striatal dopaminergic, glutamatergic, and GABAergic neurotransmission systems	[94]
Progesterone	Methamphetamine-injected ovariectomized mice	Prevented the striatal dopamine and serotonin depletion	[95]
Progesterone	Methamphetamine-injected gonadectomized male mice	Attenuated striatal dopamine depletion	[96]
Progesterone and estrogen	Primate model of ovariectomy	Improved the TH-IR in the striatum and protected dopamine neurons	[97]
Progesterone	Embryonic stem cells	Increased the number of TH-positive cells during differentiation	[98]
Progesterone	6-OHDA unilaterally lesioned male rats	Chronic administration exacerbated motor impairments, and dopamine turnover in the striatum	[99]
Allopregnanolone	6-OHDA hemiparkinsonian rats	Improved the contralateral rotational behavior, a sign of motor degeneration	[105]
Allopregnanolone	6-OHDA-lesioned male rats	Chronic postlesion treatment improved the cognitive deficits in spatial and recognition memories	[106]
Allopregnanolone	6-OHDA-injured SH-SY5Y cells	Increased TH expression dependent on activation of $GABA_A$ receptors and modulation of CaMKIIδ3/BDNF signaling pathway	[107]
Progesterone and pregnenolone	3-nitropropionic acid-injected rats model of HD	Progesterone improved motor performance, antioxidant enzymes and attenuated oxidative stress and inflammatory cytokines; pregnenolone reversed these effects	[109]
Allopregnanolone and progesterone	Cultured astrocytes	Reduced mutant huntingtin (mHtt) aggregates by inducing mTOR-dependent autophagy	[110]
Progesterone	Wobbler mice model of ALS	Increased GABAergic interneurons and granule cells, decreased astrocyte number and increased *BDNF* mRNA levels in the hippocampus; no influence on neurogenesis	[117]
Progesterone	Wobbler mice model of ALS	Improved motor neuron morphology and Na^+,K^+-ATPase sodium pump mRNA levels; attenuated neuropathy	[118]
Progesterone	Wobbler mice model of ALS	Increased ChAT-IR and BDNF mRNA levels in spinal cord motoneurons	[119]
Progesterone	Wobbler mice model of ALS	Decreased GFAP-positive astrocytes and increased ChAT-IR in the spinal cord motoneurons	[120]
Progesterone	Wobbler mice model of ALS	Increased *BDNF* mRNA levels and oligodendrocyte density in spinal cord motoneurons	[121]
Progesterone and norethindrone	Wobbler mice model of ALS	Progesterone reversed the proinflammatory macroglial phenotype and inflammatory mediators and enhanced ChAT expression; norethindrone inhibited these effects	[122]
Progesterone and allopregnanolone	Wobbler mice model of ALS	Acute treatment: improved neuronal vacuolation, nitric oxide synthase hyperactivity and cell survival markers. Chronic treatment: improved manganese superoxide dismutase (MnSOD)-IR, BDNF mRNA levels, and muscle performance	[123]
Progesterone	Mutant human superoxide dismutase 1 (G93A-SOD1) transgenic mouse model of ALS	Reduced spinal cord motor neuron death, delayed motor neuron dysfunction progression and increased animal lifespan associated with autophagic flux activation and downregulation of the mutant SOD1	[124]
Nestorone	Wobbler mice model of ALS	Restored ChAT-IR; decreased motoneuron vacuolization, astrogliosis, microgliosis, and proinflammatory markers	[125]
Progesterone and pregnenolone	Mouse model of sciatic nerve injury; rat dorsal root ganglia	Increase in progesterone or pregnenolone levels enhances myelin sheath formation rate by Schwann cells in peripheral nerves; progesterone improved axon myelination in rat dorsal root ganglia in vitro	[132]

Table 1 (continued)

Hormones	Model	Main outcomes	Reference
Progesterone	Organotypic slice cultures of rat cerebellum	Increased proliferation rate of OPC via classical PR activation; enhanced differentiation of OPCs into mature myelinating oligodendrocytes	[133]
Progesterone and allopregnanolone	Organotypic slice cultures of rat cerebellum	Upregulated gene expression of myelin basic protein (MBP) dependent on PR and $GABA_A$ receptors activation	[134]
Progesterone	Spinal cord injury rat model	Increased OPC proliferation; upregulated mRNA levels of transcription factors (Olig1, Olig2, and Nkx2.2) required for oligodendrocyte differentiation and myelin repair; increased mRNA and protein levels of MBP and proteolipid protein (PLP); increased mature oligodendrocytes and remyelination	[135]
Progesterone	Spinal cord injury rat model	Stimulation of oligodendrocyte differentiation and maturation, and late remyelination; inhibition of astrocyte and microglia proliferation and activation	[136]
Progesterone	Cuprizone-induced demyelination mouse model of MS	Switch from M1 (proinflammatory) to M2 (anti-inflammatory) phenotype in microglial cells and NLRP3 inflammasome suppression	[137]
Progesterone	Experimental autoimmune encephalomyelitis MS model	Reduced inflammatory cell infiltration in the injured spinal cord, prevented demyelination, and attenuated disease severity	[138]

AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; BDNF, brain-derived neurotrophic factor; ChAT, choline acetyltransferase; E2, 17β-estradiol; GABA, γ-aminobutyric acid; GFAP glial fibrillary ccidic protein; 6-OHDA, 6-hydroxydopamine; MPA, medroxyprogesterone acetate; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MS, multiple sclerosis; OPC, oligodendrocyte precursor cells; TH, tyrosine hydroxylase; IR, immunoreactivity.

neuronal toxicity by inactivating Jun N-terminal kinase (JNK) and activating PGRMC1 in cultured cortical neurons [35]. More recently, PGRMC1-mediated Ras signaling activation was reported to be involved in progesterone's antiapoptotic effects in rat primary cortical neurons challenged with $A\beta_{25-35}$ [36].

Regarding CNS protection, there are complex interactions between neurosteroids. For example, estrogen, but not progesterone, exerted neuroprotective actions preventing cognitive deficits and Aβ accumulation in ovariectomized triple-transgenic AD mice (3xTg-AD). In contrast, progesterone diminished tau hyperphosphorylation alone and when in combination with estrogen, while it blocked estrogen-mediated Aβ reduction [37]. Interestingly, progesterone alone and in combination with estrogen decreases phosphorylated abnormal tau (AT8 site) in continuous or cyclic administration, but Aβ was decreased only with cyclic progesterone administration, suggesting that estrogen and progesterone can have better results with an optimized hormone therapy while simulating physiological fluctuations [38]. Notably, progesterone and estrogen, alone or in combination, have been shown to improve spatial learning and memory performance of ovariectomized $A\beta_{1-40}$-injected rats and cognitive protection was associated with reduced neuronal apoptosis. The authors also observed cholinergic and serotonergic protection, as evidenced by increased choline acetyltransferase (ChAT) and 5-hydroxytryptamine 2A (5-HT2A) and decreased glial fibrillary acidic protein (GFAP) expression in the hippocampus. All these effects were potentiated by a combination of estrogen and progesterone [39]. Despite the growing evidence for progesterone protection in AD, there is still some debate about progesterone antagonizing estrogen's beneficial effects. Progesterone reversed the estradiol-induced spatial memory improvements in ovariectomized middle-aged rats, as evidenced by Morris water maze test scores. However, progesterone attenuated the estradiol increased mortality in these female rats [40]. Furthermore, progesterone inhibited the neuroprotective effect of E2 against N-methyl-D-aspartate (NMDA) toxicity in hippocampal slices and reversed the estradiol-induced increase in brain-derived neurotrophic factor (BDNF) protein levels and TrkB receptor activation [41].

The endogenous neurosteroid allopregnanolone has also been evaluated for its potential to promote neuroregeneration, improve cognition, and reduce AD pathology [42, 43]. For example, physiological concentrations of allopregnanolone (0–10 μM) prevented NMDA-mediated excitotoxicity in human NT2 neurons [44]. Corroborat-

ing these findings, the evoked presynaptic glutamate release in the rat medial PFC was reduced by allopregnanolone by a mechanism dependent on the inhibition of L-type Ca^{2+} channels and PKA activation [45], and in the rat cortical terminal nerves, by activation of $GABA_A$ receptors. The decreased glutamate release resulted in reduced Ca^{2+} influx, suggesting that allopregnanolone may attenuate glutamate-induced excitotoxicity by a GABAergic-associated mechanism [46]. This progesterone metabolite has also been shown to restore hippocampal-dependent learning and memory associated with increased hippocampal neurogenesis in a male triple-transgenic mouse model of AD (3×TgAD) [47, 48]. This effect is probably related to its capacity to induce neural progenitor cell proliferation [49] and improve survival of newborn neurons [50]. In the 3×Tg-AD model, allopregnanolone reduced Aβ generation and activated microglia, increased oligodendrogenesis [50], while enhanced oligodendrocyte and neuronal differentiation [51]. These reports suggest allopregnanolone can inhibit neuroinflammation while stimulating remyelination and neurogenesis, a desirable profile for a regenerative agent for AD brain. A pharmacokinetic and pharmacodynamic study of allopregnanolone revealed that several administration routes could reach therapeutic brain and plasma concentrations resulting in increased hippocampal neurogenesis in young 3×TgAD and aged nontransgenic mice [52].

Synthetic progestins have also been studied alone or in combination with estrogens in preclinical studies with regard to cognition and neuroprotection. For example, in a rat model of transitional menopause, levonorgestrel, a commonly prescribed progestin for oral contraception and menopause hormone replacement therapy (HRT), showed significant improvement in parameters such as cognition, anxiety- and depressive-like behaviors, especially when combined with estrogen. Likewise, in this study, progesterone displayed better results in combination with estrogen [53]. Conversely, levonorgestrel and estrogen combination impaired spatial working memory in middle-aged ovariectomized rats. However, both steroids were able to improve cognitive performance if administered separately [54]. In addition, the comparison of three progestins regarding cognitive performance revealed interesting neuroprotective data in middle-aged ovariectomized rats. Norethindrone acetate and medroxyprogesterone acetate (MPA) impaired working and reference memories, while levonorgestrel improved the animal learning process [55]. Such profiles may be related to their chemical structure and steroid receptor-binding profile. MPA is a 17-α-hydroxyprogesterone derivative, while norethindrone acetate and levonorgestrel are 19-nortestosterone derivatives, from estrane and 13-ethylgonane groups, respectively, resembling testosterone chemical structure. Levonorgestrel displays higher affinity for testosterone and progesterone receptors compared to norethindrone acetate and MPA, whereas all of them have insignificant estrogenic activity [55]. Noteworthy, whether cognitive or neurodegenerative processes are affected by these different receptor binding affinities and chemical structures of progestins is a valid topic to be further investigated.

Moreover, progesterone and 19-norprogesterone, alone or in combination with estrogen, were able to protect hippocampal neurons against glutamate toxicity [56]. 19-Norprogesterone exhibits potent progestogenic, but no glucocorticoid, estrogenic, or androgenic activities [57]. In contrast, MPA did not provide this protection and reduced the estrogen-mediated benefits when administered together [56]. This was corroborated in another study, showing that MPA increased glutamate excitotoxicity in rat hippocampal neurons [58]. One hypothesis for this divergence could be attributed to BDNF gene expression and protein levels, which can be positively modulated by progesterone, while MPA did not present this profile, in cortical organotypic explants [59]. Finally, MPA treatment has also been demonstrated to impair Aβ proteolytic degradation in rat glial cells by reducing metalloproteinase 9 expression, suggesting that it may hamper Aβ degradation in vivo [60]. This growing evidence suggests the neuroprotective and cognitive effects depend largely on the type of progestin.

Neuronal Metabolism and Bioenergetics

Some lines of evidence suggest that progesterone might influence neuronal metabolism, bioenergetics, and glucose uptake via nonclassical pathways. For example, progesterone improved learning and memory and upregulated GLUT3, GLUT4, CREB, and PPARγ in the cerebral cortex of APP/PS1 mice and primary cortical neuron cultures. The increase in neuronal glucose uptake was due to activation of the PGRMC1/CREB/GLUT3 and PGRMC1/PPARγ/GLUT4 pathways [61]. Interestingly, progesterone and other neurosteroids exhibited beneficial effects in the bioenergetic deficits of AD cell models overexpressing APP/Aβ, wtTau, and the mutant Tau P301L. All of the neurosteroids tested improved mitochondrial membrane potential and ATP production in APP/Aβ cells. In contrast, only progesterone and estradiol increased ATP levels in tau P301L cells [62]. Indeed, brain mitochondria treated with estrogen or progester-

one exhibit improved respiratory function through the upregulation of complex IV (cytochrome *c* oxidase) expression and attenuated oxidative stress. Hence, this could be the mechanism involved in the enhanced mitochondrial bioenergetics promoted by progesterone [63]. In addition, allopregnanolone has also been shown to improve bioenergetics in the female 3×TgAD model improving mitochondrial respiration, biogenesis and enzyme activity, together with decreased lipid peroxidation and AD pathology genes expression [64]. Moreover, pretreatment with allopregnanolone mitigated $A\beta_{25-35}$-induced neuronal death in PC12 cells and attenuated oxidative stress markers [65].

Metabolic analyses revealed that estrogen or progesterone alone improved mitochondrial respiratory capacity of toxin-challenged hippocampal neurons. However, coadministration of these two steroids decreased mitochondrial respiration. Additionally, estrogen prevented toxin-cell death, and progesterone did not, suggesting that combined therapy may not improve the mitochondrial deficits associated with AD [66]. These observations may be because progesterone largely antagonizes the estrogen-induced gene expression responses. In the brains from ovariectomized AD female macaques, genes related to mitochondrial function were upregulated by estrogen and downregulated by progesterone. While these genes upregulated by estrogen in macaques were found to be downregulated in postmortem brains of AD female patients. This wide genomic screening indicates that estrogen decrease during menopause contributes to increased AD risk in women [67]. Therefore, experiments comparing continuous and cyclic progesterone combined with estrogen administration are necessary to help to clarify these questions and unravel their neural interactions [38].

Progestogens in Epidemiological Studies and Clinical Trials

Some evidence suggests that the age-related decrease in neurosteroid production is a crucial contributing factor to AD pathogenesis [3]. However, evidence from epidemiological studies and clinical trials are still controversial, probably due to the divergence in the time of HRT initiation, the total time exposure to hormones, and the type of progestin used, which can influence the cognitive outcomes and AD risk. Table 2 summarizes the main clinical reports discussed here. For example, a randomized double-blind controlled trial administering sequential E2 (2 mg/day) and oral natural progesterone (100 mg/day) in early postmenopausal women revealed improvements in the PFC cognitive activity [68]. Postmenopausal women who received combined estrogen and progestin as an HRT had higher spatial cognitive test scores than the estrogen alone group. Also, serum testosterone levels were positively associated with spatial memory scores [69]. Postmenopausal women diagnosed with MCI benefited from long-term (24 months) percutaneous estrogen (2 mg/day) plus oral micronized progesterone (100 mg/day) treatment displaying better cognitive scores than the placebo group [70]. When evaluating daily life activities, a randomized prospective study reported improved scores for AD women taking conjugated equine estrogen (0.625 mg/day) plus micronized progesterone (100 mg/day) compared to tacrine. However, this HRT exhibited an equivalent efficacy on mood and cognition compared to tacrine. In addition, tacrine showed better outcomes in APOE ε4-negative patients [71].

In a retrospective case-control study, it was reported that the number of pregnancies was positively correlated with the risk of AD development, and with earlier disease onset. The AD-affected group had more pregnancies than the control group, and the authors correlate the AD group risk with lifetime higher levels of exposure to natural estrogen and progesterone [72]. Additionally, case-control studies reported differences regarding HRT time exposure and AD risk. On the other hand, a prospective cohort study showed that postmenopausal hormone therapy was not associated with an overall cognitive improvement in aged women. The authors also reported an increase in the risk of cognitive decline in long-term users of estrogen plus progestin or estrogen alone, and the risk increased further in women who initiated the replacement at older ages [73]. Similarly, a pilot cohort study revealed better cognitive test performance in women with early HRT initiation around menopause than individuals who initiated therapy later or were never treated. HRT was defined as with estrogen alone or estrogen plus progestin. Therefore, the timing of HRT initiation has a critical window of therapeutic opportunity [74] with a clear indication of better outcomes with early HRT initiation.

Corroborating these findings, the population-based prospective Cache County Study investigated and identified relationships between the timing of use of HRT and AD risk. When any HRT is initiated within 5 years after menopause begins, AD risk is reduced, especially for more than 10 years of use. In contrast, AD risk was not modified in individuals starting therapy more than 5 years after menopause [75], further suggesting a therapeutic window for HRT. Moreover, postmenopausal women undergoing HRT with estrogen or progestogen alone or combined for up to 10 years exhibited a slight

Table 2. Epidemiological studies and clinical trials associating HRT with the risk to develop neurodegenerative diseases or modify the disease course

Hormones	Subjects	Type of study	Main outcomes	Reference
E2 and oral natural progesterone	Early postmenopausal women	Randomized, double blind, placebo-controlled crossover study	Improvements in the PFC cognitive activity	[68]
Estrogen alone or combined with a progestin	Postmenopausal women	Cross-sectional study	Higher spatial cognitive test scores for women currently receiving estrogen plus progestin compared to estrogen alone; testosterone levels correlated positively with higher spatial test scores	[69]
Long-term percutaneous estrogen plus oral micronized progesterone	Postmenopausal women diagnosed with MCI	Randomized, placebo-controlled clinical trial	Better cognitive scores and slow progression rate to dementia in the HRT group compared to placebo	[70]
Progesterone plus estrogen compared to tacrine	Postmenopausal AD patients	Randomized open-label, prospective clinical trial	HRT improved scores in daily life activities but had an equivalent efficacy compared to tacrine on cognition and mood	[71]
Progestin plus estrogen or estrogen alone	Postmenopausal women aged 71–81 years	Prospective cohort study	Postmenopausal hormone therapy was not associated with an overall cognitive improvement; increase in the risk of cognitive decline in long-term users, particularly those who initiated the HRT at older ages	[73]
HRT with estrogen alone or combined with progestin	Menopausal and postmenopausal women	Pilot cohort study	Early HRT initiation around menopause resulted in better cognitive test performance than individuals who initiated therapy later or were never treated	[74]
HRT	Postmenopausal women	Population-based prospective observational study	Reduced AD risk when HRT is initiated within 5 years after menopause; AD risk was not changed when therapy started more than 5 years after menopause	[75]
HRT with estrogen or progestogen alone or combined	Postmenopausal women	Case-control study	HRT for up to 10 years resulted in a slight increase in AD risk; more than 10 years of HRT with estrogen alone decreased AD risk; exposure to progestogen alone or combined did not modify the risk for AD; HRT was not considered a determinant in AD risk	[76]
HRT with estrogen or progestogen alone or combined	Postmenopausal women	Nationwide case-control study	Any HRT slightly increased risk to develop AD, independent of the age of therapy initiation, and type of progestogen used	[77]
Conjugated equine estrogen and MPA	Postmenopausal women over 65 years old	Randomized placebo-controlled clinical trial	HRT increased the risk of dementia and did not protect the women from MCI development	[78]
Conjugated equine estrogen alone or combined with MPA	Postmenopausal women 65–79 years-old	Randomized placebo-controlled clinical trial	Estrogen alone did not reduce incidence of MCI or dementia; pooled results of estrogen alone, and estrogen plus MPA showed an increase in the risk for both outcomes	[79]
Conjugated equine estrogen plus MPA	–	Systematic review	Increased risk of AD development	[80]
HRT or oral contraceptive use	–	Meta-analysis	No significant alteration in the risk of PD development	[100]

Table 2 (continued)

Hormones	Subjects	Type of study	Main outcomes	Reference
Estrogen alone and estrogen plus progestin	Postmenopausal women	Case-control study	Estrogen alone increases the risk of PD in hysterectomized postmenopausal women; estrogen plus progestin did not alter PD risk in women with natural menopause	[101]
Conjugated equine estrogen followed by MPA	Postmenopausal women aged 45–75 years old	Double-blind, placebo-controlled, crossover study	HRT reduced levodopa-induced dyskinesia in PD postmenopausal patients	[102]
Esterified or conjugated estrogen alone or combined with a progestin	Idiopathic PD women from 35 to 89 years old and age-matched controls	Population-based case-control study	Increased in PD risk for esterified estrogen combined with a progestin; no alteration in PD risk for conjugated estrogen alone or combined with a progestin	[103]
Progesterone or E2	Postmenopausal PD women	Placebo-controlled randomized clinical trial	Antidopaminergic effect for progesterone in the motor function of PD patients; E2 administration presented no effect	[104]
HRT	Postmenopausal women and controls	Case-control study	Both HRT during postmenopause and reproductive factors showed no significant association with ALS risk	[127]
HRT	ALS patients and matched controls from the Netherlands, Ireland, and Italy	Case-control study	No alteration in ALS risk and estrogen and progestogen exposure; only in the Netherlands HRT was associated with a decreased risk for ALS	[128]
HRT	Premenopausal and postmenopausal women with MS	Retrospective pilot study	HRT users reported an improvement in MS symptoms severity	[139]
HRT	Menopause women with MS	Systematic review	Inconclusive association between age at menopause, HRT, and MS disease severity	[140]
HRT with at least 1 year of systemic estrogen with or without a progestin	Postmenopausal MS women and age-matched controls	Cohort observational study	Systemic HRT use was associated with better physical quality of life in women with MS	[141]
Nomegestrol acetate plus transdermal estradiol	Women in the postpartum phase	Randomized, placebo-controlled double-blind clinical trial	Nomegestrol acetate (19-norprogesterone derivative) and estrogen reduced MS relapse in the postpartum phase	[142]

AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; E2, 17β-estradiol; HRT, hormone replacement therapy; MCI, mild cognitive impairment; MPA, medroxyprogesterone acetate; MS, multiple sclerosis; PD, Parkinson's disease.

increase in AD risk. However, those with more than 10 years of HRT with estrogen alone had decreased AD risk. On the other hand, exposure to progestogen alone or combined did not modify the risk for AD development. This study suggests that HRT is not a determinant in AD risk and should not be indicated as a preventative strategy for cognitive impairment and dementia [76]. Another case-control study of HRT in postmenopausal women also did not detect protective effects against AD development. In a comprehensive study conducted in Finland between 1999 and 2013, women treated with any HRT presented a slightly increased risk to develop AD compared to nontreated women, independent of the age of therapy initiation and type of progestogen used [77].

Studies evaluating specific progestins were also conducted. For example, a randomized placebo-controlled clinical trial of postmenopausal women over 65 years old treated with conjugated equine estrogen (0.625 mg/day) and progestin MPA (2.5 mg/day) concluded that HRT increased the risk of dementia and did not protect the women from MCI development [78]. Similarly, another clinical trial evaluating conjugated equine estrogen alone (0.625 mg/day) or combined with MPA (2.5 mg/day) revealed that estrogen alone did not reduce incidence of

MCI or dementia and, when the results of both HRT were pooled, it was observed an increase in the risk for both outcomes. Therefore, the authors did not recommend HRT as a preventive strategy for cognitive impairment or dementia in aged women [79]. Finally, a systematic review concluded that the use of conjugated equine estrogen plus MPA was associated with increased risk of AD development [80].

Currently, two completed clinical trials in AD prevention assessing estrogen plus progesterone (NCT00000176 and NCT00006399), one trial with MPA and estrogen (NCT00066157) have been conducted with no published results with regard to progesterone or progestins and another trial with postmenopausal women using HRT including progesterone for AD neuroprotection (NCT04312399) is recruiting. A phase 1b/2a clinical trial (NCT02221622) evaluating intravenous single and multiple ascending doses for allopregnanolone (2–18 mg) in MCI due to AD or mild AD has been completed with promising results with regard to safety and tolerability [81]. Additionally, a phase 2 trial (NCT04838301) evaluating intravenous allopregnanolone in mild AD and another phase 1 trial (NCT03748303) testing intramuscular allopregnanolone as a regenerative agent for early AD are not yet recruiting. Noteworthy, allopregnanolone is an approved medication for postpartum depression due to its GABAergic modulation of the hypothalamic-pituitary axis [82].

Taken together, although some controversial reports are found, epidemiological and clinical trials on HRT indicate that early HRT initiation (around beginning of menopause) and natural progesterone administered alone or in combination with estrogen could result in favorable cognitive outcomes and reduce risk of AD. In contrast, some synthetic progestins such as MPA may not share this beneficial profile. Therefore, they should be further evaluated and compared for their efficacy in clinical trials and epidemiological studies.

Parkinson's Disease

Parkinson's disease (PD) is a movement disorder characterized by tremor, rigidity, and bradykinesia. Due to the loss of dopaminergic neurons in the substantia nigra pars compacta, reduced dopamine in the striatum, and intracellular α-synuclein inclusions, PD is classified as a neurodegenerative disorder. Several in vitro and in vivo studies support a potential neuroprotective role of progestogens in PD. Indeed, reports show alterations in neurosteroid levels and their synthetic enzymes in PD patients.

For example, the levels of allopregnanolone and 5α-dihydroprogesterone, but not progesterone, were found to be reduced in the cerebrospinal fluid and plasma of PD patients [83]. A parallel study with postmortem PD brains presented reduced mRNA levels of key neurosteroid biosynthesis enzymes, neurosteroid-modulated $GABA_A$ receptor subunits, and hormone receptors in the substantia nigra and striatum [84]. These results have led to the proposal that PD patients might present reduced de novo neurosteroid biosynthesis [85].

The results of the human studies have been corroborated in animal models [86, 87]. Significant alterations were observed in neurosteroid progestogens in the brains of 6-hydroxydopamine (6-OHDA)-lesioned animals. Moreover, reduced levels of dihydroprogesterone were detected in the striatum and cerebral cortex, and pregnenolone was reduced in the striatum. Notably, isopregnanolone was increased in both brain regions. These data indicate that progesterone metabolism is compromised in the 6-OHDA PD model [88].

Previous studies demonstrated that progestogens protect dopaminergic neurotransmission in PD animal models. More specifically, in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-injected mice, progesterone and E2 prevented striatal depletion of dopamine and its metabolites [89] and prevented dopamine transporter (DAT) downregulation in the striatum and substantia nigra [90]. Interestingly, progesterone administered after an MPTP insult also avoided reductions in dopaminergic parameters [91, 92]. Progesterone increases striatal dopamine, DAT, vesicular monoamine transporter 2 (VMAT2), and BDNF levels and reduces GFAP expression in the striatum of MPTP-injected mice [92]. It has been proposed that progesterone is a potential disease-modifying treatment for the prodromal phase of PD [92]. Additionally, progesterone has neuroprotective and immunomodulatory properties in the myenteric plexus of MPTP-lesioned mice. Progesterone has been shown to prevent MPTP-induced decreases in dopamine neurons and BDNF levels and increases in GFAP and proinflammatory gut macrophages [93]. This suggests progesterone can protect gut myenteric plexus and prevent gastrointestinal alterations in PD [93]. Progesterone elicited neuroprotective and neuromodulatory effects on striatal dopaminergic, glutamatergic, and GABAergic neurotransmission systems in 6-OHDA unilaterally injected rats [94]. In addition, progesterone avoided the methamphetamine-induced striatal dopamine and serotonin depletion in ovariectomized

mice [95] and significantly attenuated methamphetamine-induced striatal dopamine depletion in gonadectomized male mice [96]. In a primate model of ovariectomy, progesterone and estrogen replacement, alone or combined, improved the tyrosine hydroxylase (TH, enzyme of dopamine biosynthesis) immunoreactivity in the striatum, suggesting both hormones can protect dopamine neurons [97]. These data are corroborated by the finding that progesterone increases the number of TH-positive cells in embryonic stem cells during differentiation [98]. Together, these preclinical data suggest an important role for progesterone in dopaminergic pathway neuroprotection. Despite several reports about the beneficial effects of progesterone in preclinical PD models, controversial findings have been published. For example, chronic progesterone administration exacerbated motor impairments and dopamine turnover in the striatum of 6-OHDA unilaterally lesioned male rats [99]. This result suggests possible adverse outcomes for male PD patients taking progesterone.

A meta-analysis relating environmental and familial factors with early nonmotor characteristics found no significant alteration in risk of PD associated with HRT or oral contraceptive users [100]. A case-control study observed that conjugated estrogen alone (most prescribed dose was 0.625 mg/day) increases the risk of PD in postmenopausal women with hysterectomy. However, no alteration in PD risk was detected with estrogen plus progestin (MPA) in women with natural menopause. The most prescribed dose for estrogen was 0.625 mg/day ranging from 0.3 to 1.25 mg and for MPA 5 mg/day ranging from 2.5 to 10 mg [101]. Conversely, a conjugated equine estrogen (0.625 mg/day) followed by MPA (10 mg/day) administration reduced levodopa-induced dyskinesia in postmenopausal PD patients [102]. Another case-control study found that esterified estrogen administered alone or in combination with progestin increased PD risk. The same study also showed that conjugated estrogen alone or combined with progestin did not modify PD risk [103], suggesting that the conjugated form of estrogen maybe be safer. Moreover, a clinical trial evaluating motor function impairment in PD patients revealed an antidopaminergic effect for progesterone treatment (100 mg/day), whereas E2 administration (2 mg/day) presented no effect [104]. Despite several lines of preclinical evidence of progesterone improvements in PD models, these findings are not supported by epidemiological studies that show no alterations or even increase in PD risk for progestins combined with estrogen, and further epidemiological and mechanistical studies are needed to elucidate this topic. Currently, there are no studies registered on clinicaltrials.gov assessing progestins for PD.

Allopregnanolone as a neuroprotective agent in PD is a relatively new area of research. The ipsilateral injection of allopregnanolone in 6-OHDA hemiparkinsonian rats improved the contralateral rotational behavior, considered a sign of motor degeneration [105]. Moreover, early progesterone treatment enhanced the ipsilateral activity and expression of 3α-hydroxysteroid oxidoreductase, which is involved in converting progesterone to allopregnanolone. Thus, some progesterone-mediated neuroprotective effects could actually be mediated by allopregnanolone [105]. Chronic postlesion allopregnanolone treatment improved the cognitive deficits in spatial and recognition memories in 6-OHDA-lesioned male rats [106]. Allopregnanolone also protected 6-OHDA-injured SH-SY5Y cells resulting in increased tyrosine-hydroxylase expression. This effect was dependent on activation of $GABA_A$ receptors and modulation of Ca^{2+}/calmodulin-dependent protein kinase II δ3 (CaMKIIδ3)/BDNF signaling pathway [107]. Currently, to our knowledge, there are no epidemiological studies or ongoing clinical trials evaluating allopregnanolone's potential to halt PD progression.

Huntington's Disease

Huntington's disease (HD) is a progressive neurodegenerative disease caused by a polyglutamine repeat in the huntingtin gene, ultimately transcribed and translated into mutant huntingtin (mHtt) protein. This disease leads to a progressive loss of striatal GABAergic neurons, causing cognitive, neuropsychiatric, and motor impairments such as tremor, chorea, and dystonia. Both genders have equal prevalence because of their inherited autosomal dominant pattern, but neurosteroids such as estrogens have provided neuroprotection in experimental models [86, 108].

The mitochondrial complex II inhibitor, 3-nitropropionic acid, produces selective striatal lesions and has been systemically administered in rodents to model HD. In this model, chronic treatment with progesterone improved motor performance and antioxidant enzymes and attenuated oxidative stress and inflammatory cytokines. In contrast, pretreatment with pregnenolone, a $GABA_A$ receptor-negative modulator, reversed the beneficial progesterone-mediated effects [109]. This observation suggests that progesterone's protective effects might be mediated by its metabolite allopregnanolone, a $GABA_A$ re-

ceptor-positive modulator. In addition, the neurosteroids allopregnanolone and progesterone reduced mHtt aggregates in cultured astrocytes by inducing mTOR-dependent autophagy [110]. Progestogens are relatively unexplored compounds for HD with a few preclinical studies published, and currently, to our knowledge, there are no ongoing clinical trials evaluating progesterone or allopregnanolone neuroprotection to modify HD course.

Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disorder also known as motoneuron disease or Lou Gehrig's disease. It causes the progressive death of motoneurons from the brain stem and spinal cord, leading to several symptoms such as muscle spasms, weakness and atrophy, pain, cognitive and emotional alterations, and respiratory failure. The latter is commonly the cause of death between 3 and 5 years from final diagnosis [111, 112]. Some lines of evidence point out a possible protective role for progesterone in ALS. It has been demonstrated elevated progesterone serum levels in ALS patients compared to controls and a positive correlation with better prognosis such as survival time; whereas this protective profile was not shared by cortisol [113, 114]. Additionally, the classical progesterone receptors PR-A and -B were found to be increased in the human spinal cord in ALS, especially in the lumbar and cervical parts, in axons and blood vessels, with their immunoreactivity increased in nerve roots and large arteries [115]. This might suggest a protective role for progesterone in an attempt to repair tissue degeneration.

Genetic mouse models have been developed to partially resemble some ALS features. For example, the wobbler mice show spontaneous spinal cord and brain stem motoneuron degeneration and astrogliosis [112]. Similar to the human findings, increased progesterone, allopregnanolone, and 20α-dihydroprogesterone levels were found in the brain, spinal cord, and also in the adrenal glands of wobbler mice [116]. Progestogens have exhibited beneficial effects in ALS models characterized by spinal cord motor neuron degeneration. In the brain of these animals, progesterone increased GABAergic interneurons and granule cells, along with decrease in astrocytes number in the hippocampus; however, no influence on neurogenesis was observed by the authors [117]. Treatment of wobbler mice with progesterone attenuated neuropathy, improved motor neuron morphology, and restored Na^+,K^+-ATPase pump mRNA levels [118]. ChAT immunoreactivity was also increased in motoneurons after progesterone administration [119, 120]. The beneficial effects on wobbler mice neuropathology might be related to increased BDNF mRNA levels both in spinal cord motoneurons [119, 121] and in the hippocampus [117]. Glial cells are also positively influenced by progestogens. For instance, GFAP-positive astrocytes were decreased by progesterone in the spinal cord motoneurons [120]. The oligodendrocyte density in the spinal cord gray matter of wobbler mice was increased by progesterone treatment [121], indicating its remyelinating potential (see multiple sclerosis (MS) session). In the same model, progesterone reversed the proinflammatory macroglial phenotype and inflammatory mediators, together with enhanced ChAT expression, effects counteracted by the synthetic progestin norethindrone. This progestin is a 19-nortestosterone derivative exhibiting estrogenic and androgenic activities besides the PR activation which may lead to unwanted outcomes [122]. These results indicate that the type of progestin used may produce different results probably related to the hormone steroid receptor profile activation. Progesterone and allopregnanolone have also been shown to improve several parameters in wobbler mice. These hormones improved neuronal vacuolation, nitric oxide synthase hyperactivity, and cell survival markers after acute treatment. Also, both molecules improved manganese superoxide dismutase (MnSOD) immunoreactivity, BDNF mRNA levels, and muscle performance after chronic treatment [123]. In another transgenic mouse model of ALS expressing a mutant human superoxide dismutase 1 (G93A-SOD1), progesterone reduced spinal cord motor neuron death, delayed motor neuron dysfunction progression, and increased animal lifespan. It was demonstrated that these effects were associated with autophagic flux activation and downregulation of the mutant SOD1 expression [124].

Other synthetic progestins such as nestorone have been tested for alleviating ALS symptoms and neuropathology [111]. Interestingly, nestorone-treated wobbler mice showed improvement in several spinal cord abnormalities, i.e., restored ChAT-IR; decreased motoneuron vacuolization, astrogliosis, and microgliosis; and downregulated proinflammatory markers. In addition, a slight enhancement in forepaw anatomy was observed after nestorone, supporting this progesterone receptor agonist as a promising strategy for ALS [125]. Nestorone, a 19-norprogesterone derivative, has a unique profile among progestins with stronger progestogenic activity than progesterone itself due to its high affinity for PR and very low activities at androgen, estrogen, and glucocorticoid receptors [126].

Currently, there are no studies on clinicaltrials.gov evaluating progestogens repurposing for ALS. Nonetheless, epidemiological studies were conducted to assess a possible relationship between menopause, HRT, and ALS development. A case-control study found no association between several reproductive factors (such as age at menarche and final menstrual period, type of menopause, and others) and ALS risk. Additionally, HRT during postmenopause showed a slight but insignificant association with ALS risk [127]. A large case-control study revealed no significant association between estrogen and progestogen exposure and a possible reduced ALS risk. Notably, among the three countries assessed, HRT was only associated with decreased ALS risk in the Netherlands [128].

Multiple Sclerosis

Another important aspect of progesterone therapeutic profile is its reported role in myelin formation and remyelinating processes. In this sense, the use of natural progesterone or synthetic progestins is considered an attractive therapeutic approach for treating demyelinating diseases, such as MS or inducing myelin repair after injuries [129]. It was observed that levels of neurosteroids, particularly progesterone and testosterone metabolites, are altered in the cerebrospinal fluid and plasma of male MS patients [130]. For a review of the levels and sex differences of steroid hormones in neurodegenerative diseases, see Giatti et al. [131].

In a mouse model of sciatic nerve injury, it was observed that progesterone is generated from pregnenolone by Schwann cells in peripheral nerves, and an increase in progesterone or pregnenolone levels augment myelin sheath formation rate. A positive progesterone effect on axon myelination was also demonstrated in rat dorsal root ganglia in vitro [132]. These benefits are suggested to be related to progesterone actions in oligodendrogenesis and myelin formation in the CNS and PNS [129]. Progesterone increased the proliferation rate of oligodendrocyte precursors cells (OPC) via classical PR activation in organotypic slice cultures of the rat cerebellum [133], stimulated the differentiation of OPCs into mature myelinating oligodendrocytes [133], and upregulated the gene expression of myelin basic protein (MBP), a myelin sheath component, a process that is dependent on PR activation [134]. Allopregnanolone could also increase MBP expression in a $GABA_A$ receptor-dependent manner [134].

In a spinal cord injury rat model, progesterone treatment after lesion increased OPC proliferation and upregulated the mRNA levels of transcription factors Olig2 and Nkx2.2, which are required for oligodendrocyte differentiation, and later Olig1, which is involved in myelin repair. Progesterone also increased the mRNA and protein levels of MBP and proteolipid protein (PLP). These effects resulted in increased mature oligodendrocytes and remyelination [135]. Besides stimulating oligodendrocyte differentiation and maturation, progesterone reduces astrocyte and microglia proliferation and activation [136].

In a demyelination mouse model, the effects of progesterone on microglial cells are reported to involve a switch from M1 (proinflammatory) to M2 (anti-inflammatory) phenotype and NLRP3 inflammasome suppression [137]. Similar effects were observed in an MS model induced by autoimmune encephalomyelitis. In this model, progesterone reduced inflammatory cell infiltration in the injured spinal cord, prevented demyelination, and attenuated disease severity [138]. Therefore, the evidence suggests that progesterone can act as a remyelinating and anti-inflammatory agent, suppressing reactive gliosis in MS.

There is also evidence from clinical studies on the possible benefits of treating MS patients with progesterone. In a retrospective pilot study, women with MS were questioned about the disease severity. The majority (82%) of the premenopausal women reported worse symptoms during the premenstrual period, 54% of postmenopausal women reported increased disease severity after menopause, and 75% of HRT users reported an enhancement in symptoms severity [139]. Conversely, a systematic review with menopausal MS patients reported an inconclusive association between age at menopause, use of HRT, and disease severity [140]. Still, a cohort observational study revealed that HRT (at least 1 year of systemic estrogen with or without progestin) in the postmenopausal phase resulted in a better physical quality of life in women with MS [141]. In a randomized controlled clinical trial (NTC00127075), the administration of nomegestrol acetate (a 19-norprogesterone derivative, 10 mg/day) and transdermal estradiol (75 μg/week) to MS women in the postpartum phase reduced disease relapse [142].

Conclusions and Future Perspectives

This review summarized preclinical and clinical studies addressing the progestogen potential for some of the most common neurodegenerative diseases: AD, PD, HD,

ALS, and MS. There are still many challenges from basic experimental science to clinical translation for effective HRT in neuroprotection. For example, evidences from animal models demonstrate that cyclic administration of progesterone and estrogen resembling the natural menstrual cycle yields better results than continuous treatment [38]. Also, the benefits of HRT seem to be higher with early initiation around menopause rather than late usage [73–75]. Thus, estrogen-combined and cyclic treatment of progestogens in early menopause might provide important results in clinical trials for neurodegenerative disorders. Some studies reveal a promising profile for natural progesterone with regard to AD risk and progression than synthetic progestins, especially MPA, which appears to increase the risk [75, 78, 80]. Nestorone shows a promising profile for ALS in preclinical studies [111, 125]. In addition, the progesterone metabolite allopregnanolone showed very promising results in preclinical studies, and the ongoing and future trials may confirm its regenerative potential.

In summary, despite reports of noneffectiveness or reversion of beneficial estrogen-related effects, preventive and therapeutic use of progesterone, allopregnanolone, and synthetic progestins are important to be considered in future studies, regarding the mechanism of action, once it may modify the course of some neurodegenerative conditions. In this sense, dose, administration regimen, timing, the involved complex intracellular signaling pathways, and the potential benefits of postmenopausal progestogen therapy need to be more thoroughly evaluated, especially when administered in combination with estrogen.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

The authors thank the Fundação de Amparo à Pesquisa do Estado de São Paulo – FAPESP: 2016/20796-2 (RPU), 2020/04709-8 (RPU), 2018/02762-9 (RBO), 2017/23616-8 (TBB); and Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) code 001 (CSB).

Author Contributions

Taysa Bervian Bassani drafted the work and performed the research and interpretation of data. Taysa Bervian Bassani and Rodrigo Portes Ureshino concieved the idea and revised and corrected the final version. Cynthia Silva Bartolomeo and Rafaela Brito Oliveira drew the figures and revised the manuscript. All authors approved the final version of the manuscript.

References

1 Giatti S, Garcia-Segura LM, Barreto GE, Melcangi RC. Neuroactive steroids, neurosteroidogenesis and sex. Prog Neurobiol. 2019;176:1–17.
2 Rossetti MF, Cambiasso MJ, Holschbach MA, Cabrera R. Oestrogens and progestagens: synthesis and action in the brain. J Neuroendocrinol. 2016;28(7):1–11.
3 Hasanpour M, Nourazarian A, Geranmayeh MH, Nikanfar M, Khaki-Khatibi F, Rahbarghazi R, et al. The dynamics of neurosteroids and sex-related hormones in the pathogenesis of alzheimer's disease. Neuromolecular Med. 2018;20(2):215–24.
4 Céspedes Rubio ÁE, Pérez-Alvarez MJ, Lapuente Chala C, Wandosell F. Sex steroid hormones as neuroprotective elements in ischemia models. J Endocrinol. 2018;237(2):R65–81.
5 Kastner P, Krust A, Turcotte B, Stropp U, Tora L, Gronemeyer H, et al. Two distinct estrogen-regulated promoters generate transcripts encoding the two functionally different human progesterone receptor forms A and B. EMBO J. 1990;9(5):1603–14.
6 Garg D, Ng SSM, Baig KM, Driggers P, Segars J. Progesterone-mediated non-classical signaling. Trends Endocrinol Metab. 2017;28(9):656–68.
7 Kowalik MK, Rekawiecki R, Kotwica J. The putative roles of nuclear and membrane-bound progesterone receptors in the female reproductive tract. Reprod Biol. 2013;13(4):279–89.
8 Thomas P, Pang Y, Dong J. Enhancement of cell surface expression and receptor functions of membrane progestin receptor α (mPRα) by progesterone receptor membrane component 1 (PGRMC1): evidence for a role of PGRMC1 as an adaptor protein for steroid receptors. Endocrinology. 2014;155(3):1107–19.
9 González SL, Coronel MF, Raggio MC, Labombarda F. Progesterone receptor-mediated actions and the treatment of central nervous system disorders: an up-date of the known and the challenge of the unknown. Steroids. 2020;153:108525.
10 Moussatche P, Lyons TJ. Non-genomic progesterone signalling and its non-canonical receptor. Biochem Soc Trans. 2012;40(1):200–4.
11 Cabeza M, Heuze Y, Sánchez A, Garrido M, Bratoeff E. Recent advances in structure of progestins and their binding to progesterone receptors. J Enzyme Inhib Med Chem. 2015;30(1):152–9.
12 Gonzalez S. Progesterone for the treatment of central nervous system disorders: the many signaling roads for a single molecule. Neural Regen Res. 2020;15(10):1846.
13 Diviccaro S, Cioffi L, Falvo E, Giatti S, Melcangi RC. Allopregnanolone: an overview on its synthesis and effects. J Neuroendocrinol. 2022;34(2):e12996.
14 Thomas P, Pang Y. Anti-apoptotic actions of allopregnanolone and ganaxolone mediated through membrane progesterone receptors (PAQRs) in neuronal cells. Front Endocrinol. 2020;11:417.
15 Wirth MM. Beyond the HPA axis: progesterone-derived neuroactive steroids in human stress and emotion. Front Endocrinol. 2011;2:19.

16 Charalampopoulos I, Alexaki VI, Tsatsanis C, Minas V, Dermitzaki E, Lasaridis I, et al. Neurosteroids as endogenous inhibitors of neuronal cell apoptosis in aging. Ann N Y Acad Sci. 2006;1088(1):139–52.
17 Melcangi RC, Giatti S, Calabrese D, Pesaresi M, Cermenati G, Mitro N, et al. Levels and actions of progesterone and its metabolites in the nervous system during physiological and pathological conditions. Prog Neurobiol. 2014;113:56–69.
18 Yilmaz C, Karali K, Fodelianaki G, Gravanis A, Chavakis T, Charalampopoulos I, et al. Neurosteroids as regulators of neuroinflammation. Front Neuroendocrinol. 2019;55:100788.
19 Lei B, Mace B, Dawson HN, Warner DS, Laskowitz DT, James ML, et al. Anti-inflammatory effects of progesterone in lipopolysaccharide-stimulated BV-2 microglia. PLoS One. 2014;9(7):e103969.
20 He J, Evans CO, Hoffman SW, Oyesiku NM, Stein DG. Progesterone and allopregnanolone reduce inflammatory cytokines after traumatic brain injury. Exp Neurol. 2004;189(2):404–12.
21 Jolivel V, Brun S, Binamé F, Benyounes J, Taleb O, Bagnard D, et al. Microglial cell morphology and phagocytic activity are critically regulated by the neurosteroid allopregnanolone: a possible role in neuroprotection. Cells. 2021;10(3):698.
22 Si D, Yang P, Jiang R, Zhou H, Wang H, Zhang Y, et al. Improved cognitive outcome after progesterone administration is associated with protecting hippocampal neurons from secondary damage studied in vitro and in vivo. Behav Brain Res. 2014;264(57):135–42.
23 Weill-Engerer S, David JP, Sazdovitch V, Liere P, Eychenne B, Pianos A, et al. Neurosteroid quantification in human brain regions: comparison between alzheimer's and nondemented patients. J Clin Endocrinol Metab. 2002;87(11):5138–43.
24 Luchetti S, Huitinga I, Swaab DF. Neurosteroid and GABA-A receptor alterations in Alzheimer's disease, Parkinson's disease and multiple sclerosis. Neuroscience. 2011;191:6–21.
25 Luchetti S, Bossers K, Van de Bilt S, Agrapart V, Morales RR, Frajese GV, et al. Neurosteroid biosynthetic pathways changes in prefrontal cortex in Alzheimer's disease. Neurobiol Aging. 2011;32(11):1964–76.
26 Marx CE, Trost WT, Shampine LJ, Stevens RD, Hulette CM, Steffens DC, et al. The neurosteroid allopregnanolone is reduced in prefrontal cortex in alzheimer's disease. Biol Psychiatry. 2006;60(12):1287–94.
27 Schaeffer V, Patte-Mensah C, Eckert A, Mensah-Nyagan AG. Modulation of neurosteroid production in human neuroblastoma cells by Alzheimer's disease key proteins. J Neurobiol. 2006 Jul;66(8):868–81.
28 Guerra-Araiza C, Amorim MAR, Camacho-Arroyo I, Garcia-Segura LM. Effects of progesterone and its reduced metabolites, dihydroprogesterone and tetrahydroprogesterone, on the expression and phosphorylation of glycogen synthase kinase-3 and the microtubule-associated protein Tau in the rat cerebellum. Dev Neurobiol. 2007 Mar;67(4):510–20.
29 Pinto-Almazán R, Calzada-Mendoza CC, Campos-Lara MG, Guerra-Araiza C. Effect of chronic administration of estradiol, progesterone, and tibolone on the expression and phosphorylation of glycogen synthase kinase-3β and the microtubule-associated protein tau in the hippocampus and cerebellum of female rat. J Neurosci Res. 2012;90(4):878–86.
30 Guerra-Araiza C, Amorim MAR, Pinto-Almazán R, González-Arenas A, Campos MG, Garcia-Segura LM, et al. Regulation of the phosphoinositide-3 kinase and mitogen-activated protein kinase signaling pathways by progesterone and its reduced metabolites in the rat brain. J Neurosci Res. 2009;87(2):470–81.
31 Amorim MAR, Guerra-Araiza C, Pernía O, Da Cruz E Silva EF, Garcia-Segura LM. Progesterone regulates the phosphorylation of protein phosphatases in the brain. J Neurosci Res. 2010;88(13):2826–32.
32 Hong Y, Wang X, Sun S, Xue G, Li J, Hou Y, et al. Progesterone exerts neuroprotective effects against Aβ-induced neuroinflammation by attenuating ER stress in astrocytes. Int Immunopharmacol. 2016;33:83–9.
33 Hong Y, Liu Y, Yu D, Wang M, Hou Y. The neuroprotection of progesterone against Aβ-induced NLRP3-Caspase-1 inflammasome activation via enhancing autophagy in astrocytes. Int Immunopharmacol. 2019;74(12):105669.
34 Hong Y, Liu Y, Zhang G, Wu H, Hou Y. Progesterone suppresses Aβ42-induced neuroinflammation by enhancing autophagy in astrocytes. Int Immunopharmacol. 2018;54(12):336–43.
35 Qin Y, Chen Z, Han X, Wu H, Yu Y, Wu J, et al. Progesterone attenuates Aβ25-35-induced neuronal toxicity via JNK inactivation and progesterone receptor membrane component 1-dependent inhibition of mitochondrial apoptotic pathway. J Steroid Biochem Mol Biol. 2015;154:302–11.
36 Wu Z, Wu H, Sun S, Wu H, Shi W, Song J, et al. Progesterone attenuates Aβ25–35-induced neuronal toxicity by activating the Ras signalling pathway through progesterone receptor membrane component 1. Life Sci. 2020;253:117360.
37 Carroll JC, Rosario ER, Chang L, Stanczyk FZ, Oddo S, LaFerla FM, et al. Progesterone and estrogen regulate Alzheimer-like neuropathology in female 3xTg-AD mice. J Neurosci. 2007;27(48):13357–65.
38 Carroll JC, Rosario ER, Villamagna A, Pike CJ, Amorim MAR, Guerra-Araiza C, et al. Continuous and cyclic progesterone differentially interact with estradiol in the regulation of alzheimer-like pathology in female 3×Transgenic-alzheimer's disease mice. J Neurosci Res. 2010;151(6):2713–22.
39 Hu Z, Yang Y, Gao K, Rudd JA, Fang M. Ovarian hormones ameliorate memory impairment, cholinergic deficit, neuronal apoptosis and astrogliosis in a rat model of Alzheimer's disease. Exp Ther Med. 2016;11(1):89–97.
40 Bimonte-Nelson HA, Francis KR, Umphlet CD, Granholm AC. Progesterone reverses the spatial memory enhancements initiated by tonic and cyclic oestrogen therapy in middle-aged ovariectomized female rats. Eur J Neurosci. 2006;24(1):229–42.
41 Aguirre CC, Baudry M. Progesterone reverses 17β-estradiol-mediated neuroprotection and BDNF induction in cultured hippocampal slices. Eur J Neurosci. 2009;29(3):447–54.
42 Irwin RW, Brinton RD. Allopregnanolone as regenerative therapeutic for Alzheimer's disease: translational development and clinical promise. Prog Neurobiol. 2014;113:40–55.
43 Irwin RW, Solinsky CM, Brinton RD. Frontiers in therapeutic development of allopregnanolone for Alzheimer's disease and other neurological disorders. Front Cell Neurosci. 2014;8:1–19.
44 Lockhart EM, Warner DS, Pearlstein RD, Penning DH, Mehrabani S, Boustany RM, et al. Allopregnanolone attenuates N-methyl-D-aspartate-induced excitotoxicity and apoptosis in the human NT2 cell line in culture. Neurosci Lett. 2002;328(1):33–6.
45 Hu AQ, Wang ZM, Lan DM, Fu YM, Zhu YH, Dong Y, et al. Inhibition of evoked glutamate release by neurosteroid allopregnanolone via inhibition of L-type calcium channels in rat medial prefrontal cortex. Neuropsychopharmacology. 2007;32(7):1477–89.
46 Chang Y, Hsieh HL, Huang SK, Wang SJ. Neurosteroid allopregnanolone inhibits glutamate release from rat cerebrocortical nerve terminals. Synapse. 2019 Mar;73(3):e22076.
47 Wang JM, Singh C, Liu L, Irwin RW, Chen S, Chung EJ, et al. Allopregnanolone reverses neurogenic and cognitive deficits in mouse model of Alzheimer's disease. Proc Natl Acad Sci U S A. 2010;107(14):6498–503.
48 Singh C, Liu L, Wang JM, Irwin RW, Yao J, Chen S, et al. Allopregnanolone restores hippocampal-dependent learning and memory and neural progenitor survival in aging 3xTgAD and nonTg mice. Neurobiol Aging. 2012;33(8):1493–506.
49 Wang JM, Johnston PB, Ball BG, Brinton RD. The neurosteroid allopregnanolone promotes proliferation of rodent and human neural progenitor cells and regulates cell-cycle gene and protein expression. J Neurosci. 2005;25(19):4706–18.

50 Chen S, Wang JM, Irwin RW, Yao J, Liu L, Brinton RD, et al. Allopregnanolone promotes regeneration and reduces β-amyloid burden in a preclinical model of Alzheimer's disease. PLoS One. 2011;6(8):e24293.
51 Chen S, Wang T, Yao J, Brinton RD. Allopregnanolone promotes neuronal and oligodendrocyte differentiation in vitro and in vivo: therapeutic implication for alzheimer's disease. Neurotherapeutics. 2020;17(4):1813–24.
52 Irwin RW, Solinsky CM, Loya CM, Salituro FG, Rodgers KE, Bauer G, et al. Allopregnanolone preclinical acute pharmacokinetic and pharmacodynamic studies to predict tolerability and efficacy for alzheimer's disease. PLoS One. 2015;10(6):e0128313.
53 Koebele SV, Hiroi R, Plumley ZMT, Melikian R, Prakapenka AV, Patel S, et al. Clinically used hormone formulations differentially impact memory, anxiety-like, and depressive-like behaviors in a rat model of transitional menopause. Front Behav Neurosci. 2021;15:696838.
54 Prakapenka AV, Hiroi R, Quihuis AM, Carson C, Patel S, Berns-Leone C, et al. Contrasting effects of individual versus combined estrogen and progestogen regimens as working memory load increases in middle-aged ovariectomized rats: one plus one does not equal two. Neurobiol Aging. 2018;64:1–14.
55 Braden BB, Andrews MG, Acosta JI, Mennenga SE, Lavery C, Bimonte-Nelson HA, et al. A comparison of progestins within three classes: differential effects on learning and memory in the aging surgically menopausal rat. Behav Brain Res. 2017;322:258–68.
56 Nilsen J, Brinton RD. Impact of progestins on estrogen-induced neuroprotection: synergy by progesterone and 19-norprogesterone and antagonism by medroxyprogesterone acetate. Endocrinology. 2002;143(1):205–12.
57 Sitruk-Ware R. Pharmacological profile of progestins. Maturitas. 2004;47(4):277–83.
58 Nilsen J, Morales A, Brinton RD. Medroxyprogesterone acetate exacerbates glutamate excitotoxicity. Gynecol Endocrinol. 2006;22(7):355–61.
59 Jodhka PK, Kaur P, Underwood W, Lydon JP, Singh M. The differences in neuroprotective efficacy of progesterone and medroxyprogesterone acetate correlate with their effects on brain-derived neurotrophic factor expression. Endocrinology. 2009;150(7):3162–8.
60 Porter KN, Sarkar SN, Dakhlallah DA, Vannoy ME, Quintana DD, Simpkins JW, et al. Medroxyprogesterone acetate impairs amyloid beta degradation in a matrix metalloproteinase-9 dependent manner. Front Aging Neurosci. 2020 Apr 7;12:92.
61 Wu H, Wu ZG, Shi WJ, Gao H, Wu HH, Bian F, et al. Effects of progesterone on glucose uptake in neurons of Alzheimer's disease animals and cell models. Life Sci. 2019;238:116979.
62 Grimm A, Biliouris EE, Lang UE, Götz J, Mensah-Nyagan AG, Eckert A, et al. Sex hormone-related neurosteroids differentially rescue bioenergetic deficits induced by amyloid-β or hyperphosphorylated tau protein. Cell Mol Life Sci. 2016;73(1):201–15.
63 Irwin RW, Yao J, Hamilton RT, Cadenas E, Brinton RD, Nilsen J, et al. Progesterone and estrogen regulate oxidative metabolism in brain mitochondria. Endocrinology. 2008;149(6):3167–75.
64 Wang T, Yao J, Chen S, Mao Z, Brinton RD. Allopregnanolone reverses bioenergetic deficits in female triple transgenic alzheimer's mouse model. Neurotherapeutics. 2020;17(1):178–88.
65 Qian X, Cao H, Ma Q, Wang Q, He W, Qin P, et al. Allopregnanolone attenuates Aβ25-35-induced neurotoxicity in PC12 cells by reducing oxidative stress. Int J Clin Exp Med. 2015;8(8):13610–5.
66 Yao J, Chen S, Cadenas E, Brinton RD. Estrogen protection against mitochondrial toxin-induced cell death in hippocampal neurons: antagonism by progesterone. Brain Res. 2011;1379:2–10.
67 Ratnakumar A, Zimmerman SE, Jordan BA, Mar JC. Estrogen activates Alzheimer's disease genes. Alzheimers Dement. 2019;5(1):906–17.
68 Girard R, Météreau E, Thomas J, Pugeat M, Qu C, Dreher JC, et al. Hormone therapy at early post-menopause increases cognitive control-related prefrontal activity. Sci Rep. 2017;7(1):44917.
69 Doty RL, Tourbier I, Ng V, Neff J, Armstrong D, Battistini M, et al. Influences of hormone replacement therapy on olfactory and cognitive function in postmenopausal women. Neurobiol Aging. 2015;36(6):2053–9.
70 Yoon BK, Chin J, Kim JW, Shin MH, Ahn S, Lee DY, et al. Menopausal hormone therapy and mild cognitive impairment: a randomized, placebo-controlled trial. Menopause. 2018;25(8):870–6.
71 Yoon BK, Kim DK, Kang Y, Kim JW, Shin MH, Na DL, et al. Hormone replacement therapy in postmenopausal women with Alzheimer's disease: a randomized, prospective study. Fertil Steril. 2003;79(2):274–80.
72 Colucci M, Cammarata S, Assini A, Croce R, Clerici F, Novello C, et al. The number of pregnancies is a risk factor for Alzheimer's disease. Eur J Neurol. 2006;13(12):1374–7.
73 Kang JH, Weuve J, Grodstein F. Postmenopausal hormone therapy and risk of cognitive decline in community-dwelling aging women. Neurology. 2004;63(1):101–7.
74 MacLennan AH, Henderson VW, Paine BJ, Mathias J, Ramsay EN, Ryan P, et al. Hormone therapy, timing of initiation, and cognition in women aged older than 60 years: the REMEMBER pilot study. Menopause. 2006;13(1):28–36.
75 Shao H, Breitner JCS, Whitmer RA, Wang J, Hayden K, Wengreen H, et al. Hormone therapy and alzheimer disease dementia: new findings from the Cache county study. Neurology. 2012;79(18):1846–52.
76 Imtiaz B, Taipale H, Tanskanen A, Tiihonen M, Kivipelto M, Heikkinen AM, et al. Risk of Alzheimer's disease among users of postmenopausal hormone therapy: a nationwide case-control study. Maturitas. 2017;98:7–13.
77 Savolainen-Peltonen H, Rahkola-Soisalo P, Hoti F, Vattulainen P, Gissler M, Ylikorkala O, et al. Use of postmenopausal hormone therapy and risk of Alzheimer's disease in Finland: nationwide case-control study. BMJ. 2019;364:l665.
78 Shumaker SA, Legault C, Rapp SR, Thal L, Wallace RB, Ockene JK, et al. Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women - the women's health initiative memory study: a randomized controlled trial. J Am Med Assoc. 2003;289(20):2651.
79 Shumaker SA, Legault C, Kuller L, Rapp SR, Thal L, Lane DS, et al. Conjugated equine estrogens and incidence of probable dementia and mild cognitive impairment in postmenopausal women: women's Health Initiative Memory Study. J Am Med Assoc. 2004;291(24):2947.
80 Hersi M, Irvine B, Gupta P, Gomes J, Birkett N, Krewski D, et al. Risk factors associated with the onset and progression of Alzheimer's disease: a systematic review of the evidence. Neurotoxicology. 2017;61:143–87.
81 Hernandez GD, Solinsky CM, Mack WJ, Kono N, Rodgers KE, Wu CY, et al. Safety, tolerability, and pharmacokinetics of allopregnanolone as a regenerative therapeutic for Alzheimer's disease: a single and multiple ascending dose phase 1b/2a clinical trial. Alzheimers Dement. 2020;6(1):e12107.
82 Meltzer-Brody S, Kanes SJ. Allopregnanolone in postpartum depression: role in pathophysiology and treatment. Neurobiol Stress. 2020;12:100212.
83 di Michele F, Longone P, Romeo E, Lucchetti S, Brusa L, Pierantozzi M, et al. Decreased plasma and cerebrospinal fluid content of neuroactive steroids in Parkinson's disease. Neurol Sci. 2003;24(3):172–3.
84 Luchetti S, Bossers K, Frajese GV, Swaab DF. Neurosteroid biosynthetic pathway changes in substantia nigra and caudate nucleus in parkinson's disease. Brain Pathol. 2010;20(5):945–51.
85 Di Michele F, Luchetti S, Bernardi G, Romeo E, Longone P. Neurosteroid and neurotransmitter alterations in Parkinson's disease. Front Neuroendocrinol. 2013;34(2):132–42.
86 Smith KM, Dahodwala N. Sex differences in Parkinson's disease and other movement disorders. Exp Neurol. 2014;259:44–56.
87 Bourque M, Morissette M, Di Paolo T. Repurposing sex steroids and related drugs as potential treatment for Parkinson's disease. Neuropharmacology. 2019;147:37–54.

88 Melcangi RC, Caruso D, Levandis G, Abbiati F, Armentero MT, Blandini F, et al. Modifications of neuroactive steroid levels in an experimental model of nigrostriatal degeneration: potential relevance to the pathophysiology of Parkinson's disease. J Mol Neurosci. 2012;46(1):177–83.
89 Grandbois M, Morissette M, Callier S, Di Paolo T. Ovarian steroids and raloxifene prevent MPTP-induced dopamine depletion in mice. Neuroreport. 2000;11(2):343–6.
90 Callier S, Morissette M, Grandbois M, Pélaprat D, Di Paolo T. Neuroprotective properties of 17β-estradiol, progesterone, and raloxifene in MPTP C57Bl/6 mice. Synapse. 2001;41(2):131–8.
91 Bourque M, Morissette M, Al Sweidi S, Caruso D, Melcangi RC, Di Paolo T, et al. Neuroprotective effect of progesterone in MPTP-treated male mice. Neuroendocrinology. 2016;103(3–4):300–14.
92 Litim N, Morissette M, Di Paolo T. Effects of progesterone administered after MPTP on dopaminergic neurons of male mice. Neuropharmacology. 2017;117:209–18.
93 Jarras H, Bourque M, Poirier AA, Morissette M, Coulombe K, Di Paolo T, et al. Neuroprotection and immunomodulation of progesterone in the gut of a mouse model of Parkinson's disease. J Neuroendocrinol. 2020; 32(1):e12782.
94 Casas S, Giuliani F, Cremaschi F, Yunes R, Cabrera R. Neuromodulatory effect of progesterone on the dopaminergic, glutamatergic, and GABAergic activities in a male rat model of Parkinson's disease. Neurol Res. 2013;35(7):719–25.
95 Yu L, Liao PC. Estrogen and progesterone distinctively modulate methamphetamine-induced dopamine and serotonin depletions in C57BL/6J mice. J Neural Transm. 2000; 107(10):1139–47.
96 Yu L, Cherng CG, Chen H. Central effects of gonadal hormones neurotoxicity in mice gonadectomized at 4 weeks postpartum. 2002; 70101:282–7.
97 Kritzer MF, Adler A, Bethea CL. Ovarian hormone influences on the density of immunoreactivity for tyrosine hydroxylase and serotonin in the primate corpus striatum. Neuroscience. 2003;122(3):757–72.
98 Díaz NF, Díaz-Martínez NE, Velasco I, Camacho-Arroyo I. Progesterone increases dopamine neurone number in differentiating mouse embryonic stem cells. J Neuroendocrinol. 2009;21(8):730–6.
99 Chao OY, Huston JP, von Bothmer A, Pum ME. Chronic progesterone treatment of male rats with unilateral 6-hydroxydopamine lesion of the dorsal striatum exasperates parkinsonian symptoms. Neuroscience. 2011;196:228–36.
100 Noyce AJ, Bestwick JP, Silveira-Moriyama L, Hawkes CH, Giovannoni G, Lees AJ, et al. Meta-analysis of early nonmotor features and risk factors for Parkinson disease. Ann Neurol. 2012;72(6):893–901.
101 Popat RA, Van Den Eeden SK, Tanner CM, McGuire V, Bernstein AL, Bloch DA, et al. Effect of reproductive factors and postmenopausal hormone use on the risk of Parkinson disease. Neurology. 2005;65(3):383–90.
102 Nicoletti A, Arabia G, Pugliese P, Nicoletti G, Torchia G, Condino F, et al. Hormonal replacement therapy in women with Parkinson disease and levodopa-induced dyskinesia: a crossover trial. Clin Neuropharmacol. 2007;30(5):276–80.
103 Lundin JI, Ton TGN, Lacroix AZ, Longstreth WT, Franklin GM, Swanson PD, et al. Formulations of hormone therapy and risk of Parkinson's disease. Mov Disord. 2014; 29(13):1631–6.
104 Strijks E, Kremer JAM, Horstink MWIM. Effects of female sex steroids on Parkinson's disease in postmenopausal women. Clin Neuropharmacol. 1999;22(2):93–7.
105 Yunes R, Casas S, Gaglio E, Cabrera R. Progesterone exerts a neuromodulatory effect on turning behavior of hemiparkinsonian male rats: expression of 3α-Hydroxysteroid oxidoreductase and allopregnanolone as suggestive ofGABAAReceptors involvement. Parkinsons Dis. 2015;2015:1–9.
106 Nezhadi A, Sheibani V, Esmaeilpour K, Shabani M, Esmaeili-Mahani S. Neurosteroid allopregnanolone attenuates cognitive dysfunctions in 6-OHDA-induced rat model of Parkinson's disease. Behav Brain Res. 2016; 305:258–64.
107 Wang T, Ye X, Bian W, Chen Z, Du J, Li M, et al. Allopregnanolone modulates GABAAR-dependent CaMKIIδ3 and BDNF to protect SH-SY5Y cells against 6-OHDA-induced damage. Front Cell Neurosci. 2019; 13:569.
108 Langbehn DR, Brinkman RR, Falush D, Paulsen JS, Hayden MR. A new model for prediction of the age of onset and penetrance for Huntington's disease based on CAG length. Clin Genet. 2004;65(4):267–77.
109 Kumar P, Kumar P, Khan A, Deshmukh R, Lal Sharma P. Role of neurosteroids in experimental 3-nitropropionic acid induced neurotoxicity in rats. Eur J Pharmacol. 2014; 723(1):38–45.
110 Kim HN, Lee SJ, Koh JY. The neurosteroids, allopregnanolone and progesterone, induce autophagy in cultured astrocytes. Neurochem Int. 2012;60(2):125–33.
111 Sitruk-Ware R, Bonsack B, Brinton R, Schumacher M, Kumar N, Lee JY, et al. Progress in progestin-based therapies for neurological disorders. Neurosci Biobehav Rev. 2021;122:38–65.
112 De Nicola AF, Meyer M, Garay L, Kruse MS, Schumacher M, Guennoun R, et al. Progesterone and allopregnanolone neuroprotective effects in the wobbler mouse model of amyotrophic lateral sclerosis. Cell Mol Neurobiol. 2021;42(1):23–40.
113 Gargiulo Monachelli G, Meyer M, Rodríguez GE, Garay LI, Sica REP, De Nicola AF, et al. Endogenous progesterone is associated to amyotrophic lateral sclerosis prognostic factors. Acta Neurol Scand. 2011;123(1):60–7.
114 Monachelli GG, Meyer M, Rodríguez G, Garay L, Sica RE, De Nicola AF, et al. Progesterone and cortisol levels in sporadic amyotrophic lateral sclerosis (sALS): correlation with prognostic factors. Horm Mol Biol Clin Investig. 2011;6(1):167–73.
115 Gargiulo-Monachelli GM, Campos-Melo D, Droppelmann CA, Keller BA, Leystra-Lantz C, De Nicola AF, et al. Expression and cellular localization of the classical progesterone receptor in healthy and amyotrophic lateral sclerosis affected spinal cord. Eur J Neurol. 2014;21(2):273–e11.
116 Gonzalez Deniselle MC, Liere P, Pianos A, Meyer M, Aprahamian F, Cambourg A, et al. Steroid profiling in male wobbler mouse, a model of amyotrophic lateral sclerosis. Endocrinology. 2016 Nov;157(11):4446–60.
117 Meyer M, Gonzalez Deniselle MC, Gargiulo-Monachelli G, Lima A, Roig P, Guennoun R, et al. Progesterone attenuates several hippocampal abnormalities of the wobbler mouse. J Neuroendocrinol. 2013;25(3):235–43.
118 Gonzalez Deniselle MC, López-Costa JJ, Saavedra JP, Pietranera L, Gonzalez SL, Garay L, et al. Progesterone neuroprotection in the Wobbler mouse, a genetic model of spinal cord motor neuron disease. Neurobiol Dis. 2002;11(3):457–68.
119 Gonzalez Deniselle MC, Garay L, Gonzalez S, Saravia F, Labombarda F, Guennoun R, et al. Progesterone modulates brain-derived neurotrophic factor and choline acetyltransferase in degenerating Wobbler motoneurons. Exp Neurol. 2007;203(2):406–14.
120 Meyer M, Gonzalez Deniselle MC, Garay LI, Monachelli GG, Lima A, Roig P, et al. Stage dependent effects of progesterone on motoneurons and glial cells of wobbler mouse spinal cord degeneration. Cell Mol Neurobiol. 2010 Jan;30(1):123–35.
121 Meyer M, Gonzalez Deniselle MC, Gargiulo-Monachelli G, Garay LI, Schumacher M, Guennoun R, et al. Progesterone effects on neuronal brain-derived neurotrophic factor and glial cells during progression of Wobbler mouse neurodegeneration. Neuroscience. 2012;201:267–79.
122 Gargiulo-Monachelli G, Meyer M, Lara A, Garay L, Lima A, Roig P, et al. Comparative effects of progesterone and the synthetic progestin norethindrone on neuroprotection in a model of spontaneous motoneuron degeneration. J Steroid Biochem Mol Biol. 2019;192:105385.
123 Meyer M, Garay LI, Kruse MS, Lara A, Gargiulo-Monachelli G, Schumacher M, et al. Protective effects of the neurosteroid allopregnanolone in a mouse model of spontaneous motoneuron degeneration. J Steroid Biochem Mol Biol. 2017;174:201–16.

124 Kim J, Kim TY, Cho KS, Kim HN, Koh JY. Autophagy activation and neuroprotection by progesterone in the G93A-SOD1 transgenic mouse model of amyotrophic lateral sclerosis. Neurobiol Dis. 2013;59:80–5.
125 Meyer M, Gonzalez Deniselle MC, Garay L, Sitruk-Ware R, Guennoun R, Schumacher M, et al. The progesterone receptor agonist Nestorone holds back proinflammatory mediators and neuropathology in the wobbler mouse model of motoneuron degeneration. Neuroscience. 2015;308:51–63.
126 Kumar N, Koide SS, Tsong YY, Sundaram K. Nestorone®: a progestin with a unique pharmacological profile. Steroids. 2000;65(10–11):629–36.
127 Popat RA, Van Den Eeden SK, Tanner CM, Bernstein AL, Bloch DA, Leimpeter A, et al. Effect of reproductive factors and postmenopausal hormone use on the risk of amyotrophic lateral sclerosis. Neuroepidemiology. 2006;27(3):117–21.
128 Rooney JPK, Visser AE, D'Ovidio F, Vermeulen R, Beghi E, Chio A, et al. A case-control study of hormonal exposures as etiologic factors for ALS in women. Neurology. 2017;89(12):1283–90.
129 Schumacher M, Hussain R, Gago N, Oudinet JP, Mattern C, Ghoumari AM, et al. Progesterone synthesis in the nervous system: implications for myelination and myelin repair. Front Neurosci. 2012;6:10.
130 Caruso D, Melis M, Fenu G, Giatti S, Romano S, Grimoldi M, et al. Neuroactive steroid levels in plasma and cerebrospinal fluid of male multiple sclerosis patients. J Neurochem. 2014;130(4):591–7.
131 Giatti S, Diviccaro S, Serafini MM, Caruso D, Garcia-Segura LM, Viviani B, et al. Sex differences in steroid levels and steroidogenesis in the nervous system: physiopathological role. Front Neuroendocrinol. 2020 Jan;56:100804.
132 Koenig HL, Schumacher M, Ferzaz B, Thi AN, Ressouches A, Guennoun R, et al. Progesterone synthesis and myelin formation by Schwann cells. Science. 1995;268(5216):1500–3.
133 Ghoumari AM, Baulieu EE, Schumacher M. Progesterone increases oligodendroglial cell proliferation in rat cerebellar slice cultures. Neuroscience. 2005;135(1):47–58.
134 Ghoumari AM, Ibanez C, El-Etr M, Leclerc P, Eychenne B, O'Malley BW, et al. Progesterone and its metabolites increase myelin basic protein expression in organotypic slice cultures of rat cerebellum. J Neurochem. 2003;86(4):848–59.
135 Labombarda F, González SL, Lima A, Roig P, Guennoun R, Schumacher M, et al. Effects of Progesterone on oligodendrocyte progenitors, oligodendrocyte transcription factors, and myelin proteins following spinal cord injury. Glia. 2009;57(8):884–97.
136 Labombarda F, González S, Lima A, Roig P, Guennoun R, Schumacher M, et al. Progesterone attenuates astro- and microgliosis and enhances oligodendrocyte differentiation following spinal cord injury. Exp Neurol. 2011;231(1):135–46.
137 Aryanpour R, Pasbakhsh P, Zibara K, Namjoo Z, Beigi Boroujeni F, Shahbeigi S, et al. Progesterone therapy induces an M1 to M2 switch in microglia phenotype and suppresses NLRP3 inflammasome in a cuprizone-induced demyelination mouse model. Int Immunopharmacol. 2017;51:131–9.
138 Garay L, Deniselle MCG, Lima A, Roig P, De Nicola AF. Effects of progesterone in the spinal cord of a mouse model of multiple sclerosis. J Steroid Biochem Mol Biol. 2007;107(3–5):228–37.
139 Smith R, Studd JWW. A pilot study of the effect upon multiple sclerosis of the menopause, hormone replacement therapy and the menstrual cycle. J R Soc Med. 1992;85(10):612–3.
140 Karageorgiou V, Lambrinoudaki I, Goulis DG. Menopause in women with multiple sclerosis: a systematic review. Maturitas. 2020;135:68–73.
141 Bove R, White CC, Fitzgerald KC, Chitnis T, Chibnik L, Ascherio A, et al. Hormone therapy use and physical quality of life in postmenopausal women with multiple sclerosis. Neurology. 2016;87(14):1457–63.
142 Vukusic S, Ionescu I, El-Etr M, Schumacher M, Baulieu EE, Cornu C, et al. The prevention of post-partum relapses with progestin and estradiol in multiple sclerosis (POPART'MUS) trial: rationale, objectives and state of advancement. J Neurol Sci. 2009;286(1–2):114–8.