Review

Progesterone receptors: Form and function in brain

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Abstract

Emerging data indicate that progesterone has multiple non-reproductive functions in the central nervous system to regulate cognition, mood, inflammation, mitochondrial function, neurogenesis and regeneration, myelination and recovery from traumatic brain injury. Progesterone-regulated neural responses are mediated by an array of progesterone receptors (PR) that include the classic nuclear PRA and PRB receptors and splice variants of each, the seven transmembrane domain 7TMPRβ and the membrane-associated 25-Dx PR (PGRMC1). These PRs induce classic regulation of gene expression while also transducing signaling cascades that originate at the cell membrane and ultimately activate transcription factors. Remarkably, PRs are broadly expressed throughout the brain and can be detected in every neural cell type. The distribution of PRs beyond hypothalamic borders, suggests a much broader role of progesterone in regulating neural function. Despite the large body of evidence regarding progesterone regulation of reproductive behaviors and estrogen-inducible responses as well as effects of progesterone metabolite neurosteroids, much remains to be discovered regarding the functional outcomes resulting from activation of the complex array of PRs in brain by gonadally and/or glial derived progesterone. Moreover, the impact of clinically used progestogens and developing selective PR modulators for targeted outcomes in brain is a critical avenue of investigation as the non-reproductive functions of PRs have far-reaching implications for hormone therapy to maintain neurological health and function throughout menopausal aging.
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1. Introduction

It has become increasingly evident that the functions of gonadal steroid hormones, such as progesterone (P_4),

extend well beyond reproduction. Multiple regions within the central nervous system (CNS) beyond the hypothalamus are targeted by P_4, including the hippocampus and cortex. In recent years, both of these extrahypothalamic sites have garnered increasing interest from endocrinologists based on accumulating evidence that P_4 has potent and direct neuroprotective and neuroregenerative effects in these brain regions while also regulating estrogen action [20,44,91,94, 102,127,135,172,182,201,202,214,231,232,243,244,246,295, 299]. The non-reproductive neural effects of P_4 have

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substantial clinical significance, as progestogens are administered in conjunction with estrogens in hormone therapy to counter the proliferative effect of estrogen on the uterine epithelium. Estrogen, 17β-estradiol (E_2), acts in concert with progesterone to regulate multiple non-reproductive brain functions, such as cognition and neuroprotection [201, 42,99,100,126,161,203,228,242,254,93]. Perhaps the best-known neural effect of estrogen is its ability to protect neurons against a wide variety of insults including glutamate excitotoxicity, amyloid beta (Aβ), and oxidative stress [201,202,42,99,100,126,161,228,242,254,39,38,64,253,292, 306]. On the other hand, the neuroprotective role of P_4 [42,99,100,126,161,228,242,101,162,156,98] is just emerging. From a reproductive gonadal hormone perspective, progesterone always acts in concert with E_2. However, this is not the case for glial derived progesterone [244,18] or for current and future therapeutic uses of progesterone [244,18,258,259]. Here, we discuss the non-reproductive neural functions of P_4 as well as the possible mechanisms by which P_4 achieves these effects, including 'classical' progesterone receptor-mediated pathways and alternate 'non-genomic' mechanisms.

2. Progesterone receptors from membrane to nucleus

The classical nuclear progesterone receptor (cPR) was first characterized in the 1970s and since this time, has been localized to many regions of the CNS, including the hippocampus, cortex, hypothalamus, and cerebellum [117,116, 115,114,43,147,120,121,145,146]. Like most steroids, P_4 exerts its effects by binding and activating specific cellular receptors. According to the common theory of steroid action, P_4 effects are mediated by binding to its cognate receptors (PR), classically defined as ligand-activated transcription factors. In the absence of hormone, PRs are complexed with several chaperone molecules, including heat shock protein (hsp) 90, hsp70, and hsp40. The interaction of PRs with the chaperones is a prerequisite for hormone binding [218,219]. The chaperones also serve to link the PR with protein trafficking systems. Upon P_4 binding, PR undergoes conformational changes, dissociates from the chaperone proteins, dimerizes, and directly interacts with specific response elements (PREs) in the promoters of target genes [173,59,66,3]. When bound to PREs, PRs interact with components of the basal transcription machinery by binding to steroid receptor co-activators. These co-activators bind to PR via a conserved LXXLL amphipathic helix or nuclear-receptor box motifs, which make initial contacts with several helices in the AF-2 (activation function) region of the PR ligand-binding domain [192,289]. Classical PREs are not required for P_4-induced gene upregulation, as P_4 has been shown to increase expression of genes lacking these elements [110,226,208]. These non-classical responses may occur through alternative genomic mechanisms, such as PR tethering to the SP1 transcription factor [208] or non-genomic mechanisms, such as activation of second messenger signaling cascades [201,202,166].

3. Progesterone receptors in the brain: the case for multiple isoforms

Two major isoforms of cPR are known to exist, the full-length B isoform (PRB) and the N-terminal-truncated A isoform (PRA) [55]. Both isoforms are encoded by a single gene (with 8 exons), with translation being initiated from separate start codons (Fig. 1). Like other steroid nuclear receptors, cPR is composed of a variable N-terminal region (encoded by exon 1), a conserved DNA-binding domain (encoded by exons 2 and 3), a variable hinge region (encoded by part of exon 4), and a conserved ligand-binding domain (encoded by exons 4–8). The N-terminal 164-amino acids of PRB, known as B-upstream segment or BUS (absent in PRA), constitute an additional activation function (AF-3), which is made up of two LXXLL motifs and a conserved tryptophan residue. Although the role of cPRs in reproductive function has been extensively studied, the receptors that mediate the neuroprotective and neurotrophic effects of P_4 have yet to be identified.

Splice variants other than the classical PRA and PRB variants have been identified [130,129]. These include variants with insertions of 'intronic' exons and exon-skipped variants (Fig. 2). The intronic exons T [129] and S can be inserted between exons 3 and 4, while exons i45a and i45b can be inserted between exons 4 and 5 (Fig. 2A). Exon-skipped variants include PR-c, PR-s, and PR-t. These variants are generated through omission of exon 1 (PR-c) or exons 1–3 (PR-s and PR-t). Both PR-s and PR-t also retain 5′ untranslated exons (Fig. 2B). Other exon-skipped mRNA variants include del 2, del 4, del 6, del 5+6, del 4+6, del 4+5+6, del 3+4, and del 3+4+5+6. Interestingly, some of these variants have a defective DNA-binding domain and also lack the nuclear localization signal (NLS). PR splice variants lacking NLS, which would be expected to result in cytoplasmic localization, and contain the intact proline rich (PXXP) domain, would be expected to displace the intramolecular occupation of SH3 in Src, enabling them to activate Src and mitogen-activated protein kinases (MAPK) in the cytosol. PRs lacking a functional DNA-binding domain and a NLS could serve as a membrane-associated PR.

Although cPR is expressed in the hippocampus and frontal cortex [117,116,115,114,43], P_4 effects have been reported in the CNS of PR knockout mice, indicating that receptors other than cPR may mediate P_4 signaling in the brain [157]. A novel P_4-binding protein that is distinct from the cPR has been identified as a membrane protein, known as 7TMPR for its seven transmembrane domains [312,313], has characteristics of a G protein-coupled receptor. When bound to progestin, this receptor blocks the activity of adenylyl cyclase, the enzyme that catalyzes production of the intracellular second-messenger cAMP [313]. Three isoforms of 7TMPR have been identified—7TMPRα, β, and γ. The open reading frames (ORFs) of 7TMPRα from human, pig, and mouse are 1038–1053 nucleotides in length and encode peptides 346–350 amino acids in length. These
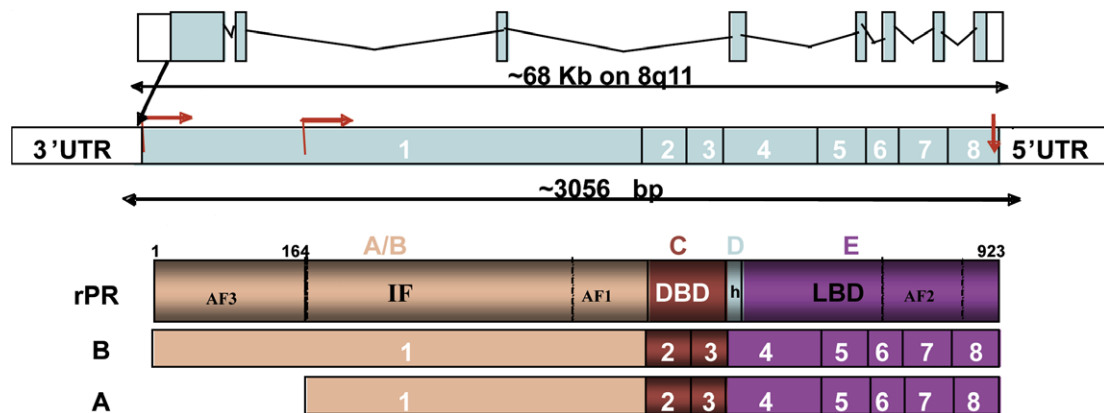
Fig. 1. Gene structure and functional domains of rat cPRA and cPRB. In rat, the classical progesterone receptor is composed of 8 exons with a 3100-bp coding region and 5′- and 3′-untranslated region. Both cPRB and cPRA are transcribed from this gene, but use alternative initiation codons (red horizontal arrows) driven by different promoters. The cPRs have a highly conserved DNA-binding domain (DBD), an activation function1 (AF1) domain immediately upstream of the DBD, a hinge region downstream of the DBD, as well as a ligand-binding domain (LBD) and a C-terminal AF2 domain. An inhibition factor (IF) is present upstream of AF1. The N-terminus of cPRB contains an AF3 domain, which acts in synergy with AF1 and AF2.
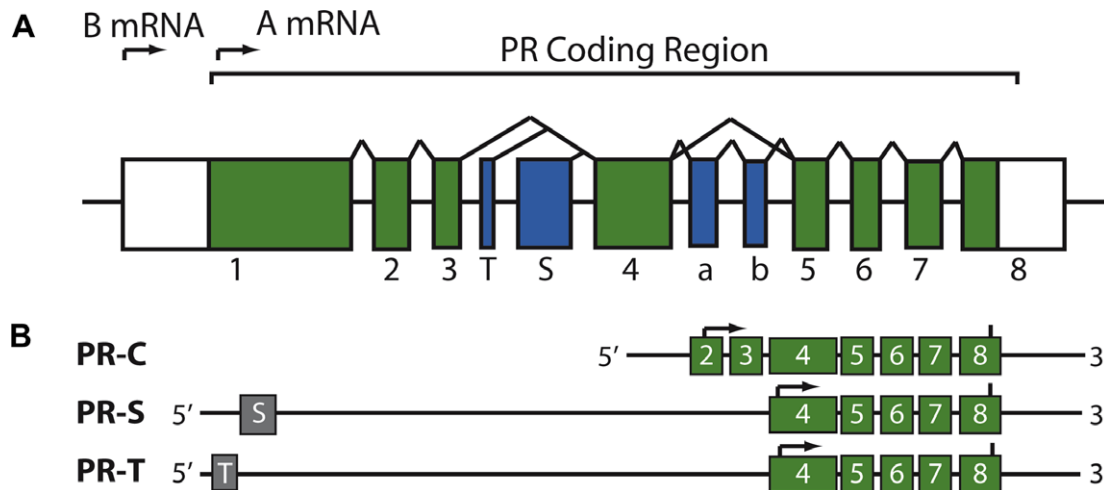

Fig. 2. Splice variants of cPR. (A) Variants can be generated through insertion of T or S between exon 3 and 4 as well as through insertion of a or b between exon 4 and 5. (B) Alternatively, variants can be generated through exon skipping. In PR-c, exon 1 is omitted. In PR-S and PR-T, exons 1–3 are omitted, but the 5′-untranslated exons S and T are retained.

peptides are similar in size to 7TMPR of spotted seatrout (352 amino acids) and zebrafish (354 amino acids). The ORFs of 7TMPRβ from mammals, zebrafish, and *Xenopus laevis* are 1064/1065 nucleotides in length and encode 352–354-amino acid peptides. The 7TMPRγ are slightly shorter, at approximately 330 amino acids.

An additional putative membrane-bound PR has been cloned in multiple different species. The initial isolation and cloning of this protein from pig and rat revealed the presence of a single transmembrane domain. Humans contain two orthologous genes, hpr6.6 (chromosome X, 195 amino acids) and Dg6 (chromosome 4, 223 amino acids). The rat homologue is a 25 kDa, 223-amino acid protein (25-Dx) possessing a hydrophobic domain of 14 residues and a proline-rich domain in the N-terminal region. Independent isolation of rat adrenocortical innerzone-specific antigen (IZAg) by affinity chromatography revealed this protein to be identical to 25-Dx. Overexpression of 25-Dx in CHO cells has been shown to increase P_4 binding to the microsomal fraction [70]. This 25-Dx-enriched microsomal fraction has moderate affinity for testosterone and weak affinity for corticosterone and cortisol. In contrast, it does not bind to either estradiol (E_2) or aldosterone. In human sperm, blockade of 25-Dx with a specific antibody inhibits P_4-induced increases in intracellular Ca^{2+}, providing further support that this protein serves as a membrane PR [70].

4. Localization of progesterone receptors in the brain

Progesterone receptors are broadly expressed throughout the brain, with no apparent restriction to specific cell types. Nevertheless, PR expression may vary depending on the brain region, cell type, or hormonal status

(Fig. 3). Both of the classical PR isoforms (PRA and PRB) are expressed in the hippocampus and frontal cortex of the rat (Fig. 3). PR immunoreactivity is especially high within the bed nucleus of the stria terminalis (BST), in particular the medial division of the medial nucleus of the BST (the principal nucleus of the BST). Immunoreactivity is lower in the intermediate and lateral divisions of the medial nucleus of the BST. In the centromedial amygdala, PR expression is prominent in the posterodorsal part of the medial amygdaloid nucleus, but lower in surrounding areas. No sex differences have been observed in PR expression in the BST and centromedial amygdala [9]. In the brainstem, PR immunoreactivity is present in the norepinephrine neurons of the nucleus tractus solitarius, the region from which projections to the hypothalamic supraoptic nuclei arise. Guerra-Araiza et al. have used quantitative RT-PCR analysis to characterize sex differences in the regulation of PR isoform expression by sex steroid hormones in the rat cerebellum [116]. PR isoform expression in female rats was not altered by estrogen or P_4, while PRA was selectively induced by estrogens in the male cerebellum. Similarly, in the rat hippocampus and olfactory bulb, E_2 induces PRA isoform expression, whereas P_4 does not affect the expression of any PR isoforms [117,116]. In rodents, PR is present in the ventromedial hypothalamus [148]. Auger et al. have reported PR-immunoreactive cells within the preoptic area, the ventromedial and dorsomedial nucleus of the hypothalamus, and the arcuate nucleus of the female rat [9].

Dot blot analysis of 7TMPR expression in human tissue has shown that the α form (from a testicular library) is mainly localized to reproductive tissues such as the placenta, testis, and ovary. In contrast, the γ form (from a colon library) is present in the kidney, fetal kidney, colon, a lung carcinoma, and HeLa 53 cells [313]. The β form (from a brain library) is exclusively localized to neural tissues [313]. These include the cerebral cortex, cerebellum, caudate nucleus, thalamus, pituitary gland, and spinal cord, as shown by dot blot hybridization or tissue array with Northern hybridization.

5. Mechanisms of progesterone action

Progesterone produces multiple effects in the brain through three principle mechanisms: regulation of gene expression, modulation of neurotransmitter systems, and activation of signaling cascades. Classification of the determinant pathways and identification of the specific receptors mediating activation of each of these pathways would be expected to uncover new targets and enable development of improved therapeutic strategies. The effects of P_4 are historically thought to be mediated by PRA or PRB-induced gene transcription [173,55,4]. Available evidence suggests that PRA and PRB shuttle between the nucleus and the cytoplasm, with ligand binding inducing interactions between the receptor and nuclear co-activators [173,4]. PRA and PRB differentially regulate gene transcription, increasing the complexity of this regulatory system [10,37]. For example, PRA is a less potent transactivator than PRB. Also, PRA exerts transrepressional activity on PRB in a promoter- and cell type-dependent manner [10,37]. The P_4-inducible genetic network is further refined

PR A and B Isoforms in Rat Brain

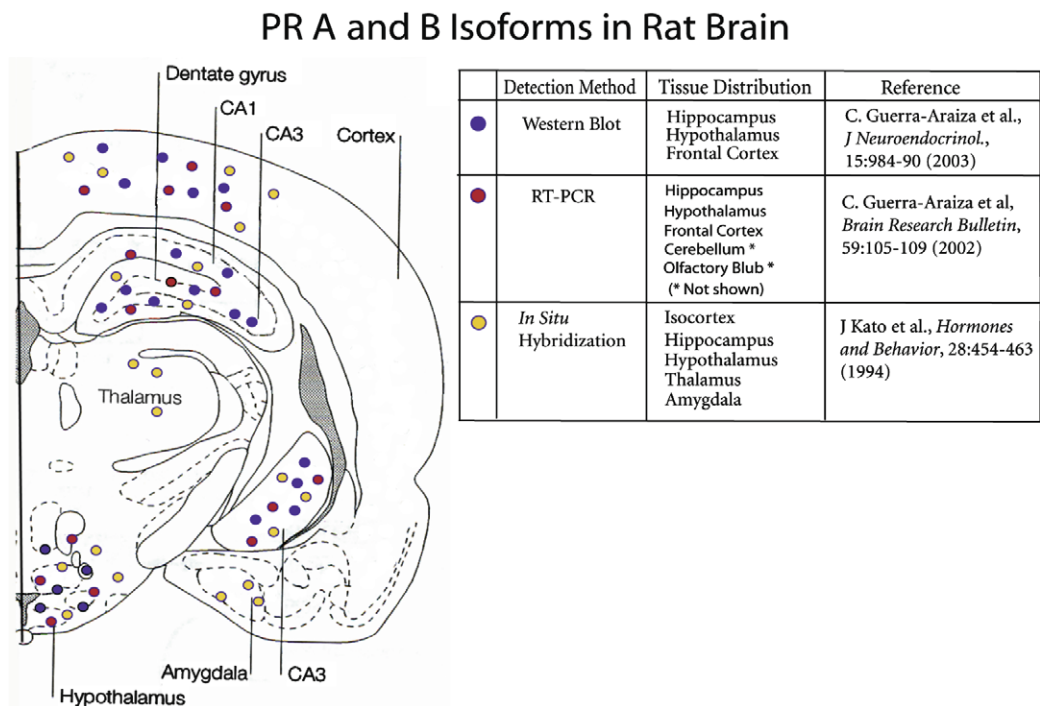|	Detection Method	Tissue Distribution	Reference
●	Western Blot	Hippocampus Hypothalamus Frontal Cortex	C. Guerra-Araiza et al., *J Neuroendocrinol.*, 15:984-90 (2003)
●	RT-PCR	Hippocampus Hypothalamus Frontal Cortex Cerebellum * Olfactory Blub * (* Not shown)	C. Guerra-Araiza et al, *Brain Research Bulletin*, 59:105-109 (2002)
○	*In Situ* Hybridization	Isocortex Hippocampus Hypothalamus Thalamus Amygdala	J Kato et al., *Hormones and Behavior*, 28:454-463 (1994)

Fig. 3. Distribution of the 25-Dx PR transmembrane domain in the rat brain. The classical progesterone receptors PRA and PRB have been localized to regions throughout the brain using the indicated methods.

by the expression of PR splice variants with variable ligand affinities and transactivational activities [187].

The effects of P_4 may be attributed to mechanisms apart from the 'classical' gene transcription mediated by PRA and PRB. Recently, P_4 binding sites have been detected at the surface of hypothalamic and spinal neurons [157,237]. These binding sites, identified as 25-Dx (also known as PGRMC1), mediate the antiapoptotic actions of P_4 in granulose and luteal cells [212,211]. In the ovary, 25-Dx complexes with the plasminogen activator inhibitor RNA-binding protein 1 (25-Dx/SERBP1) to activate cGMP-dependent protein kinase [68]. P_4 signaling may also be mediated by several putative Src homology domains present in 25-Dx [210]. However, the P_4-activated signaling pathways that are mediated by 25-Dx have yet to be determined in neurons. Like 25-Dx, the seven transmembrane putative progesterone receptor 7TMPR may regulate P_4 signaling. The 7TMPR has been shown to activate a pertussis toxin-sensitive inhibitory G protein, resulting in activation of the MAPK pathway through inhibition of cAMP production [271,312].

Progestereone and its 5α-reduced derivatives dihydroprogesterone (DHP) and tetrahydroprogesterone (THP or allopregnanolone), can promote Schwann cell proliferation and activation of the myelinating program of these cells [183]. Melcangi and colleagues demonstrated that P_4 and its derivatives increased expression of the transcription factors Sox-10 and Krox-20, both of which play a key role in Schwann cell physiology and in their myelinating program. Western blot analyses indicated that Krox-20 was increased after 3 h of treatment with P_4, dihydroprogesterone, or tetrahydroprogesterone, whereas P_4 or dihydroprogesterone stimulated expression of Sox-10 after 6 h of exposure. Analysis of rat and human promoters for these two transcription factors indicated that putative P_4-response elements are present in the Krox-20 gene but not in Sox-10. These findings suggest that P_4 and its neuroactive derivatives could coordinate the Schwann cell-myelinating program utilizing different intracellular pathways [183].

Although mPR binds P_4 with high selectivity and affinity, it does not bind many of the synthetic progestins including norethisterone, norgestrel, promesgestrone, and demegestone [271]. This differential binding may underlie the distinct differences in neuroprotection and MAPK activation elicited by P_4 and synthetic progestins [201,202]. However, the neuronal expression of mPR has not yet been determined. The various progestin-activated signaling pathways can be combined synergistically or antagonistically in an intriguing number of ways to regulate development, survival, and electrical activity in the CNS. Each step of this signaling network can be influenced in a cell type- or brain region-specific manner through alterations in receptor expression or ligand structure, opening up a wide array of therapeutic possibilities.
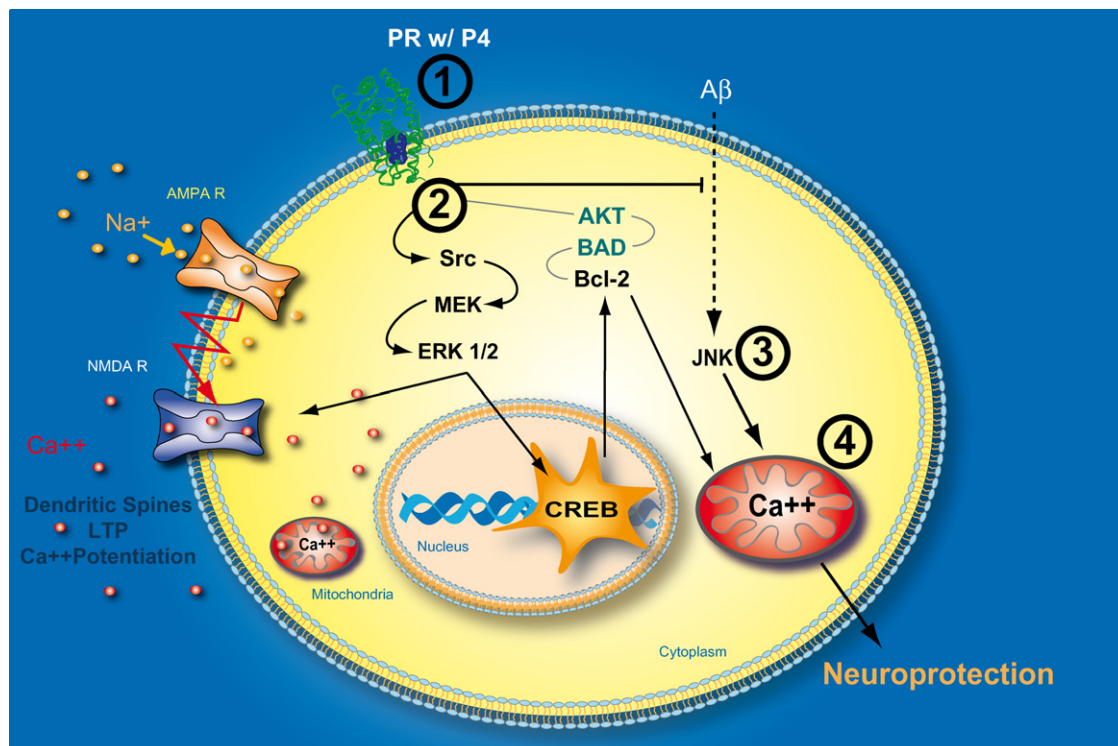

Fig. 4. Model of progesterone-induced neuroprotective signaling. Progestogen prevents synaptic dysfunction associated with aging and neurodegeneration through (1) ligand activation of a progesterone receptor, (2) which initiates second messenger signaling cascades, (3) to promote neuronal survival. These signaling cascades converge on mitochondrial function to protect against toxic insults and include the indirect prevention signaling pathway and the direct protection signaling pathway. In the indirect prevention signaling pathway, both ERK/CREB/bcl-2 and Akt pathways are simultaneously activated, which (4) enhances mitochondrial function and enables neurons to better withstand neurodegenerative insults. The direct protection pathway acts to block Aβ-induced JNK activation and mitochondrial dysfunction.

The MAPKs modulate cellular differentiation, proliferation, survival, and death. Activation of the MAPK, extracellular signal regulated kinase (ERK), is required for E_2-induced neuroprotection (Fig. 4) [253]. We and others have demonstrated that both E_2 and P_4 activate the ERK signaling pathway [201,202,254,253]. However, nuclear activation of ERK is not induced by medroxyprogesterone acetate (MPA), a progestin that lacks neuroprotective effects [202]. Phosphorylation of the MAPK substrate, cAMP response element binding protein (CREB), is associated with increased resistance to ischemic injury [72,77], and CREB is activated in response to ovarian hormones [118,168,281,301,309,311]. CREB, in turn, can upregulate *bcl-2* expression [77,301]. Accordingly, E_2 and P_4 upregulate *bcl-2* in hippocampal neurons [201]. In contrast to P_4, MPA does not activate CREB, nor does it increase bcl-2 expression [201]. On the contrary, MPA blocked E_2-induced CREB activation and bcl-2 upregulation in primary hippocampal neurons.

Estrogen and P_4 simultaneously activate the MAPK/ ERK pathway as well as an alternate pro-survival pathway, the Akt pathway [254]. . Activation of Akt by E_2 and P_4 in cortical slice cultures is associated with increase neuronal survival [254]. However, use of mixed cell types in these slice cultures precludes differentiation between direct and indirect effects of the steroids on neural cells. In primary hippocampal neuron cultures, E_2 and P_4 directly activate Akt in neurons. Western blot analysis of whole-cell lysates revealed that E_2 (10 ng/mL) and P_4 (10 ng/mL), either alone or in combination, significantly increased Akt phosphorylation within 20 min of treatment. Treatment of primary hippocampal neurons with MPA did not alter Akt phosphorylation, but blocked E_2-induced Akt phosphorylation.

More recently, it has been recognized that these steroids also regulate metabolic functions sustaining the energetic demands of this neuronal activation [205,204,206,200,283, 34,252,227]. Recent findings from Nilsen and colleagues indicate that P_4 significantly increased mitochondrial respiration 24 h following a single *in vivo* exposure at a magnitude comparable to E_2 [135]. Consistent with an increase in oxidative respiration, P_4 and E_2 significantly increased COXIV enzyme activity and expression of COXIV mRNA. Both P_4 and E_2 reduced free radical leak indicating greater efficiency of electron transport, which was evidence in a reduced generation of free radicals, P_4 and E_2 induced a significant reduction in mitochondrial lipid peroxidation. The reduction in lipid peroxidation suggests the activation of mechanisms beyond solely mitochondrial efficiency. P_4 induced a significant increase in MnSOD expression as did E_2 and E_2/P_4. In contrast, the expression of peroxiredoxin V was only increased by E_2 but not in the P_4- and P_4 blocked the E_2 induction of peroxiredoxin V. These results indicate that both P_4 and E_2 can promote dismutation of the superoxide anion O_2^- by increasing MnSOD to form H_2O_2 whereas only E_2 induces peroxiredoxin V that promotes clearance of H_2O_2 and prevention of oxidative

damage. Further, P_4 and E_2 directly regulate mitochondrial function and are not due to an increase in the number of mitochondria as neither P_4 nor E_2 nor their combination induced evidence for mitochondrial biogenesis. While P_4 was as efficacious as E_2, the combination of P_4 and E_2 led to reduced efficacy. On all outcome measures, the combination of P_4 and E_2 resulted in a substantial decrement in response magnitude.

6. Neuroprotective actions of progesterone and progestin in the CNS

P_4 has established neuroprotective actions that likely involve several different mechanisms. Anxiolytic effects are one way by which P_4 can reduce neural injury. Diverse stimuli including kainate [25], pilocarpine [275], and pentylenetetrazole [143] elicit stereotypic seizure behaviors and within several hours to a few days, significant neuronal loss in select brain regions such as the hippocampus. In these paradigms, P_4 treatment attenuates not only seizure behaviors ([131], Rhodes, 2004 #2538; [225]), but also neuronal injury [52]. The primary mechanism of neuroprotection in these models appears to involve the P_4 metabolite, allopregnanolone (APα, also known as 5α-pregnan-3a-ol-20-one and 3a,5a-tetrahydroprogesterone). P_4 is metabolized to APα following the sequential action of 5α-reductase and 3α-hydroxysteroid dehydrogenase. APα acts as potent modulator of γ-aminobutyric acid subtype A (GABA$_A$) receptors, increasing chloride conductance evoked by GABA [20,174]. This serves to decrease excitatory signaling and thus, antagonize seizure activity. Support for an APα-mediated mechanism of P_4 neuroprotection is provided by the finding that (i) APα is as effective as P_4 in seizure paradigms [52,224,27,81,78,80] and (ii) molecular [82,221] or pharmacological [224,80,155,276] inhibition of P_4 metabolism to APα blocks the protective actions of P_4. Interestingly, APα has also been implicated in the neuroprotective effects of P_4 following oxygen–glucose deprivation of rat Purkinje cells [7] and traumatic injury [126,61,60,230].

P_4 likely triggers multiple neuroprotective mechanisms. For example, in neuronal cultures, P_4 activates MAPK/ ERK [201,202,254] and Akt [254] signaling pathways, both of which are associated with neuroprotection [254,253,314]. Recent evidence suggests that, in spinal cord injury models, P_4 neuroprotection is associated with upregulation of brain-derived neurotrophic factor (BDNF) [283,34,252] increased levels and activity of choline acetyltransferase [252], and a reduction in mitochondrial dysfunction [227]. In cerebral ischemia models, the protective effects of P_4 are attributed, in part, to suppression of inflammatory responses and nitric oxide synthase-2 expression [95]. In addition to its direct effects on neurons, P_4 may exert indirect neuroprotective effects by acting on non-neuronal target cell populations. For example, P_4 reduces blood–brain barrier leakage [232], decreases glial activation [111], and increases myelination [12,154].

P_4 and E_2 are known to modulate the activity of one another, sometimes antagonistically. Thus, it is of interest to determine the effect of P_4 and progestogens on the neuroprotective effects of E_2. The antagonistic relationship between P_4 and E_2 is illustrated by the finding that P_4 can block E_2-induced increases in spine density in the hippocampus [295,197]. P_4 can also attenuate E_2-induced upregulation of BDNF, neurotrophin 3, and nerve growth factor in the entorhinal cortex, but not in hippocampus, of female rats [30]. P_4 reverses estrogen-induced enhancement of spatial memory in ovariectomized female rodents [315]. Recent results from our group demonstrate that both P_4 and MPA block the neuroprotective effect of E_2 in the hippocampus following kainate lesion in young female rodents [233] and reproductively senescent female rodents (Carroll and Pike, unpublished observations). P_4 treatment decreases the estrogen receptor hybridization signal in monkey brain [119], indicating that P_4 may limit E_2 signaling. However, in both a systemic kainate lesion model [11] and an ischemic stroke model [272], acute P_4 treatment was not neuroprotective and did not significantly affect E_2 neuroprotection.

The neuroprotective action of P_4 in traumatic brain injury has been extensively studied by Stein and colleagues. Results of their extensive body of work indicate that a single injection of P_4 attenuated cerebral edema when administered during the first 24 h after traumatic brain injury (TBI) in rats whereas 5 days of P_4 injection resulted in improved spatial learning performance and reduced sensory neglect [246]. In subsequent analyses, Grossman et al. [111] found that P_4 reduced edema levels, as in previous studies, while increasing the accumulation of activated microglia in traumatic brain injured rat brain [127]. However, a parallel analysis indicated that P_4 and allopregnanolone reduced both IL-1β and TNF-α 3 h post-traumatic brain injury, when the expression of these cytokines peaked in the untreated animals [127]. Progesterone-induced reduction in inflammatory cytokines was also observed in a medial frontal cortex model of traumatic brain injury [214]. Progesterone inhibited the injury-induced rise in complement factor C3, GFAP, and nuclear factor kappa beta (NFkappaB) [214]. The paradox of the dual effect of P_4 to induce accumulation of activated microglia and reduce inflammatory immune cytokines remains unresolved.

The contributions of gender and gonadal hormones in the cascade of events following brain injury were investigated and revealed that normally cycling females exhibited significantly less edema than males following traumatic brain injury and that pseudopregnant females were virtually spared from postinjury edema. Subsequent studies of ovariectomized females, with or without hormone treatment, indicated that the reduction of cerebral edema was associated primarily with the presence of circulating progesterone [229]. The Stein group then went onto to determine whether P_4 metabolite neurosteroids mediated the neuroprotection of exogenous or endogenous P_4.

One day after traumatic brain injury, both P_4-treated (16 mg/kg) and allopregnanolone (8 or 16 mg/kg)-treated rats showed less caspase-3 activity, and rats treated with allopregnanolone (16 mg/kg) showed less DNA fragmentation in the lesion area, indicating reduced apoptosis. Nineteen days after the injury, rats treated with P_4 or allopregnanolone (8 or 16 mg/kg) showed no difference in necrotic cavity size but had less cell loss in the medio-dorsal nucleus of the thalamus and less learning and memory impairments compared with the injured vehicle-treated rats. The results from their analyses indicated that P_4 and allopregnanolone had similar neuroprotective efficacy after traumatic brain injury, but that allopregnanolone appeared to be more potent than P_4 in promoting CNS repair [60]. A follow-up study compared the effects of P_4 and its metabolite, allopregnanolone, on the early injury cascade (apoptosis) and long-term functional deficits after traumatic brain injury [61]. Progesterone (16 mg/kg) or allopregnanolone (4, 8, or 16 mg/kg) were injected at 1, 6 h, and then for five consecutive days after bilateral contusions of the frontal cortex in adult male rats. Within 1 day after injury, P_4 and allopregnanolone reduced expression of pro-apoptotic proteins caspase-3 and Bax, and apoptotic DNA fragmentation. Progesterone and allopregnanolone also reduced the size of glial fibrillary acid protein (GFAP)-positive astrocytes at the lesion site 24 h after injury. At 19 days postinjury, rats given P_4 or allopregnanolone (8 mg/kg) showed improved performance in a spatial learning task compared to injured rats given only the vehicle [61].

The extensive body of basic science *in vivo* evidence indicating that P_4 was highly efficacious in reducing or preventing the neurological consequences of traumatic brain injury [259], led Stein and colleagues to conduct a clinical trial of P_4 in human victims of moderate to severe coma associated traumatic brain injury [299]. In a phase II, randomized, double-blind, placebo-controlled trial conducted at an urban Level I trauma center with 100 adult trauma patients who arrived within 11 h of injury with a postresuscitation Glasgow Coma Scale score of 4–12 (scores associated with moderate to severe degrees of coma) were enrolled with proxy consent. Neurologic outcome was assessed 30 days postinjury. Seventy-seven patients received progesterone, 23 received placebo. No serious adverse events were attributed to progesterone. Adverse and serious adverse event rates were similar in both groups, except that patients randomized to P_4 had a lower 30-day mortality rate than controls. Thirty days postinjury, the majority of severe traumatic brain injury survivors in both groups had relatively poor Glasgow Outcome Scale-Extended and Disability Rating Scale scores. Moderate traumatic brain injury survivors who received P_4 were more likely to have a moderate to good outcome than those randomized to placebo. The authors concluded that results of this small study, P_4 caused no discernible harm and showed potential benefit [299].

7. Progesterone regulation of memory and neuronal excitability

After more than three decades of research, it is now well established that the ovarian hormone, E_2, exerts a wide variety of effects on neural structures and function, particularly within the hippocampus [191,298,296]. Electrophysiological studies have shown that E_2 enhances hippocampal CA1 synaptic transmission and plasticity by increasing NMDA and AMPA receptor activity, which results in neuronal excitation [268,75,293,294]. While the above studies have focused exclusively on the effect of E_2 on brain structure and function, more recent studies have investigated the effect of P_4 and its neuroactive metabolites APα and pregnanolone (PREG) on cognitive function and neural excitability.

Long-term potentiation (LTP) is considered to be the best cellular model of memory trace formation in the brain, at least for certain forms of memory in the hippocampus and neocortex [16,33,165]. The phenomenon opposite to LTP is long-term depression (LTD), which was first demonstrated in cerebellar cortex by Ito in 1982 [136]. LTD has also been demonstrated in the hippocampus and neocortex and like LTP, is considered a mechanism for memory storage [22,65]. Although the molecular mechanisms underlying LTP (and LTD) have been extensively investigated, there is a relative paucity of studies demonstrating the critical role of LTP in behavioral learning and memory [248]. Nonetheless, LTP (and LTD) are the best current models of synaptic plasticity, which may underlie memory storage [29]. In the CA1, the most widely studied form of LTP involves glutamate activation of NMDA receptors, which augments AMPA receptor function for the expression and maintenance of LTP. However, this is not the sole form of LTP in the CA1, as Teyler and associates have demonstrated a form of tetanus-induced LTP in the CA1 that is independent of NMDA receptors and involves voltage-dependent calcium channels [112].

Few studies have examined the acute effects of P_4 on synaptic transmission and plasticity, with the results of these studies being mostly contradictory. P_4 (10 μM) reportedly has no effect on LTP (CA1 slices from 4-week-old rats), but no non-drug control was used in this study [137]. In another study, P_4 (8–10 M, in CA1 slices) significantly enhanced synaptic transmission, as seen by an increased field potential and population spike amplitude; however, following a seizure-induced tetanus, P_4 decreased the field potential, the population spike responses, and the duration of after-discharges [67]. In whole cell patch clamp of pyramidal neurons from slices of prelimbic cortex, P_4 (100 μM) had no effect on the frequency of excitatory postsynaptic currents (EPSCs), but inhibited dopamine-induced increases in EPSCs [71]. P_4 dose–response functions were not obtained in any of these studies. In primary hippocampal neurons, P_4 as well as E_2 enhances glutamate-mediated increases in intracellular calcium, with E_2 having a greater effect. P_4 appears to interfere with E_2 enhancement of synaptic transmission, as seen by the finding that co-treatment with P_4 and E_2 enhances glutamate-mediated increases in intracellular calcium to the same degree as P_4 alone [201].

Clinical investigations have been performed to understand the effect of P_4 on moods associated with premenstrual dysphoric disorder (PMDD) [290]. PMDD is defined in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV, APA 1994) as a cluster of both negative mood symptoms and physical symptoms that occur during the luteal phase of the menstrual cycle (when P_4 and APα levels are high) and disappear several days following the onset of menstruation (when P_4 and APα levels are low). The increase in P_4 (and APα) levels that occurs during the luteal phase of the menstrual cycle is considered to be at least partly responsible for the negative mood changes associated with PMDD [290,13]. Although ovarian steroids are required for onset of premenstrual symptoms, women with PMDD are thought to exhibit an altered GABA receptor sensitivity [264]. Support for the association of P_4 with negative mood symptoms comes from the finding that postmenopausal women exhibiting intermediate APα plasma concentrations subjectively rated themselves as having significantly more negative mood symptoms during P_4 treatment than during treatment with unopposed E_2 or placebo [6]. P_4 concentrations (measured via radioimmunoassay) in the amygdala, cerebellum, and hypothalamus are significantly higher in fertile women in the luteal phase of menstruation than in postmenopausal controls [31]. Moreover, in fertile women, APα concentrations are highest in substantia nigra and basal hypothalamus, suggesting that the pattern of steroid secretion during the menstrual cycle is reflected in specific brain tissues [31].

P_4 and APα are known to regulate cognitive function, particularly those functions related to mood and/or associated with changes in the menstrual cycle (e.g., postpartum depression, major depression, epilepsy) [14]. The GABAergic system also participates in major depression (for review, see [35]). The GABA$_A$ receptor mediates the majority of rapid (1–100 ms) synaptic inhibition in the mammalian brain, and APα and PREG exert both anxiolytic and anesthetic effects by enhancing GABA-stimulated chloride conductance. This enhanced conductance serves to hyperpolarize postsynaptic membranes and results in neuronal inhibition [186,185]. Recent evidence suggests that specific neurosteroids 'fine-tune' neural inhibition via the GABAergic system [195]. In another recent study, the ability of P_4 to influence cognition and memory of biologically salient stimuli was investigated in healthy young women [278]. Here, a single dose of P_4 was orally administered to women who were then asked to memorize and recognize faces while undergoing functional magnetic resonance imaging. The results revealed that P_4 decreases recognition accuracy without affecting reaction times. P_4 also decreased amygdala and fusiform gyrus activity elicited by faces during memory encoding, supporting the conclusion that P_4 alters memory function by influencing amygdala activity [278,279].

In animals, P_4 and its metabolites severely impair learning and memory performance immediately following administration in the Morris water maze test [142,250]. Although the mechanism underlying this impairment is unknown, a recent study demonstrated that pretreatment of rats with APα induces a partial tolerance against the acute effects of APα in the Morris water maze test [274]. These authors suggest that prolonged exposure to APα in women (e.g., pregnancy, postmenopausal hormone replacement therapy, menstrual cycle) may alter cognitive behavior such as learning and memory, possibly through a GABAergic-dependent mechanism.

Excitatory synapses, which can be approximated by dendritic spine density, serve as the substrate for learning and memory. A significant amount of literature describes the effects of estrogen and P_4 on dendritic spine formation in hippocampal pyramidal neurons [104]. In rats, ovariectomy results in a decrease (over 6 days) in the density of dendritic spines, which can be prevented and reversed by E_2 treatment [295]. Administration of P_4 after estrogen treatment initially augments the effects of E_2 (and sexual behavior such as lordosis). However, 6 h later, P_4 rapidly decreases spine density to the very low levels, which are equivalent to levels seen 18 h after ovariectomization. Indeed, the number of dendritic spines in specific brain regions fluctuates over the 4–5 day estrous cycle in accordance with estrogen and P_4 levels [76]. The down regulation of dendritic spines by P_4 is blocked by the P_4 antagonist, RU-38486, consistent with the presence of intracellular PRs in the hippocampus. Electron microscopic studies have demonstrated the presence of non-nuclear PRs in glia and dendritic spines in the hippocampus [191]. Also, P_4 acts directly on GABAergic receptors to enhance GABA inhibition and thus, counter the effects of E_2 [197,291].

During the ovulatory cycle, extensive tissue remodeling occurs throughout the body, including certain brain regions. Some of the most profound changes occur in uterine tissue, which undergoes extensive angiogenesis and cell proliferation during the follicular phase. In the absence of a blastocyst, the uterine growth phase is terminated by resorption or exfoliation of epithelial and vascular cells. Numerous inflammatory mediators are cyclically regulated during both the growth and exfoliative phase [73,158,180]. These cyclically-regulated genes encode diverse proteins, many of which function in apoptosis such as Fas, caspase-3, M30 [8], complement C3 [180,178], and secretory leukocyte proteinase inhibitor (SLPI) [149]. Progestins regulate the expression of many of these genes. For example, progestins antagonize estrogens in regulation of C3 [180,178], whereas P_4 acts in synergy with the proinflammatory cytokine, IL-1, to induce expression of SLPI, an antimicrobial peptide important in host defense [149].

In contrast to uterine remodeling during the estrous cycle, brain 'remodeling' is more modest and does not involve major changes in the proportions of cell populations. In the rodent hippocampus, certain synaptic beds implicated in declarative memory undergo striking, transient changes during the estrous cycle. The dendritic spine density of CA1 pyramidal cells undergoes cyclic changes, which are strongly correlated with sensitivity to NMDA receptor-mediated synaptic responses [296,298]. There is also increased aggregation of MAP2 in apical dendrites [223] as well as an increased expression of syntaxin, synaptophysin (presynaptic), and spinophilin (postsynaptic) [51]. The increase in dendritic spines is driven by elevations in E_2 during the preovulatory follicular phase, whereas the rapid regression of these spines after ovulation depends upon elevation of P_4 from the corpus luteum [295]. Administration of the PR antagonist, RU 486, during proestrus inhibits the decrease in spine density after proestrus [295]. Like the CA1, the hypothalamic arcuate nucleus undergoes remodeling in response to the preovulatory luteinizing hormone surge. In this region, astrocyte volume changes have been associated with altered GABAergic contacts on gonadotropin-releasing hormone axons [134,198]. There is now a significant literature concerning the effects of estrogen and progesterone on dendritic spine formation in hippocampal pyramidal neurons [104]. In brief, ovariectomy (in rats) causes a decrease (over 6 days) in the density of dendritic spines, which can be prevented and reversed by estradiol treatment [295]. Progesterone treatment subsequent to estrogen treatment initially augments the effects of estradiol (and sexual behavior, e.g., lordosis) and then (after 6 h) results in a rapid decrease in spine density to the very low values seen in ovariectomized animals by 18 h. Indeed, the number of dendritic spines in specific brain regions fluctuates over the 4–5 day estrous cycle in accordance with estrogen and progesterone levels [297]. The down regulation of dendritic spines by progesterone is blocked by the progesterone antagonist, RU-38486, consistent with the presence of intracellular progesterone receptors (PR). Electron microscopic studies also indicated the presence of non-nuclear PRs in glia and dendritic spines in hippocampus [191]. Progesterone can also act directly on GABAergic receptors to enhance GABA inhibition, thus countering the effects of E_2 [197,291].

8. Progesterone regulation of glial cell function and response

Progesterone regulates responses in each of the major glial cell types, astrocytes, microglia, oligodendrocytes and Schwann cells. During the estrous cycle astrocyte size varies with CA1 astrocytes shrinking immediately before increases in spine density [153]. Astrocytes also decrease in size in the rostral preoptic location of gonadotropin-releasing hormone cell bodies [45]. Astrocyte size is strongly associated with the expression of glial fibrillary acidic protein (GFAP), which varies during the estrous cycle in the dentate gyrus [262]. Progesterone, and its neurosteroid metabolite dihydroprogesterone induced a significant elevation of GFAP mRNA levels in type 1 astrocytes within hours of exposure with direct administration of dihydroprogesterone inducing an increase within 2 h whereas P_4 required 6 h for increased GFAP expression.

These findings suggest that the effect of P_4 is likely due to metabolism to DHP. The requirement for conversion of P_4 to increase GFAP protein level was confirmed through the addition of finasteride (a specific blocker of the 5α-reductase) which completely abolished the effect of P_4 [92].

In astrocytes, P_4 regulates production of multiple proteins including those shown to be involved in regulating synaptic plasticity such as ApoE which is secreted by astrocytes may be an important player in synaptic remodeling, since this protein transports cholesterol and other lipids to outgrowing neurites [184]. Glial apoE mRNA changes cyclically in the CA1 and arcuate nucleus [261,199], supporting a role for this protein in synaptic remodeling. During pregnancy, twofold increases in uterine apoE levels are associated with increased import of maternal lipids [277]. Also, estrogen-dependent sprouting of perforant path fibers to the hippocampus is absent in apoE-knockout mice [263,199,267]. Complex heterotypic cellular interactions that occur in response to ovarian steroids extend beyond astrocytic–neuronal interactions. Although ApoE is secreted by astrocytes, astrocytic responses to estrogen require interactions with microglia, as evidenced in monotypic astrocyte cultures which are much less sensitive to estrogen than mixed glial cultures containing microglia [262]. Besides E_2, Premarin® also induced ApoE expression in mixed glia [235]. P_4 increased ApoE secretion in macrophages (microglia also express apoE mRNA) by acting on the C-terminal lipid-binding domain of ApoE to block its intracellular degradation [63]. The effect of other clinical progestins on glial apoE expression remains to be determined.

In many organ systems, estrogen actions are attenuated or antagonized by progestins. As discussed above, E_2 drives increases in CA1 spine density (growth phase), while P_4 promotes the regression of dendritic spines (during the proestrus to estrus transition). In mouse hippocampal slice cultures, mossy fiber sprouting into the molecular layer of the dentate gyrus is induced by deafferentation of the entorhinal cortex [267]. In this system, E_2 (100 pM) increases sprouting by 75%. This concentration of E_2 also induces maximal apoE induction in mixed glia [236]. E_2-dependent sprouting can be blocked by P_4 or tamoxifen [267]. P_4 appears to differ from MPA in its ability to regulate synaptic plasticity. Preliminary results from our laboratory show that MPA, but not P_4, inhibits E_2-mediated sprouting. This difference is consistent with recent findings by Nilsen and Brinton that P_4, but not MPA, is neuroprotective against excitotoxicity and stimulates nuclear activation of ERK. Further, MPA, but not P_4, blocked the neuroprotective effects of E_2 [202]. Additional studies will be necessary to evaluate the differences and similarities of MPA and P_4.

In some models, P_4 has been reported to have anti-inflammatory activities. After stab wounds, P_4 decreased reactive astrocytes to a greater extent than E_2, but less than pregnenolone[88,87]. In a model of cerebral concussion, male rats given an i.p. injection of P_4 of had less edema

[111] and lipid peroxidation [232] than their untreated counterparts. On the other hand, P_4 had a negligible effect on glial activation or neuronal loss in this model [111]. In accord with findings from the cerebral concussion model, P_4 inhibited the level of clinical neurogenic edema, possibly by reducing meningeal release of substance P [113]. Of course, P_4 has many complex interactions with neurotransmitters, which may underlie this and other anti-inflammatory effects (e.g., activation of the GABA receptor by P_4 and other C21 steroids [79]).

Progesterone regulation of myelination is now well documented and is a compelling example of the profound direct effects of P_4. The sciatic nerve, and Schwann cells in particular, are capable of synthesizing P_4 and possess the enzymes necessary to convert P_4 to the 5α-reduced and the 3α–5α-reduced derivatives of P_4: dihydroprogesterone and tetrahydroprogesterone [188]. Progesterone receptor has been detected in both sciatic nerve and in Schwann cell cultures. P_4 and its metabolite neurosteroids regulate expression of two major proteins of the peripheral nervous system (PNS): the glycoprotein Po (Po) and peripheral myelin protein 22 (PMP22). Melcangi and colleagues have shown that: (a) dihydroprogesterone enhanced the low mRNA levels of Po in the sciatic nerve of aged male rats; (b) P_4 and its derivatives stimulates the gene expression of Po in the sciatic nerve of adult rats and in Schwann cell cultures; (c) tetrahydroprogesterone increased PMP22 gene expression in the sciatic nerve of adult rats and in Schwann cell cultures. They further demonstrated that P_4 and its derivatives control Po gene expression via the PR, while tetrahydroprogesterone modulated expression of PMP22 through the GABAA receptor[188]. Melcangi and coworkers went on to demonstrate that P_4 and its derivatives regulate other myelin proteins [i.e., myelin-associated glycoprotein (MAG) and myelin and lymphocyte protein (MAL)] in sex-specific cultures of rat Schwann cells [182]. Progesterone or dihydroprogesterone induced a stimulatory effect on P0 mRNA levels in male but not in female Schwann cells. In contrast, treatment with tetrahydroprogesterone increased gene expression of P0 in female derived Schwann cells. A similar sex-difference was also evident for other myelin proteins. PMP22 expression was increased by P_4 in male derived Schwann cell cultures, whereas tetrahydroprogesterone induced an increase of mRNA levels in female derived cells. Moreover, MAG was stimulated by tetrahydroprogesterone treatment in male cultures only, whereas MAL expression was unaffected by neuroactive steroid treatment in both male and female cultures. Collectively these findings indicate that P_4 and its metabolite neuroactive steroids on regulate myelin protein expression in a sexually dimorphic manner. This finding might represent an important background for sex-specific therapies of acquired and inherited peripheral neuropathies [182,188]. Melcangi and colleagues pursued the relevance of these findings for age-associated myelin loss and morphological alterations of myelinated fibers in the sciatic nerve of 22–24-month-old male rats. The sciatic nerves of untreated

old male rats, showed a general disorganization and a significant reduction in the density of myelinated fibers, compared to nerves from 3-month-old male rats. The effect of aging was particularly evident in myelinated fibers of small caliber (<5 μm in diameter). In addition, the sciatic nerves of old rats showed a significant increase in the number of fibers with myelin infoldings in the axoplasm and in the number of fibers with irregular shapes. Treatments of old rats with P, DHP and THP resulted in a significant increase in the number of myelinated fibers of small caliber, a significant reduction in the frequency of myelin abnormalities and a significant increase in the g ratio of small myelinated fibers. Furthermore, P_4 significantly reduced the frequency of myelinated fibers with irregular shapes. Results of these *in vivo* animal studies indicate that in the aged male rat P_4 and its neuroactive metabolites reduced aging-associated morphological abnormalities of myelin and aging-associated myelin fiber loss in the sciatic nerve [12].

In the central nervous system P_4 and its neurosteroid metabolites were found to promote glial functions, such as the synthesis of myelin proteins. In glial cell cultures prepared from neonatal rat brain, P_4 increased the number of oligodendrocytes expressing myelin basic protein and the 2′,3′-cyclic nucleotide-3′-phosphodiesterase (CNPase), the third most abundant myelin protein in the CNS [18]. The role of P_4 in myelination is extensively covered in several excellent reviews by Schumacher and colleagues and the reader is referred to these for further reading [243,244,18].

9. Progesterone regulation of meiosis and mitosis

During development of both vertebrates and invertebrates, P_4 promotes meiosis to generate germ cells [19,47,240]. P_4 induced re-entry into the cell cycle at mediated by a membrane-bound PR [19,17,21,270,123].

P_4 promotion of meiosis is mediated by a rise in intracellular Ca^{2+} [24,196,286]. In *Xenopus* oocytes, P_4 induces the resumption of meiosis (maturation) through a non-genomic mechanism involving inhibition of adenylyl cyclase and reduction of intracellular cAMP. However, P_4 action in *Xenopus* oocytes is not blocked by pertussis toxin, indicating that inhibition of the oocyte adenylyl cyclase is not mediated by the α subunit of classical G_i-type G proteins [181]. Subsequent analyses indicate that P_4 is likely inducing maturation by antagonizing constitutive Gβγ-mediated inhibition of cell cycle progression [181].

Intracellular Ca^{2+} influx and inhibition of Gβγ are not the sole requirements for P_4 regulation of meiosis. Multiple laboratories have demonstrated that P_4 activates MAPK signaling pathway in oocytes and that this pathway is required for promotion of meiosis by P_4 [69,144,74]. P_4 activation of MAPK leads to the formation of the M-phase promoting protein complex (CDC2 and cyclin B), which promotes G2 to M phase transition [171,189].

Mitotically, P_4 has a complex function in the uterus and can be both inhibitory and stimulatory for proliferation depending upon cell type (endometrial or stromal) the reg-

imen of treatment, the type of PR that is activated (PRA versus PRB), the dose of E2 and P_4 , and when in the cycle P_4 is administered [56–58,96,133,150]. In the endometrium, P_4 inhibits proliferation of endometrial cells whereas P_4 is a proliferative agent in the stromal cells of the uterus. Further, P_4 inhibited proliferation in E2 primed uterus but not when administered alone or with low dose E2. A progestinal agent in hormone therapy is added to antagonize endometrial cell proliferation in the uterus [249]. In addition to P_4 action in the uterus, P_4 can promote proliferation in the breast [151,215,26,50].

In the Women's Health Initiative, in which medroxyprogesterone acetate (MPA) was used as the progestinal agent, an increased risk of breast cancer in the hormone therapy (HT) trial was observed which did not occur in the estrogen only therapy (ET) [50,300,288,36,269,86]. The WHI HT trial also revealed an increased risk of invasive ovarian cancer and a reduced risk of endometrial cancer [5,234]. The use of the progestin, MPA, in the WHI HT trials has been proposed to be a major factor contributing to the increased cancer risk seen in this trial. However, the tumorgenic properties of different progestogens have not been systematically studied, and not all progestogen molecules have the same antagonistic or agonistic profiles [256,257,15]. The impact of different progestogens on the proliferation of neural stem cells or neural progenitors is currently unknown.

10. Progesterone and estrogen regulation of neurogenesis and neural progenitor proliferation

As in the uterus [56,105], P_4 regulation of mitosis of neural progenitors in brain has a complex profile. Tanapat et al. have shown that ovariectomized rats treated with a high level of E_2 have enhanced hippocampal cell proliferation, whereas subsequent exposure to P_4 resulted in blockade of the E_2-induced enhancement of cell proliferation [266]. In contrast to P_4 regulation of E_2-induced neurogenesis *in vivo*, we have demonstrated that P_4 alone enhances cell proliferation *in vitro* [284]. More recent results indicate that P_4 induced a dose dependent significant increase in rat neural progenitor cells (rNPC) proliferation as measured by BrdU incorporation over a 24-h exposure period with an EC100 value of 100 pM. Unlike its metabolite steroid APα, the dose–response curve for P_4 was shallow but linear up to 1 μM whereas the dose–response for APα was steeply linear followed by an inverse function at 1 μM. Further, when compared to the dose–response for E2-induced rNPC proliferation (EC100 of 250 nM), P_4 induced a more consistent enhancement of rNPC proliferation. The time course of P_4-induced rNPC proliferation generated 2 important outcomes. First, P_4-induced DNA synthesis occurred rapidly within the first 1–4 h of P_4 exposure. Second, it appears that P_4-induced DNA synthesis does not persist beyond 6 h and that by 8 h, P_4 no longer induces DNA synthesis. These data suggest that P_4 is not driving rNPCs into prolonged or uncontrolled proliferation.

Lastly, we conducted a steroid specificity analysis which indicates that P_4 and its metabolite $AP\alpha$ are both proliferative agents [40].

Our own work has demonstrated that the neurosteroid P_4 metabolite, $AP\alpha$ is a potent, stereoisomer-specific promoter of neurogenesis of both rat hippocampal neural progenitor cells and human cortical neural stem cells [284]. Allopregnanolone-induced proliferation was isomer and steroid specific, in that the stereoisomer 3β-hydroxy-5β-pregnan-20-one and related steroids did not increase 3H-thymidine uptake. Immunofluorescent analyses for the neural progenitor markers, nestin and Tuj1, indicated that newly formed cells were of neuronal lineage. Furthermore, microarray analysis of cell cycle genes and real time RT-PCR and western blot validation revealed that allopregnanolone increased the expression of genes, which promote mitosis and inhibited the expression of genes that repress cell proliferation. Allopregnanolone-induced proliferation was antagonized by the voltage gated L-type calcium channel blocker nifedipine consistent with the finding that allopregnanolone induces a rapid increase in intracellular calcium in hippocampal neurons via a GABA type A receptor activated voltage gated L-type calcium channel [285]. These data demonstrate that $AP\alpha$ significantly increased rNPC and hNSM proliferation with concomitant regulation in mitotic cell cycle genes via a voltage gated L-type calcium channel mechanism.

$AP\alpha$-induced neurogenesis is a dose-dependent process, with concentrations in the low to mid nanomolar range promoting proliferation and concentrations exceeding $1\ \mu M$ significantly inhibiting neurogenesis. The biphasic dose–response profile of $AP\alpha$-induced neurogenesis could account for the disparity between our *in vitro* data and reports that $AP\alpha$ decreases neurogenesis in the rat dentate gyrus *in vivo*. In these *in vivo* studies, $AP\alpha$ inhibited neurogenesis of rat SVG cells following intracerebral ventricular injection of 7.8 mmol of $AP\alpha$ [91,92]. Considering that the injected concentration is diluted into the cerebrospinal fluid and the volume of the cerebrospinal fluid in a 300-g rat is $\sim$580 μl [163], the final concentration of $AP\alpha$ would be more than 50 μM. Thus, inhibition of neurogenesis at micromolar concentrations of $AP\alpha$ in this study is consistent with our dose–response data, which demonstrates inhibition of neural progenitor cells proliferation at micromolar concentrations and promotion of neurogenesis at nanomolar concentrations [284]. Griffin and Mellon found that early administration of $AP\alpha$ substantially delays progression and severity of symptoms in a transgenic mouse model of Niemann-Pick Type C, a disease characterized by disrupted neurosteroidogenesis [109].

While production of new neurons from proliferating stem/progenitor cells in the SGZ of the dentate gyrus is maintained throughout life in multiple species including humans [103,83], the magnitude of neurogenesis declines with age. Age-associated decline in neurogenic potential in the dentate gyrus has been observed as early as middle age [159,220] and has been proposed to contribute to age-related learning and memory impairments [62,84,89,1]. The mechanism underlying age-associated decline in neurogenesis remains to be fully determined. However, loss of the growth factors FGF-2, IGF-1, and VEGF in the microenvironment of the SGZ is a prime contributor to the reduced neurogenic potential of the SGZ [122]. Recent studies have demonstrated that the levels of these three multiple stem/progenitor cell proliferation factors decline early on during the course of aging in the hippocampus [28,247]. Hippocampal levels of FGF-2, IGF-1, and VEGF are more than 50–60% decline lower in adult rats than in young rats [247]. These findings suggest that the dramatic decline in dentate neurogenesis could be linked to reduced concentrations of FGF-2, IGF-1, and VEGF in the hippocampus, as each of these factors can individually influence the proliferation of stem/progenitor cells in the SGZ of the dentate gyrus. For example, FGF-2 enhances dentate neurogenesis in both neonatal and adult brain [247,209,222,273,48,49,282,85], and intracerebroventricular (ICV) infusions of FGF-2 upregulate dentate neurogenesis in the aged brain [159,85,132,141,160]. Likewise, ICV administration of IGF-1 increased dentate neurogenesis in the adult and aged brain [1,2,176]. VEGF can promote dentate neurogenesis in both the intact and the injured adult brain following ICV administration [265,139,140]. During neurogenesis, VEGF may act as a chemoattractant that specifically targets FGF2-stimulated neural progenitors [308].

Growth factors regulate a myriad of cellular processes aside from neurogenesis. For example, EGF has well-characterized proliferative effects on the endometrium. EGF gene expression dramatically increases in the endometrial glands of pregnant mares at approximately 40 days after ovulation [260]. This upregulation is maintained until at least day 250 of gestation and is associated with an increase in EGF receptor binding sites in the endometrium [170]. The expression of both IGF and TGFb1 is also upregulated during this time [169]. Administration of varying doses and combinations of P_4 and estrogen for 35 days yields negative or only weakly positive EGF expression, whereas administration of only P_4 for 40 days strongly upregulated EGF expression irrespective of additional treatment with estrogen [90]. These findings underscore the importance of P_4 in regulation of growth factors and reveal a mechanism for P_4-associated cell proliferation *in vivo*.

Similar to EGF, IGF, and TGF, expression of brain derived neurotrophic factor (BDNF) is positively correlated with E_2 and P_4 levels and negatively correlated with menopausal age [23]. Hormone replacement therapy restored plasma BDNF levels to levels seen in fertile women during the follicular phase [23]. Circulating plasma levels of BDNF change during the menstrual cycle, suggesting that P_4 may regulate neurotrophin expression [23]. Modifications in BDNF circulating levels during the menstrual cycle suggest a potential role for gonadal sex hormones in regulating neurotrophin expression, which

has implications for sustaining the regenerative milieu of the brain during the menopausal years.

Regulation of cell cycle entry by progesterone and its neurosteroid metabolites as therapeutic regenerative agents will require careful analysis prior to development for restoration of neurons lost due to neurodegenerative disease. In Alzheimer's disease (AD), cell cycle-specific gene expression is upregulated [32] and, evidence indicates that mitotic signaling is dysregulated [305]. In the aged and AD brain, both the pool of neural stem cells and their proliferative potential are markedly diminished [159,177]. In addition, the level of potential regenerative factors is reduced in the brains of AD patients compared to age-matched controls [287]. Herrup and colleagues have found that ectopic expression of cell cycle proteins predicts the site of neuronal cell death in the AD brain [41], leading these investigators to propose that dysregulation of various elements of the cell cycle contributes to regionally specific neuronal death in AD. They also found that DNA replication precedes neuronal death in AD brain [304]. More disturbing, cell cycle events precede neuronal death at *all* stages of AD, from mild cognitive impairment to advanced AD [305]. This finding has important implications for strategies targeting neurogenesis in the AD brain. Specifically, it suggests that promoting entry into the cell cycle could potentially be a double-edged sword, with benefit to healthy brains but with exacerbation of ectopic mitosis in brains destined to develop AD or with existing AD.

11. Progesterone and regulation Alzheimer's disease pathology

A key hypothesis linking P_4 to AD posits that P_4 acts as an endogenous regulator of β-amyloid (Aβ) metabolism. According to the widely but not universally embraced 'amyloid cascade hypothesis,' AD pathogenesis is triggered by any of a number of events that have the final common endpoint of increasing the pool of soluble Aβ [125,124,255]. In turn, elevated soluble Aβ leads to the formation of an array of soluble oligomeric, minimally soluble aggregated, and eventually insoluble fibrillar Aβ species, all of which are linked in a variety of ways to neurodegenerative cascades [53,217,216,245,179,190,251,164]. Thus, factors that have the net effect of reducing the pool of soluble Aβ are thought to represent potentially powerful strategies for preventing the development of AD [97,152].

Neurosteroids have recently been measured in various brain regions of aged Alzheimer's disease patients and aged non-demented controls by GC/MS [241]. In Alzheimer's patients, there was a general trend toward lower levels of neurosteroids in different brain regions, and neurosteroid levels were negatively correlated with two biochemical markers of Alzheimer's disease, the phosphorylated tau protein and the β-amyloid peptides [241]. The formation of these metabolites within distinct brain regions negatively correlated with the density of β-amyloid deposits.

Available evidence suggests that E_2, like P_4, may influence Aβ levels. In women, E_2 status has been linked to the development of AD [15]. Schonknecht and colleagues found that levels of E_2 in cerebral spinal fluid are lower in AD patients than in non-AD controls and that, in the AD group, E_2 levels are inversely correlated with $Aβ_{1-42}$ levels [239]. In accord with this finding, several cell culture studies have shown that E_2 decreases Aβ production, presumably increasing the non-amyloidogenic cleavage of amyloid precursor protein (APP) via α-secretase [46,138,302,303,280,107]. The physiological significance of this effect has been confirmed by *in vivo* studies investigating the relationship between circulating E_2 concentrations and brain levels of Aβ. Depletion of endogenous E_2 via ovariectomy results in a significantly increases levels of soluble Aβ in brains of mice [238] and guinea pigs [213]. Importantly, this effect is partially reversed by E_2 replacement. Furthermore, E_2 reduces pools of soluble [175,310] and deposited Aβ [310] in mouse models of AD, strongly implicating E_2 as a regulator of AD pathogenesis. Unexpectedly, two recent studies using transgenic mouse models of AD have found weak [106] or absent evidence [128] that E_2 reduces insoluble pools of Aβ. Several factors may have contributed to these negative results, including the transgenic strains, the relevant pool of Aβ, and the difference between estrogen levels in circulation and in the brain [307]. Prior investigations of Aβ regulation by ovarian sex steroids have used ovariectomy models (which depletes endogenous E_2 and P_4) combined with E_2, but not P_4, replacement [213,175,310,106,128].

While E_2 replacement is beneficial in regulation of Aβ metabolism, the interaction between E_2 with P_4 is more clinically relevant. That is, how are Aβ levels affected when P_4 acts in concert with E_2? Our group has recently addressed this question in the 3xTg-AD mouse model of AD. Our results suggest that continuous E_2, but not P_4 treatment attenuates the acceleration of Aβ accumulation and memory deficits observed in ovariectomized mice. More importantly, in animals receiving both hormones, P_4 blocked the beneficial effect of E_2 on Aβ accumulation [44].

12. Progestogens, progestins and metabolism

Many progestogens are used therapeutically among these, P_4 is the only naturally occurring progestogen (see Table 1). The remainder, which are synthetic, are referred to as progestins (see Table 1) [257]. Progestins are classified on the basis of their chemical structure, since the structures of these molecules vary widely. Progestins can be divided into those related in chemical structure to P_4 and those related chemically to testosterone. The classification scheme and the names of progestins in each of the categories are summarized in Table 1. This classification scheme does not denote the chemical source of the compounds.

Progestins related to P_4 are characterized by the presence or absence of a methyl group on carbon 10, and are subdivided into pregnanes (21 carbons) and 19-norpregn-

Table 1
Classification of progestogens

I. Natural	II. Synthetic progestins	
	Structurally related to progesterone	Structurally related to androgen

Progesterone	1. Pregnane derivatives
	  a. *Acetylated:* medroxyprogesterone acetate, megestrol acetate, cyproterone acetate, chlormadinone acetate, medrogestone
	  b. *Non-acetylated:* dydrogesterone
		1. Ethinylated
		  a. *Estranes:* norethindrone, norethynodrel, lynestrenol, norethindrone acetate, ethynodiol diacetate, tibolone
		  b. *Gonanes:* levonorgestrel, desogestrel, norgestimate, gestodene

	2. 19- Norpregnane derivatives
	  a. *Acetylated:* nomegestrol acetate
	  b. *Non-acetylated:* demegestone, trimesgestone, promgeestone, nesterone
		2. Non-ethinylated: dienogest, drospirenone

anes (20 carbons) (see Tables 1 and 2) [258]. The pregnanes and 19-norpregnanes can be further separated into compounds with and without an acetyl group. One of the best-known and most widely used of these progestins is MPA, which is classified as an acetylated pregnane. All of the 19-norpregnane progestins have been used primarily in Europe and not in the United States.

Unlike the progestins related to P_4, which are first subdivided on the basis of the number of carbons (21 versus 20), those related to testosterone are first subdivided on the basis of whether or not they contain an ethinyl group. The ethinylated progestins are subdivided further into those related to the parent steroid, estrane, and those related to 13-ethylgonane. Both estranes and 13-ethylgonanes lack a methyl group at carbon 10. The estrane group of progestins consists of norethindrone and its prodrugs, namely norethindrone acetate, ethynodiol diacetate, norethynodrel, and lynestrenol. These prodrugs, which are considered part of the norethindrone family, have been widely used for hormone therapy and/or contraception. Although tibolone is also a prodrug and is listed in the estrane category, it is not converted to norethindrone. Instead, it is transformed to other active metabolites.

The 13-ethylgonanes contain an ethyl group on carbon 13 of the basic steroid nucleus (gonane). This category of progestins, sometimes referred to as the levonorgestrel family, consists of levonorgestrel and the levonorgestrel derivatives desogestrel, norgestimate, and gestodene. The latter three progestins are often referred to as the new progestins, as they have been marketed relatively recently. In contrast, levonorgestrel has been used for many years.

Norgestimate and desogestrel, but not gestodene, are prodrugs. However, only norgestimate is converted to levonorgestrel. Norgestimate is also converted to deacetylated norgestimate (levonorgestrel-3-oxime), which has progestational activity. Desogestrel is converted to its active form, 3-ketodesogestrel. Gestodene has inherent progestational activity, but is not approved for use in the United States.

13. Progestogen metabolism

With the exception of P_4, little is known about the metabolism of most progestogens. Baulieu first discovered
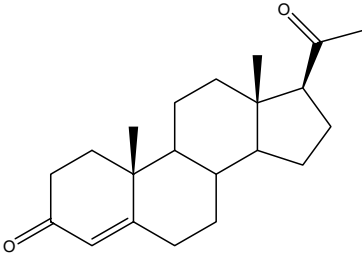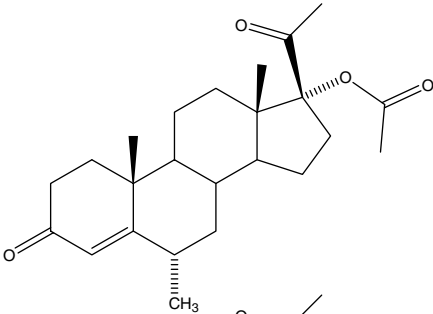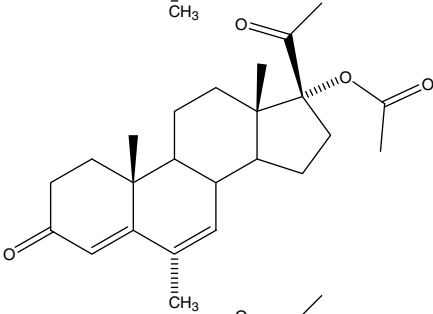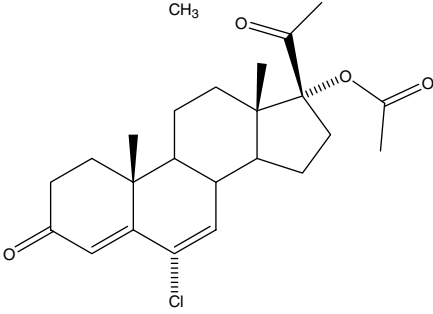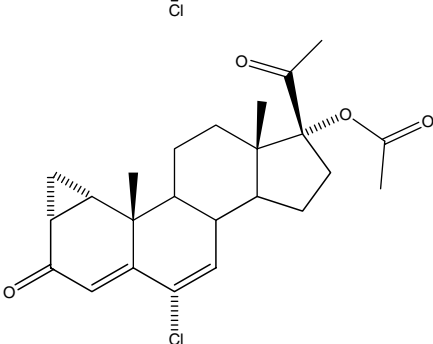
that P_4 is converted to neuroactive metabolites in the brain [20,243,242]. This has now been well established by many laboratories and documented in multiple species including the rodent and human. Neurosteroids such as APα are synthesized in the central and peripheral nervous system, primarily by myelinating glial cells, but also by astrocytes and several neuron types [243,193,194,54]. A region-specific expression pattern of P_4-converting enzymes in brain is evident in both the hippocampus and cortex of rodent and human brain [193,194,54,108]. The P_4-converting enzymes 5α-reductase and 3α-hydroxysteroid dehydrogenase are expressed in the hippocampus of both the rodent and human brain and convert P_4 to its 5α, 3α-reduced metabolites (e.g., APα). Remarkably, these enzymes are also present and functional in pluripotential progenitors [167]. The conversion of P_4 to its 5α, 3α-reduced metabolites can be blocked by 5α-reductase inhibitors, such as finasteride.

Of the progestins, the metabolism of norethindrone and levonorgestrel is the best characterized (see Table 2). These compounds undergo extensive reduction at the double bond between carbons 5 and 6 and the carbonyl group at carbon 3, resulting in the formation of dihydro- and tetrahydroderivatives. They can also undergo hydroxylation. Surprisingly little is known about the metabolism of the most widely used progestin, MPA. This compound, like other progestins structurally related to P_4 or testosterone, contains a double bond between carbons 5 and 6 as well as a ketone group at carbon 3. Therefore, it is likely to undergo extensive reduction at these functional groups. Unlike the neuroactive metabolites of P_4 (e.g., APα), exceedingly little is known about the neuroactive properties of progestin metabolites.

14. Progesterone and PRs: translational and therapeutic challenges

Relative to estrogen neurobiology, the non-reproductive neural functions of P_4 and the basic genomic, signaling and cell biology of these processes are just emerging. Progesterone and its neuroactive metabolites can promote the viability of neurons and function of glial cells within both the central and peripheral nervous system.

Table 2
Structures of selected progestogens and list of their active metabolites

Category	Progestogens	Structure	Active compound of prodrug
Natural progestogens	Progesterone		
Pregnane (Acetylated)	Medroxyprogesterone acetate		
	Megestrol acetate		
	Chlormadionone acetate		
	Cyproterone acetate		

Table 2 (*continued*)
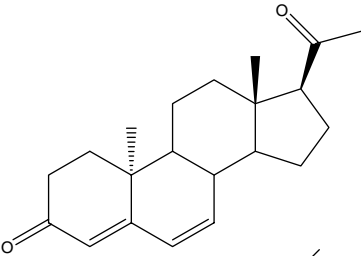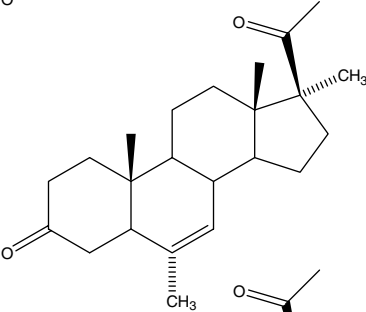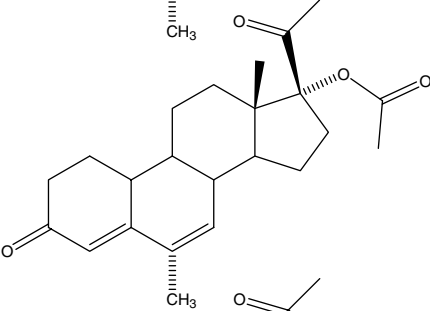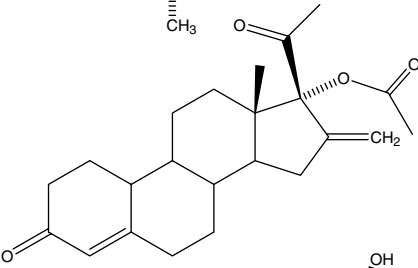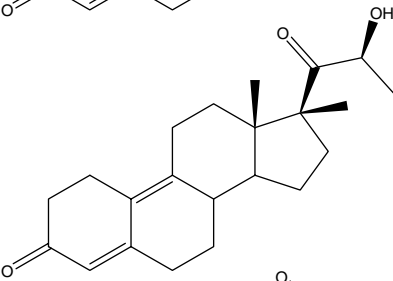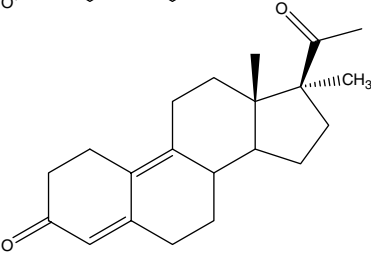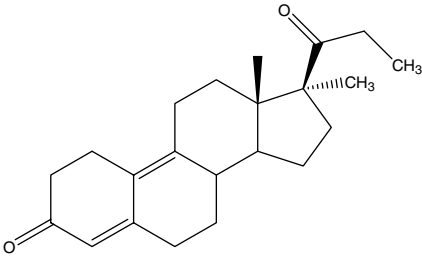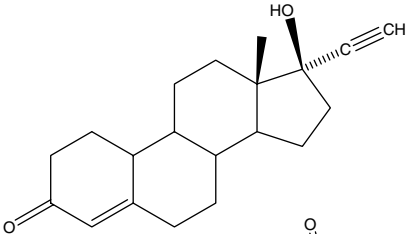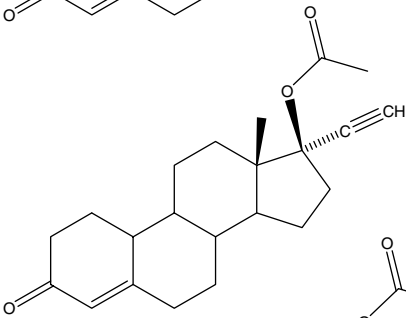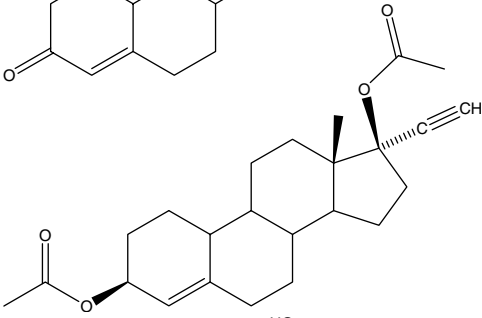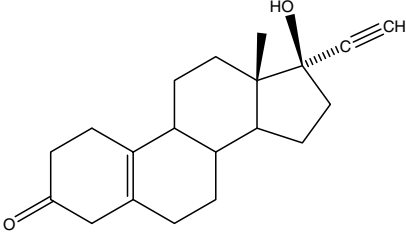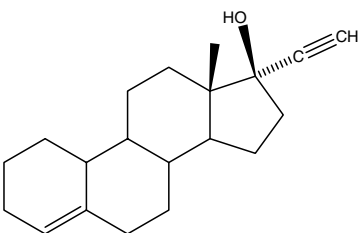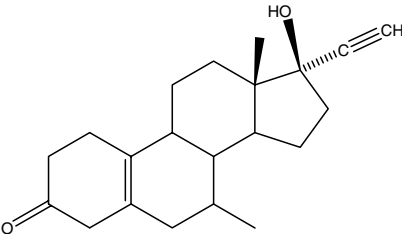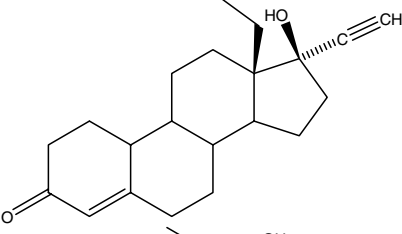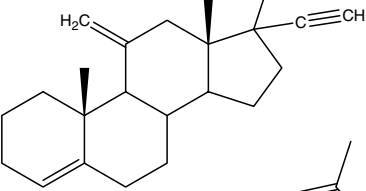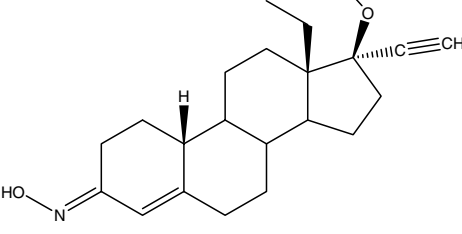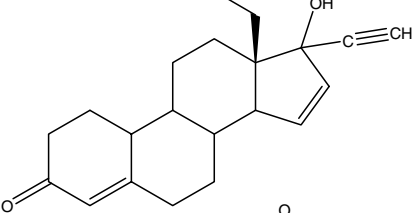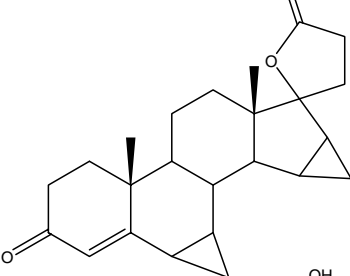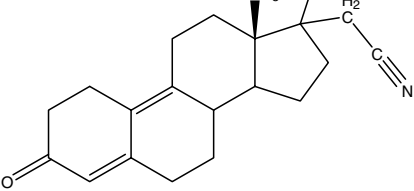
Category	Progestogens	Structure	Active compound of prodrug
Pregnane (Non-acetylated)	Dydrogesterone		
	Medrogestone		
19-Norpregnane (Acetylated)	Nomegestrol acetate		
	Nesterone		
Norpregnane (Non-acetylated)	Trimegestone		
	Demegestone		

Table 2 (*continued*)

Category	Progestogens	Structure	Active compound of prodrug
	Promegestone		
Tesosterone derivative (Estranes)	Norethindrone		
	Noethindrone acetate		Norethindrone
	Ethynodiol diacetate		Norethindrone
	Norethynodrel		Norethindrone
	Lynestrenol		Norethindrone

Table 2 (*continued*)

Category	Progestogens	Structure	Active compound of prodrug
	Tibolone		Δ4-Tibolone 3α-OH-Tibolone 3β-OH-Tibolone
Testosterone derivatives (Gonanes)	Levonorgestrel		
	Desogestrel		3-Ketodesogestrel
	Norgestimate		Levonorgestrel-3-oxime Levonorgestrel
	Gestodene		
Testosterone derivatives (Non-ethinylated)	Drospirenone		
	Dienogest		

While there is a substantial body of evidence regarding the pleiotrophic actions of P_4 [244], much remains to be determined regarding the specific PR required and the associated effector mechanism(s) of action. The use of P_4 as a myelinating agent and as a treatment for traumatic brain injury highlight the basic science and clinical importance of understanding the direct effects of P_4 and other progestogens. It is interesting to note that women have a greater risk of developing the demyelinating disease multiple sclerosis with a frequent onset at menopause [207]. Given the significant impact of P_4 and its metabolite, allopregnanolone (tetrahydroprogesterone) on remyelination following injury and preventing age-associated myelin loss, the potential therapeutic use of P_4 for remyelination is substantial in both men and women. Of particular concern, given the results of the WHI and WHIMS trials, is the impact of clinically used progestins on neurological function. While progestogens in hormone therapy are given to reduce the risk of uterine cancer, these agents potentially exert effects in brain. Collectively, we know little regarding the impact of different progestins on neural function either acutely or chronically. The wide distribution of progesterone receptors in brain suggests that this gonadally and brain derived steroid plays a significant role in neural function, which awaits continued discovery.

Acknowledgments

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