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Progesterone Modulates Neuronal Excitability Bidirectionally

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Abstract

Progesterone acts on neurons directly by activating its receptor and through metabolic conversion to neurosteroids. There is emerging evidence that progesterone exerts excitatory effects by activating its cognate receptors (progesterone receptors, PRs) through enhanced expression of α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors (AMPARs). Progesterone metabolite 5α,3α-tetrahydro-progesterone (allopregnanolone, THP) mediates its anxiolytic and sedative actions through the potentiation of synaptic and extrasynaptic γ-aminobutyric acid type-A receptors ($GABA_A$Rs). Here, we review progesterone's neuromodulatory actions exerted through PRs and THP and their opposing role in regulating seizures, catamenial epilepsy, and seizure exacerbation associated with progesterone withdrawal.

Keywords

Progesterone; Progesterone receptors; Allopregnanolone; Catamenial epilepsy; AMPA receptors; GABA-A receptors

Introduction:

Progesterone synthesized in the ovaries and adrenocortical glands can easily cross the blood-brain barrier and can also be synthesized locally in the brain from cholesterol. Neurons, glia, and microglia express enzymes that can convert cholesterol to progesterone [7, 124, 150]. The progesterone distribution across the brain is not uniform due to local synthesis and metabolism. Its cortical and striatal levels correlate with the circulating hormone, but the concentration in the hypothalamus is independent of the serum levels [13]. Circulating progesterone can passively diffuse into the brain. Most circulating steroids are bound to hormone-binding proteins, including albumin, limiting their free transport across the membrane; however, this does not seem to affect progesterone transport across the blood-

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brain barrier [165]. Thus, progesterone metabolism and local synthesis are most likely to underlie its non-uniform distribution across the brain [3].

Circulating progesterone levels are low (<1.5 ng/mL) during the follicular phase. They reach a peak (> 7 ng/mL) during the luteal phase of the menstrual cycle [19]. Blood progesterone also cycles during the rodent/murine female reproductive cycle, the estrous cycle, which lasts 4–5 days, reaching a peak on proestrus evening in rats and during the diestrus stage in mice [90, 141]. Although the plasma progesterone levels are higher in females, the brain progesterone levels are comparable between male and female mice, and in humans, the cerebrospinal fluid progesterone levels are similar in men and women [96, 177], suggesting local synthesis and a neuromodulatory role in males.

Several progesterone-effector molecules are present in the brain (Fig. 1). The most commonly studied molecule is its metabolite allopregnanolone (THP). These effects are rapid and potentiate the inhibitory neurotransmission mediated through the $GABA_A$Rs. PRs are also expressed in the brain and play a critical role in regulating reproductive hormone synthesis [85, 149]. Two lesser-studied effector molecules include membrane progesterone receptors (mPRs) and progesterone receptor membrane component 1 (pgrmc1). Both are present in the brain; the mPRs seem to regulate the secretion of female reproductive hormones, whereas the function of pgrmc1 proteins is unclear [69, 95, 102, 126, 140, 158].

The role of PRs in regulating neuronal excitability outside the hypothalamus has started to emerge. We will primarily discuss progesterone's novel actions exerted through PR activation and discuss their role in regulating seizures in women with epilepsy.

Progesterone receptors:

PRs, which belong to the nuclear receptor family, mediate progesterone's genomic effects [131, 146]. The two main isoforms of PRs, PR-A and PR-B, are encoded from a single locus. PR-B is 164 amino acids longer than PR-A [14, 22, 81] (Fig. 2). The PR peptide is comprised of an N terminal activation function (AF) domain, a DNA binding domain, a hinge region, and a C terminal ligand-binding domain. The hinge region encompasses a nuclear localization signal necessary for nuclear transport of the ligand-bound activated receptor. The N terminal amino acids of PR-B form an AF3 domain, which renders the receptor a more robust transcription activator function. Additional truncated isoforms of PRs may also exist; but, it is unclear whether they are expressed in the brain [14].

PR-B regulates the expression of many more genes than PR-A [120]. The AF3 domain of PR-B and differential interaction of the two isoforms with other transcription factors and coactivators confers this distinction [157]. Under *in vitro* conditions, PR-A, when expressed in excess, can repress the transcriptional activity of PR-B and other nuclear hormone receptors, including glucocorticoid receptors (GRs) and androgen receptors (ARs) [128, 162].

PRs bind to the palindromic progesterone response element (PRE) in the genes' regulatory regions under their control. DNA footprinting studies using the long terminal repeat of mouse mammary tumor virus (MMTV) identified PR binding to TGTTCT motif [20]. The

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optimal PRE sequence is RGnACAnrnTGTnCY, although transcriptional activation can occur even with suboptimal sequences [58]. Furthermore, the analysis of several progesterone-regulated genes has revealed that ½ PRE sites are more common than the perfect palindromes and that binding of PR monomers to these sites triggers transcription [20, 58]. PR also regulates the expression of transcription factors FOXO1, STAT5, and cFos, which are themselves coregulators of PR-dependent transcription. Steroid receptor coactivators (SRC) 1, 2, and 3 also play a role in PR-regulated transcription [81]. Since cFos is an activity-triggered transcription factor, through this association, PRs may regulate activity-dependent neuronal plasticity.

Progesterone also induces post-translational modifications of PRs, particularly of PR-B, which can significantly alter PR function [24, 41]. Phosphorylation of serine residues and acetylation, ubiquitination, or sumoylation of lysine residues can alter the stability of PRs, influence their transcriptional activity, and enhance their interaction with other transcription factors and enhancer proteins [41]. For example, the L388 sumoylation represses PR function, whereas phosphorylation of S294 and S345 by mitogen-activated protein kinases removes this repression and stimulates the transcriptional activity. Furthermore, phospho-S294 deficient PRB isoform is transcriptionally inactive in breast cancer cells [135]. Most of these studies were performed using exogenous expression systems or in the human uterine or the breast tissue and cell lines. Whether post-translational modifications regulate endogenous PR functions in the brain is unclear. Calcium influx through glutamatergic receptors and voltage-gated calcium channels regulate protein kinase activity in the brain, which may change PR function in an activity-dependent manner.

PR expression in the brain:

Progesterone uptake is comparable between the hypothalamus, hippocampus, and cortex [164], which raises the possibility that PR expression between these regions may also be similar. The hypothalamus, medial preoptic area, hippocampus, frontal cortex, olfactory bulbs, and cerebellum of female and male animals express PR mRNA and protein [6, 18, 36–39, 42, 56, 70]. However, studies comparing potential differences in their expression levels across these regions are lacking. Hippocampus, entorhinal cortex (EC), and amygdala play a critical role in limbic seizure generation and propagation. In the hippocampus's principal neurons, the PR immunoreactivity is spread over the entire neuron, including cell soma, axons, dendrites, and PRs also seem to be present at the synapses [97, 167]. On the other hand, the expression of PRs in the extra-hippocampal limbic regions is not well-understood.

The hippocampus and hypothalamus express both the principal PR isoforms. Semi-quantitative measurements suggest equal PR-A and PR-B expression in female rats' hypothalamus and hippocampus [36]. PR-B but not PR-A mRNA expression seems to fluctuate during the estrous cycle in the hypothalamus and frontal cortex. In contrast, it remains stable in the hippocampus [36]. However, the PR-A and PR-B protein changes studied later by the same group appear to follow distinct trends [39]. The semi-quantitative measurement of mRNA levels and the use of an antibody without confirmed specificity against PRs are some of the limitations of these studies, contributing to the observed

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discrepancy. Since PR-A could potentially suppress PR-B's transcriptional activity, differences in these isoforms' relative expression could impact progesterone-induced gene expression. Hence, assessing whether brain regions differ in the PRA and PR-B expression ratio will be critical to understanding PR effects on neuronal function.

Estrogen stimulates PR expression; an estrogen response element is present in the promoter region of PRs. The presence of ER-α seems to be essential for this regulation, as estrogen-induced PR expression is blocked in the ER-α knockout mice [53, 87, 137]. Estrogen stimulates the expression of both the PR isoforms in the hypothalamus, but PR-B is more responsive than PR-A. On the other hand, PR expression in the frontal cortex is maintained independently of circulating steroid hormones. A prior study has also found that the hypothalamic binding of PR ligand R5020 binding is reduced in ovariectomized animals, but, the hippocampal and cortical tissue was unaffected [87]. Since progesterone and estrogen are synthesized from cholesterol in the brain, the de novo synthesis of these hormones could also add to the complexity of PR expression's hormonal regulation. Progesterone suppresses the estrogen-stimulated PR expression [39], perhaps by reducing ER expression [60]. This complex interplay between estrogen- and progesterone-regulation of PR expression is evident during the estrous cycle, as hypothalamic and hippocampal PR expression fluctuates during the estrous cycle [36, 39, 45, 139]. However, the estrous cycle-associated PR expression changes are not uniform across brain areas, indicating that additional factors are likely involved.

PR-mediated regulation of neurotransmission:

Recent studies have found that progesterone upregulates the expression of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors (AMPARs) and that this action is dependent on PRs [68]. Anti-progestin RU-486 pretreatment and PR deletion block the progesterone-induced AMPAR upregulation, whereas a specific PR agonist Nestorone mimics the progesterone effects [68]. The upregulation of AMPAR expression following progesterone treatment is also associated with enhanced AMPAR-mediated synaptic transmission of CA1 pyramidal neurons [68].

Similar to the changes triggered by exogenous progesterone administration, estrous cycle-linked hormone fluctuations also influence AMPAR expression. The GluA1 and GluA2 subunit expression is more in the hippocampi of rats in the estrus stage than in diestrus animals and is dependent on PR activation [68]. Corresponding distinctions in the AMPAR-mediated mEPSCs of CA1 pyramidal neurons are also present [68]. PR blockade with RU-486 also blocked the estrus-associated potentiation of AMPAR expression, indicating that PRs mediated this effect.

Progesterone increases BDNF expression via PR-regulated mechanisms [62]. BDNF levels also change during the estrous cycle. The expression is higher in animals in proestrus and estrus stages than that during the metestrus stage [130]. Since BDNF is known to increase AMPAR expression [17, 82], the progesterone-PR-BDNF signaling may contribute to the estrous cycle-linked plasticity of AMPARs.

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The glutamatergic receptors are primarily located on the dendritic spines, and female reproductive hormones regulate the spine density in CA1 pyramidal neurons. Studies by Woolley and colleagues have extensively characterized estrogen and progesterone's influence on CA1 neurons' spines. Ovariectomy reduces dendritic spines' density, and estrogen treatment reverses this decline [94, 170]. Progesterone treatment initially promotes estrogen-induced spine formation; however, it subsequently causes a sharp decrease in the spines [170]. PRs appear to regulate some of these effects since RU-486 treatment inhibits the estrous cycle-linked spine density changes [170].

In addition to the regulation of neurotransmitter receptor expression and spine density, PRs in the hypothalamus interact with proteins including synapsin, Cam Kinase II, protein phosphatase 2B, and Rab and α subunit of AP2 complex [2], which control the stability of glutamate receptors at synapses [57, 73, 145]. PRs may also regulate synaptic strength through these interactions.

PR activation also regulates the expression of α2 subunits of the γ-aminobutyric acid type-A receptors ($GABA_A$Rs). Progesterone withdrawal after a 7-day treatment upregulates the hippocampal expression of α2 subunit mRNA expression in female mice [114]. This upregulation is substantially higher in the PR knockout mice than in the wild-type mice, indicating that PR-regulated mechanisms could counteract signaling underlying the α2 subunit upregulation.

PR regulation of neuronal excitability:

In agreement with the fluctuations in PR expression and the changes in the strength of glutamatergic and GABAergic neurotransmission during the estrous cycle, the neuronal activity also varies between stages of the estrous cycle. GnRH neurons are more active during estrus than during the diestrus [79, 80]. The expression of immediate early gene *cfos*, a surrogate of neuronal activity, in LHRH and LH neurons also fluctuates during estrous cycles [5, 54, 79]. In the LHRH neurons, cfos expression is seen during the proestrus hormonal surge but not during other estrous cycle stages. In contrast, in the LH neurons, cfos expression is more during the metestrus stage than during the proestrus stage. PRs could regulate some of these changes since PR knockout animals have several reproductive abnormalities and endocrine deficits [21, 85]. The absence of PR expression in kisspeptin neurons of anteroventral periventricular nucleus impairs LH surge, and estradiol-induced cfos expression in these neurons is also attenuated in the knockout animals [149].

Progesterone exerts inhibitory actions through THP activation of $GABA_A$Rs:

In contrast to PR activation's excitatory effects, progesterone metabolite THP reduces excitability by enhancing inhibitory neurotransmission mediated by $GABA_A$Rs. Several recent reviews have described these effects in detail [9, 63, 112]. Here, we will discuss these inhibitory effects only briefly.

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$GABA_A$Rs mediate the anticonvulsant action of THP. These pentameric receptors are assembled from a combination of 19 subunits ($\alpha_{1–6}$, $\beta_{1–3}$, $\gamma_{1–3}$, δ, ε, θ, π, $\rho_{1–3}$); most of the receptors contain 2α and 2β subunits, and the 5th subunit is variable. Ligand-binding opens up the channel pore to allow passage of chloride or bicarbonate ions into the cells under most conditions. The receptors containing a δ subunit, present in the peri- and extrasynaptic membrane, are more sensitive to THP modulation than receptors containing a γ2 subunit [10, 64]. THP and other neurosteroids act as positive allosteric modulators at physiological concentrations and increase the GABA efficacy of these receptors, whereas, at higher concentrations, they exert agonist-like actions [12]. The neurosteroid binding site is located between α and β subunits of $GABA_A$Rs [55].

The α1β2/3γ2 subunit-containing receptors are the most widely expressed $GABA_A$R in the brain. On the other hand, some subunits have a more localized expression. For example, the δ subunits are primarily expressed on hippocampal and cerebellar granule neurons, the α4 subunits are also highly expressed in the DGCs, and the α5 subunits are expressed in the CA1 pyramidal neurons [106, 169]. The α6 subunit expression, on the other hand, is restricted to cerebellar granule neurons.

Acute application of progesterone or neurosteroids to brain slices reduces neuronal excitability [35, 61, 105, 148], and these changes are associated with an increase in the amplitude of synaptic $GABA_A$R-mediated currents and/or prolongation of the current decay [148, 151, 176]. Extrasynaptic $GABA_A$Rs mediate a persistent form of inhibition called tonic inhibition, which is measured as holding current or membrane noise. The tonic current is also potentiated by THP [90, 107, 148]. The neurosteroid modulation of tonic current is significantly attenuated in the mice lacking δ subunit-containing $GABA_A$Rs [32], and neurosteroids also fail to control the excitability of hippocampal and cerebellar granule neurons in the δ subunit knockout animals. The variable distribution of $GABA_A$R subtypes across the brain influences effect of pharmacological agents, including neurosteroid sensitivity [101, 138]. Because of the higher neurosteroid sensitivity of the δ subunit-containing $GABA_A$Rs, neurons that express these receptors are more responsive to neurosteroids than other neurons. For example, medroxyprogesterone acetate causes a considerable prolongation of decay of synaptic currents of DGCs, which have a strong expression of the δ subunit-containing $GABA_A$Rs than those of the CA1 pyramidal neurons, which have a weak expression of these receptors [8].

In addition to the rapid allosteric modulation and potentiation of GABAergic inhibition, progesterone and THP also affect the strength of GABAergic inhibition by changing the subunit expression. Two to three-day exposure to progesterone or THP increases the hippocampal α4 and δ subunit expression but reduces α1 subunit expression, likely as a compensatory effect [40, 134]. However, the extended treatment causes a depression of the α4 subunit expression [143]. The subunit expression is again upregulated after discontinuation of progesterone or THP treatment [142, 143]. The endogenous hormonal fluctuations similarly affect $GABA_A$R subunit expression such that the expression of the δ and γ2 subunits following opposite directions [90, 125]. During pregnancy, elevated progesterone levels upregulate the δ subunit expression and down-regulate the γ2 subunit expression [127]. There is an acute decline in the δ subunit expression during post-partum

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concomitant with the fall in progesterone levels, whereas the α4 and γ2 subunit expression increases transiently [127]. These changes in hormone levels and $GABA_AR$ expression affect the excitability of CA1 neurons [133]. Prolonged blockade or potentiation of neuronal activity triggers homeostatic plasticity, which restores the neuron's target firing rate [44, 109, 153, 160]. The reduction in γ2 and α4 subunit expression following prolonged progesterone exposure or upregulation of their expression following progesterone withdrawal likely represent homeostatic alterations.

The efficacy of the anticonvulsant action of progesterone also depends on the expression of $GABA_ARs$. Strong expression of δ subunit-containing $GABA_ARs$ in the hippocampal DGCs plays a critical role in restricting the spread of activity into the hippocampus proper. However, the $GABA_ARs$ expressed in epilepsy patients have altered pharmacological properties, including reduced sensitivity to THP [31, 59, 67, 123, 154]. In these patients, the diminution of neurosteroid sensitivity of $GABA_ARs$ is accompanied by increased expression of α4γ2 subunit-containing receptors [67]. The down-regulation of δ subunit-containing receptors and diminished neurosteroid potentiation of the tonic current of DGCs during the epileptogenic period is associated with a compromised dentate "gating" function [66, 104, 105]. Hippocampi of epileptic animals have upregulated expression of α4γ2 subunit-containing receptors decreased expression of the δ subunit-containing $GABA_ARs$ [33, 66, 72, 105, 107, 176]. These alterations result in diminished neurosteroid sensitivity of receptors [66, 72, 98, 105, 107, 176]. The expression of α4 subunits is also transiently upregulated in the hippocampus following spontaneous seizures [34] and could cause a brief localized impairment of neurosteroid control of neuronal activity.

Besides allosteric modulation of $GABA_ARs$, THP also exerts inhibitory actions by binding to mPRs, which are G-protein coupled receptors. In a recent study, mPR agonist or THP seemed to increase the phosphorylation of $GABA_ARs$ through mechanisms involving protein kinase A and C activation [103]. These effects appear to be longer-lasting than the rapid effects of THP exerted through the allosteric modulation.

Progesterone and catamenial epilepsy:

The hormonal influence on neuronal activity and circuit function is reflected in functional connectivity changes, differences in alpha oscillations, and changes in glucose metabolism during phases of the menstrual cycle [4, 16, 119]. The diagnosis of epilepsy onset may cluster around menarche [52, 74] (but also [152]) or menopause [1], and seizure patterns may also change during puberty and menopause [43]. Additionally, some epilepsies, such as juvenile myoclonic epilepsy, first manifest during adolescent years [86]. Women who have reproductive-cycle linked fluctuations in seizures, called catamenial epilepsy, experience a decline in seizures at menopause [43].

The most prominent clinical effect of hormonal regulation of neuronal activity is seen in women with epilepsy. A third of women with epilepsy could experience cyclic seizure exacerbation associated with specific phases of the menstrual cycle. This seizure pattern is called catamenial epilepsy [46] and can be divided into three types, based on the phase of the cycle linked to seizure precipitation. Perimenstrual seizure precipitation is typical in

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women who suffer from catamenial seizure precipitation (type II catamenial epilepsy) [46]. The seizure precipitation can also occur during the preovulatory phase (type I). The type II seizure exacerbation is due to progesterone withdrawal, whereas type I seizures occur due to a high estrogen to progesterone ratio. The third type of catamenial seizures is observed in women in which the progesterone levels do not rise sufficiently during the luteal phase. Type II seizure exacerbation is the best-studied hormonal regulation of neuronal activity.

Some progesterone metabolites, including pregnenolone sulfate (PS) and 3β-hydroxylated progesterone derivatives, suppress GABAergic inhibition [25, 99, 166] and enhance NMDA receptor currents [168, 172]. These compounds exert a proconvulsant action; PS enhances the convulsive effect of pentylenetetrazole [116], and NMDA [76, 91], and its infusion in the hippocampal triggers SE [168]. PS levels also vary during the menstrual cycle and could contribute to differences in seizure susceptibility.

Estrous cycle-linked changes in seizure susceptibility also occur in experimental animals. For example, rats in the estrus stage of the cycle have a lower threshold for electroconvulsive and bicuculline-induced seizures than rats in the diestrus stage [26, 171]. Latency to picrotoxin-induced seizures is lower in rats in the proestrus stage than in the estrus stage [156]. In contrast, another study did not find differences in seizure susceptibility in kindled rats [165]. Susceptibility to prolonged seizures of status epilepticus (SE) is also influenced by the estrous cycle stage [88, 90]. The incidence of SE is lower in rats in the estrus stage than those in the other stages [129]. Mice in the estrus stage of the cycle associated with lower progesterone levels and a weaker expression of δ subunit-containing $GABA_A$Rs in the hippocampus are also more susceptible to SE than animals in the diestrus stage [90]. Besides, deletion of the δ subunits abolishes the resistance seen in animals in the diestrus stage. In general, progesterone appears to exert antiseizure effects, and seizure susceptibility is inversely correlated to the serum progesterone levels [63, 110], whereas estrogen primarily seems to exert proconvulsant effects [163]. However, the use of different stimuli to generate seizures, non-uniform selection of estrous cycle stages for comparison, and variation in the parameters assessed to evaluate seizure susceptibility make it challenging to compare these studies' findings and draw firm conclusions. Furthermore, since the expression of $GABA_A$Rs, NMDARs, and AMPARs varies during the estrous cycle, the selection of chemoconvulsant agents used to trigger seizures may have also influenced the findings.

High progesterone levels during pregnancy are predicted to reduce seizure susceptibility. However, pseudopregnant animals are not protected from PTE-evoked seizures, and pregnant mice appear to be more susceptible to fluorothyl-induced seizures [115, 144]. The frequency of recurrent spontaneous seizures is also unaffected in pseudopregnant animals [78]. Progesterone and estrogen levels are elevated in pregnant/pseudopregnant animals and their contrasting actions may mask the anticonvulsant effects of progesterone. Additionally, the PR-regulated potentiation of glutamatergic transmission may also counteract the THP-mediated neuroprotective effects in pseudopregnant/pregnant animals.

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PR activation and regulation of catamenial seizures in experimental animals:

We have found that PR activation also regulates seizures using two models of catamenial epilepsy in rats. In the first model, female epileptic animals were treated with pregnant Meyer's serum gonadotropin (PMSG) followed by human chorionic gonadotropin to elevate progesterone levels [68, 115]. Administration of finasteride, which prevents progesterone to THP conversion by blocking enzyme 5α -reductase activity, to the hormone-primed animals caused a 20-fold increase in the seizure frequency. Co-treatment of the animals with anti-progestin RU-486 during the hormone-priming period caused a substantial attenuation of withdrawal-induced seizures [68]. In the second model, female epileptic animals were treated daily with progesterone for a week and the effect of withdrawal was assessed during the subsequent week. A majority of animals experienced a doubling of seizures during the withdrawal, and RU-486 treatment simultaneous with progesterone prevented this increase [136]. These findings suggest that PR activation could enhance seizure susceptibility. Although we could not rule out an anti-glucocorticoid receptor effect in the studies done using RU-486, results using a specific PR agonist Nestorone also support PR activation's seizure-promoting effect [136]. Nestorone neither activates nor blocks glucocorticoid receptors, and it also does not modulate the activity of $GABA_A$Rs [77], and Nestorone treatment of epileptic animals increases the seizure frequency [136].

Studies using PR knockout animals also complement these findings obtained with pharmacological blockade of PRs with RU-486. Kindling epileptogenesis is slower in the PR knockout animals [117]. Also, the anticonvulsant effects of progesterone are amplified in the PR knockout animals [113]. Furthermore, an epidemiological survey of women with epilepsy has also found that progestin-only contraceptives may increase the risk of seizures in women with epilepsy [51, 92]. The putative seizure-promoting effects of PR activation may explain the increased risk seen in these surveys.

The findings of these recent studies contrast with the rapid sedative, anesthetic, and anticonvulsant action of progesterone known for decades [132, 174]. Blockade of progesterone metabolism to THP could cause seizure exacerbation in humans [50]. Progesterone protects from seizures evoked by chemical or electrical stimulation, but blockade of THP production removes this protection [27, 75]. Finasteride, which blocks 5α-reductase, causes a dramatic seizure exacerbation in female and male epileptic animals, although the extent of seizure precipitation is far more in females than in males [65, 68, 78]. Finasteride treatment also accelerates epileptogenesis [11, 66]. In contrast, THP alone is sufficient to suppress evoked and recurrent spontaneous seizures [29, 93, 174].

Mutations that cause THP deficiency are associated with epilepsy in humans. Dysregulation of AKR1C2 *and* AKR1C3 genes that encode proteins involved in neurosteroid synthesis, is seen in patients of protocadherin 19 (PCDH19) female-limited epilepsy who have an infantile seizure onset [155]. Serum levels of THP and other steroids, including progesterone, pregnanolone sulfate, and cortisol, are lower in the PCDH19 patients [155, 159]. Furthermore, mice lacking *Pcdh19* are also more susceptible to seizures triggered by electrical or chemical stimulation [108].

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Progesterone clinical trial of seizures in women with epilepsy:

Clinical trials have revealed that progesterone's efficacy to suppress seizures is limited [47, 48, 174]. In two double-blind studies, progesterone treatment was no different from placebo treatment in treating seizures [23, 49] (but also see [100], although women who have a severe form of perimenstrual seizure exacerbation may benefit from progesterone treatment [49].

To reconcile progesterone's contrasting effects, we propose that progesterone can exert seizure-suppressant or seizure-promoting effects (Fig. 3). The effects exerted through PR activation involving stimulation of gene expression could potentiate AMPAR-mediated synaptic transmission and increase network excitability. These changes occur through transcriptional regulation and are likely to be longer-lasting than the rapid non-genomic effects exerted through THP-induced potentiation of GABAergic inhibition. High progesterone levels during the luteal phase would activate PRs and enhance AMPAR-mediated glutamatergic transmission. As the levels decline during the perimenstrual phase, the THP-mediated inhibitory effects would also reduce. This could lead to an imbalance between inhibitory and excitatory neurotransmission and create a window of heightened seizure susceptibility.

One way to avoid the detrimental effects of PR activation while preserving the neuroprotective effects of THP is to use synthetic neurosteroids or agents which increase neurosteroid levels. In experimental animals, Ganaxolone blocks chemically or electrically-evoked seizures [30, 83, 118, 175] and reduces SE [111]. However, the effects of Trilostane, which blocks inhibits 3β-hydroxysteroid dehydrogenase/Δ5–4 isomerase and increases brain progesterone, THP, and pregnenolone levels, on SE appear to be complex. In the Trilostane-treated rats, severe convulsive seizures triggered by kainic acid started earlier, but the seizure duration was substantially shorter [84].

Ganaxolone use in a phase II trial to treat partial-onset seizures in adults has shown encouraging results [147], and it also appears to be effective against treatment-resistant infantile spasms [71]. However, a recently concluded phase III trial of Ganaxolone to treat adult focal-onset seizures did not achieve the primary endpoint: seizure suppression compared to that in the placebo-treated group. Synthetic neurosteroids Brexanolone and Ganaxolone have also been tested to treat super-refractory SE in pediatric and adult patients [15, 121, 161]. However, in phase III, multicenter randomized, placebo-controlled trial Brexanolone was no different from placebo in regulating seizures following weaning of coma-inducing agents or concerning the risk of mortality [122]. The reasons for the failure of synthetic neurosteroids or agents which alter neurosteroid levels to treat seizures in patients or experimental animals are unclear. THP regulates the expression of $GABA_AR$s [28, 89, 144, 173], and chronic exposure to THP or synthetic neurosteroids could alter $GABA_AR$ expression and induce tolerance [144].

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Conclusions:

Decades of research have revealed the anticonvulsant action of progesterone exerted through its metabolite THP. These actions involve allosteric potentiation of $GABA_AR$s, particularly those containing a δ subunit which are highly sensitive to THP. The allosteric actions are exerted within minutes of THP application and suppress evoked seizures or status epilepticus. However, prolonged exposure to progesterone/THP alters the $GABA_AR$ subunit expression and could cause tolerance to these agents.

In contrast to the anticonvulsant actions, recent studies have found that activation of PRs may counteract the effects of THP and increase neuronal excitability through the potentiation of AMPARs. These findings are intriguing and warrant further investigation since the potentiation of AMPAR-mediated synaptic transmission termed long-term potentiation is also critical for cognitive processes. Thus, progesterone appears to exert complex effects in the brain and affects neuronal function. The effector molecules play a critical role in determining whether the effects are beneficial or detrimental.

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Highlights:

- Progesterone regulation of neuronal activity and seizures
- Progesterone receptor activation exerts seizure-promoting effects
- Progesterone receptor activation could contribute to catamenial seizure exacerbation
- Allopregnanolone suppresses seizure activity through potentiation of $GABA_A$ receptors

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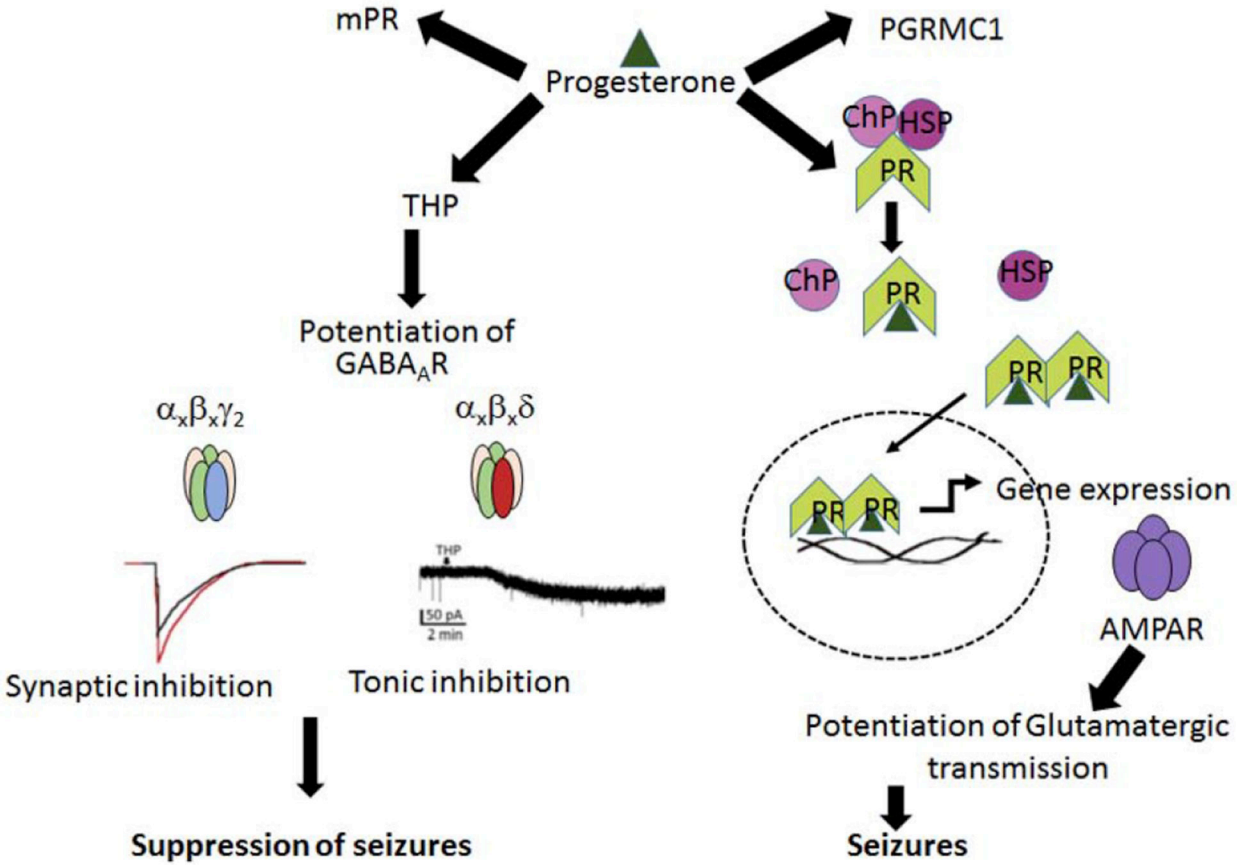

Figure 1:

A schematic illustrating the cellular actions of progesterone. Four progesterone effector molecules, THP, PRs, mPRs, and PGRMC1 are present in the brain. Progesterone metabolite THP is a potent modulator of $GABA_A$Rs and enhances synaptic and tonic GABAAR-mediated inhibition. These effects are rapid and suppress seizures. Binding of progesterone to PRs leads to dissociation of heat shock proteins (HSP) and other chaperon proteins (ChP). The ligand-bound PRs dimerize and are translocated to the nucleus. PRs bind to the hormone response elements and trigger gene expression. PR activation upregulates AMPAR expression, which would lead to potentiation of glutamatergic transmission. PR activation exerts a seizure promoting effect. The role of mPRs and PGRMC1 in the regulation of neuronal function is incompletely understood.

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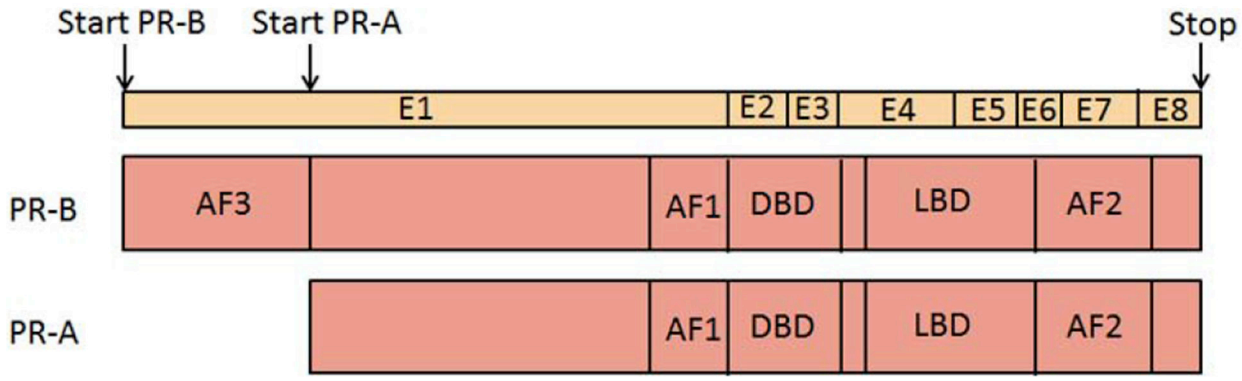

Figure 2:

A schematic showing the components of PR-A and PR-B peptides. The exons E1 to E8 are marked, the corresponding functional domains are illustrated below the coding region. PR-B contains extra N terminal amino acids that form the activation function (AF) 3 domain. This domain is thought to contribute to the stronger transactivation function to PR-B. The activation function 1 and 2 domains are common between PR-A and PR-B. DBD and LBD represent the DNA and ligand-binding domains respectively.

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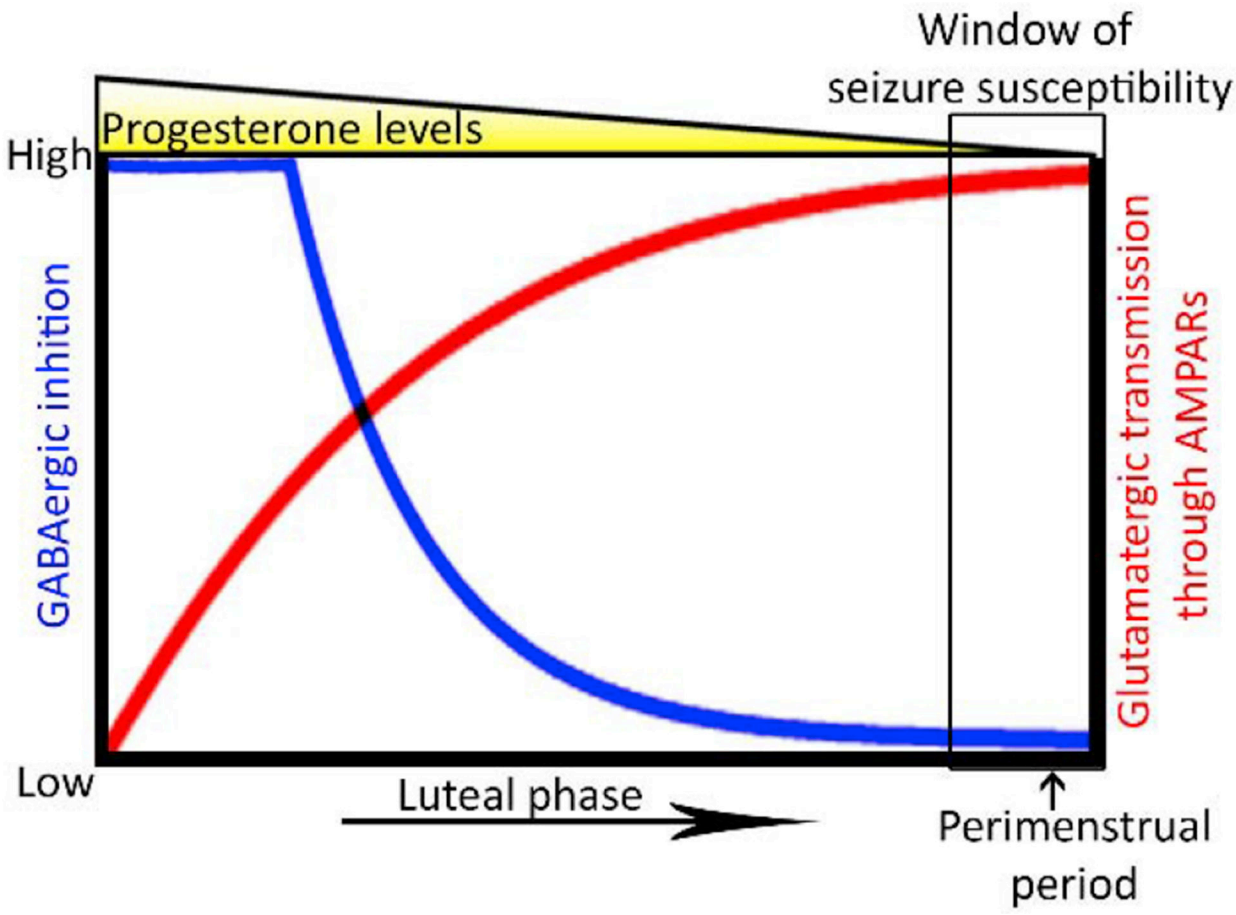

Figure 3:

Progesterone exerts rapid effects through THP, which potentiates GABAergic inhibitory neurotransmission. On the other hand, PR-mediated effects are slower but longer-lasting, since they involve changes in gene expression. The GABAergic inhibition is strong during the luteal phase when progesterone levels are high. However, the decline in progesterone levels later in the luteal phase diminishes GABAergic inhibition. On the other hand, high progesterone levels during the luteal phase would also activate PRs and enhance AMPAR-mediated glutamatergic transmission. This could cause an imbalance between excitation and inhibition and create a perimenstrual window of seizure susceptibility.