Review

Georgina MacKenzie and Jamie Maguire*

Neurosteroids and GABAergic signaling in health and disease

Abstract: Endogenous neurosteroids such as allopregnanolone, allotetrahydrodeoxy corticosterone, and androst anediol are synthesized either de novo in the brain from cholesterol or are generated from the local metabolism of peripherally derived progesterone or corticosterone. Fluctuations in neurosteroid concentrations are important in the regulation of a number of physiological responses including anxiety and stress, reproductive, and sexual behaviors. These effects are mediated in part by the direct binding of neurosteroids to γ-aminobutyric acid type-A receptors (GABA A Rs), resulting in the potentiation of GABA A R-mediated currents. Extrasynaptic GABA A Rs containing the δ subunit, which contribute to the tonic conductance, are particularly sensitive to low nanomolar concentrations of neurosteroids and are likely their preferential target. Considering the large charge transfer generated by these persistently open channels, even subtle changes in neurosteroid concentrations can have a major impact on neuronal excitability. Consequently, aberrant levels of neurosteroids have been implicated in numerous disorders, including, but not limited to, anxiety, neurodegenerative diseases, alcohol abuse, epilepsy, and depression. Here we review the modulation of GABA A R by neurosteroids and the consequences for health and disease.

Keywords: allopregnanolone; γ-aminobutyric acid (GABA); neurosteroids; allotetrahydrodeoxy corticosterone (THDOC).

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Introduction

The term neurosteroids was first introduced in the 1980s by Baulieu to describe steroids produced de novo in the brain from cholesterol; it was later expanded to include those derived from the local metabolism of peripherally derived steroid precursors such as, progesterone, corticosterone, or testosterone (1–3). Neurosteroids are modulators of aminobutyric acid type A receptors (GABA A Rs) and can induce analgesic, anxiolytic, sedative, anesthetic, and anticonvulsant effects (4, 5). The ability of neurosteroids to modulate GABA A R function was first shown in 1984 by Harrison and Simmonds who demonstrated that allopregnanolone, a synthetic neuroactive steroid with anesthetic properties, potently potentiated GABA A R currents (6). This result was repeated shortly afterward with the endogenous neurosteroids 5α-pregnan-3α,21-diol-20-one (allopregnanolone) and 5α-pregnan-3α,21-diol-20-one (THDOC) (7). Fluctuations in the concentration of endogenous neurosteroids and changes in GABAergic signaling have been implicated in a variety of physiological and pathophysiological conditions including stress, pregnancy, reproductive/sexual behaviors, depression, and epilepsy (8–15). Here we review the neurosteroid-mediated regulation of GABAergic transmission, the effects on neuronal excitability, and the implications for health and disease.

Neurosteroidogenesis

There are three main classes of neurosteroids: the pregnane (e.g., allopregnanolone), the sulfated (e.g., dehydroepiandrosterone sulfate, or DHEAS), and the androstane (e.g., androstanediol), which are classified according to their structural homology (9) (Figure 1). The 3α-hydroxy ring A-reduced pregnane steroids, such as allopregnanolone and THDOC, are the most potent positive modulators of GABA A Rs and will be the focus of this review whereas; the sulfated neurosteroids are often inhibitory and act as noncompetitive antagonists at GABA A Rs (16). Allopregnanolone and THDOC can be synthesized from cholesterol by a series of steroidogenic enzymes [for reviews, see (2, 5, 17, 18)] (Figure 1). Briefly, the key pathways are as follows: cholesterol is transported into the inner mitochondrial membrane via the steroidogenic acute regulatory protein (StAR) and translocator protein 18 kDa (TSP0), also known...
as the peripheral benzodiazepine receptor (19). Here, mitochondrial cholesterol side-chain cleavage enzyme (cytochrome P450scc) catalyzes a side chain cleavage to convert cholesterol into pregnenolone, an important rate-limiting step for the production of allopregnanolone and THDOC. Pregnenolone is then converted by 3β-hydroxysteroid dehydrogenase (3β-HSD) into progesterone with further metabolism of progesterone by 21 hydroxylase (p450c21), yielding deoxycorticosterone. Finally, progesterone and deoxycorticosterone are metabolized by 5α-reductase followed by 3α-hydroxysteroid dehydrogenase (3α-HSD), to yield allopregnanolone and THDOC, respectively. In addition, androstanediol, another potent positive modulator of GABA\textsubscript{A}Rs, also utilizes the 5α-reductase/3α-HSD metabolic pathway to catalyze its synthesis from testosterone (3, 9) (Figure 1).

The steroidogenic enzymes are not uniformly distributed throughout the brain but are localized in specific brain regions and cell types (20). Cytochrome p450scc, for example, is expressed in both principal neurons and glial cells in various brain regions including the amygdala, hypothalamus, thalamus, cortex, and hippocampus.
(21). Furthermore, both 5α-reductase protein and 3α-HSD mRNA have been shown to colocalize in principal neurons in the thalamus, striatum, cerebellum, cortex, amygdala, and hippocampus, indicating that these are likely sites of neurosteroidogenesis (22). However, there is limited or no expression in interneurons with weak 5α-reductase/3α-HSD expression found only in the granule cells of the cerebellum and olfactory bulb (22). As neurosteroids are produced in the same neurons that express GABA_A Rs, they may act in an autocrine as well as a paracrine fashion to alter neuronal excitability. Interestingly, p450c21 mRNA has so far only been found in the brain stem and at very low levels in the cerebellum, suggesting that local metabolism of steroid hormone precursors from the periphery might be the prominent pathway for neuronal THDOC synthesis, which coincides with the observation that THDOC is not detectable in the brains of adrenalectomized animals (20, 23). Indeed, because steroid hormones are small and lipophilic, peripherally derived hormones from the adrenal cortex, placenta, or gonads can readily cross the blood-brain barrier and plasma membrane, where they can be locally metabolized into neurosteroids (24). It has also been observed that some steroidogenic enzymes are found in more than one subcellular compartment. For instance, cytochrome p450c17, an important enzyme in the pathway that mediates the conversion of pregnanolone into DHEAS and androstenediol, is found in the cell body, axon, and dendrites of embryonic basal ganglia and cerebellum neurons (21, 25). Therefore, neurosteroids may be synthesized at some distance away from the cell body, and thus, it can be hypothesized that distantly synthesized or trafficked neurosteroids could mediate effects in brain regions apparently devoid of the necessary enzymes for neurosteroid synthesis (21). However, due to technical difficulties in the quantification of neurosteroids, it is difficult to directly measure local neurosteroid production.

Baseline circulating plasma neurosteroid levels and levels in the brain are generally low, but they increase in response to certain physiological triggers such as stress, the ovarian cycle, and pregnancy. The basal THDOC concentration in the plasma of rats (26, 27) and humans (28, 29) is approximately ≤5 nM at rest. However, a stressful episode activates the hypothalamic-pituitary-adrenal axis, resulting in the release from the adrenal gland of corticosterone in rats and cortisol in humans (30). Plasma levels of THDOC increase approximately threefold to fourfold in rats subjected to an acute swim stress (26) and in humans responding to panic induction with cholecystokinin-tetrapeptide (29), which parallels changes in corticosterone/cortisol levels. The peak THDOC response occurs 10–30 min after the cessation of the stress and can be prevented by the 5α-reductase inhibitor, finasteride (23, 26, 27, 31). Allopregnanolone is also found at low nanomolar concentrations in the plasma of both humans (32, 33) and rats (34–36) and fluctuates in response to stress (23, 36, 37) stage of menstrual/estrous cycle (32, 38) and pregnancy (33, 37, 39–41), reflecting changes in peripheral progesterone levels. During pregnancy, plasma allopregnanolone levels have been shown to reach concentrations ranging from 40 nM to >100 nM in both rats (35) and humans (33, 37, 39–41). Similarly, allopregnanolone levels have been shown to increase during pregnancy in the rat cerebral cortex, peaking by day 19 and returning to control levels upon parturition (day 21) (35). It is important to note that although basal and peak neurosteroids levels have been detected at nanomolar concentrations under normal physiological circumstances, these concentrations are sufficient to positively modulate GABA_A Rs. Further, neurosteroid concentrations may be significantly higher at specific neuronal locations reflecting local synthesis, diffusion barriers, and metabolism.

Although neurosteroid concentration measurements have been made in the central nervous system (CNS) of both rats (23, 35, 36, 42, 43) and humans (44–46), accurately measuring neurosteroid concentrations is difficult and reflected in the range of neurosteroid concentrations reported in the literature. Radioimmunoassays are commonly used to measure neurosteroid levels and are highly sensitive. However, sample contamination, antibody cross-reactivity, and different sample extraction, and purification procedures likely underscore some of the variability in the literature. Alternative approaches include separation of cross-reacting steroids followed by enzyme-linked immunosorbent assays (47) and liquid or gas chromatography coupled with mass spectrometry, which have provided lower estimates of brain-derived neurosteroids [for reviews, see (48, 49)]. However, despite the difficulties in accurately measuring neurosteroid levels in both plasma and the CNS, the relative changes in neurosteroid concentration during different physiological states are likely to be accurate (48) and will have important implications for neuronal and network excitability.

Neurosteroid modulation of GABARs

GABA_A Rs are assembled from a combination of 19 subunits (α_1–6, β_1–3, γ_1–3, δ, ε, θ, π, ρ_1–3) to form a heteropentameric structure around a central ion channel pore, which fluxes chloride (50–52). The exact receptor subunit combination determines not only its pharmacological and
biophysical properties but also its subcellular localization. For instance, receptor combinations containing the γ subunit are found predominantly at the synapse where they mediate rapid synaptic (phasic) transmission (53, 54). Meanwhile, assemblies containing the δ subunit have a high affinity for GABA and are found either perisynaptically or extrasynaptically (54–57). These properties make them ideally suited to sense the nanomolar concentrations of ambient GABA predicted to be found in the extrasynaptic space with persistent receptor activation resulting in the generation of a tonic chloride conductance (54, 58, 59).

Positive neurosteroids such as allopregnanolone and THDOC are potent modulators of GABA Rs and act by increasing the open probability of the channel without changing the single channel conductance (60, 61). At low nanomolar concentrations, neurosteroids act as positive allosteric modulators. Indeed, in recombinant expression systems, neurosteroids have been shown to potentiate the peak current generated by the majority of GABA R subtypes in response to subsaturating GABA concentrations (62). Yet, at higher micromolar concentrations, neurosteroids directly activate the receptor in the absence of GABA (63). However, not all neurosteroids are positive modulators of GABA R. Adding to the diversity of neurosteroid-mediated regulation, two members of the sulfated neurosteroid family, pregnanolone sulfate and DHEAS, inhibit GABA R subtypes. For instance, receptor combinations containing the δ subunit have a high affinity for GABA and are found either perisynaptically or extrasynaptically (54–57). These properties make them ideally suited to sense the nanomolar concentrations of ambient GABA predicted to be found in the extrasynaptic space with persistent receptor activation resulting in the generation of a tonic chloride conductance (54, 58, 59).

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Although more efficacious at δ-subunit-containing receptors, neurosteroids can potentiate the effects of GABA at receptors containing most isoforms. In fact, the binding site for neurosteroids does not involve the δ subunit. Using a combination of site-directed mutagenesis, electrophysiology, and homology modeling, two neurosteroid-binding sites have been identified on GABA Rs composed of α,β,γ subunits (63). First, threonine 236 on the α subunit, which lies close to the α/β interface, and tyrosine 284 on the β subunit are essential for the direct activation of the receptor by allopregnanolone. Second, the α-subunit residue glutamine 241 located on transmembrane 1 is crucial for mediating both the allosteric potentiation and direct neurosteroid activation of the receptor (63, 72–74), although neighboring residues are also likely to be important for forming the steroid-binding site (75, 76). Recently, photoaffinity labeling using (3α,5β)-6-azi-pregnanolone identified phenylalanine 301 in the β subunit as a unique residue for neurosteroid binding, which likely forms part of the direct activation site (77). It will be of interest to modify this residue and examine both neurosteroid potentiation and direct activation of α,β,γ-GABA Rs subtypes using electrophysiology. In addition, photoaffinity labeling of native receptors subtypes could be used to distinguish those residues that are involved in the direct activation vs. allosteric modulation by neurosteroids (75, 78).

Despite being shown to potentiate the majority of GABA R subtypes, the actions of positive neurosteroids at GABA R subtypes containing the ε subunit (ε-GABA Rs) are less clear. Compared with other GABA R subtypes, ε-GABA Rs are relatively insensitive to the potentiating effects of a number of intravenous anesthetics including the neurosteroid allopregnanolone (62, 79, 80) [but see (81)]. However, pregnane neurosteroids have been shown to directly activate ε-GABA Rs in the absence of endogenous agonist (62, 82–84). As inclusion of the ε subunit has been shown to confer constitutive activity to the GABA R in recombinant expression systems (81, 84, 85), it is difficult to determine whether neurosteroid action is mediated by allosteric potentiation of spontaneous openings or via steroid binding to the direct activation site (86). Furthermore, understanding the actions of neurosteroids at ε-GABA Rs is complicated because neurosteroid actions may be influenced by receptor stoichiometry (83). Therefore, further studies using native receptor populations such as in vitro slice models are required for the actions of neurosteroids at ε-GABA Rs to be fully understood. For example, recent evidence from brain stem respiratory
neurons of the ventral respiratory column showed an increased in ε-GABAₐₐRs subunit expression during pregnancy and reduced sensitivity to intravenous anesthetics. These data suggest that increased expression of ε-GABAₐₐRs during pregnancy might protect against respiratory depression despite elevated neurosteroid levels (87).

**Regulation of GABAₐₐRs and changes in neuronal excitability**

The presence of low concentrations (i.e., 10–30 nM) of neurosteroids results in the potentiation of extrasynaptic GABAₐₐRs. Although the magnitude of potentiation will depend on receptor subtype, local GABA concentration, and steroid metabolism, the large charge transfer generated by these persistently open channels means that even a small increase in the tonic conductance will have a major impact on excitability. Generally, an increase in the tonic conductance will reduce the input resistance narrowing the temporal and spatial integration of synaptic events and increasing the amount of excitatory input required to generate an action potential (54, 88). In addition, changes in tonic inhibition can impact the sensitivity of a neuron to changes in inputs (the neuronal gain) by shunting the background synaptic noise (54, 88, 89) [but see (90)]. Larger increases in neurosteroid concentration (i.e., ≥100 nM) will reduce neuronal excitability further by potentiating the phasic component of GABAergic inhibition by prolonging IPSPs as well as enhancing tonic GABAergic inhibition (64). Therefore, as neurosteroid concentrations vary under both physiological and pathological conditions, GABAergic signaling requires dynamic regulation to maintain optimal levels of inhibition [for a review, see (91)].

Fluctuations in steroid hormones, such as those that occur during stress, the ovarian cycle, and pregnancy, have been shown to correspond to changes in GABAergic inhibition and subunit expression (8, 10, 35, 92–97). For example, the δ subunit has been shown to increase while the γ₂ subunit decreases in mouse hippocampus at times of the ovarian cycle when progesterone levels are high, resulting in an increase in tonic inhibition and decreased levels of anxiety and seizure susceptibility (95). Similar changes have been observed in the periaqueductal gray matter (98) and the CA1 region of the hippocampus in response to elevated steroid levels (97). These changes in subunit expression can be prevented by blocking neurosteroid synthesis with finasteride and can be mimicked in males by progesterone administration (11). Similar changes have also been demonstrated in response to elevations in neurosteroids following acute stress (11). However, no changes in GABAₐₐR mRNA expression levels were found in gonadotropin-releasing hormone neurons in the medial preoptic area in cycling mice (99), suggesting that steroid-mediated modulation of GABAₐₐR expression is likely cell type-specific.

The conditions in which there are prolonged changes in neurosteroid levels, such as during pregnancy, has been shown to induce alterations in the cerebrocortical and hippocampal expression of the GABAₐₐR γ₂ subunit (35, 94, 100, 101) and the hippocampal GABAₐₐR δ subunit (94), which can be prevented by blocking the neurosteroid synthesis with finasteride (35, 100, 101). These changes in GABAₐₐR subunit expression during pregnancy are correlated with alterations in network excitability (10). Further, hippocampal expression of the α4 subunit has also been shown to fluctuate in response to changes in progesterone concentration (8, 96, 102, 103). Therefore, neurosteroids can alter GABAergic inhibition via the direct modulation of GABAergic inhibition as well as by altering GABAₐₐR subunit expression, which exerts dramatic effects on neuronal excitability. Thus, the neurosteroid regulation of GABAergic inhibition has significant implications for neuronal excitability in health and disease.

**Role of neurosteroids in disease**

Neurosteroids have been implicated in numerous disorders, including, but not limited to, depression, anxiety, alcohol abuse, epilepsy, and neurodegenerative diseases (104–111). The evidence of altered neurosteroid levels associated with several neuropsychiatric and neurological disorders has generated a great deal of enthusiasm for targeting neurosteroids or their site of action for treatment [for a review, see (9)]. Furthermore, the actions of neurosteroids on specific GABAₐₐR subtypes have further increased enthusiasm for the therapeutic potential of these compounds. The following section will review the role of neurosteroids in disease as well as the therapeutic potential of targeting neurosteroids, focusing specifically on neurosteroids that exhibit positive modulation of GABAₐₐRs.

**Depression**

Neurosteroid levels are abnormal in patients with major depression [for a review, see (112)]. For example,
allopregnanolone levels are decreased in patients with major depression compared with healthy controls [for a review, see (112)]. Conversely, the levels of the stress-derived neurosteroid, THDOC, are elevated in patients with major depression [for a review, see (112)]. Antidepressant treatment normalizes the neurosteroid levels in depressed patients (106, 107, 112–114), which is thought to mediate the antidepressant effects of these drugs (107, 113, 114). These data implicate altered neurosteroid levels in the pathophysiology of depression as well as a role in the effectiveness of antidepressant treatment. Selective serotonin reuptake inhibitors (SSRIs) enhance the antidepressant effects of these drugs via increasing GABAergic tone (115), which are independent of effects on serotonergic transmission (113–115), suggesting that the antidepressant effects of SSRIs and allopregnanolone are mediated via the GABAergic system rather than the serotonergic system. Consistent with the role of neurosteroids in depression, exogenous administration of allopregnanolone exerts antidepressant effects in animal models (115, 116). Further, mice with deficits in the primary target for neurosteroid action in the brain, the δ-subunit-containing GABA\(_A\)Rs (\(\text{Gabrd}^{-}\) mice), exhibit depression-like behavior during the postpartum period (10, 94).

Neurosteroids have also been implicated in mood disorders associated with the ovarian cycle. Allopregnanolone levels during the luteal phase are associated with symptom severity in patients with premenstrual dysphoric disorder (PMDD) (117) [for a review, see (118)], and increased levels are correlated with symptom improvement (119) [for reviews, see (120, 121)]. However, there are conflicting results regarding alterations in neurosteroid levels in patients with PMDD. Many studies suggest that there is no significant difference in allopregnanolone levels in patients with PMDD compared with controls, whereas other studies suggest that allopregnanolone levels are decreased or increased in patients with PMDD [for a review, see (118)]. Given that there are no clear differences in neurosteroid levels in patients with PMDD, it has been proposed that these patients have altered responses to neurosteroids or the site of action of neurosteroids (95). Although the exact nature of the relationship remains unclear, these data demonstrate a role for neurosteroids and their site of action in the pathophysiology of depression.

### Anxiety

Patients with generalized anxiety disorders have altered neurosteroid levels. Allopregnanolone levels are significantly decreased in patients with posttraumatic stress disorder (122) and in patients with panic disorder (123). Following experimentally induced panic attacks, allopregnanolone levels are decreased in patients with a history of panic disorders compared with healthy controls (124, 125), suggesting that there are deficits in neurosteroid signaling in patients with anxiety disorders. Together, these findings suggest that neurosteroids play a role in the pathophysiology of anxiety and panic disorders (126). However, the most convincing evidence for neurosteroid involvement in anxiety disorders is the potent anxiolytic actions of neurosteroids (127–131). Allopregnanolone (129, 132–134) and THDOC (127, 134) have been shown to exhibit anxiolytic properties in many different behavioral paradigms. However, the anxiolytic effects of neurosteroids appear to be state-dependent because neurosteroids do not exhibit anxiolytic properties following stress (135).

### Epilepsy

Neurosteroids exhibit robust anticonvulsant actions in the pentylenetetrazol (PTZ), pilocarpine, kindling, bicuculline, and maximal electroshock models of epilepsy [for reviews, see (9, 38)]. In addition to their ability to decrease seizure susceptibility, neurosteroids also delay the progression of epileptogenesis (136, 137) and are neuroprotective against seizure-induced cell death (138). Furthermore, alterations in the expression of δ-subunit-containing GABA\(_A\)Rs, the primary target of neurosteroids, have been observed in the pilocarpine model of temporal lobe epilepsy (139) and have been proposed to play a role in the process of epileptogenesis. Consistent with the anticonvulsant role of neurosteroids, neurosteroid withdrawal has been demonstrated to increase seizure frequency and decrease the anticonvulsant effects of GABA agonists (140–142). These data implicate alterations in neurosteroid levels and/or their site of action in epileptogenesis and seizure susceptibility.

It has been proposed that neurosteroids are particularly therapeutically relevant for the treatment of catamenial epilepsy. Catamenial epilepsy is thought to result from changes in hormone levels during the menstrual cycle, resulting in increased seizure frequency at certain stages of the cycle (143). Progesterone has been used as an add-on therapy for the treatment of catamenial epilepsy (144, 145), with some success. Interestingly, simultaneous treatment with finasteride blocks the anticonvulsant actions of progesterone (146), demonstrating that the anticonvulsant effects of progesterone are mediated by neurosteroids. Progesterone withdrawal (147) and
neurosteroid withdrawal (148) increases seizure susceptibility, which is thought to represent an animal model of catamenial epilepsy. Interestingly, following neurosteroid withdrawal, the anticonvulsant actions of the synthetic neuroactive steroid ganaxolone are enhanced (149), which may be due to alterations in the expression of neurosteroid-sensitive GABA A Rs (150). Animal models have demonstrated alterations in GABA A Rs associated with changes in hormone levels, which are thought to underlie the changes in neuronal excitability related to the estrous cycle (95, 96). Therefore, the evidence supports a role for altered neurosteroid levels and/or their site of action in the pathophysiology of epilepsy, particularly catamenial epilepsy.

Alcohol

Both neurosteroids and ethanol have a shared pharmacological target, GABA A Rs (7, 151, 152). A neurosteroid-binding site has been identified on the α/β interface of GABA A Rs (72), demonstrating the direct modulation of GABA A Rs by neurosteroids. Further, GABA A R δ-subunit-containing receptors confer sensitivity to neurosteroids and are thought to mediate the majority of their effects on GABAergic inhibition (62, 64, 65, 67) (see Neurosteroid Modulation of GABA A Rs). Because ethanol does not interfere with neurosteroid actions, it is thought to exert its actions on GABA A Rs via a site independent of the neurosteroid-binding site [for a review, see (153)]. However, the direct actions of ethanol on specific GABA A R subtypes have been more controversial. Studies have demonstrated that ethanol enhances tonic GABAergic inhibition (154–156) likely via actions on GABA A R δ-subunit-containing receptors (157–159). However, as stated, these findings remain controversial and have not been able to be replicated by other investigators [for reviews, see (160, 161)].

Ethanol has been shown to increase circulating concentrations of neurosteroids (162–166), which plays a role in modulating the sensitivity to ethanol [for reviews, see (167–169)]. For example, ethanol-induced elevations in neurosteroid levels mediate the sedative properties of ethanol (170), ethanol-induced impairments in memory (171, 172), the anxiolytic and antidepressant properties of ethanol (173, 174), as well as the anticonvulsant effects (165). However, neurosteroids do not mediate the ethanol-induced motor impairments (175). These data demonstrate that ethanol induces elevations in neurosteroid levels, which, in part, mediate the behavioral effects of alcohol.

Neurodegeneration

Decreased levels of neurosteroids have been observed in patients with neurodegenerative diseases [for a review, see (176)]. Allopregnanolone levels are decreased in patients with Alzheimer disease (AD), Parkinson disease (PD), multiple sclerosis (MS), and Niemann-Pick type C disease [for reviews, see (176, 177)]. The expression of StAR, (178) one of the major neurosteroidogenic enzymes, is elevated in patients with AD. Similarly, there are changes in the expression of neurosteroidogenic enzymes in PD, MS, and Niemann-Pick type C disease [for a review, see (177)]. Increased expression of the enzymes involved in neurosteroidogenesis has been proposed to reflect compensatory changes due to the decreased levels of neurosteroids related to neurodegeneration (176). Consistent with the involvement of neurosteroid deficits in neurodegenerative diseases, neurosteroids have been shown to have neuroprotective properties in numerous different animal models [for a review, see (179)]. For instance, in a rodent model of Niemann-Pick type C disease, a lysosomal storage disorder with neuronal loss and a reduction in neurosteroidogenesis, administration of a single dose of allopregnanolone in the neonatal period significantly prevented neuronal cell death and a delay in the development in neurological symptoms. Although the exact mechanisms underlying the protective effects of allopregnanolone are unclear, these studies demonstrate the therapeutic potential of neurosteroids for some neurodegenerative disorders (180, 181) [for a review, see (182)]. Thus, several studies implicate neurosteroids in the pathophysiology of several neurodegenerative disorders, including AD, PD, MS, and Niemann-Pick type C disease.

Therapeutic potential of neurosteroids

Neurosteroids have been demonstrated to have a therapeutic potential, particularly in patients with epilepsy (144, 145). However, naturally occurring neurosteroids have several limitations, which minimize their therapeutic potential. First, neurosteroids are rapidly metabolized and thus have low bioavailability [for a review, see (9)]. In addition, neurosteroids can be converted to compounds that can act on steroid hormone receptors (183), thus mediating unwanted actions that may offset the desired effects of these compounds. Due to these limitations, synthetic neurosteroids have been designed that exhibit a better pharmacological profile than endogenous neurosteroids.
For example, ganaxolone is a synthetic analogue of allo-pregnanolone developed as a potential therapeutic agent [for reviews, see (184, 185)]. Ganaxolone has been shown to be effective in animal models of, infantile spasms (186), catamenial epilepsy (149), PTZ-induced seizures (187, 188), and kindling (140). In clinical trials, ganaxolone has shown to significantly improve seizure frequency in epileptic adults and infants/children (184, 186, 189) and was explored as a sleep aide [for reviews, see (184, 185)]. However, the enthusiasm for the therapeutic potential of ganaxolone has diminished due to the adverse side effects, the most common of which were somnolence and nausea [for reviews, see (69, 184)].

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References


64. Stell BM, Brickley SG, Tang CY, Farrant M, Mody I. Neuroactive steroids reduce neuronal excitability by selectively enhancing tonic inhibition mediated by delta subunit-containing GABA(A) receptors. Proc Natl Acad Sci USA 2003; 100: 14439–44.
107. Guidotti A, Costa E. Can the antidysphoric and anxiolytic profiles of selective serotonin reuptake inhibitors be related to their ability to increase brain 3 alpha, 5 alpha-tetrahydroprogesterone (allopregnanolone) availability? Biol Psychiatry 1998; 44: 865–73.


154. Wei WZ, Faria LC, Mody I. Low ethanol concentrations selectively augment the tonic inhibition mediated by delta subunit-containing GABA(A) receptors in hippocampal neurons. J Neurosci 2004; 24: 8379–82.


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