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Neurosteroid Influence on Affective Tone

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Abstract

Affective disorders such as depression and anxiety are among the most prevalent psychiatric illnesses and causes of disability worldwide. The recent FDA-approval of a novel antidepressant treatment, ZULRESSO® (Brexanolone), a synthetic neurosteroid has fueled interest into the role of neurosteroids in the pathophysiology of depression as well as the mechanisms mediating the antidepressant effects of these compounds. The majority of studies examining the impact of neurosteroids on affective states have relied on the administration of exogenous neurosteroids; however, neurosteroids can also be synthesized endogenously from cholesterol or steroid hormone precursors. Despite the well-established influence of exogenous neurosteroids on affective states, we still lack an understanding of the role of endogenous neurosteroids in modulating affective tone. This review aims to summarize the current literature supporting the influence of neurosteroids on affective states in clinical and preclinical studies, as well as recent evidence suggesting that endogenous neurosteroids may set a baseline affective tone.

Keywords

neurosteroids; neurosteroidogenesis; allopregnanolone; depression; anxiety; PTSD

Introduction

Psychiatric disorders are among the most prevalent forms of disability worldwide, with affective disorders such as depression and anxiety being the most common (Center for Behavioral Health Statistics, 2017; Evaluation, 2019; James et al., 2018). Upwards of 50% of individuals diagnosed with an affective disorder fail to achieve full symptom remission, and almost a third of those treated exhibit treatment resistance with currently available antidepressant and antipsychotic treatments (Fournier et al., 2010; Howes et al., 2021; John Rush et al., 2006; Zhdanava et al., 2021). Of particular concern is the length of

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time it takes these treatments to become effective, a delay which poses a significant risk for treatment noncompliance as well as increased suicide risk (Fergusson et al., 2005; Hammad et al., 2006; Healy & Aldred, 2009; Jick et al., 2004; Simon & Savarino, 2007; Stone et al., 2009). Therapeutic advances for affective disorders have been delayed due to the complex neurobiological heterogeneity of these disorders. Numerous mechanisms have been implicated in the pathophysiology of mood disorders, such as the predominant monoamine hypothesis of depression (Hirschfeld, 2000) as well as newer theories including the GABAergic hypothesis of depression (Lüscher et al., 2011).The GABAergic hypothesis of depression has gained recent interest and validation (Lüscher et al., 2011) given the FDA-approval of, ZULRESSO® (Brexanolone), a synthetic neurosteroids as an antidepressant with a novel mechanism of action as a positive allosteric modulator of $GABA_A$ receptors ($GABA_A$Rs) (Althaus et al., 2020; Epperson et al., 2023; Lüscher & Möhler, 2019a).

Neurosteroids are a class of steroids that are endogenously synthesized in the brain *de novo* from cholesterol or from steroid hormone precursors; whereas neurosteroids are steroids which, independent of their origin, can exert actions in the brain. Neurosteroids have been shown to exert anxiolytic and antidepressant effects (Zorumski et al., 2012, 2019; Zorumski & Mennerick, 2013), demonstrating their ability to modulate affective tone. In fact, treatment of affective disorders with exogenous neurosteroids has demonstrated effectiveness in clinical studies (Arnaud et al., 2021; Epperson et al., 2023; Meltzer-Brody et al., 2018; Suthoff et al., 2022). Despite the well-established influence of exogenous neurosteroids on affective states, we still lack an understanding of the role of endogenous neurosteroids in modulating affective tone. This review aims to summarize the current literature supporting the influence of neurosteroids on affective states in clinical and preclinical studies as well as recent evidence suggesting that endogenous neurosteroids may set a baseline affective tone, one which is impacted by risk factors for psychiatric illnesses and may be a useful target for the treatment of mood disorders. The neurosteroids that are discussed in this review are listed in table 1.

1. Endogenous Neurosteroid Synthesis

Etienne Baulieu coined the term, “neurosteroid” in 1981, describing steroid hormones synthesized endogenously in the brain that are derived from cholesterol. Endogenous neurosteroid synthesis requires the sequential action of enzymes 5α-reductase and 3α-hydroxysteroid dehydrogenase (3α-HSD) (Figure 1). Both 5α-reductase types I and II convert either a. progesterone into 5α-dihydroprogesterone or b. deoxycorticosterone into 5α-deoxycorticosterone. 3α-HSD bidirectionally reduces 5α-dihydroprogesterone into allopregnanolone (Figure 1). The same steroidogenic enzymes utilized in the endogenous production of neurosteroids, 5α-reductase and 3α-HSD, are present outside of the brain to synthesize neurosteroids in the adrenal glands, reproductive organs, placenta, and skin (Liang & Rasmusson, 2018; Mellon & Griffin, 2002). Within the brain however, transcriptional expression of these enzymes is temporally- and regionally- specific, implicating their role in development and maintenance of neuronal circuits.

5α-reduced metabolites are synthesized in both neurons and glial cells. Key enzymes necessary for the synthesis of endogenous neurosteroids have been discovered in the brain of

several mammals, submammalian vertebrates, and invertebrates. While technical limitations have hindered the precise localization of protein levels of some steroidogenic enzymes and neurosteroids, mRNA of 5α-reductase type I and 3α-HSD have both been found to colocalize in glutamatergic pyramidal neurons and glial cells in brain regions rich in white matter such as the cortex, hippocampus(CA1–3), olfactory bulb, striatum, thalamus, amygdala, corpus callosum and cerebellum (Agís-Balboa et al., 2006). 3α-HSD has been discovered to be expressed in the hypothalamus, thalamus, caudate nucleus, frontal cortex, olfactory bulb, and olfactory tubercle (For review see (Mellon, 2007)). Genes for enzymes in the Cytochrome P450 family that catalyze the cleavage of cholesterol into pregnenolone, are present in white matter throughout the brain as well as in cerebellum, hypothalamus, cortex, hippocampus, and amygdala(Compagnone et al., 1995). These regions are considered the main hubs for neurosteroidogenesis in the brain, as genes for both 5α-reductase and 3α-HSD enzymes have also been discovered in these regions (For review see (Mellon, 2007)). These hubs for neurosteroidogenesis are also key nodes for emotional processing, consistent with the impact of neurosteroids on affective states.

2. Effect of 5α-reduced neurosteroids on affective tone

Steroid hormones are known to exert their biological effects by binding to their intracellular receptors, translocating to the nucleus, and regulating gene transcription. However, steroid hormones have also been shown to exert rapid effects on neuronal excitability by interacting with specific neurotransmitter receptors, including $GABA_A$Rs and NMDA receptors (for review see (Carver & Reddy, 2013; Park-Chung et al., 1997; Rasmusson et al., 2022; Rupprecht & Holsboer, 1999; Ziolkowski et al., 2021)). While there are three main classes of neurosteroids that exist based on their structural characteristics (pregnane, sulfated, and androstane), this review will focus on 5α-reduced neurosteroids that have been indicated in a variety of affective states (for review see (Reddy & Bakshi, 2020)). 5α-reduced metabolites of both progesterone and testosterone (3α-diol) have been demonstrated to impact affective states (see review (Melcangi et al., 2021)), although there is more evidence supporting a role for 5α-reduced progesterone metabolites and will therefore be the focus of this review.

2.1 Clinical evidence

While some of the first clinical observations of neurosteroids demonstrated their potent anesthetic and sedative properties, accumulating evidence has highlighted their efficacy as antidepressants, anxiolytics, and antipsychotic treatments.

2.1.1. Anxiety—Fluctuations in neurosteroid levels have been observed throughout the human lifespan, with more drastic changes across the estrous cycle, pregnancy, and a decline in late adulthood (Figure 2). These changes have been observed to occur in concert with changing $GABA_A$R expression during periods with increased risk of developing an anxiety disorder (Figure 2). Researchers have identified significantly lower levels of pregnenolone in patients with generalized anxiety disorder (GAD) (Semeniuk et al., 2001). Dysregulation of $GABA_A$/benzodiazepine receptor complexes have also been noted in individuals with GAD (Semeniuk et al., 2001), suggesting impaired neurosteroid signaling and inhibitory tone that may contribute to anxiety pathology. In line with this notion, disequilibrium

of neurosteroids in individuals with premenstrual syndrome have also been noted where lower levels of progesterone during the luteal phase were correlated with increase symptom severity with PMS (Wang et al., 1996). Conversely, in individuals with panic disorders it was demonstrated that plasma concentrations of allopregnanolone were elevated while progesterone and *5*α-DHP were comparable to levels of healthy controls (Ströhle et al., 2002). Elevated plasma levels of allopregnanolone were also observed in women during the follicular and premenstrual phase of the estrous cycle, periods where anxiety and other symptoms of premenstrual dysphoric disorder (PMDD) arise (Brambilla et al., 2003). These findings could be in part due to the increase in HPA-axis activation during panic attacks that would result in the hypersecretion of neurosteroids as a counter-regulatory mechanism against this anxiogenic condition. In follow up studies where panic attacks were induced using sodium lactate or cholecystokinin-tetrapeptide in individuals with a history of panic attacks, both allopregnanolone and pregnanolone were significantly reduced compared to levels in healthy controls without a history of panic attacks (Ströhle et al., 2002, 2003).

2.1.2. Depression—Following parturition there is a rapid decline in neurosteroid levels, particularly in levels of allopregnanolone that might trigger symptoms of postpartum depression in a subset of individuals. This precipitous decline in endogenous allopregnanolone levels is thought to create a window of vulnerability to mood disorders during this period and spurred interest in developing an exogenous neurosteroid analog to target the underlying pathology of postpartum depression. Clinical trials have demonstrated the efficacy of this treatment modality where administration of a synthetic allopregnanolone analog ZULRESSO® (Brexanolone), to individuals with severe postpartum depression resulted in a significant reduction in depressive symptoms, anxiety, and insomnia (Epperson et al., 2023; Kanes, Colquhoun, Doherty, et al., 2017; Kanes, Colquhoun, Gunduz-Bruce, et al., 2017; Meltzer-Brody et al., 2018). Treatment responses with ZULRESSO® (Brexanolone) were rapid and durable, persisting up to 90 days post-treatment (Epperson et al., 2023; Meltzer-Brody et al., 2018; Patterson et al., 2022). Follow-up studies utilizing a similar allopregnanolone analog for treatment of major depressive disorder demonstrated a significant reduction in symptoms of depression in response to 14 days of oral treatment (Gunduz-Bruce et al., 2019). In postmenopausal women with major depression that were treatment-resistant to classical antidepressants selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs), the use of a synthetic allopregnanolone analog, Ganaxalone, improved mood symptoms and insomnia associated with depression following an 8-week treatment period (Dichtel et al., 2020). Allopregnanolone concentrations have been demonstrated to be ~60% lower in patients with unipolar depression. Interestingly, treatment with SSRIs such as fluoxetine or paroxetine are able to normalize CSF allopregnanolone concentrations without altering levels of progesterone or pregnanolone, the timing of which correlates with the antidepressant treatment response (Uzunova et al., 1998). Postmortem analysis of tissue samples from patients with depression demonstrated that mRNA expression of 5α-reductase type I is downregulated in Brodmann's area 9 (BA9) of the prefrontal cortex (Agís-Balboa et al., 2014). In patients that received antidepressant treatment, allopregnanolone levels in BA9 were significantly increased when compared to those with depression that went untreated (Agís-Balboa et al., 2014). To further probe this mechanism, in vitro studies utilizing rat and

human purified 3α-HSD isoforms to evaluate the impact of SSRIs on neurosteroid synthesis revealed that fluoxetine, sertraline, and paroxetine directly decrease the affinity for 3α-HSD to the substrate DHP. This occurrence indicates that SSRIs influence neurosteroidogenesis by shifting the preference of 3α-HSD to favor its reductive reaction to convert DHP to allopregnanolone (Griffin & Mellon, 1999). These findings thus indicate that neurosteroid synthesis after SSRI treatment may contribute to the mechanism underlying the effectiveness of these therapies to aid in alleviating mood symptoms in individuals with affective disorders. To further support this hypothesis, low dose treatment with SSRIs like fluoxetine that are not sufficient to fully block serotonin reuptake, are sufficient to recover brain levels of neurosteroids and improve mood symptoms such as aggression (Pinna et al., 2003). Such findings emphasize an important mechanism of antidepressant action outside of the monoamine hypothesis of depression, to alleviate mood symptoms through normalizing neurosteroid synthesis.

In men and women, midlife (40–70 years of age) marks a downward shift in levels of neurosteroids (Figure 2). For one of the most abundant neurosteroids, dehydroepiandrosterone (DHEA), this decrease has been reported at a rate of 1–4% per year until ~80 years of age when levels begin to remain steady (Muller et al., 2003; Tannenbaum et al., 2004). Midlife also marks a period of vulnerability for many agerelated psychiatric illnesses that may be driven in part by this shift in neurosteroid production (Muller et al., 2003; Tannenbaum et al., 2004). Additionally, it has been demonstrated that DHEA levels are lower in individuals with a history of major depressive disorder and may be utilized as a predictive biomarker in individuals experiencing their first episode of depression (Agorastos et al., 2023). Previous clinical trials utilizing a sixweek treatment protocol with DHEA indicated a reduction in depressive-symptoms in individuals with midlife-onset depression (Schmidt et al., 1996, 2005). Replacement therapy with DHEA has been shown to not only be capable of restoring serum levels of neurosteroids but also improved overall mood and depression symptoms (Binder et al., 2009; Bloch et al., 2012; Morales et al., 1994; Wolkowitz et al., 1997, 1999). These findings indicate that exogenous neurosteroid treatment may be effective for both reproductive and non-reproductive mood disorders.

2.1.3. PTSD—In individuals with posttraumatic stress disorder (PTSD), deficits in emotional-processing and emotional-regulation can be attributed in part to hyperactivation of brain regions that govern emotional regulation, including the prefrontal cortex, amygdala, insula, and anterior cingulate (Sripada, King, et al., 2012). Exogenous neurosteroid treatment in individuals with PTSD decreased neuronal activity in the amygdala and insula, while increasing activity in the prefrontal cortex and rostral anterior cingulate cortex (Sripada, Marx, et al., 2012). Such findings demonstrate the ability of exogenous neurosteroid treatments to impact neural circuits that govern emotional regulation. While one clinical trial utilizing Ganaxalone, a neuroactive allopregnanolone analog, failed to show efficacy in individuals with PTSD, the dosing of Ganaxalone may have been below the necessary therapeutic level (Rasmusson et al., 2017).

There are known sex differences in the alterations of neurosteroids in male and female individuals with PTSD (Rasmusson et al., 2006, 2019). In women with PTSD, deficits

in CSF levels of allopregnanolone are apparent without changes in progesterone or 5α-DHP levels, indicating an impairment in synthesis through the 3α-HSD enzyme (Rasmusson et al., 2006). Conversely, in men with PTSD, whose 3α-HSD function was not impacted, deficits in CSF levels of allopregnanolone as well as pregnanolone levels were nonetheless observed, indicating an impairment in synthesis through the 5α-reductase enzyme (Rasmusson et al., 2019). In a separate study, men with PTSD from two independent cohorts were found to have decreased allopregnanolone levels (Marx, 2018). Pregnenolone treatment in these individuals improved the primary behavioral endpoints in this study and correlated with a potential enhancement of white matter integrity (Marx, 2018). These results are supported by the findings of a functional gene variant of 5α-reductase type II that has been shown to exert influence on PTSD risk and symptom severity only in men (Gillespie et al., 2013). Further, these studies highlight the ability of exogenous neurosteroid treatment to reverse the circuit level neuropathology observed in psychiatric diseases (for review see (Almeida et al., 2021; Rasmusson et al., 2022)).

2.1.4. Bipolar Disorder—Emotional lability is a hallmark symptom of bipolar disorders (i.e., cyclical shifts of manic or hypomanic episodes and depressive states). During active depressive states in individuals with bipolar disorder, it has been demonstrated that CSF levels of pregnenolone are reduced compared to individuals without an affective illness (George et al., 1994). An association has been made between a single nucleotide polymorphism in the gene encoding TSPO in individuals with bipolar disorder that may lead to impaired neurosteroidogenesis (Colasanti et al., 2013). Low serum progesterone levels were also found to be associated with a single nucleotide polymorphism in the gene AKR1C4 that encodes for the steroidogenic enzyme 3α-HSD in men with a history of manic or hypomanic irritability; the effect was not found in females with similar diagnoses (Johansson et al., 2011). This resulting functional missense mutation may increase the risk for developing manic or hypomanic irritability, as it impairs the conversion of progesterone to allopregnanolone, resulting in less anxiolytic capacity of neurosteroid signaling during states of intense mood shifts. Conversely, in women with the same AKR1C4 missense mutation, elevated serum progesterone levels have been reported that were shown to be protective against paranoia in women with bipolar disorder during manic or hypomanic episodes. These studies also identified a mutation in the HSD3B2 gene, which encodes for the steroidogenic enzyme 3β-HSD, that was shown to be associated with an increased risk of paranoid ideation (Johansson et al., 2012).

Individuals with bipolar disorder have been demonstrated to have the highest rate of comorbid substance use disorders, with cannabis being the most abused drug (Leweke & Koethe, 2008). In bipolar depressed individuals, it has been demonstrated that previous cannabis use disorders were associated with increased basal CSF levels of pregnenolone while allopregnanolone levels were attenuated (Mason et al., 2017). These findings suggest that prior cannabis use may increase risk for bipolar disorder through preferencing neurosteroidogenesis to pregnanolone synthesis over allopregnanolone. In a randomized, double-blind, placebo-controlled trial in which individuals with bipolar disorder received 500mg of pregnenolone per day, those with bipolar disorder reported significantly reduced depressive symptoms as determined by the Hamilton Rating Scale for Depression (Brown

et al., 2014; Hamilton, 1960). Furthermore, administration of pregnenolone increased serum levels of allopregnanolone, pregnenolone, and pregnanolone from baseline measurements, which may have contributed to the higher rate of symptom remission post-treatment (Brown et al., 2014). Consistent with the proposed efficacy of exogenous neurosteroids in the treatment of symptoms present in bipolar disorder, treatment with atypical antipsychotics (i.e. olanzapine, clozapine, and lithium), increase levels of pregnenolone and allopregnanolone (Marx et al., 2008; Marx, Shampine, et al., 2006). The resulting increase in neurosteroid levels may contribute to the efficacy of these therapies in stabilizing mood (for review see ((Carta et al., 2012)).

2.1.5. Schizophrenia—Neurosteroids have been linked to the pathology of schizophrenia (for review see (Cai et al., 2018; Michele et al., 2008; Ritsner, 2010)). Two brain regions that have been indicated for hypofunction and grey matter deficits in first-episode and progressive schizophrenia are the posterior cingulate cortex and the parietal cortex (Liang et al., 2020; Mitelman et al., 2005; Northoff et al., 2005). Post-mortem analysis of neurosteroid levels in individuals with schizophrenia demonstrated that pregnenolone and DHEA levels were higher in the posterior cingulate and parietal cortex, compared to individuals without a psychiatric diagnosis (Marx, Stevens, et al., 2006). Allopregnanolone levels in the parietal cortex were found to be decreased in individuals with schizophrenia (Marx, Stevens, et al., 2006). Treatment with neurosteroids have been shown to alleviate negative, depressive, and anxiety symptoms in individuals with schizophrenia. In several studies, individuals diagnosed with schizophrenia that received DHEA or pregnenolone treatment in addition to their regular antipsychotic medication demonstrated significant improvements in negative, anxiety, and depressive symptoms without varying impact on cognitive and positive symptoms associated with schizophrenia (Marx et al., 2017; Marx et al., 2009; Ritsner et al., 2014; Strous et al., 2003). These individuals had an increase in plasma neurosteroid levels that correlated with their improvement in negative symptoms (Marx et al., 2017; Marx et al., 2009; Strous et al., 2003). A separate study evaluating the impact of add-on treatment with pregnenolone to improve neurocognitive dysfunction in individuals with schizophrenia found that pregnenolone significantly reduced deficits in visual attention, sustained attention, and executive functioning (Kreinin et al., 2017). These improvements were demonstrated to occur independent of the type of antipsychotic therapy individuals were also taking or the duration of their illness (Kreinin et al., 2017). Interestingly, similar to treatment in bipolar disorder, it has been noted that second-generation antipsychotics such as clozapine, increase neurosteroid levels, an effect which may contribute to their efficacy for both positive and negative symptoms of schizophrenia (Barbaccia et al., 2001; Marx et al., 2003; Marx, Shampine, et al., 2006).

2.1.6 5α-reductase Deficiency and Post-Finasteride Syndrome—In 1974, an article was published detailing the impact of a genetic mutation found in a group of children leading to deficiencies in 5α-reductase and dihydrotestosterone. Further studies identified that 5α-reductase type 2 is the primary isozyme absent in these individuals with no significant impairment in the expression or function of 5α-reductase type 1. Males with this mutation present with ambiguous sexual features until maturity when they present with prostate hypoplasia. Additional studies identified that these individuals do not develop

androgenic alopecia, also known as male pattern hair loss. This discovery prompted interest in the development of 5α-reductase inhibitors for the treatment of both androgenic alopecia and prostate hyperplasia.

Currently there are two 5α-reductase inhibitors that are FDA-approved for the treatment of benign prostate hyperplasia and androgenic alopecia. The first in this class, Finasteride (Propecia™ or Proscar™), is a competitive 5α-reductase inhibitor with preferential inhibition of the type 2 isozyme. The second, Dutasteride (Avodart™), is a selective inhibitor for both type 1 and type 2 isozymes. Several side effects have been noted in individuals that received these therapies, even after discontinuation of the drug, including anxiety, depression, and suicidal ideation (Ganzer et al., 2014; Irwig, 2012; Melcangi et al., 2017; Rahimi-Ardabili et al., 2006; Traish et al., 2015), now termed post-finasteride syndrome (for review see (Diviccaro et al., 2019)). CSF measurement in individuals that discontinued treatment with finasteride conclude that 5α-reduced neurosteroids remained altered in these individuals which is considered to contribute to the pathology of their mood symptoms (Caruso et al., 2015; Melcangi et al., 2013, 2017) (Figure 3).

2.2. Preclinical evidence

2.2.1. Preclinical Models Relevant to Anxiety—Neurosteroids have also proven efficacious in improving affective deficits observed in preclinical models. To measure affective responses in rodents, several behavioral tasks are utilized such as the forced swim test, tail suspension test, open field, light/dark box, and elevated plus maze test (Cryan et al., 2002). In the forced swim test, experimenters place a rodent individually into a cylinder filled with water and measure the amount of time the rodent remains mobile as a proxy for antidepressant responsiveness (Porsolt et al., 1977). Use of exogenous neurosteroids has been shown to increase the total time rodents remain mobile in the forced swim test indicating an antidepressant response of these compounds (Frye et al., 2004; Frye & Walf, 2002; Khisti et al., 2000; Khisti & Chopde, 2000; Martínez-Mota et al., 1999). In open field testing, anxiety behavior has been inferred from the lack of avoidance behaviors measured as the number of entries and time spent in the center of the chamber. After receiving exogenous neurosteroids, rodents display less avoidance behaviors, performing more center entries and spending more time in the center of the chamber (Antonoudiou et al., 2022; Frye et al., 2004; Wieland et al., 1991). Opposingly, rodents treated with finasteride display behaviors consistent with increased anxiety and depressive responses when subjected to the forced swim and open field tests (Frye & Walf, 2002). In the light/dark box the number of transitions an animal makes between the light and dark chambers is also a measure of avoidance behaviors and used as a proxy for anxiety behaviors, whereby an increase in transitions signifies anxiolytic behavior. Following neurosteroid exposure, rodents are observed to have a decrease in anxiogenic behavior demonstrated by an increase in light/dark chamber transitions (Wieland et al., 1991). Similar results are seen in the elevated plus maze following neurosteroid treatment, where rodents display more anxiolytic behavior demonstrated by spending more time in the open arm of the maze (Frye et al., 2004). Additionally, these anxiolytic effects of exogenous neurosteroids are seen in rodents that have been devoid of peripheral neurosteroid secretion, an effect associated with dose-dependent increases in brain levels of neurosteroids (Bitran et al., 1993). Cumulatively, these

studies suggest that treatment with exogenous neurosteroids have behavioral effects in part due to their ability to modulate endogenous neurosteroid levels. Another preclinical measure of rodent behavior is the Geller-Seifter conflict paradigm, in which rodents are subjected to an operant chamber that produces a reward followed by increasing amplitudes of foot shocks (Pollard & Howard, 1979). After receiving exogenous neurosteroids, rodents demonstrate an increase in anti-conflict behaviors measured as an increase in lever pressing for a reward despite the conflict of being shocked (Brot et al., 1997).

2.2.2 Preclinical Models Relevant to Depression—Chronic stress is a known precipitating factor in the emergence of depressive disorders and has been utilized in several preclinical protocols to induce behavioral deficits similar to the symptoms manifest in depression (for review see (Willner, 1984, 1990)). In work from our laboratory and others using rodent models of depression, allopregnanolone levels in the amygdala and frontal cortex have been demonstrated to decline (Uzunova et al., 2003; Walton et al., 2023). Coinciding with the decline in allopregnanolone, 5α-reductases have also been demonstrated to be reduced in the amygdala following chronic stress (Walton et al., 2023). Though acute stress has shown to briefly elevate neurosteroid levels (Purdy et al., 1991), several models of chronic stress have demonstrated deficits in neurosteroids that may contribute to the emergence of affective disorders (Dong et al., 2001; Walton et al., 2023). The use of exogenous neurosteroids has also been shown to prevent the behavioral deficits posed by chronic stress by lowering anxiety and avoidance behavioral measures (Antonoudiou et al., 2022; Evans et al., 2012; Walton et al., 2023). If treatment occurred after the period of chronic stress, the use of exogenous neurosteroids was capable of restoring behavioral measures to baseline outcomes (Antonoudiou et al., 2022; Evans et al., 2012).

2.2.3. Preclinical Models Relevant to PTSD—It has been demonstrated that neurosteroid biosynthesis is disrupted in several corticolimbic brain regions in preclinical rodent models of PTSD (for review see (Almeida et al., 2021; Aspesi & Pinna, 2019; Guidotti et al., 2001; Locci & Pinna, 2019b; Pinna, 2018)). Social isolation has been proven to induce enhanced contextual fear, impaired contextual fear extinction, as well as symptoms of anxiety and depression (Locci & Pinna, 2019a; Pibiri et al., 2008; Pinna et al., 2003; Rau et al., 2005). Following protracted social isolation, pregnenolone, 5α-DHP, 5α-reductase type I, and allopregnanolone are decreased in the frontal cortex as compared to group housed mice (Dong et al., 2001; Serra et al., 2000). Socially isolated mice also exhibit a downregulation of 5α-reductase type I in layer v-vi, CA3, dentate gyrus, and BLA, as well as a downregulation of 3α-HSD in the dentate gyrus (Agís-Balboa et al., 2007).

Treatment with neurosteroids prior to exposure of a traumatic event is protective against anxiogenic behaviors in rodent models of PTSD (Bitran et al., 2000). Restoring brain allopregnanolone levels with SSRI treatment (fluoxetine) following protracted social isolation has been demonstrated to reduce aggression that is induced by this model (Pinna et al., 2003). The aggressive phenotype displayed in this model has been attributed in part to reductions in brain levels of allopregnanolone, insofar as the intensity of aggressive behavior is dose-dependently reduced with allopregnanolone (Pinna et al., 2003). Additionally, (S)-norfluoxetine (S-NFLX), an active metabolite of fluoxetine that does not impact

serotonin reuptake, was demonstrated to be more potent than fluoxetine in normalizing brain allopregnanolone levels and further, reduced the enhanced contextual fear-conditioned response that is elicited by social isolation (Pibiri et al., 2008). In preclinical models of PTSD there have also been noted reductions in the $GABA_AR$ signaling, demonstrated by a reduction in their responsiveness to GABA agonists and a decrease of α1, α2, and γ2 subunits with an increase in α4 and α5 subunits (Matsumoto et al., 2009). These changes in $GABA_AR$ subunit assembly may be attributed to the downregulation of allopregnanolone synthesis that occurs during social isolation. It has been demonstrated that $GABA_AR$ positive allosteric modulation with benzodiazepines (midazolam), which are commonly used to treat anxiety, enhances long term potentiation in the hippocampus through a mechanism dependent on neurosteroid signaling (Tokuda et al., 2010). Collectively, these findings further establish the ability of exogenous neurosteroids to impact anxiogenic behaviors in rodents and support the role of neurosteroids in maintaining affective tone despite known precipitating factors for psychiatric illnesses like PTSD.

2.2.4. Preclinical Models Relevant to Bipolar Disorder—Historically, lithium has been the gold standard in treatment for bipolar I and II to prevent manic/hypomanic and depressive episodes (Volkmann et al., 2020). In rodents, exposure 10 days of lithium treatment was demonstrated to lower brain levels of DHEA in the frontal cortex and hippocampus (Maayan et al., 2004). Serum levels of DHEA were also found to be impaired following lithium treatment (Maayan et al., 2004). Conversely, serum levels of allopregnanolone and pregnenolone were demonstrated to increase following lithium treatment. Other mood stabilizers including clozapine and olanzapine, which are also used for the treatment of bipolar disorder, have been shown to increase levels of pregnenolone in the rat hippocampus, cerebral cortex, and serum (for review see (Carta et al., 2012).

2.2.5. Preclinical Models Relevant to Schizophrenia—The stress-diathesis model provides one explanation for the increased vulnerability to the development of schizophrenia in individuals that have been chronically exposed to stressors during development (Walker & Tessner, 2008). This model has been applied in rodents utilizing isolation rearing, where rodents are subjected to chronic social deprivation from weaning until adulthood. Following isolation rearing, neurosteroids have also been found to be impacted through impairment of 5α-reductase synthesis (Paba et al., 2011). Additionally, rodents exhibit several behavioral and biochemical aberrations that are observed in individuals with schizophrenia, including: hyper-reactivity to a novel environment, impaired sensorimotor gating, anxiogenic-behaviors, anhedonia, cognitive deficits, and excess dopamine secretion (for review see (Fone & Porkess, 2008; Walker, 1994)) (Figure 3).

Dopamine hyperactivity has also been indicated in schizophrenia (for review see (Howes & Kapur, 2009), a condition in which individuals have difficulty filtering sensorimotor stimuli to effectively respond to the environment. Sensorimotor gating may be measured using prepulse inhibition (PPI) where rodent motor responses are measured during a first introduction to a weak acoustic stimulus preceding a startle-inducing acoustic stimulus. Dopaminergic agonists have been shown to produce deficits in PPI, where subsequent exposure to a startle-inducing stimulus results in a lower startle amplitude (Bortolato et

al., 2008; Frau et al., 2014). Inhibition of 5α-reductase by finasteride blocks the effects of dopaminergic agonists on PPI (Bortolato et al., 2008; Frau et al., 2014). Following treatment with finasteride, reversal of PPI deficits induced by dopamine agonists was only effective after use of a D1 agonist (Frau et al., 2014). The contribution of dopamine receptors in mediating these effects of impaired 5α-reductases is further discussed in the below section titled: “Proposed mechanisms mediating effects of 5α-reduced neurosteroids on affective tone”.

3. Proposed mechanisms mediating the effects of 5α-reduced neurosteroids on affective tone

3.1. Ionotropic

In the mammalian brain, $GABA_A$-receptors ($GABA_A$Rs) mediate most of the inhibitory control over neurotransmission (Ghit et al., 2021; Michels & Moss, 2007). $GABA_A$Rs are heteropentameric ligand gated chloride ion selective channels, composed of five subunit variants from 19 subunit isoforms (α1–6, β1–3, γ1–3, δ, ε, q, π, and r1–3). $GABA_A$R subunit composition expression varies throughout neuronal circuits, with both regional and neuronal specificity (Michels & Moss, 2007; Nakamura et al., 2015). Compositional diversity of $GABA_A$Rs differs between synaptically or extrasynaptically located receptors and further, determines the biophysical responses of these receptors to pharmacological manipulations and therefore their downstream impacts on behavior (Michels & Moss, 2007).

Finasteride has been demonstrated to prevent the estrous cycle-related changes in GABAergic inhibition, suggesting that these effects are mediated by endogenous neurosteroids (Maguire & Mody, 2007). Proteomic analyses indicate that treatment with finasteride results in dysregulation of pathways involved in GABA synthesis and degradation, synaptic transmission, fatty acid metabolism and steroid biosynthesis (Soggiu et al., 2016). Sub-chronic treatment with finasteride followed by withdrawal has been shown to induce downregulation of both α4- and β3-subunit containing $GABA_A$Rs in the cerebral cortex in conjunction with a downregulation of estrogen receptor-α and −β (Giatti et al., 2016). The effects of finasteride on the downregulation of β3-subunit containing $GABA_A$Rs was also observed in the gut following finasteride withdrawal (Diviccaro et al., 2022). These findings support the notion that endogenous neurosteroids impact $GABA_A$Rs, which may contribute to their influence over affective tone.

Nonsulfated 5α-reduced neurosteroids act as positive allosteric modulators of $GABA_A$Rs, increasing the frequency and duration of ion channel opening (Akk et al., 2005). Neurosteroid access to intracellular $GABA_A$Rs is largely via lateral membrane diffusion; however, they are also capable of binding to $GABA_A$Rs upon extracellular membrane sites (Akk et al., 2005). These actions by neurosteroids have been demonstrated to occur at low nanomolar (~10nM) concentrations in the presence of GABA, through a highly conserved binding site on α- subunits, however, in the absence of GABA, neurosteroids at micromolar concentrations have been shown to directly activate $GABA_A$Rs through a binding site at the interphase of α/β subunits (Chen et al., 2019; Hosie et al., 2006). Neurosteroid sensitivity for $GABA_A$Rs is influenced by $GABA_A$R subunit composition (Akk et al., 2005,

2008; Belelli & Lambert, 2005; Hosie et al., 2006). Specifically, extrasynaptic δ-subunit containing $GABA_A$Rs are more sensitive to neurosteroid modulation in comparison to synaptically located γ-subunit containing $GABA_A$Rs (Belelli & Lambert, 2005; Carver & Reddy, 2016; Reddy, 2018). In addition to their extrasynaptic location, δ-subunit containing $GABA_A$Rs also differ from γ-subunit containing $GABA_A$Rs by their contribution to a tonic inhibition firing pattern, activated by low concentrations of GABA (Mody & Pearce, 2004). This contrasts with benzodiazepines, classically used for treatment of anxiety and depressive disorders, which bind to $GABA_A$Rs at the interphase between α1–3, α5 and γ subunits yet α4/6 containing receptors are insensitive to benzodiazepines (Morlock & Czajkowski, 2011; Richter et al., 2012). Fluctuations in expression of δ-subunit containing $GABA_A$Rs have been noted across estrous states as well as in affective disorders including postpartum depression, major depression, and anxiety disorders (Gilfarb & Leuner, 2022; Lüscher & Möhler, 2019; Maguire et al., 2005). Many of these fluctuations have been demonstrated to occur in concert with changing neurosteroid levels, suggesting that impairments in GABAergic functioning and neurosteroid signaling may underlie some of the neuropathology of affective disorders.

3.2. Metabotropic

3.2.1. Membrane Progesterone Receptors—5α-reduced neurosteroids also act upon receptors of the progestin and adipoQ receptor (PAQR) family, which are a g-protein coupled receptor family comprised of membrane progesterone receptors (mPRs) (Pang et al., 2013; Rupprecht et al., 1993). Neurosteroid binding of mPRs activates a signaling cascade that promotes the surface expression of α4βδ-containing $GABA_A$Rs (Abramian et al., 2014; Davies et al., 2017; Parakala et al., 2019). This has been shown to occur via the phosphorylation of a key regulatory residue, serine 408/409, in the β3 subunit (Modgil et al., 2017; Parakala et al., 2019). Along with the induction of cell surface expression, neurosteroid phosphorylation of the β3 subunit has been demonstrated to potentiate GABAergic inhibition (Modgil et al., 2017; Parakala et al., 2019). Evidence supports that these metabotropic actions of neurosteroids aid in facilitating anti-apoptotic actions in brain regions that coordinate emotional responses (i.e., hypothalamus, amygdala, pituitary gland, forebrain, and corpus callosum), where mPRs are abundantly expressed (Pang et al., 2013). These metabotropic actions highlight the potential for neurosteroids to impact affect tone through the preservation of cell circuits that facilitate emotional responses.

3.2.2. Mesolimbic dopamine system—Neurosteroids have been demonstrated to modulate the dopaminergic mesolimbic system (Dornellas et al., 2021; Mosher et al., 2019). In rodents treated with finasteride, increased anxiety-like behaviors in the open field where correlated with decreased dopamine synthesis in the frontal cortex, hippocampus, caudate putamen, and nucleus accumbens (Li et al., 2018). As previously mentioned, dopamine hyperactivity has been indicated in psychiatric illnesses such as schizophrenia, and results in impaired rodent responses to PPI. While treatment with finasteride was demonstrated to reverse the deficits of PPI induced by dopamine agonists, this was shown only to be effective with use of a D1 agonist (Frau et al., 2014). These effects were not seen following use of a selective D2 agonist or with the use of a non-selective D1/D2 agonist, indicating that

finasteride effects sensorimotor gating primarily through D1 receptors (Frau et al., 2014). Further investigation has also identified the role of finasteride in reversing the effects of the dopaminergic agonist, pramipexole, that has high selectivity for D3 receptors and a lesser affinity for D2 receptors (Floris et al., 2022). Finasteride reversed the pramipexole-induced upregulation of D3 receptors in the nucleus accumbens (Floris et al., 2022). D1 and D3 receptors are known to form complexes that increases the affinity of dopamine. Following finasteride treatment, coimmunoprecipitation of D1- and D3-receptor complexes was dampened (Fanni et al., 2019). These actions of finasteride indicate the capacity of impaired synthesis of 5α-reductase in modulating the functional relationship of D1-and D3- receptor complexes and subsequently dopamine signaling through a key brain region involved in the dopamine mesolimbic system.

3.3. Inflammation

In addition to the ability of stress to induce alterations in neurosteroid levels, stress also induces changes in neuroimmune signaling that may contribute to the emergence of psychiatric disease states (Brenhouse et al., 2019; Bullmore, 2018; Walter et al., 2017). Recent studies have indicated that allopregnanolone and pregnenolone are capable of inhibiting neuroimmune signaling by mediating interactions with toll-like receptors (Balan et al., 2019, 2023). Toll-like receptors (TLRs) and their downstream effects on neuroimmune signaling have been previously implicated in the pathology of neuropsychiatric disorders (Liu et al., 2014). TLRs are dependent upon adaptor proteins including myeloid differentiation primary response 88 (MyD88) and TIR-domain-containing adapter-including interferon-β (TRIF) to activate cytokine and chemokine signaling pathways. Upon lipopolysaccharide (LPS)-mediated activation of neuroimmune signaling, neurosteroids including allopregnanolone and pregnenolone inhibit the levels of proinflammatory mediators (i.e. high mobility group box-1 (HMGB1), monocyte chemoattractant protein-1 (MCP-1), and tumor necrosis factor alpha (TNFα)) in addition to transcription factors (i.e. the p50 subunit of nuclear factor kappa B (NF-kB p50), (phosphorylated p65 subunit of nuclear factor kappa B (pNF-kB p65), phosphorylated cyclic-AMP response element binding protein (pCREB), phosphorylated transforming growth factor-β-activated kinase-1 (pTAK1), and tumor necrosis factor receptorassociated factor 6 (TRAF6)) (Balan et al., 2019). These effects have been shown to be due in part by the ability of these neurosteroids to prevent the TLR4/MD-2 complex, which would initiate LPS-mediated TLR4 signaling (Balan et al., 2019). Finasteride has been observed to induce activation of pro-inflammatory mediators in the gut-brain axis following treatment withdrawal. In rodents, 20 days of treatment followed by one month of withdrawal, gut levels of TNFα and Interleukin-1β (IL-1β) were found to be elevated (Diviccaro et al., 2022). Brexanolone was shown to inhibit pro-inflammatory pathways in individuals with postpartum depression (Balan et al., 2023). Specifically, it was demonstrated that following the 60-hour infusion of Brexanolone, TNFα and IL-6 levels were reduced in whole blood samples and were significantly correlated with improvements in HAM-D scores (Balan et al., 2023). Further studies have demonstrated that Brexanolone blunted LPS-induced TLR activation through inhibition of TLR4 and TLR7 (Balan et al., 2023) which is in alignment with previous observations that allopregnanolone inhibits TLR activation through MyD88-dependent signaling and not TRIF signaling (Balan et al., 2021). Collectively these findings highlight a novel mechanism by which

neurosteroids may mitigate neuropsychiatric disease states by dampening pro-inflammatory pathways.

3.4. Network states/Connectivity

Exogenous administration of neurosteroids has been demonstrated to alter network states in amygdalocortical brain regions critical for emotional processing across several species (Antonoudiou et al., 2022). Administration of neurosteroid analogs has been shown to alter the patterns of electroencephalographic (EEG) activity in humans and local field potential recording in rodents, potentiating the power of high theta (6–12Hz) frequency oscillations known to govern safety behavioral responses (Antonoudiou et al., 2022). Interestingly, this network effect on high theta oscillations is distinct from the effects of other positive allosteric modulators of $GABA_A$Rs, suggesting a unique mechanism of action (Antonoudiou et al., 2022). Moreover, the effects on high theta power do not occur in mice lacking δ-subunit containing $GABA_A$Rs, indicating that the ability of neurosteroid analogs to alter oscillations in the theta frequency are mediated through δ-subunit containing $GABA_A$Rs (Antonoudiou et al., 2022).

Neurosteroid actions in limbic brain regions including the amygdala have previously been shown to mediate anxiolytic and antidepressant effects (Antonoudiou et al., 2022; Walton et al., 2023). Exogenous administration of neurosteroids either directly to the amygdala or systemically result in changes in connectivity within the amygdala as well as the regions to which it projects (Antonoudiou et al., 2022; Sripada et al., 2014; Van Wingen et al., 2008). Cortical thickness and associated disruptions in connectivity have been associated with multiple psychiatric disorders (Paus, 2021). In disorders where neurosteroid levels are impaired, there have been observed correlations in the degree of cortical thickness to serum neurosteroid levels such that a higher degree of cortical thinning and symptom severity tracks with lower levels of neurosteroids (Kinzel et al., 2020). Chronic stress has also been shown to induce brain wide alterations in network connectivity (Antonoudiou et al., 2022; Negrón-Oyarzo et al., 2016; Woo et al., 2021). These alterations are prevented with the treatment of exogenous neurosteroids during the experience of chronic stress, suggesting that neurosteroids may coordinate network activity through multiple brain regions that are necessary to maintain affective tone.

4. Therapeutic Potential of Targeting Endogenous Neurosteroidogenesis

As highlighted in this review and others, endogenous neurosteroidogenesis has been indicated in the neuropathology of several psychiatric illness (for further review see (Pinna, 2020; Porcu et al., 2016; Walton & Maguire, 2019)). Treatment with neurosteroids or pharmacological treatments (i.e., antidepressants, antipsychotics, and mood stabilizers) that increase neurosteroid levels (Table 2) have demonstrated efficacy in improving symptoms of psychiatric illnesses. This suggests that neurosteroids may contribute to the therapeutic efficacy of these treatments, in addition to potentially contributing to the underlying neuropathology of these illnesses. Known precipitating factors to the emergence of psychiatric illnesses such as social isolation and chronic stress have been shown to elicit deficits in neurosteroids. Importantly, many of these induced deficits in neurosteroidogenesis

have been discovered in brain regions that mediate emotional responses, suggesting a key role for neurosteroids in maintaining affective tone.

Most reports on the impact of neurosteroids have been based on the use of exogenous neurosteroids or their inhibitors. Recently, it was demonstrated that increasing neurosteroidogenesis by directly overexpressing 5α-reductases is sufficient to ameliorate behavioral deficits that are induced by chronic stress (Walton et al., 2023). These findings further support the role of endogenous neurosteroids in maintaining affective tone reinforce the potential of targeting neurosteroidogenesis for treatment of several affective illnesses. Harnessing the body's ability to synthesize endogenous neurosteroids offers a superior therapeutic approach, ensuring synthesis and delivery at the endogenous site of action, largely in limbic regions, limiting off target and unwanted side effects. Future studies are required to explore this promising, novel therapeutic avenue.

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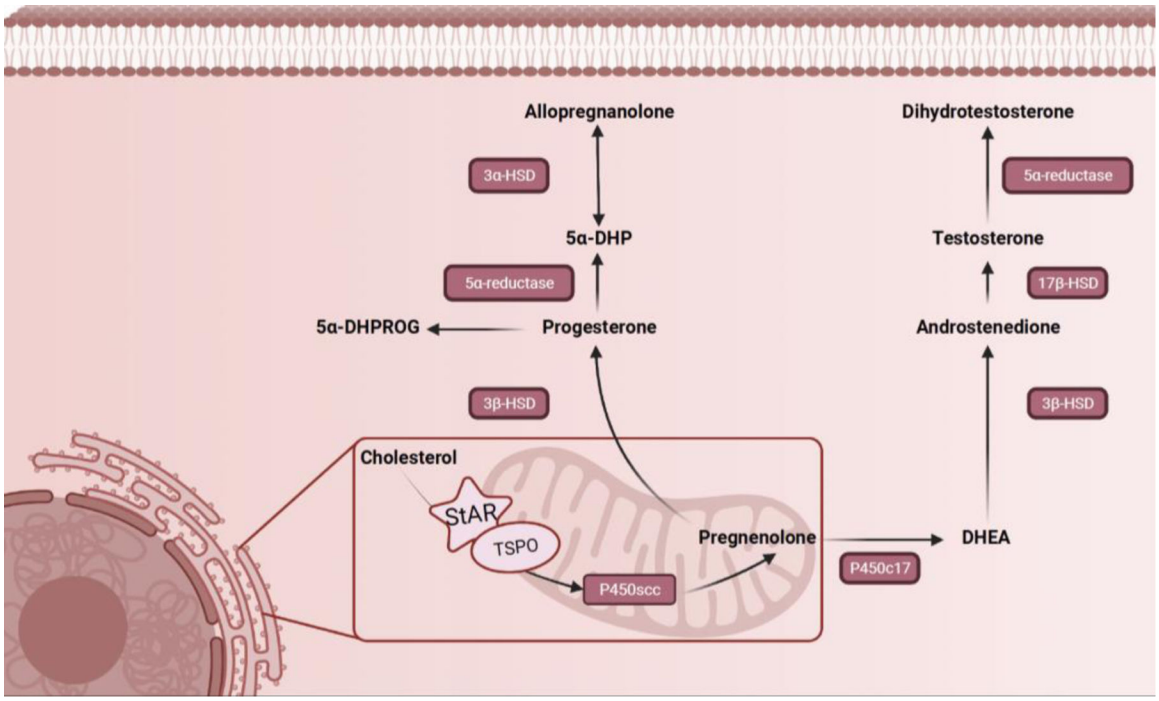

Figure 1. 5α-reduced neurosteroid synthesis.

Illustration of the synthesis pathway for 5α-reduced metabolites of progesterone described in this review.

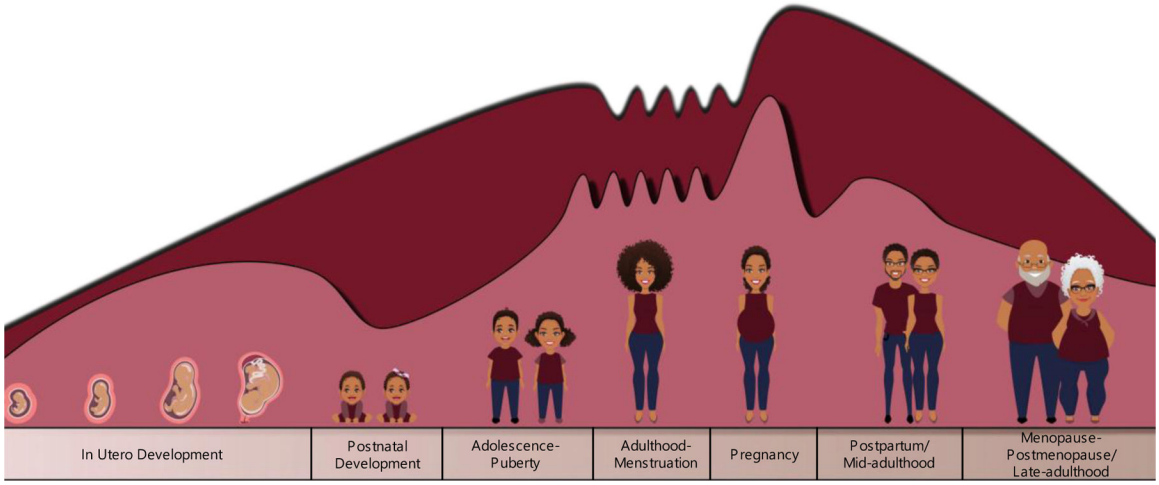

Figure 2. Neurosteroid and $GABA_AR$ expression across the lifespan.

Illustration of the relative fluctuation of neurosteroid and $GABA_AR$ expression across the lifespan. These fluctuations also occur in men with a downward shift in neurosteroid expression occurring in mid-adulthood. (for review see Muller et al. 2003; Tannenbeaum et al. 2004; Mellon & Griffin, 2002; Gilfarb and Leuner, 2022; Maguire and Mody, 2008).

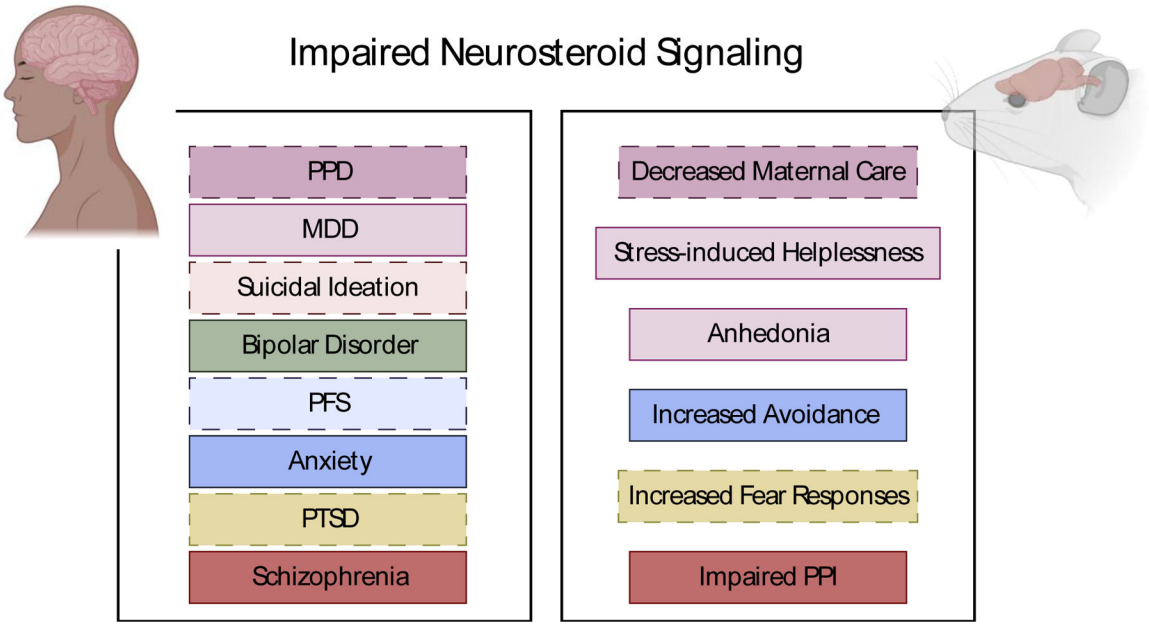

Figure 3. Clinical and Preclinical Consequences of Impaired Neurosteroid Signaling.
Descriptions of preclinical and clinical symptoms associated with impaired neurosteroid levels.

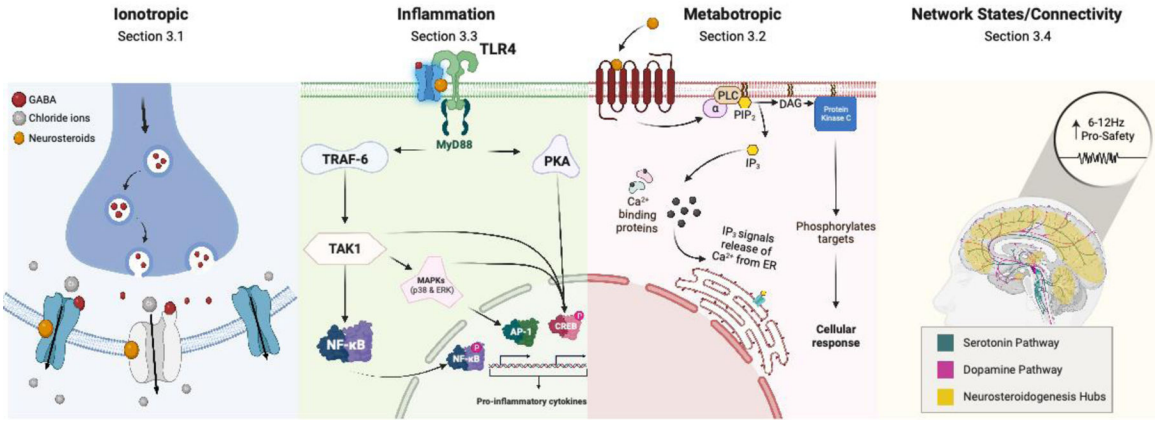

Figure 4. Mechanisms Mediating 5α-reduced neurosteroids on affective tone.

Illustration depicting the mechanisms highlighted in this review whereby 5α-reduced neurosteroids may impact affective tone. *Abbreviations:* Toll-like Receptor 4 (TLR4), myeloid differentiation primary response 88 (MyD88), tumor necrosis factor receptor-associated facto- 6(TRAF-6), protein kinase A(PKA), phosphorylated cyclic-AMP response element binding protein(pCREB), transforming growth factor-b-activated kinase-1(TAK1), nuclear factor kappa B(NF-kβ), phosphorylated nuclear factor kappa B(pNF-kβ), mitogen-activate protein kinases(MAPKs), activator protein-1(AP-1), phospholipase C(PLC), phosphatidylinositol 4,5-biphosphate(PIP_2), diacylglycerol(DAG), inositol triphosphate(IP_3), Calcium(Ca^{2+}), Endoplasmic Reticulum(ER).

Table 1.

List of neurosteroids and analogs described in this review

Steroids/Neurosteroids
Pregnenolone
Progesterone
Dihydroprogesterone (5a-DHP)
5a-Dihydroprogesterone (5a-DHPROG)
Allopregnanolone (ALLO)
Dehydroepiandrosterone (DHEA)
Androstenedione
Testosterone (T)
Dihydrotestosterone (DHT)
Neurosteroid Analogs
Zuranolone (SAGE-217)
ZULRESSO® (Brexanolone)
Ganaxolone

Table 2.

Pharmacological treatments interact with neurosteroid synthesis.

MEDICATION	CLASS	INDICATION	IMPACT ON 5a-REDUCED NEUROSTEROIDS	REFERENCE
		ANTIDEPRESSANTS		
AMITRIPTYLINE	Tricyclic	MDD *Off-label*: anxiety, insomnia, treatment-resistant depression	+	(Jaworska-Feil et al., 2000)
DOXEPIN	Tricyclic	MDD, insomnia *Off-label*: anxiety	?	
IMIPRAMINE	Tricyclic	MDD *Off-label*: insomnia	no effect	(Haduch et al., 2011; Uzunov et al., 1996; Guidotti & Costa, 1998)
TRAZODONE	Atypical	MDD *Off-label*: insomnia, anxiety	+	(Korade et al., 2017)
MIRTAZAPINE	Atypical	MDD *Off-label*: panic disorder, GAD, PTSD	+	(Schüle et al., 2006)
FLUOXETINE	SSRI	MDD, OCD, panic disorder, treatment-resistant depression, acute depression in Bipolar I disorder, PMDD. *Off-label*: social anxiety disorder and PTSD	+	(Griffin & Mellon, 1999; Guidotti & Costa, 1998; Pinna et al., 2003; Uzunova et al., 1998; Guidotti & Costa, 1998)
PAROXETINE	SSRI	MDD, OCD, GAD, PTSD, social anxiety disorder, PMDD	+	(Griffin & Mellon, 1999; Alessandr o Guidotti & Costa, 1998)
SERTRALINE	SSRI	MDD, panic disorder, OCD, PTSD, social anxiety disorder, PMDD *Off-label*: GAD	+	(Griffin & Mellon, 1999)
CITALOPRAM	SSRI	MDD *Off-label*: PMDD, OCD, panic disorder, GAD, PTSD, social anxiety disorder	?	
ESCITALOPRAM	SSRI	MDD, GAD *Off-label*: panic disorder, OCD, PTSD, social anxiety disorder, PMDD	+	(Haduch et al., 2011)
VENLAFAXINE	SNRI	MDD, GAD, social anxiety disorder *Off-label*: PMDD	+	(Haduch et al., 2011)
DESVENLAFAXINE	SNRI	MDD	?	
DULOXETINE	SNRI	MDD, GAD	?	
BUPROPION	Atypical	MDD, Seasonal affective disorder	?	
PHENELZINE	“Irreversible” MAOI	MDD, treatment-resistant depression	?	
ISOCARBOXAZID	“Irreversible” MAOI	MDD	?	
TRANYLCYPROMINE	“Reversible” MAOI	MDD *Off-label*: treatment-resistant depression, social anxiety disorder, panic disorder, atypical depression	?	
SELEGILINE	“Reversible” MAOI	MDD	?	
BREXANOLONE	Neurosteroi d Analog	PPD	+	(Balan et al., 2023)
KETAMINE	Dissociative Anesthetic	Treatment-resistant depression	+	(Korneyev et al., 1993; Li et al., 2016)

MEDICATION	CLASS	INDICATION	IMPACT ON 5a-REDUCED NEUROSTEROIDS	REFERENCE
		ANXIOLYTICS		
ALPRAZOLAM	Benzodiaza pine	GAD, panic disorder, anxiety associated with depression. *Off-label*: PMS, PMDD, insomnia, adjunct with acute mania, acute psychosis	?	
CHLORDIAZEP OXIDE	Benzodiaza pine	GAD	*?*	
CLONAZEPAM	Benzodiaza pine	Panic disorder *Off-label*: adjunct treatment of acute mania, acute psychosis, or insomnia	no effect	(Korneyev et al., 1993; Tokuda et al., 2010)
DIAZEPAM	Benzodiaza pine	anxiety disorder *Off-label*: insomnia	*+*	(Wolf et al., 2015)
LORAZEPAM	Benzodiaza pine	anxiety disorder *Off-label*: insomnia, panic disorder, adjunct with acute mania or acute psychosis	*?*	
HYDROXYZINE	Antihistamine	Anxiety	*?*	
MADAZOLAM	Benzodiaza pine	Anxiety	*+*	(Dhir & Rogawski, 2012; Tokuda et al., 2010)
ETIFOXINE	Benzooxazine	Anxiety	*+*	(Luc Do Rego et al., 2015; Wolf et al., 2015)
BUSPIRONE	Azapirone	GAD	*?*	
		ANTIPSYCHOTICS		
OLANZAPINE	Thio-Benzodiaze pine	Schizophrenia, Bipolar I Disorder, treatment-esistant depression	*+*	(Marx et al., 2003; Marx, Shampine, et al., 2006)
QUETIAPINE	Dibenzo-Thiazepine Derivative	Schizophrenia, depressive episodes in Bipolar I disorder, adjunctive treatment in MDD	no effect	(Marx, Shampine, et al., 2006)
RISPERIDONE	Benzisoxazole Derivative	Schizophrenia, acute mania/ mixed episodes due to Bipolar I dDsorder, irritability associated with autism spectrum disorder	no effect	(Marx et al., 2003)
ZIPRASIDONE	Benzo-Thiazolyl-Piperazine Derivative	Schizophrenia, acute mania/ mixed episodes due to Bipolar I Disorder	no effect	(Marx, Shampine, et al., 2006)
ARIPIPRAZOLE	Benzisoxazole Derivative	Schizophrenia, Bipolar I Disorder	no effect	(Marx, Shampine, et al., 2006)
CLOZAPINE	Dibenzo-Diazepine	Schizophrenia, suicidality in Schizophrenia	*+*	(Barbacci a et al., 2001; Marx et al., 2003; Marx, Shampine, et al., 2006)
THIOTHIXENE	Thioxanthene Derivative	Schizophrenia	*?*	
THIORIDAZINE	Piperidine Phenothiazine	Schizophrenia. *Off-label*: depression with psychotic features	*+*	(Haduch et al., 2011)
CHLORPROMA ZINE	Dimethylamine Phenothiazine Derivative	Schizophrenia, psychoses, hyperexcitability, combative behavior in children *Off-label*: Bipolar I Disorder	*?*	
HALOPERIDOL	Butyrophen one	Schizophrenia, manic states, drug-induced psychoses, hyperexcitability, agitation	no effect	(Barbaccia et al., 2001; Marx et al., 2003)

MEDICATION	CLASS	INDICATION	IMPACT ON 5a-REDUCED NEUROSTEROIDS	REFERENCE
PALIPERIDONE	Benzisoxazole Derivative	schizophrenia, schizoaffective disorder	*?*	
ASENAPINE	Dibenzo-Oxepino Pyrrroles	schizophrenia, manic/mixed episodes associated with bipolar I disorder	*+*	(Danek et al., 2021)
LURASIDONE	Benzisoxaz ole Derivative	schizophrenia, depressive episodes in Bipolar I disorder	*+*	(Danek & Daniel, 2022)
ILOPERIDONE	Benzisoxaz ole Derivative	schizophrenia	*+*	(Danek & Daniel, 2021)
CARIPRAZINE	Atypical	schizophrenia, acute mania/ mixed episodes due to bipolar I disorder	*?*	
BREXPIPRAZO LE	Serotonin-Dopamine Activity Modulators (SDAM)	schizophrenia, adjunct treatment of MDD	*?*	
		MOOD STABILIZERS		
LITHIUM	Antimanic	Bipolar I Disorder	*+*	(Marx et al., 2008; Maayan et al., 2004)
CARBAMAZEPI NE	Anticonvuls ant	Bipolar I Disorder	*+*	(Eagle et al., 2020; Jaworska-Feil et al., 2000; Yoshizaw a et al., 2020)
DIVALPROEX	Anticonvuls ant	Bipolar Disorder	*?*	
LAMOTRIGINE	Anticonvuls ant	Bipolar Disorder	*?*	

+ indicates evidence of an interaction with the specified drug and neurosteroid synthesis,

? indicates no known evidence of an interaction. Abbreviations: Major Depressive Disorder (MDD), Generalized Anxiety Disorder (GAD), Post Traumatic Stress Disorder (PTSD), Obsessive Convulsive Disorder (OCD), Premenstrual Dysphoric Disorder (PMDD), Postpartum Depression (PPD), Premenstrual Syndrome (PMS).