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Neuroactive steroids role in mood disorders and PTSD☆

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Neurosteroids are steroids that are synthesized in the brain without the aid of peripheral sources (Baulieu, 1997). For steroids, e.g., allotetrahydrodeoxycorticosterone, lacking certain enzymes of the steroid synthesis machinery in the brain but not in the periphery, e.g, the 5α-reductase, which is the first step in the formation of metabolites of progesterone and deoxycorticosterone, the term neuroactive steroids has been coined (Rupprecht and Holsboer, 1999). Especially 3α-reduced neurosteroids such as allopregnanolone are known for decades as powerful allosteroic modulators of γ-aminobutyric acid type A ($GABA_A$) receptors, which may exert anxiolytic and even antidepressant effects in rodent models (Rupprecht and Holsboer, 1999). As such, the question has arisen whether these neurosteroids as endogenous modulators of neuronal excitability contribute to the pathophysiology of mood and anxiety disorders and whether they may even have a therapeutic potential. To address these questions studies have been performed in depressed patients (Romeo et al.,1998, Uzunova et al., 1998) and patients with anxiety disorders (Ströhle et al., 2003) that revealed an altered equilibrium of 3α-reduced neurosteroids which might contribute to the pathophysiology of these disorders. Intriguingly, antidepressants such as selective serotonin reuptake inhibitors (SSRIs) or mirtazapine have been found to directly interact with the 3α-reductase, the second neurosteroidogenic enzyme, by shifting its activity towards reduction, i.e. towards an enhanced synthesis of endogenous 3α-reduced neurosteroids (Griffin and Mellon, 1999; Schüle et al., 2006). As such, interference of antidepressants with the neurosteroid enzyme machinery might also contribute to their mechanisms of action in anxiety disorders.

Another step forward was the discovery of ligands of the translocator protein 18 kDa (TSPO), a mitochondrial channel protein crucial for steroid synthesis (Papadopoulos et al., 2006), as rapidly acting anxiolytics in animals and humans which lack benzodiazepine-inherent side effects such as tolerance development and abuse liability (Rupprecht et al., 2009: Rupprecht et al., 2010). Moreover, etifoxine, a benzoxazine with TSPO and $GABA_A$ receptor affinity, is approved in France for the treatment of anxiety syndromes (Rupprecht et al., 2010, 2022). Finally, the development of brexanolone (Kanes et al., 2018) and zuranolone introduced exogenous neurosteroid application as therapeutics in major depression (Meltzer-Brody et al., 2018) and postpartum depression (Deligiannidis et al., 2021). Meanwhile, brexanolone and zuranolone have been approved for treatment of post partum depression by the FDA (Deligiannidis, Metzer-Body, 2025; Wilson et al., 2025), whereas the approval of zuranolone for major depressive disorder is still pending (Riebel et al., 2024).

The current special issue "Neuroactive steroids and neuropsychiatry" edited by Marco Bartolato and Graziano Pinna contains a cluster of four papers covering the role of neuroactive steroids in mood disorders and PTSD, which highlight recent developments in the field building up on the aforementioned achievements.

The contribution of Leslie Morrow and colleagues focusses on the interplay between neurosteroids and immune cells and their putative involvement in mood disorders and alcohol abuse disorders (Morrow et al., 2024). The described inhibitory effects of neurosteroids on toll-like receptor mediated immune signals constitutes a novel mechanism of action which might contribute to the pathophysiology of these disorders, which show discrete signs of neuroinflammation (Rupprecht et al., 2022) and may even contribute to the therapeutic efficacy of exogenously applied neurosteroids.

The paper of Liisa Hantsoo and Jennifer Payne focuses on the pathophysiology of premenstrual dysphoric disorder (PMDD) (Hantsoo and Payne, 2023). They discuss the differential mode of action of synaptic and extrasynaptic $GABA_A$ receptors and their differential sensitivity to neurosteroids. Clinically, they describe putative differences in $GABA_A$ receptor subunit expression in PMDD, which might contribute to different subtypes of PMDD regarding responsiveness to treatment with SSRIs. These findings are of particular relevance given the recent approval of brexanolone and zuranolone for postpartum depression.

Najah Walton et al. (Walton et al., 2023) review the impact of endogenous and exogenously applied neurosteroids on the affective tone. They underline the importance of the neurosteroid synthesis enzyme machinery and the effects of a broad spectrum of psychopharmacological compounds in this context. Moreover, they point out the importance of neurosteroid regulation also for posttraumatic stress disorder (PTSD) and schizophrenia and of 5α-reductase deficiency.

☆ Neurosteroids in affective disorders: fiction or future?

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PTSD is also the topic of the contribution of Graziano Pinna and colleagues (Pinna et al., 2025). They discuss the equilibrium between inhibitory and excitatory neurosteroids for the pathophysiology, the putative therapeutical impact of TSPO ligands and the potential use of sophisticated neurosteroid profiling as a potential biomarker for PTSD subtypes.

In conclusion, the cluster of papers on neurosteroids and mood disorders summarizes and extends findings on the role of neurosteroids in the pathophysiology of these disorders and their putative therapeutic potential. Given the development of exogenous neurosteroids such as brexanolone and zuranolone together with the putative therapeutic impact of TSPO ligands promoting endogenous neurosteroidogenesis, the neurosteroid field hopefully will put forward innovative neuropsychopharmacological approaches in affective disorders.

Data availability

No data was used for the research described in the article.

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