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Commentary: Neuroactive steroids and the dopaminergic system

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Neuroactive steroids (i.e., steroids directly synthesized in the nervous system or from peripheral glands and affecting nervous function) play important physiopathological roles in the nervous system, such as the modulation of different neurotransmitter systems. Among these, it is interesting to highlight the effects on the dopaminergic system, because this neurotransmitter is crucial for regulating mood, motivation, reward, and motor control. In this special issue dedicated to the role of neuroactive steroids in neuropsychiatry, four different review articles have discussed, in human and animal studies, the interactions between neuroactive steroids and the dopaminergic system. As discussed by Scheggi et al. (2024), neuroactive steroids interact directly or indirectly with the dopaminergic system, modulating release, reuptake, and receptor sensitivity. Alterations of neurosteroid levels and alterations of the dopaminergic system were associated with depression, anxiety, schizophrenia, addiction and gambling disorders, Parkinson's disease, and prenatal cannabis exposure. In particular, as demonstrated in patients with post-traumatic stress disorders or hepatic encephalopathy, low or high levels of allopregnanolone were observed, respectively. These levels correlate with cognitive and behavioral deficits, supporting the role of neurosteroids in these disorders. Indeed, some neurosteroids, like, for instance, pregnenolone, allopregnanolone, and dehydroepiandrosterone, have been suggested to be promising therapeutic strategies for dopaminergic-related disorders. For instance, animal studies demonstrated dose- and state-dependent effects of allopregnanolone on dopamine release. In particular, low doses of this neurosteroid enhance mesolimbic dopamine, while high doses inhibit it via GABA-A receptors. In this context, Seib et al. (2023) focused their attention on the role exerted by neuroandrogens and neuroestrogens in the mesocorticolimbic system. Indeed, as discussed in this review, animal studies show that this brain area expresses the steroidogenic enzymes involved in the biosynthesis of these molecules as well as their receptors, like, for instance, androgen receptors, estrogen receptor isoforms alpha and beta, and the membrane-associated G-protein coupled estrogen-receptor 1. Accordingly, androgens and estrogens regulate dopamine synthesis through tyrosine hydroxylase, dopamine receptor subtypes, and particularly the D1/D2 ratio, depending on age and sex. These findings provide valuable insights into the mechanisms of neurosteroid action. However, there are notable differences and limitations when comparing these results to human studies, like, for instance, the complexity of the human brain and behavior, hormonal variability (i.e., humans exhibit greater variability in hormone levels due to age, sex, menstrual cycle, stress, and lifestyle), ethical and practical constraints, and translational gaps (e.g., testosterone effects on cognitive flexibility in rodents may not directly apply to humans, where results are mixed and context-dependent).

As reported by Branca and Bortolato (2024), neuroactive steroids, such as dehydroepiandrosterone sulfate and allopregnanolone, have a role in tic disorders, particularly Tourette syndrome. Indeed, the levels of dehydroepiandrosterone sulfate are elevated in boys with this syndrome, and its surge during adrenarche coincides with the onset of tics. Androgens like testosterone and dehydroepiandrosterone sulfate may contribute to male predominance in TS (3–4:1 ratio), though their exact roles remain to be explored. Stress worsens tics, and patients with Tourette syndrome show dysregulated HPA axis activity, with altered cortisol and ACTH responses. In particular, allopregnanolone is linked to stress-induced exacerbation of tics, acting as a modulator of GABA-A receptors, which are implicated in tic pathophysiology. In conclusion, these human studies provide clinical relevance, while animal models give mechanistic insights and platforms for testing novel therapy to be applied in tic disorders. Neuroactive steroids may also have a role in Parkinson's disease. Indeed, in this special issue, Bourque et al. (2024) discussed their neuroprotective and neuromodulatory effects in this neurodegenerative disorder. In particular, males have a higher incidence of this neurodegenerative disorder, suggesting a protective role for female sex hormones like estrogen. Women with longer exposure to endogenous estrogen (e.g., late menopause) show reduced risk of Parkinson's disease, while surgical menopause increases risk. In animal models, not only estrogens, which reduce dopaminergic neuron loss, but also other neuroactive steroids show neuroprotective effects. For instance, allopregnanolone seems to be particularly active in early pathological stages, while dehydroepiandrosterone and pregnenolone improve motor symptoms through anti-inflammatory effects. In

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addition, neuroactive steroids, such as estrogens and pregnenolone, reduce L-Dopa-induced dyskinesias. Altogether, human and animal studies show similarities but also differences. For instance, both types of study support a protective role for estrogens in Parkinson's disease, and particularly in females. However, human studies often report conflicting results due to methodological variability, whereas animal studies provide more consistent but simplified models of PD pathology.

In summary, these four reviews support a key role of neuroactive steroids in regulating the dopaminergic system. Their interactions with GABAergic and glutamatergic systems further underscore their importance in brain function and behavior. Understanding these mechanisms offers new insights into the pathophysiology of neuropsychiatric disorders and opens avenues for novel therapeutic interventions with potential advantages over traditional dopamine-targeting drugs. However, even if this is a rapidly evolving field, several key mechanistic, therapeutic, and translational questions remain unexplored. In particular, more human studies, sex-stratified analyses, and a better mechanistic understanding, including studies on their possible side effects, are needed.

Data availability

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

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