Targeting neurosteroidogenesis as therapeutic strategy for dopamine-related neuropsychiatric disorders

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Neurosteroids are a subclass of steroids synthesized de novo in the brain, which modulate the actions of several neurotransmitters, including dopamine. The involvement of neurosteroids in brain function has recently attracted much interest with respect to their therapeutic potential in psychiatric treatment. In particular, we have investigated the role of 5a-reductase (5AR), the key enzyme in neurosteroidogenesis, in animal models of neuropsychiatric disorders linked to dopaminergic dysfunctions. Our preclinical and clinical findings suggest that 5AR inhibitors, such as finasteride, may elicit antidopaminergic effects in a number of disorders associated with dopaminergic hyperactivity, including Tourette syndrome and schizophrenia. Unlike benchmark antidopaminergic therapies, however, the effects of 5AR inhibitors are not accompanied by extra-pyramidal symptoms, and appear to be contributed by the negative modulation of D1 and D3 receptor signaling in the nucleus accumbens. Notably, we identified that inhibitors of 17α-hydroxylase/17,20-lyase (CYP450-C17), the rate-limiting enzyme in androgen synthesis, elicit behavioral effects akin to those produced by finasteride. Taken together, these data suggest that 5α-reduced androgens may play a critical role in the modulation of dopaminergic signaling in the nucleus accumbens, and offer a potential theoretical platform to account for the male predominance of Tourette syndrome and schizophrenia.

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