



Commentary

Neurosteroidogenesis: a New Pharmacological Target for Tourette Syndrome?

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Tourette Syndrome (TS) is a childhood-onset neurological disorder characterised by multiple motor tics and one or more phonic tics. Number, frequency and tic complexity vary over time. Although clinical and epidemiological studies indicate that TS is a partially inherited disorder, its pathogenesis remains poorly understood (Singer, 2005). One of the main features of TS is that its prevalence in children is significantly higher than in adults; in most TS patients, tic severity follows a characteristic time course, with onset at 5–7 years of age, followed by an increase in frequency and intensity until the age 10 and 12 years, and a later remission phase after puberty (Leckman et al., 1998).

Several clinical studies have highlighted male sex and environmental stress as risk factors in TS pathogenesis. TS has a strong male predominance, with a male:female ratio estimated at 4:1; furthermore, the severity of tics and accompanying symptoms (such as perceptual alterations, anxiety and obsessive-compulsive behaviours) are typically exacerbated by environmental stress (Cohen, Leckman & Bloch, 2013). In consideration of the role of steroids in the regulation of sex differences and stress response, these premises suggest that these molecules may be implicated in the etiology and pathophysiology of TS. In particular, our research focuses on neurosteroids, a family of steroids synthesized by the brain. A schematic diagram of steroidogenesis is presented in Fig. 1.

The key rate-limiting enzyme in androgens and neurosteroids synthesis, 5- α reductase (5AR), catalyses the saturation of the 4,5 double bond of the A ring of Δ^4 -3-ketosteroid substrates, such as deoxycorticosterone, progesterone, androstenedione and testosterone. Through this irreversible reaction, Δ^4 -3-ketosteroid substrates are converted into their pregnane and androstane

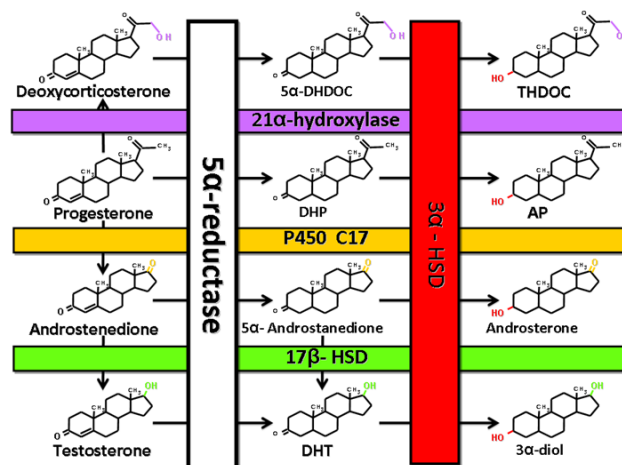


Figure 1: Simplified pathway of neurosteroidogenesis. 3- α HSD, 3- α hydroxysteroid dehydrogenase; P450-C17, steroid 17 α -hydroxylase/17,20 lyase; 17- β -HSD, 17- β -hydroxysteroid dehydrogenase (modified from Paba et al., 2011).

metabolites. The physiological importance of 5AR in the brain derives from its capability to convert testosterone to the more potent brain active androgen dihydrotestosterone (DHT), and to convert progesterone and deoxycorticosterone to their respective 5 α -reduced metabolites. These are precursors of allopregnanolone and tetrahydrodeoxycorticosterone, two neurosteroids directly implicated in the regulation of stress response through the positive modulation of the γ -amino-butyric acid (GABA)_A receptor and HPA axis in response to stress. Among the five types of 5AR enzymes characterised to date, the first two isoforms (5AR1 and 5AR2) play major roles in brain steroidogenesis. The two isoforms are differently expressed and regulated: 5AR1 is the only isoform present in the glial

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cells; the expression of 5AR2 is under the positive control of testosterone and DHT, while the expression of 5AR1 is negatively regulated by the same androgens.

Over the years, our group has demonstrated that the pharmacological inhibition of 5AR elicits therapeutic effects in animal models of TS (Bortolato et al., 2013). In particular, we found that the 5AR inhibitors finasteride and dutasteride normalised the disruption of sensorimotor gating, induced by the non-selective DAergic agonists amphetamine and apomorphine (Bortolato et al., 2008). Gating deficits, as measured by the paradigm of prepulse inhibition (PPI) of the acoustic startle reflex, have been shown to be highly relevant to the sensory dysregulation described in TS. In fact, PPI deficits are exhibited by TS patients, and are posited to indicate the impaired ability to filter out irrelevant stimuli. Although the primary symptoms of TS are motor and vocal tics, several researchers have pointed out the role of sensory phenomena in the pathogenesis of tics. Sensory experiences affect tics and, in turn, tics are generated in response to intrusive sensory phenomena.

The most commonly prescribed drugs for TS are primarily dopamine antagonists, such as neuroleptics (e.g. haloperidol), benzamides (e.g. sulpiride) or atypical antipsychotics (e.g. risperidone). While finasteride exhibited robust anti-dopaminergic mechanisms similar to those elicited by haloperidol across several behavioral tasks, its effects were not supported by a direct antagonism of dopamine receptors. Accordingly, unlike dopaminergic antagonists, finasteride failed to induce extrapyramidal side-effects. These latter findings are in line with our subsequent studies, in which we analyzed the neurobiological bases of the antipsychotic-like mechanisms of finasteride. We found that the effects of systemic finasteride are mediated by a negative modulation of D₁ (but not D₂) receptors in both rats and mice (Frau et al., 2016, 2013). Specifically, the systemic finasteride administration reverted the PPI deficits produced by the selective D₁ agonist SKF-82958 in Long Evans and C57BL/J mice, rat and mice strains, with higher sensitivity to the effects of dopamine D₁ receptor activation. Furthermore, the fact that finasteride did not counteract the behavioural alterations mediated by the D₂ agonists sumanirole and quinpirole, justifies the lack of catalepsy in both species, even at the higher dose tested.

Our results are particularly relevant in view of recent evidence supporting the therapeutic efficacy of D₁ receptor antagonists in TS. Indeed, by a multicenter, non-randomized, open-label study, Gilbert and co-workers (2014) suggest the pharmacologic antagonism of dopamine D₁ receptors as a novel approach to tic reduction in TS. They found a significant reduction in tic severity, with the selective D₁ antagonist ecopipam and a

double-blind trial is ongoing to confirm the efficacy of this pharmacological approach.

Prompted by these preclinical results, we studied the therapeutic potential of finasteride in adult male TS patients. Of note, finasteride, at the same dose used for the treatment of benign prostatic hyperplasia (5 mg/day), led to a gradual improvement of motor and vocal tics in TS patients, as assessed by the Yale Tic Severity Scale, with no reported side effects. Furthermore, the discontinuation of the chronic treatment resulted in an abrupt, dramatic exacerbation of the symptoms, which was countered by the reinstatement of the 5AR inhibitor (Bortolato, Muroi & Marrosu, 2007). Importantly, these preliminary findings have been confirmed in a following open-label study, in which adult male patients show a significant decrease of severity of tics by the sixth week of therapy, with a plateau in the therapeutic effects by the 12th week of finasteride administration. Notably, as in rodents, finasteride did not elicit extrapyramidal side effects in patients (Muroi, Paba, Puligheddu, Marrosu & Bortolato, 2011).

Our preclinical and clinical findings clearly indicated that 5AR plays a key role in the pathophysiology of TS, through the modulation of DA neurotransmission and signalling. In addition, recent preclinical results from our group have suggested that other steroidogenic enzymes might be involved in the pathogenesis of TS. Accordingly, the systemic and intracerebral injections of abiraterone, inhibitor of CYP450 C17, the alternative enzyme responsible of androgens formation, show beneficial effects in animal model of TS, further pointing to the implication of androgen synthesis in TS pathogenesis (Frau et al., 2014). The findings that abiraterone and finasteride elicit similar effects is of particular interest, in view of the convergent neurosteroidogenic pathways and consequent similar substrate and product steroids, and of the translational potential of our results for the clinical practice. Furthermore, it is worth noting that, as reported in TS, the peak age of onset of schizophrenia in males is concomitant with highest testosterone levels at adolescence. In addition, studies in the adolescent striatum and substantia nigra of male rats have shown that testosterone led to increases of tyrosine hydroxylase, D₁-, D₂-, D₅-receptor mRNA and dopamine transporter protein. These data, combined with our previous findings, suggests that the dopaminergic system is upon direct influence of androgen signaling throughout the pubertal/peripubertal period in brain areas with relevance to neurological and neuropsychiatric disorders, including TS and Schizophrenia (Purves-Tyson et al., 2012, 2014). Thus, it is not surprising that imbalances of androgen- or other neurosteroid signaling, specifically during a critical window of brain development, might affect the dopaminergic system. As mentioned above,

a genetic contribution in the etiology of TS has been consistently shown. Although the data from our and other group do not lead to drawn conclusions regarding the functional outcomes, it is feasible that in individuals with an underlying susceptibility for TS, the increase in circulating testosterone at adolescence may serve as trigger for the presentation of dopamine-related tic disorder. In this view, since its role in androgen and neurosteroid synthesis, 5AR may provide a unique biological target in those diseases with male predominance and particular sensitivity to the effects of stress contingencies, in which TS perfectly matches.

Although finasteride is typically well-tolerated, the clinical applications of this drug on TS therapy remain limited; in fact, finasteride cannot be prescribed in children, who represent the broadest target population in this disorder. In addition, finasteride can induce enduring psychoendocrinological side effects in a small subset of patients, including depression and reduction of libido (Traish, Melcangi, Bortolato, Garcia-Segura & Zitzmann, 2015). For these reasons, the identification of the neurobiological bases and molecular mechanisms underlying the effects of finasteride and other 5AR inhibitors, is crucial to overcome their limitations, and develop novel potential therapeutic tools for TS, with limited endocrine side effects.

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