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The implication of neuroactive steroids in Tourette syndrome pathogenesis: a role for 5α-reductase?

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Abstract

Tourette syndrome (TS) is a neurodevelopmental disorder characterized by recurring motor and phonic tics. The pathogenesis of TS is thought to reflect dysregulations in the signaling of dopamine (DA) and other neurotransmitters, which lead to excitation/inhibition imbalances in cortico-striato-thalamocortical circuits. The causes of these deficits may reflect complex gene × environment × sex (G×E×S) interactions; indeed, the disorder is markedly predominant in males, with a male-to-female prevalence ratio of ~4:1. Converging lines of evidence point to neuroactive steroids as likely molecular candidates to account for GxExS interactions in TS. Building on these premises, our group has begun examining the possibility that alterations in the steroid biosynthetic process may be directly implicated in TS pathophysiology; in particular, our research has focused on 5α-reductase (5αR), the enzyme catalyzing the key rate-limiting step in the synthesis of pregnane and androstane neurosteroids. In clinical and preclinical studies, we found that 5αR inhibitors exerted marked anti-DAergic and tic-suppressing properties, suggesting a central role for this enzyme in TS pathogenesis. Based on these data, we hypothesize that enhancements in 5αR activity in early developmental stages may lead to an inappropriate activation of the "backdoor" pathway for androgen synthesis from adrenarche until the end of puberty. We predict that the ensuing imbalances in steroid homeostasis may impair the signaling of DA and other neurotransmitters, ultimately resulting in the facilitation of tics and other behavioral abnormalities in TS.

Introduction

Tourette syndrome (TS) is a neurobehavioral condition characterized by recurring motor and phonic tics during childhood and adolescence. The bulk of evidence suggests that tics are the phenotypic correlate of the activation of ectopic foci in the basal ganglia, due to excitation/inhibition imbalances in cortico-striato-thalamocortical (CSTC) connections [1]. The neurobiological bases of these impairments are likely multifactorial and may reflect the molecular interplay of a broad set of genetic, environmental and gender-related variables [2]. Notably, male gender and exposure to psychosocial stress have been highlighted as key risk factors for TS pathogenesis, indicating that androgens and other neuroactive steroids

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may directly participate in the pathophysiology of this disorder. Although the neuroendocrinological alterations in TS have been the focus of little research to date, recent progress on the steroidogenic pathways may provide novel avenues to understand several critical aspects of TS pathophysiology. The present article will review the current state of the art on the implication of neuroactive steroids in TS. In particular, we will discuss our recent translational findings on 5α-reductase (5αR), the enzyme that catalyzes one of the key rate-limiting steps in the synthesis of neurosteroids and androgens. Based on emerging findings on a putative therapeutic potential of 5αR inhibitors in TS, we will outline a hypothetical mechanism whereby alterations of this enzyme may contribute to the sex differences and stress sensitivity associated with TS.

Clinical features and pathophysiology of TS

TS is a familial, childhood-onset neurobehavioral disorder characterized by multiple motor tics and at least one phonic tic, with a duration greater than one year [3]. The prevalence of the disorder has been recently estimated between 0.4 and 1% of the population [4]. In addition to tics, approximately 90% of patients are affected by comorbid psychiatric conditions, including attention-deficit hyperactivity disorder (ADHD) and obsessive-compulsive disorder (OCD), as well as reactive aggression and other impulse-control disorders (ICDs) [5, 6].

Motor tics are sudden, involuntary, non-rhythmic movements, frequently confined to the head, neck, face and mouth muscles, but also observed in the trunk and limbs [7]. Phonic tics are rapid vocalizations due to rapid air movements through the upper respiratory tract, which can sometimes be associated with copro-, echo- or palilalia [8]. Tics can also be classified as simple or complex, based on the degree of involvement of different muscles. Simple tics are brief and repetitive actions, such as eye blinking, facial grimacing, head jerking, sniffing or grunting sounds; conversely, complex tics engage multiple muscle groups in coordinated and stereotyped patterns akin to purposeful activities, including touching objects or people, hopping and jumping as well as uttering words or phrases [9].

Tics are distinctively preceded or accompanied by premonitory urges and sensory phenomena; these intrusive, uncomfortable feelings are often described as a sense of inner tension associated with focal or generalized somatic sensations, and are commonly relieved by the execution of tics [10]. While most TS-affected individuals are able to temporarily suppress tics, the ensuing buildup of tension results in an increased sense of distress and in a greater urge to tic. The dynamics of these phenomena are similar to the neuropsychological sequence of OCD, in which compulsions are typically enacted as a maladaptive coping strategy to alleviate the anxiety associated with obsessive thoughts [11].

The typical onset of TS occurs at 6–7 years of age and is characterized by the appearance of simple, recurrent motor tics, followed by the manifestation of phonic tics after several months [12]. In most children, TS symptoms undergo a progressive exacerbation, which reaches its zenith at the beginning of puberty (11–12 years of age), and is then followed by a gradual remission in the majority of patients [13]; conversely, 30–40% of TS-affected children retain their symptoms in adulthood [14]. In addition to these temporal changes, tic severity exhibits numerous fluctuations throughout life and is typically increased during periods of high mental and physical stress [15].

Although the pathophysiological bases of TS remain partially unclear, converging lines of evidence have shown that the disorder is underpinned by functional and/or morphological impairments of the CSTC pathway. As mentioned above, numerous studies support that tics may arise from multiple, heterogeneous neurobiological deficits, which ultimately lead to general imbalances of the inhibitory and excitatory inputs within the striatum and the other

basal ganglia. Specifically, these imbalances may be related to the insufficient inhibitory tone from select families of striatal interneurons [16, 17] and/or the excessive striatal activation from the cortex or other brain regions (for a comprehensive review of this issue, see [1,2]). These impairments may lead to a disproportionate striatal stimulation and the activation of ectopic foci due to the inadequacy of center-surround interactions within this brain region [18].

Multiple neurotransmitters have been implicated in TS, including dopamine (DA), serotonin, norepinephrine, acetylcholine, glutamate and γ-amino-butyric acid (GABA) [19]. In particular, ample evidence supports the involvement of DAergic dysfunctions in TS. Tics are markedly reduced by DA receptor antagonists, such as haloperidol and pimozide [20], while they are exacerbated by DAergic agonists [21]. In addition, several neuroimaging and post-mortem studies have shown excessive activity and/or innervation of the cortex and basal ganglia of TS patients [22], which may reflect dysregulations in the DAergic system [23–26].

Recent studies indicate that the key DAergic impairment in TS may consist of a sharp contrast between low tonic and high phasic DA levels in the basal ganglia [27]. This background suggests that tics may be underpinned by rapid variations in synaptic DA content, leading to a prominent activation of postsynaptic D_1 receptors in the striatum. These receptors govern the activation of the “direct pathway” projections to globus pallidus and substantia nigra *pars reticulata*, and may therefore lead to the stimulation of ectopic foci. Accordingly, the initial results of a recent clinical trial sponsored by the Tourette Syndrome Association (TSA) suggest that the D_1 receptor antagonist ecopipam may be highly effective as a therapeutic option for TS [28].

It is worth noting that the implication of the DAergic system in the pathophysiology of TS may also involve the key role of this neurotransmitter in the ventral striatum with respect to the orchestration of critical behavioral functions, such as habit formation, incentive motivation, configuration of salience maps and sensorimotor gating [29–33]. Indeed, TS patients feature alterations in all these behavioral domains [34–37].

Etiology of TS: genetic, environmental and sex factors

Over the past decade, research into the etiology of TS has afforded fundamental contributions to our current understanding of the biological bases of this disorder. In particular, a large body of evidence has indicated that, similarly to other neuropsychiatric conditions, TS is a multifactorial disorder governed by multiple genetic, environmental and sex-related factors [38–40].

Genetic factors

The genetic basis of TS was originally postulated by several groups in the late 1970’s, based on clinical observations on the high familiality of the syndrome [41, 42]. These findings spurred a great number of analyses on genetic variants in TS. Specifically, some of the first genetic studies on TS focused on genes directly implicated in DA and serotonin regulation. Recently, several candidate genes have been discovered based on sporadic and familial mutations associated with TS (Table 1). Among these genes, particular interest has been recently raised by *SLITRK1* [43–45], which encodes for a molecule involved in the organization of neurite growth.

In addition to specific studies on select genes, recent whole-genome analyses have been conducted to identify potential single-nucleotide polymorphism (SNP) variants associated with TS. Recently, the TSA International Consortium for Genetics (TSAICG) reported the

results of the first genome-wide association study (GWAS) on TS, based on the analysis of 484,000 SNPs in the DNA of 1496 TS patients and 5249 controls [46]. Although the data revealed the possible association of TS with several genes, none of the identified SNPs reached the threshold of genome-wide significance, further confirming the complex genetic architecture of TS inheritance.

An alternative approach to study inheritance patterns in TS is afforded by genetic linkage studies across families with high TS prevalence. The largest linkage study for TS and tic disorder to date, also conducted by the TSAICG [47] on 238 nuclear families and 18 large multigenerational families totaling 2040 individuals, identified regions of high linkage to the disorder in the chromosome 2p23 [47, 48].

Environmental factors

TS pathogenesis is influenced by the exposure to several environmental variables [49]. The severity of tics and other behavioral symptoms in TS is typically exacerbated by the exposure to environmental and psychosocial stress [50–54]. For example, stressful contingencies lead to a reduced ability in suppressing tics [55]. The relation between TS and stress appears to be bidirectional, insofar as patients have higher stress perception than non-affected controls, and short-term future tic severity is predicted by current levels of psychosocial stress [56]. These findings underscore a critical involvement of stress-response mechanisms in TS pathogenesis.

In addition to the emotional impact of current contingencies, TS has been associated with the occurrence of several adverse events during pre- and perinatal stages [57–59], including maternal psychosocial stress [60] as well as severe nausea and vomiting during the first gestational trimester [60]. Maternal smoking and consumption of medications are also significant risk factors for the disorder [61]. Finally, exposure to infections (particularly from β-hemolytic streptococcus) has been associated with higher incidence of TS and associated syndromes [62]. The involvement of neuroinflammatory events in TS is suggested by numerous findings [63, 64], and may also reflect the involvement of autoimmune processes [65]. The exposure to prenatal complications (including infections) may indirectly influence the clinical course of TS by altering stress reactivity [66, 67].

Sex factors and gender differences in TS

One of the most striking epidemiological aspects of TS lies in its marked gender differences. Similarly to other neurodevelopmental conditions, such as ADHD and autism-spectrum disorder (ASD), male gender is a major risk factor for TS (with a male:female prevalence ratio estimated at ~4:1) [68]. Although the biological mechanisms underlying the higher TS vulnerability in boys remain elusive, genetic studies have clearly ruled out that this phenomenon may reflect the involvement of X-linked heritability patterns.

The implication of sex factors in TS is also indirectly indicated by the observation that temporal variations of tic severity are characteristically time-locked with all the major phases of sex maturation. For example, the typical age of onset coincides with adrenarche (6–7 years old); symptoms increase in severity until the beginning of puberty (12 years old) and then undergo a spontaneous amelioration, which becomes apparent with the end of puberty (at 18–19 years of age).

In males, TS onset is characterized by anger-related manifestations and simple tics; conversely, females exhibit complex tics more often than males. TS is diagnosed later in females than males, with different age distributions [69]; furthermore, recent data indicate that, while male gender increases vulnerability for tics in childhood, female gender may predict greater tic severity in adulthood [70]. Interestingly, male TS patients exhibit

significant deficits in cortical and callosal thickness, which are not observed in females [71–73].

Neuroactive steroids in TS

The epidemiological evidence outlined in the previous section suggests that the neural underpinnings of TS may result from complex GxExS interactions. Although the molecular bases of these putative interactions remain unknown, emerging data point to neuroactive steroids as primary candidates for the mediation of these mechanisms, given their well-characterized role in the regulation of stress responses and gender differences.

Sex steroids in TS

The first studies on endocrine changes in TS were published in the late 1980's, and suggested that this disorder may feature functional alterations in the secretion of luteinizing hormone (LH), the main regulator of gonadal androgen synthesis [74, 75]. In the following years, a number of clinical observations showed that tics in TS patients could be exacerbated by anabolic androgens [76]. In addition, TS patients were found to exhibit behavioral features typically associated with androgens, including aggressiveness, precocious sex drive and pervasive erotic urges [77, 78]. Furthermore, studies on the behavioral characteristics of TS-affected children have also assessed that tic severity correlates with their preference for masculine play, irrespective of gender [79].

One of the most intriguing aspects of the postulated involvement of male sex hormones in TS is the possibility that steroidogenic enzymes and androgen receptors may serve as putative therapeutic targets for this disorder. The androgen receptor antagonists flutamide and cyproterone were tested in adult TS patients with positive results [80–82]. In particular, flutamide (750 mg/day) was tested in a cross-over, double-blind, placebo-controlled trial with 10 men and 3 women affected by TS. Treatment was evaluated for 21 days, and resulted in a very modest (7%), yet significant amelioration of motor tic severity; conversely, no significant effects were observed on phonic tics and OCD symptoms [81]. Overall, the limited and short-lived efficacy of the drug undermined its therapeutic suitability, also in consideration of its potential severe hepatic side effects [83].

Unlike males, tic severity is typically increased after puberty in females. Preliminary surveys appeared to indicate that, in women, tic severity can be conditioned by variations in hormonal profile during the menstrual cycle. In particular, 26% of females were found to experience exacerbation of tics in the estrogenic phase of the menstrual cycle, and this phenomenon was found to be correlated with increased tic severity at menarche [84]. While these data clearly support direct implication of estrogens in TS pathogenesis, evidence in this respect remains limited and controversial. Indeed, in a different study, no significant correlation was found between fluctuation in tic severity and frequency and variations in estradiol or progesterone through the menstrual cycle in female TS patients [85].

Although the neurobiology of sex steroid involvement in TS is not clear, numerous animal studies have shown that sex hormones (including testosterone, estradiol and progesterone) yield multiple modulatory effects on DAergic responses in the striatum and nucleus accumbens [86–91].

Glucocorticoids in TS

The involvement of neuroactive steroids in TS is also postulated in view of the increased stress sensitivity of TS patients [92,93], which has been linked to alterations of the hypothalamic-pituitary-adrenal (HPA) axis and glucocorticoid receptor function. Indeed, abnormal functional enhancements of HPA axis were found in TS patients in response to

stressful medical procedures [94, 95] as well as injection of the opioid antagonist naloxone [96]. Furthermore, synthetic glucocorticoid treatment increased tics in two cases of tic disorders [97]. Several rodent studies suggest that glucocorticoids modulate brain DA levels [98, 99], underscoring the possibility that this neurotransmitter may be involved in the link between these neuroactive steroids and TS. It should be noted, however, that cortisol does not appear to play a prominent role in the variations in stress responsiveness in TS; indeed, Corbett and coworkers [93] did not identify significant differences in the natural cortisol circadian variations between TS-affected children and healthy probands. Further studies are required to ascertain the degree of implication of each major glucocorticoid hormone in the modulation of TS symptoms.

Steroid 5αR: a putative candidate for GxExS interactions in TS

One of the least explored aspects of the involvement of steroids in TS concerns the existence of possible abnormalities in neurosteroidogenesis, i.e. the biosynthesis of steroids in the central nervous system, and, more specifically, in the brain. Over the past two decades, converging lines of research have elucidated that the brain and spinal cord synthesize multiple classes of endogenous steroids; these compounds act in coordination with the abundant endocrine input received from adrenal and gonadal steroids to regulate a broad set of neurobehavioral functions, including stress response and gender-related characteristics. Interestingly, various studies indicated that steroids endogenously produced in the nervous system and the regulation of neurosteroidogenesis by neurotransmitters represent pivotal processes to be considered with specific attention in the investigations aiming to clarify the mechanisms involved in various neural disorders [100, 101]. Although not all the details of neurosteroidogenic reactions have been fully elucidated, it has become clear that both the biosynthesis and metabolism of all major sex steroids can occur in the brain, through a number of tightly interwoven reactions (Fig.1).

Building on these premises, our research has been focused on the enzyme 5αR, which subserves one of the key rate-limiting steps in the synthesis of neurosteroids. 5αR catalyzes 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. This irreversible reaction is instrumental for the conversion of these compounds into their pregnane and androstane metabolites [102]. Among the many reactions catalyzed by 5αR, it is important to note that this enzyme is essential for the synthesis of 3α,5α-tetrahydroprogesterone (allopregnanolone, AP) and 3α,5α-tetrahydrodeoxycorticosterone (THDOC), two neurosteroids directly implicated in the regulation of stress response through the positive modulation of the γ-amino-butyric acid $(GABA)_A$ receptor in the brain [103]. In particular, it should be noted that THDOC has been recently shown to be the primary activator of the HPA axis in response to stress [104].

5αR also catalyzes the conversion of testosterone into its metabolite 5α-dihydrotestosterone (DHT), which is the most potent androgen hormone *in vivo* and orchestrates the development of male external genitalia and secondary sex traits. Indeed, 5αR inhibitors have been developed specifically for the reduction of DHT levels, which has been shown to have therapeutic effects for benign prostatic hyperplasia and male-pattern alopecia [102].

Of the five types of 5αR enzymes characterized to date, the first two (termed 5αR1 and 5αR2) play major roles in steroidogenesis and mediate overlapping reactions [102]; however, they differ by patterns of localization and expression. 5αR1 is highly expressed in the epidermal cells, neurons and adrenal glands; conversely, 5αR2 is predominantly expressed in the male urogenital tract, as well as genital skin, hair follicles and liver. While 5αR2 is not as abundant as 5αR1 in the brain, it can be found across most structures, and

particularly in the cortex and cerebellum [105]. The expression of 5αR2 in the brain appears to be related to the surges in testosterone levels in this organ. In fact, the expression of this enzyme has been mainly documented in early developmental stages. In adults, the expression of the enzyme is posited to depend on androgens.

Although the reactions mediated by 5αR1 and 5αR2 are largely overlapping, it is interesting to notice that 5αR2 has a higher affinity for progesterone and testosterone, possibly suggesting that these two isoenzymes may be differentially activated in the brain, in relation to different concentrations of substrates. Furthermore, unlike 5αR1, 5αR2 is distinctly absent from glial cells [105], likely signifying a topographical segregation of their functional roles.

Both 5αRs have been shown to play a role in stress response. Specifically, short-term stress increases the expression of these enzymes, thereby allowing the synthesis of neuroactive steroids. In the brain, the increased 5αR activity leads to higher synthesis of AP, THDOC and other neurosteroids, which appear to modulate stress response through multiple mechanisms, including the direct regulation of HPA axis [104]. The best characterized of such mechanisms is the positive modulation of $GABA_A$ receptor by AP; however, emerging data indicate that other 5α-reduced neurosteroids may play a key role in the responses to stress. In addition, it should be noted that, while stress-induced increases in 5αR activity have been well characterized in brain regions, recent data support that this phenomenon may also occur in peripheral organs, such as the prostate [106].

Behavioral properties of 5αR inhibitors: preclinical studies

Our preclinical studies on 5αR began with the evaluation of the anti-DAergic properties of its inhibitors finasteride and dutasteride in animal models. In particular, we originally observed that these agents could lead to a dramatic reduction of the deficits in sensorimotor gating induced by the non-selective DAergic agonists amphetamine and apomorphine [107]. Gating deficits, as measured in the paradigm of prepulse inhibition (PPI) of the acoustic startle reflex, have been shown to be highly relevant to the cognitive alterations described in TS [108]. PPI deficits are exhibited by TS patients [31, 109], and are posited to indicate the impaired ability to filter out irrelevant stimuli. This may be particularly relevant with respect to tics, which are generated in response to intrusive sensory phenomena [110–113]. Although finasteride exhibited anti-DAergic mechanisms similar to those elicited by haloperidol across several behavioral tasks, it strikingly failed to induce catalepsy [107]. Following these findings, we analyzed the neurobiological bases of the antipsychotic-like mechanisms of finasteride. In particular, we found that, in males, the effects of systemic finasteride were not affected by castration, and were mimicked by the intracerebral infusion of the drug in the nucleus accumbens [114]. Moreover, we recently found that, in mice, the mechanisms of finasteride are mediated by D_1 DA receptors [115]. This result is particularly noteworthy, in view of recent evidence supporting the therapeutic efficacy of D_1 receptor antagonists in TS [28].

Therapeutic properties of 5αR inhibitors: clinical studies

Prompted by these preclinical results, we studied the therapeutic potential of finasteride in adult male TS patients. The first patient who gave informed consent for experimental treatment with finasteride as an adjunctive therapy was a severe case of TS with explosive vocalizations, stereotyped coprolalic utterances, self-injuring motor tics and excessive sex drive. Previous therapeutic attempts with typical antipsychotics had resulted in transient improvements, but the high rate of extrapyramidal and cognitive side effects had led him to repeated withdrawals [116]. Finasteride (5 mg/day) led to a gradual improvement of his motor and vocal tics, as assessed by the Yale Tic Severity Scale with no reported side

effects. The discontinuation of the regimen after 18 weeks, however, resulted in an abrupt, dramatic exacerbation of the symptoms, which was countered by reinstatement of the 5αR inhibitor.

The therapeutic effects of finasteride as an adjunctive treatment in TS have been confirmed in a first open-label study with adult male patients, who exhibited a significant reduction of the severity of tics and associated compulsive (but not obsessive) manifestations by the sixth week of therapy [117]. At the time of this writing, the open trial of finasteride has been extended to 16 TS male adult patients. As shown in Fig.2, our patients consistently showed a fully significant reduction in tic severity by the 6^{th} week of treatment, and reached a plateau in therapeutic effects by the 12^{th} week of finasteride administration. Notably, three patients have shown that finasteride discontinuation led to a sudden exacerbation of their symptoms. Interestingly, in contrast with antipsychotics, finasteride does not elicit extrapyramidal side effects in patients [102, 117]. Our preliminary surveys on the psychological mechanisms of finasteride in tic suppression revealed that, in most patients, this drug confers an attenuation of the premonitory urges and a greater ability to control the execution of tics and other impulses, resulting in lower interference and higher functioning. In addition, our results seem to suggest that finasteride is more efficacious in reducing simple, rather than complex tics (manuscript in preparation). Following these results, our group has begun a double-blind, placebo-controlled clinical trial at the Tourette Syndrome Center of the University of Cagliari, Italy.

The idea that 5αR inhibitors may reduce tic severity by improving impulse control is indirectly supported by our recent clinical observations on the effects of finasteride in ICDs. Indeed, we found that, in males, finasteride reduced pathological gambling induced by DA receptor agonists + levodopa in Parkinson's disease patients [118].

Studies are currently ongoing to advance our understanding of the potential mechanism of action of 5αR in TS. Although the involvement of this enzyme in TS remains to be fully ascertained, the possibility that both 5αR isoenzymes may be directly involved in the genetic bases of the disorder is supported by a number of observations.

Specifically, the largest linkage study for TS and tic disorder has identified a region of high linkage in the chromosome 2p23 [47, 48], in a position directly proximal to (or partially coinciding with) the gene *SRD5A2*, which encodes for 5αR2 [119]. Furthermore, two previous TS genome scan studies pointed to chromosomal regions proximal to the gene *SRD5A1* (encoding for 5αR1) on chromosome 5p15 [120, 121].

Interestingly, both genes exhibit a number of functional polymorphic variants. In particular, several studies have associated *SRD5A2* variants with neurodevelopmental disorders with higher incidence or severity in males, such as autism and schizophrenia [122, 123], In particular, in the latter disorder, *SRD5A2* variations have been associated with increased cortisol metabolism [124].

The conundrum of the role of androgens in TS: is the key in the "back door"?

One of the most puzzling aspects about the involvement of endogenous androgens in TS pathophysiology is that the surge of gonadal androgens in the bloodstream during puberty typically coincides with a *reduction*, rather than an exacerbation, in tic severity. Interestingly, the hypothesized hyperactivity of 5αR in TS may afford a possible solution to this conundrum, in view of the newly-discovered role of this enzyme as the gatekeeper of alternative steroidogenic pathways throughout different stages of sexual development.

As noted above, the median age of TS onset coincides essentially with adrenarche, the first stage of sexual maturation characterized by the development of the inner *zona reticularis* in the adrenal cortex. The biochemical hallmark of adrenarche is the acquisition of 17,20 lyase activity by cytochrome P450 C17 (CYP17A1) [125], which is promoted by cytochrome b5 and the phosphorylation of serine residues [126–132]. The result of this process is the increased synthesis of dehydroepiandrosterone (DHEA) and androstenedione, which leads to the growth of axillary and pubic hair as well as enhancement in the oiliness of the skin [133]. The increase in 17,20 lyase activity of CYP17A1 is instrumental for the activation of the Δ^5 pathway, the predominant route of androgen synthesis in puberty and adulthood [128, 134]. This pathway consists in the conversion of 17-OH-pregnenolone into DHT through four intermediate reactions, mediated by 17,20 lyase, 3β-hydroxysteroid dehydrogenase (3β-HSD), 17β-hydroxysteroid dehydrogenase type 3 (17β- HSD3) and 5αR2 (Fig. 1).

Recent studies have documented the existence of an alternative “backdoor pathway” for the synthesis of DHT, which appears to be predominant before adrenarche. In this series of reaction, 17-OH pregnenolone is converted into 17-OH AP via the combined actions of 5αR1 and 3α-hydroxysteroid oxidoreductase (3α- HSOR). Importantly, CYP17A1 exhibits a great affinity for 17-OH-AP, which is higher than that for 17-OH-pregnenolone [135, 136] and does not require the activation of cytochrome b5 for the acquisition of 17,20 lyase activity. This enzyme converts 17-OH AP into androsterone, which is then further metabolized into 3α-androstanediol by 17β-HSD and then into DHT by oxidative 3α-HSOR [136]. The backdoor pathway has been recently demonstrated in humans [137] and is considered to play a key role in the production of DHT and other androstane derivatives in the developmental stages before adrenarche [138].

The shift from the backdoor pathway to the Δ^5 pathway is based on the functional antagonism between 5αR and CYP17A1. The prevailing activity of 5αR allows the predominance of the backdoor pathway, by facilitating the synthesis of 17-OH-AP. This premise suggests that 5αR hyperactivation in the periphery may lead to the persistence of the backdoor pathway even after adrenarche; upon these conditions, we predict that the imbalance in androgens would lead to a persistent increase in androsterone, androstanediol and DHT, as well as a relative decrease in DHEA and androstenedione. Androstane derivatives exert their effects through a vast array of receptors, including farnesoid receptor (FRX), β-estrogen receptors, which may indeed contribute to lower the threshold for tics in the presence of other predisposing variables. Alternatively, it is even possible that the persistence of 5αR2 throughout childhood may facilitate the conversion of androstenedione (which has high affinity for this isoenzyme) into androstanedione, which would then be re-converted into androsterone by 3α-HSOR. Interestingly, we recently found that blockers of CYP17A1 exert anti-DAergic actions akin to those of finasteride (manuscript submitted).

The imbalances in androgenic steroids unmasked in adrenarche could be remedied in puberty, with the full activation of Δ^5 pathway due to LH. Indeed, gonadotropins stimulate testosterone production via the Δ^5 pathway, and may inhibit the backdoor pathway in the testicles [139]. Nevertheless, it should be noted that the mechanism of involvement of puberty in tic ontogenesis is likely more complex. Indeed, puberty may actually be conducive to tic exacerbation, rather than remission, as suggested by the relatively high occurrence of tic disorders in familial male precocious puberty [140]. Thus, it is likely that the phenotypic changes associated with puberty may also involve the relation between the alterations in steroid profile and other neurodevelopmental aspects, such as the maturation of the DAergic system etc.

Furthermore, we cannot exclude that the postulated mechanism may only be applicable in males, while different mechanisms may be present in girls, depending on the relevance of aromatization processes in the aforementioned mechanisms.

A key unresolved issue concerns the possible existence of a “backdoor pathway” (or its functional equivalent) in the brain, in addition to those already documented in the adrenal cortex and gonads. Notably, all the enzymes that are required for activation of the backdoor pathway are also expressed in brain regions, including 3β-HSD, 5αR, 3α-HSOR, CYP45017A1 and 17β-HSD [141–149].

Conclusions and future perspectives

The findings and concepts delineated in this review suggest that neurosteroids may play a key role in the pathophysiology of TS, through multiple mechanisms including the modulation of DA neurotransmission and signaling.

An accurate evaluation of the role of neurosteroids in TS and other neuropsychiatric disorders is limited by numerous theoretical and practical obstacles. One of the main problems lies in the limited scope of most endocrinological analyses performed in neuropsychiatric disorders, which typically measure only a restricted number of endogenous steroids in plasma and/or urine. A possible solution for this limitation may be represented by new steroidomic techniques, based on the combination of charge tagging and liquid chromatography-tandem mass spectrometry. The utilization of these approaches, particularly if applied to CSF analyses, holds promise for a much more detailed understanding of the steroidal alterations in TS. Indeed, similar analyses have been recently conducted in healthy subject and have led to a series of surprising findings, such as an unexpected abundance of intermediate compounds of the bile biosynthetic pathways in the CSF [150]. These high-throughput strategies, together with large-scale epigenetic, transcriptomic and proteomic analyses, may prove fundamental to frame the role of neurosteroidogenesis in TS, and provide a rich sources for candidate therapeutic targets.

Our preclinical and clinical results support the possibility that 5αRs (and possibly other steroidogenic enzymes) are involved in the pathogenesis of TS. In particular, the newly-defined role of 5αR as a “gatekeeper” of alternative steroidogenic pathways at the intersection of stress-activated metabolic responses and gender differences may afford a unitary platform to explain the mechanism of potential GxExS interactions in TS. Despite the limited side effects and good tolerability profile of finasteride, the clinical applications of finasteride on TS therapy remain limited; in fact, this drug cannot be used in children, who represent the broadest target population in this disorder. In addition, recent evidence has pointed to a number of severe, permanent side effects of finasteride in a small subset of male individuals (who were prescribed this drug as a therapy for hair loss), including depression, suicidal thoughts and impotence [151–153].

In spite of these limitations, the identification of the neurobiological bases of the effects of finasteride and other 5αR inhibitors may point to novel avenues for the development of potential therapeutic tools for this disorder with limited endocrine side effects. The recent evidence that 5αR inhibition interferes with some of the behavioral effects of D_1 receptors in animal models is highly promising [115], in view of emerging evidence of the relevance of this target in TS. Further studies are warranted to establish the molecular mechanisms of neurosteroid actions and their impact on DA and other neurotransmitter systems.

From this perspective, preclinical studies on animal models are essential as a tool to test mechanistic hypotheses on the contribution of steroids in TS pathogenesis, as shown by our translational research on finasteride and 5αR inhibitors. Our studies on finasteride showed

that, despite potential differences between humans and rodents in steroidogenesis, the employment of animal models is an essential component for the enactment of effective translational strategies in TS. We are beginning to test the role of 5αR in models of TS with high face, construct and predictive validity, such as the D1CT-7 mice [154,155]. In these transgenic animals, the promoter region for the D_1 receptor was fused with the enzymatic portion of cholera toxin subunit α1 (A1) gene, which leads to a persistent activation of Gs proteins. D1CT-7 mice display explosive jerking movements of the head, trunk and limbs, which are highly reminiscent of tics [156,157]. In conformity with the gender discrepancies in TS patients, D1CT-7 male mice exhibit more tic flurries than females. Furthermore, the onset of twitching occurs at postnatal day 16 [156]; interestingly, recent studies have found that the changes in steroidal profile at day 16 in rodents are similar to those featured in adrenarche in primates [158].

Irrespective of mechanistic issues, our preliminary data on finasteride indicate that normalization of neurosteroidogenic alterations in TS may lead to significant therapeutic improvements over currently available therapies, in view of their limited set of side effects. The marked male predominance and high stress sensitivity of TS indicates that silencing the steroid-based mechanisms responsible for these phenomena may yield significant therapeutic benefits; the identification of brain-specific steroidogenic targets may allow us to harness these aspects with limited endocrinological untoward effects.

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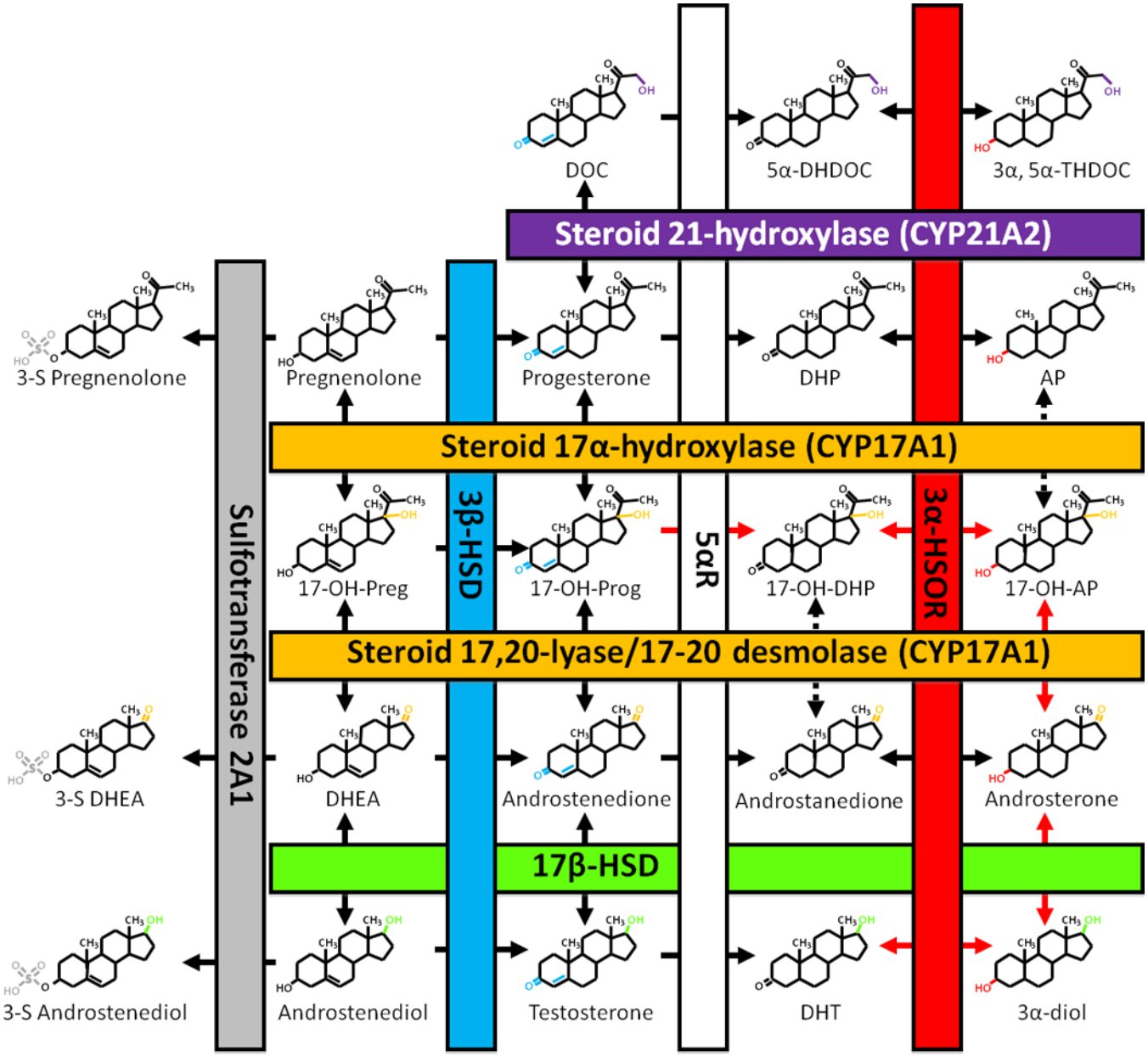

Fig. 1.

Schematization of major neurosteroidogenic pathways. Metabolic changes in steroid configurations are represented in the same color as the enzymes (boxes) catalyzing the reactions. Red arrows represent the major reactions corresponding to the “backdoor” pathway of DHT synthesis. Dotted arrows represent reactions that have been hypothesized, but not fully ascertained in the brain. Enzymes: 3β-HSD; 3β-hydroxysteroid dehydrogenase; 5αR, 5α-reductase 17β-HSD: 17β-hydroxysteroid dehydrogenase; 3α-HSOR: 3α-hydroxysteroid oxidoreductase; CYP21A2: Steroid 21-hydroxylase; CYP17A1: cytochrome P450 17A1. Steroids: DOC, deoxycorticosterone; 5α-DHDOC, 5α-dihydro deoxycorticosterone; 3α,5α-THDOC, 3α,5α-tetrahydrodeoxycorticosterone; 3S-pregnenolone, pregnenolone sulfate; DHP, 5α-dihydroprogesterone; AP, 3α,5α-tetrahydroprogesterone (allopregnanolone); 17-OH-Preg, 17-hydroxypregnenolone; 17-OH-Prog, 17-hydroxyprogesterone; 17-OH-DHP, 17-hydroxydihydroprogesterone; 17-OH-AP,

17-hydroxyallopregnanolone; 3-S DHEA dehydroepiandrosterone sulfate; DHEA, dehydroepiandrosterone; 3S- androstenediol, androstenediol sulfate; DHT, 5α-dihydrotestosterone; 3α-diol, 5α-androstane-3α,17β-diol.

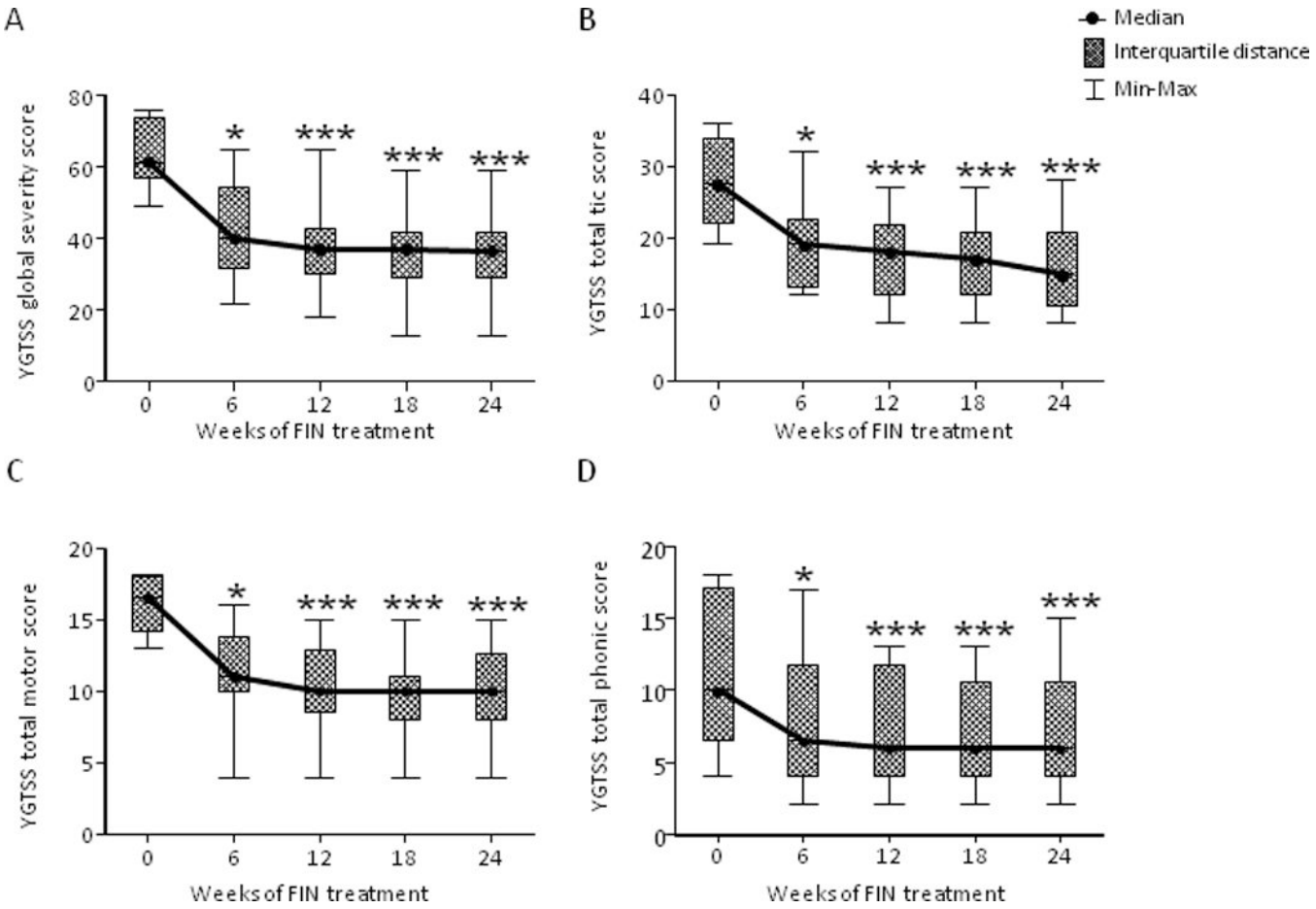

Fig. 2.

Effects of finasteride (FIN) on severity of tics in patients with Tourette syndrome (n=16). FIN induced significant reductions in the severity of (A) global symptoms [X^2 (4)=48.41, P<0.001], (B) total tics [X^2 (4)=51.07, P<0.001], (C) motor tics [X^2 (4)=50.03, P<0.001], and (D) phonic tics [X^2 (4)=47.31, P<0.001], as assessed by Yale Global Tic Severity Scale (YGTSS) scores (after adjustment for multiple comparisons). *, P<0.05; ***, P<0.001 versus baseline scores (week 0). Analyses of YGTSS scores were performed with Friedman's test, followed by Wilcoxon-Nemenyi-McDonald-Thompson test for *post-hoc* comparisons.

Table 1

List of the key genes heretofore implicated in Tourette syndrome and their chromosomal locations.

Gene	Location	References
DAT1	5p15.3	[159–161]
MAOA	Xp11.3	[160]
SLITRK1	13q31.1	[43–45]
HDC	15q21-q22	[162]
NLGN4	Xp22.33	[163]
CNTNAP2	7q35	[164]
IMMP2L	7q31	[165]