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Post-Finasteride Syndrome And Post-Ssri Sexual Dysfunction: Two Clinical Conditions Apparently Distant, But Very Close

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ABSTRACT

Post-finasteride syndrome and post-SSRI sexual dysfunction, are two poorly explored clinical conditions in which men treated for androgenetic alopecia with finasteride or for depression with SSRI antidepressants show persistent side effects despite drug suspension (e.g., sexual dysfunction, psychological complaints, sleep disorders). Because of some similarities in the symptoms, common pathological mechanisms are proposed here. Indeed, as discussed, clinical studies and preclinical data obtained so far suggest an important role for brain modulators (i.e., neuroactive steroids), neurotransmitters (i.e., serotonin, and cathecolamines), and gut microbiota in the context of the gut-brain axis. In particular, the observed interconnections of these signals in these two clinical conditions may suggest similar etiopathogenetic mechanisms, such as the involvement of the enzyme converting norepinephrine into epinephrine (i.e., phenylethanolamine N-methyltransferase). However, despite the current efforts, more work is still needed to advance the understanding of these clinical conditions in terms of diagnostic markers and therapeutic strategies.

1. Introduction

All drugs can cause adverse reactions. Therefore, when a drug is prescribed, a benefit-risk analysis which analyzes the likelihood of drug benefit against the risk of adverse reactions, is required. Examples of common drug side effects include gastrointestinal issues, skin rash or dermatitis, headache, insomnia, etc. In addition, some drugs may impair sexual function and the nervous system. In this context, it is important to highlight that persistent side effects (i.e., still present despite the drug suspension) have been recently reported in the case of inhibitors of the enzyme 5alpha-reductase (5α-R), and the case of some antidepressant drugs, such as the selective serotonin reuptake inhibitors (SSRIs), inducing post-finasteride syndrome (PFS) and post-SSRI sexual dysfunction (PSSD), respectively. In this review, we will describe these two new clinical conditions, discuss their common aspects and highlight the role of steroid molecules.

2. Neuroactive and gut steroids: production, mechanism of action and effects

Communication is an essential event for the proper orchestration of physiological functions. Within mammalian organism, several ways of communication have been established. For example, the nervous system mainly uses neurotransmitters to transfer its messages. In the context of the endocrine system, on the other hand, several hormones can play the role of messengers, spanning amino acids, proteins, or steroids. These latter are essentially produced by peripheral steroidogenic glands and released into the blood circulation, where they are distributed throughout the body through specific or nonspecific transport proteins. However, steroids can additionally have a local action (i.e., autocrine or paracrine communication), and they can also be produced by tissues that are not classically considered steroidogenic, such as the nervous system (Schumacher et al., 2003) and, as demonstrated more recently, the colon (Diviccaro et al., 2020b). All of these steroid molecules, including glucocorticoid and sex steroid hormones (i.e. adrenal- and gonadal-derived), neurosteroids (i.e. nervous system-derived), gut steroids (i.e., colon-derived), and synthetic steroids (i.e., exogenous molecules) may affect the nervous system and, accordingly, included in the so-called neuroactive steroid family (Fig. 1).

Irrespective of the tissue where steroids are produced, steroidogenesis, the process leading to steroid production, is characterized by a sequence of reactions in which the final steroid is released only when all

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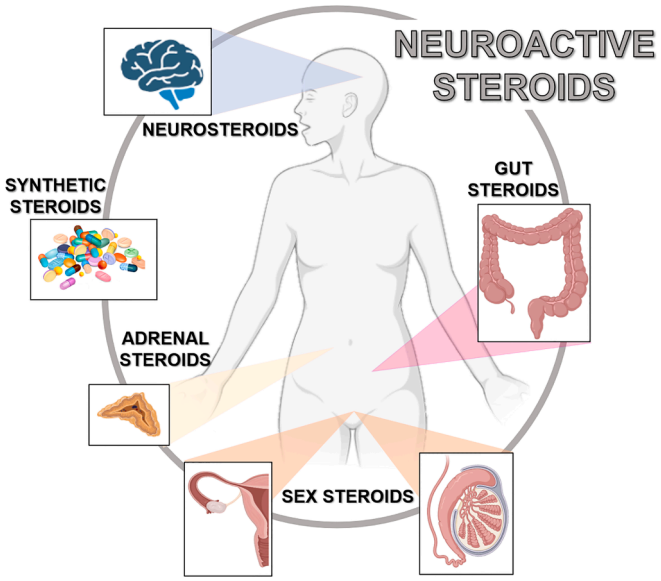

Fig. 1. Representative scheme of neuroactive steroid compounds.

the different steps of steroid synthesis have been concluded. Hence, the final steroid is an enzymatic machinery-dependent product in which steroidogenic enzymes are highly specific for their reactions, regardless of substrate.

Briefly, the steroidogenic process starts with the translocation of cholesterol, which is the precursor of all steroids, into the mitochondria (Fig. 2). This process is mediated by several proteins, but the steroidogenic acute regulatory protein (StAR) is the most relevant. StAR accumulates the free cholesterol molecules on the outer mitochondrial membrane, where other factors participate in cholesterol translocation from the outer to the inner mitochondrial membrane. This view has been then modified, suggesting that StAR can operate cholesterol translocation without the need for additional factors (Selvaraj et al., 2018). Once in the mitochondria, cholesterol is converted into pregnenolone (PREG), the first steroid, by enzymatic reaction operated by cytochrome P450 side chain cleavage (P450scc), which occurs at the matrix side of the inner mitochondrial membrane. As reviewed elsewhere (Luu-The, 2013), PREG can follow the Δ4 or the Δ5 pathway, leading to the production of progesterone (PROG) or dehydroepiandrosterone (DHEA), respectively. The production of PROG and the possibility of having the Δ4 steroids is dependent on the presence of the enzyme 3 beta-hydroxysteroid dehydrogenase (3β-HSD), whereas the production of DHEA is subordinated to the presence of 17 alpha-hydroxylase and 17,20-lyase. Then, DHEA can be converted into the other androgen, testosterone (T), thanks to the 3β-HSD activity. PROG and T can then be further converted into their reduced metabolites, dihydroprogesterone (DHP) and dihydrotestosterone (DHT), by the enzyme 5α-R. Next, the enzyme 3alpha-hydroxysteroid oxidoreductase (3α-HSOR) converts DHP and DHT into allopregnanolone (ALLO) and 3α-diol respectively. T may be also converted by the enzyme aromatase into 17β-estradiol (17β-E) (Fig. 2).

These metabolic conversions are relevant to the mechanism of action of steroids because metabolites can bind to steroid receptors with a different affinity compared with their precursors or can interact with different receptors, as described later.

All of these enzymes are located in the cytosol, more specifically in the smooth endoplasmic reticulum. Once the final steroid is produced, it is immediately released without accumulation, because of the lipid nature of these compounds.

The possibility of a tissue being responsive to a steroid is subordinated to the expression of steroid receptors (Fig. 2). Indeed, in the classical view of steroid action, these molecules exert their effects by modulating gene transcription. This is possible upon binding to their steroid receptors, such as progesterone receptor (PR) and androgen receptor (AR), which are cytosolic transcription factors that reach the nucleus after ligand binding. On the contrary, estrogen receptors (ERs), when acting as transcriptional factors, are mainly located directly in the nucleus. The classical mechanism involves gene transcription and, thus, hours to days to produce effects. However, this classical view cannot account for some more rapid effects exerted by steroid molecules. It has been demonstrated that several steroids can affect the action of membrane-bound receptors (Hara et al., 2015; Paul and Purdy, 1992;

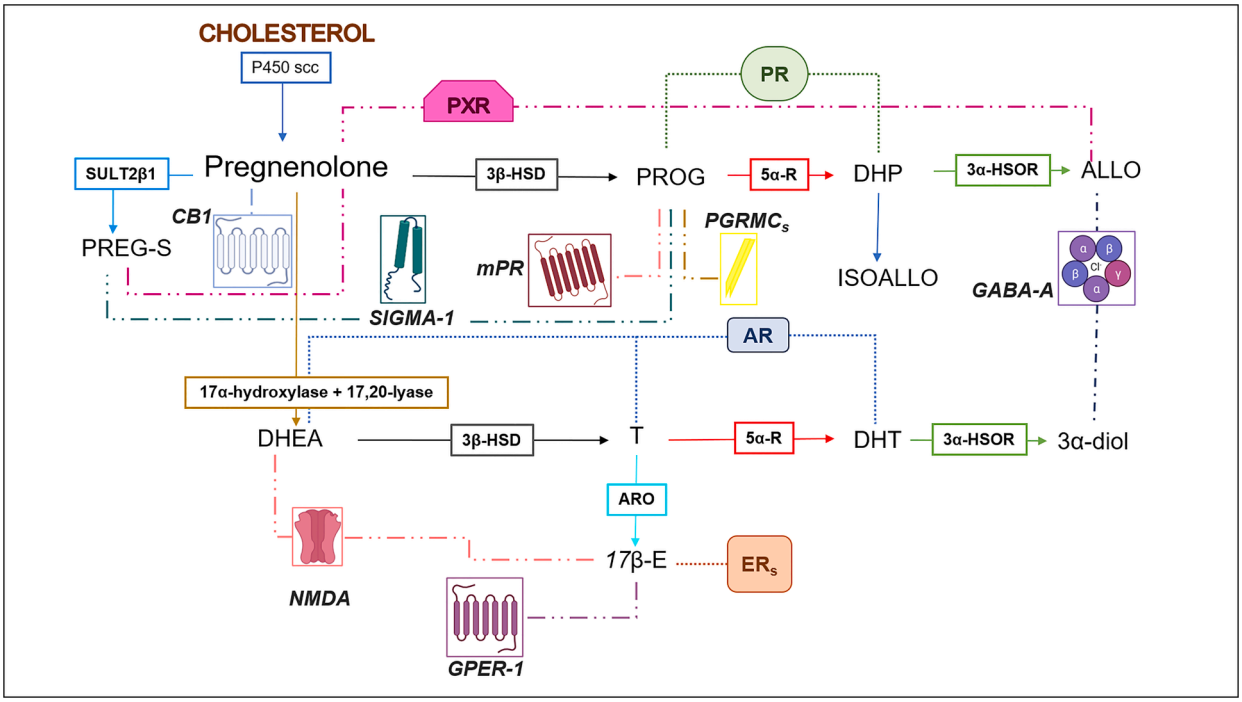

Fig. 2. Steroidogenic pathways and neuroactive steroid-related receptors. See the text for the abbreviations.

Schwartz et al., 2016). This is, for example, the case of ALLO, a PROG metabolite, whose main mechanism of action is gamma-aminobutyric acid (GABA)-A receptor binding (Follesa et al., 2006; Lambert et al., 1995). Interestingly, an allosteric modification alters the binding to the receptor, and the isomer of ALLO, the steroid isoallopregnanolone (ISOALLO), does not bind to the GABA-A receptor but interferes with ALLO binding (Hedstrom et al., 2009; Johansson et al., 2016). Other steroids that bind to membrane receptors are represented by estrogens or PROG. For instance, 17β-E binds ER type alpha also expressed in the membrane (Mazid et al., 2023) and G protein-coupled ER 1 (GPER1) (Fuentes and Silveyra, 2019). 17β-E (Tauboll et al., 2015), as well as DHEA (Bergeron et al., 1996), can potentiate N-methyl-D-aspartate (NMDA) receptor activity. Similarly, PROG can bind to membrane receptors, such as Sigma-1, membrane PRs (mPRs), and PR membrane components (PGRMCs) (Valadez-Cosmes et al., 2016). Other receptors that can be bound by steroids are, for example, the pregnane X receptor (PXR), whose action can be modulated by the sulfate form of PREG. Recently, it was indicated that cannabinoid receptor 1 (CB1) is a target of PREG (Raux et al., 2022) (Fig. 2).

In the central nervous system (CNS), nearly all cell types and brain regions express steroid receptors. Indeed, steroids exert rapid effects on neuronal membrane excitability, through membrane receptors, and long-term transcriptional actions on neurons, affecting the function of astrocytes, oligodendrocytes, microglia, and endothelial cells. These mechanisms impact, besides the well-known actions on reproduction, the mechanisms of learning, memory, synaptic plasticity, and neuronal development both during embryogenesis (Tsutsui et al., 2011) and in adult age, regulating adult neurogenesis in the subventricular zone and in the hippocampus (Fowler et al., 2008; Giachino et al., 2003). In addition, they can regulate oligodendrocyte differentiation and proliferation (Ghoumari et al., 2005; Ghoumari et al., 2003; Jung-Testas et al., 1996), cytoskeletal proteins, and the morphology of neurons and astrocytes (Guerra-Araiza et al., 2007; Reyna-Neyra et al., 2002).

The relevance of neuroactive steroids on brain functions is highlighted in situations presenting alterations in their levels. This happens, for example, in several pathological conditions affecting the CNS. Indeed, several experimental models and clinical studies have reported alterations in neuroactive steroid levels in neurodegenerative and psychiatric disorders, such as multiple sclerosis, Parkinson's disease, Alzheimer's disease, diabetic encephalopathy, stroke, traumatic brain injury, schizophrenia, major and postpartum depression, premenstrual dysphoric disorder, post-traumatic stress disorder, and impulsive aggression (Caruso et al., 2013a; Caruso et al., 2014; Caruso et al., 2008a,b; Corsi et al., 2023; Giatti et al., 2015, 2018a; Lopez-Rodriguez et al., 2015; Lopez-Rodriguez et al., 2016; Melcangi et al., 2012; Melcangi et al., 2014; Schule et al., 2014; Schumacher et al., 2003). Outside the nervous system, steroid receptors are also expressed in the colon (Asavasupreechar et al., 2020; Banibakhsh et al., 2023; Chen et al., 2019; Kliewer et al., 1998; Pfaffl et al., 2003); in fact, the involvement of sex steroids and glucocorticoids in gastrointestinal health and diseases is well established (Hogan et al., 2009; Ji et al., 2008; Kostadinova et al., 2014; Prusator and Chang, 2017). Interestingly, steroids such as PREG (Shah et al., 2007) and PROG (Stegemann et al., 2023) exert neuroprotective and anti-inflammatory effects on the intestine. Moreover, GABA–activated chloride channels modulation by ALLO treatment in a PFS model (Diviccaro et al., 2022b) and by topiramate in an inflammatory bowel disease model (Dudley et al., 2011) reduced inflammation and pathological signs.

3. Steroid environment and gut-microbiota-brain axis

The colon is not only a target for steroids, as mentioned above, but recent scientific evidence supports that it is also able to synthesize PROG, T, and their active metabolites from cholesterol (Diviccaro et al., 2020b). In addition, the higher 3α-HSOR gene expression in the rat colon compared with that in the cerebral cortex, in agreement with the higher ALLO levels in the gastrointestinal tract, is noteworthy. Indeed, this steroid is able to bind GABA-A receptors (Belelli and Lambert, 2005). Interestingly, these receptors are extensively expressed in the gastrointestinal tract (Seifi et al., 2014) and exert a prominent role in gut physiology but they are also promising in the field of neuroimmune interaction (Auteri et al., 2015). Thus, in the gut-microbiota-brain axis, specifically in the communication between the gastrointestinal tract with the CNS and microbiota, the involvement of steroid molecules is plausible and should be highlighted. In this context, it is important to note that, in the last two decades, new evidence about gut-microbiota-brain communication has changed the way some neuroscientists think about the brain. Indeed, the latest findings have supported the involvement of the microbiome in brain function, behavior, and disease (Foster et al., 2016), and for this reason, many neuroscientists have taken more seriously the microbiological field. The mutualism between the microbiome and the host genome brightens the new term "holobiont" as a new concept of human functioning (Theis et al., 2016). The gut-microbiota-brain axis is, in fact, the output of endocrine, nervous, and immune system cooperation where host-microbiota communication is fundamental. Furthermore, the gut microbiome acts as a virtual endocrine organ that arises from its metabolic capacity to synthesize several metabolites that reach the plasma, influencing distal organ function (Clarke et al., 2014). Neurosteroid levels in the brain are affected in germ-free mice (Diviccaro et al., 2021a) and in specific pathogen-free mice (Chu et al., 2021). In agreement, sex steroids also affect the gut bacterial communities (Org et al., 2016; Santos-Marcos et al., 2020), and gonadectomy influences the steroid environment in the brain as well as in the gut, differently depending on the sex (Caruso et al., 2010; Diviccaro et al., 2022a; Giatti et al., 2019). Altogether, these observations support a strict link between steroid molecules and gut microbiota in the regulation of the gut-microbiota-brain axis.

4. Side effects induced by inhibitors of the 5α-reductase

Finasteride (e.g., Propecia or Proscar) and dutasteride (e.g., Avodart) are two inhibitors of the 5α-R. Specifically, finasteride in humans has a higher affinity for type 2 of this enzyme (Finn et al., 2006; Traish et al., 2015) and was approved in 1992 for the treatment of benign prostatic hyperplasia and in 1997 for the treatment of androgenetic alopecia (AGA) (Kaufman et al., 1998). Dutasteride inhibits both 5α-R type 1 and 2 with greater potency than finasteride (Frye et al., 1998) but with similar efficacy on benign prostatic hyperplasia symptoms. Treatment with these drugs has been associated with the onset of different side effects. In particular, the most affected domains are related to sexual function. Indeed, sexual adverse events have been reported in patients with benign prostatic hyperplasia and treated with finasteride (Bruskewitz et al., 1999; Edwards and Moore, 2002; Fertig et al., 2017a,b; Fwu et al., 2014; Marberger, 1998; Nickel et al., 1996; Traish et al., 2015; Wilton et al., 1996) or dutasteride (Clark et al., 2004; Desgrandchamps et al., 2006; Fertig et al., 2017a,b; Kaplan et al., 2012; Roehrborn et al., 2002). Moreover, observational studies and clinical reports, described similar sexual complaints in male patients treated with these inhibitors for AGA (Belknap et al., 2015; Choi et al., 2016; Fertig et al., 2017a,b; Kaufman et al., 1998; Tsunemi et al., 2016). These symptoms include decreased or loss of libido, disorders of ejaculation, erectile dysfunction, testicular atrophy, orgasmic disorders, and hypogonadism, even if not confirmed by changes in T and DHT plasma levels. They are associated with increased self-harm, slow cognition, psychological pathology, changes in emotional affect, depression, sleep disturbances, skin rash, and metabolic abnormalities (Diviccaro et al., 2020a; Motofei et al., 2013; Motofei et al., 2016; Motofei et al., 2017; Traish et al., 2015; Unger et al., 2016; Welk et al., 2017).

5. Post-finasteride syndrome (PFS)

Recent observations also demonstrated that, in a subset of AGA

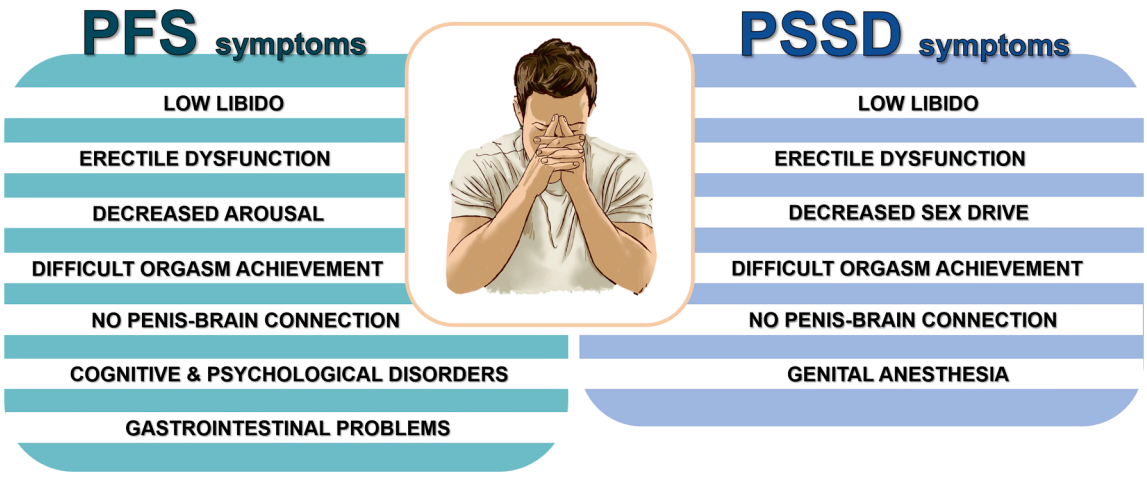

Fig. 3. Main symptoms reported by PFS and PSSD patients.

patients, side effects associated with finasteride treatment may also persist despite the drug suspension, and this happens irrespective of the patient age, drug dose, or duration of the treatment, inducing the so-called PFS.

5.1. What PFS patients reported

Several literature data have been obtained by questionnaires in which patients with PFS self-reported their symptomatology (Fig. 3) (Altomare and Capella, 2002; Asanad et al., 2022; Baas et al., 2018; Chiriaco et al., 2016; Diviccaro et al., 2020a; Fertig et al., 2017a,b; Giatti et al., 2018b; Gul et al., 2023; Healy et al., 2018; Kiguradze et al., 2017; Leliefeld et al., 2023; Shin et al., 2019; Sorbellini et al., 2018; Traish, 2020; Walf et al., 2018). In particular, as reported by Irwig and colleagues, low libido, erectile dysfunction, decreased arousal, and difficulty in achieving orgasm were mainly reported (Irwig and Kolukula, 2011). In general, these adverse events did not resolve in most subjects after 9 and 16 months of withdrawal from the drug (Irwig, 2012b). In another study, symptoms were collected in five categories: physical, sexual libido, disorder of the penis and testes, cognitive disorders, and psychological disorders (Ganzer et al., 2015). Gynecomastia represented 70 % of cases in the physical category, decreased sex drive 93 % of cases in the sexual libido category, diminished semen volume and force 82 % of cases in the disorder of penis and testes category, mental cloudiness or brain fog 75 % of cases in the cognitive disorders category, and elevated anxiety 74 % of cases in the psychological disorders category (Ganzer et al., 2015). Several subjects also reported suicidal ideation (63 %) (Ganzer et al., 2015). Another study reported a lack of connection between the brain and penis during treatment in 22 % of patients, and this percentage increased to 59 % at interview time (i.e., at least three months after finasteride discontinuation) (Giatti et al., 2018b). A similar pattern was observed for the loss of libido and sex drive, difficulty in achieving an erection, and for genital numbness or paresthesia (Giatti et al., 2018b). In addition to sexual problems, a further study reported psychological complaints (such as decreased self-confidence, irritability or easily flying into a rage, nervousness, agitation, inner restlessness, depression, hopelessness, feelings of worthlessness, suicidal thoughts, anxiety, panic attacks, sleep problems), muscular problems (tics, muscle spasms and fasciculation, tremors, involuntary muscle tension and contraction, chronic fatigue, weakness, ataxia, joint pain, and muscular ache), physical alterations (dizziness, headache, migraine, head pressure, decreased body temperature), and cognitive complains (decreased initiative and difficulty in concentration, mental confusion, forgetfulness or loss of short-term memory, losing train of thought or reasoning, slurred speech or stumbling over words) (Melcangi et al., 2017) (Fig. 3).

5.2. What has been demonstrated in PFS patients

As mentioned above, the observations presented in the literature are mainly based on symptoms self-reported by patients with PFS. Indeed, only a few studies have clinically evaluated these symptoms. For instance, impaired sexual function was confirmed by the International Index of Erectile Function and Male Sexual Health Questionnaire in 25 PFS patients (Basaria et al., 2016). In addition, another study performed on 16 PFS patients reported that 10 of them showed severe erectile dysfunction, while 6 patients showed mild-moderate one (Melcangi et al., 2017). A further study performed in 25 subjects with a history of inhibitors of 5α-R use for AGA vs. 28 controls indicated a significant difference in the total International Index of Erectile Function score; 16 of these AGA patients had a vascular abnormality on penile duplex Doppler ultrasound, and the AGA group had a higher median total Patient Health Questionnaire-9 than controls (Khera et al., 2020).

In agreement with genital numbness or paresthesia reported by the PFS patients, evidence of neuropathy involving the peripheral neurogenic control of erection was reported. Indeed, abnormal somatosensory evoked potentials of the pudendal nerve were reported in 25 % of PFS patients considered (Melcangi et al., 2017).

Clinical studies have also confirmed depressive symptoms. For instance, using the PHQ-9 depression scale, Beck Depression Inventory, and Hamilton Depression Scale 17 (Basaria et al., 2016; Irwig, 2012a) or K-10, Mini-International Neuropsychiatric Interview, and Beck Depression and Anxiety Inventories (Melcangi et al., 2017), the presence of DSM-IV major depressive disorder was confirmed in PFS patients. In addition, functional Magnetic Resonance Imaging (fMRI) in PFS patients confirmed abnormalities in brain regions implicated in depression and sexual arousal, such as the nucleus accumbens and prefrontal cortex (Basaria et al., 2016).

Finasteride treatment as well as its suspension can affect neuroactive steroid levels. This is interesting because, also in psychiatric disorders, plasma neuroactive steroid levels are modified (Bristot et al., 2014; Carta et al., 2012; Eser et al., 2006; Schule et al., 2011; Vallee, 2016). Indeed, in patients with AGA, changes in the plasma levels of steroids (i.e., decrease in DHT and increase in T and androstenedione) were reported during treatment with finasteride (Duskova et al., 2010). Moreover, three different studies were performed on PFS patients, assessing by liquid chromatography-tandem mass spectrometry (LC-MS/MS) the plasma and cerebrospinal fluid (CSF) levels of several steroids and showing the broad consequences of finasteride treatment (Caruso et al., 2015; Melcangi et al., 2013; Melcangi et al., 2017). For instance, in the plasma of PFS patients compared with those observed in healthy patients, lower levels of DHP and ALLO and higher levels of PREG, DHEA, and T were reported (Melcangi et al., 2017). Further observations

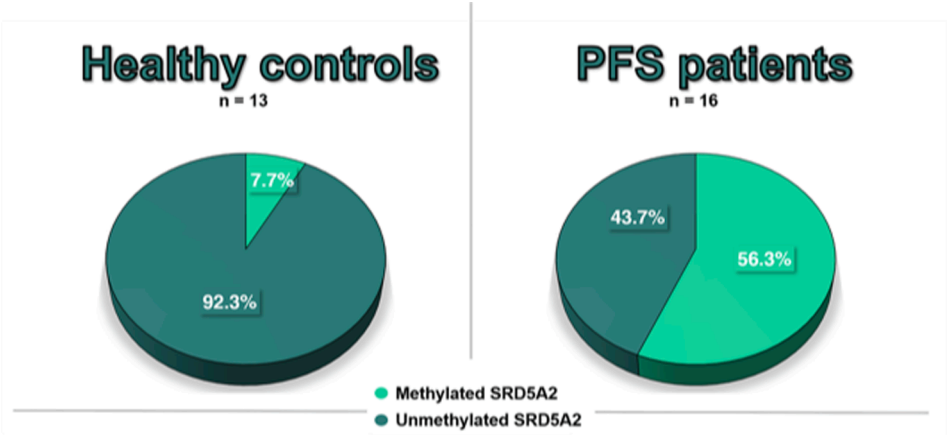

Fig. 4. Representative pie chart of methylation analysis in cerebrospinal fluid of PFS patients compared to healthy controls.

performed in different PFS patient cohort assessing serum levels, showed no changes in T and DHT (Basaria et al., 2016) or low levels of both androgens in only 9% of subjects (Irwig, 2014). Interestingly, the pattern in plasma did not exactly reflect what was observed in CSF (Melcangi et al., 2017). For instance, in contrast to what was observed in CSF, the plasma levels of PREG were significantly increased and those of PROG and T metabolites, such as DHT, 3α-diol, and 17β-E, were unaffected. In addition, the levels of ALLO that were unaffected in CSF showed a significant decrease in plasma. These findings were not surprising because, as demonstrated in various physiological or pathological conditions in several experimental models, neuroactive steroid changes occurring in plasma did not reflect exactly what occurs in CSF and the nervous system (Caruso et al., 2013b; Melcangi et al., 2014; Melcangi et al., 2016).

Not only the steroid levels themselves but also their mechanisms of action may be altered by finasteride. For instance, AR upregulation occurred in the prostate of patients treated with finasteride for benign prostatic hyperplasia (Hsieh et al., 2011) as well as in the prepuce of AGA patients showing persistent side effects (i.e., PFS patients) (Di Loreto et al., 2014). In addition, two polymorphisms in the AR gene, (CAG) rs4045402 and (GGN) rs318869, have been reported to be more frequent among AGA and PFS patients (Cecchin et al., 2014). As further demonstrated, short and/or long (CAG)n and (GGN)n repeats in the AR gene also have different frequencies according to the symptomatology reported by PFS patients (Cauci et al., 2017). Recent observations, obtained by microarray in penile skin samples of 26 PFS patients, have shown that 1.446 genes and 2.318 were overexpressed and underexpressed, respectively in PFS patients vs. healthy controls (Howell et al., 2021), suggesting that gene expression differences may be a potential etiology of side-effects occurring in PFS. In addition, a further study performed in blood samples from 3 PFS patients, suggested five potential risk genes (i.e., *CA8*, *VSIG10L2*, *HLA-B*, *KRT38*, and *HLA-DRB1*) (Li et al., 2022).

Epigenetic modifications also seem to be involved (Melcangi et al., 2019). Indeed, methylation analysis of the promoter region of the genes coding for type 1 (i.e., *SRD5A1*) and type 2 (i.e., *SRD5A2*) 5α-R performed in plasma and CSF of 16 PFS patients, indicated that *SRD5A2* promoter was more frequently methylated in CSF of PFS patients compared with healthy controls (56.3 % versus 7.7 %; Fig. 4). Importantly, this is tissue-specific methylation. Indeed, differences in *SRD5A2* promoter methylation have not been observed in plasma. Interestingly, both in plasma and CSF, the *SRD5A1* promoter was not differently methylated (Melcangi et al., 2019).

As explained in detail above (see the section "steroid environment and gut-microbiota-bran axis") host-microbes communication is fundamental and hence, the fluctuation of steroid levels may be associated with psychiatric disorders (Chen et al., 2021; Diviccaro et al., 2021a) as well as gut microbiome shaping (Huang et al., 2015; Tetel et al., 2018), which in turn contribute to the manifestation of affective disorders (Grau-Del Valle et al., 2023). In this context, it is important to highlight that finasteride treatment and suspension also affected intestinal microbiota composition. Indeed, as demonstrated in the fecal microbiota of 23 PFS patients vs. 10 healthy male subjects (Borgo et al., 2020), the α-diversity was significantly lower in the PFS group, according to the metrics Chao1 and Faith's PD, suggesting a reduction in the richness and diversity of gut microbiota structure. Moreover, β-diversity analysis based on unweighted UniFrac distance showed significant clustering of PFS patients partially confirmed by the weighted UniFrac distance, underlining the significant differences in terms of microbial composition. In particular, we reported significant changes at the phylum (i.e., decrease in *Proteobacteria* and *Actinobacteria),* family (i.e., decrease in *Acidaminococcaceae*, *Enterobacteriaceae*, *Bifidobacteriaceae*, *Christensenellaceae*, and *Desulfovibrionaceae* families), and genus levels (i.e., decrease in *Subdoligranulum*, *Phascolabacterium*, *Ruminococcaceae* UCG-002, and *Escherichia-Shigella*) (Borgo et al., 2020). In addition, in one of the sub-clusters of PFS patients analyzed, *Ruminococcaceae UCG-005* and *Faecalibacterium* were significantly decreased compared with healthy subjects. This is interesting because alterations in these populations are associated with depressive symptomatology (Liu et al., 2020) and gut dysbiosis (Sokol et al., 2008). As mentioned above, PFS patients showed depression, sleep disturbance, and sexual dysfunction. Indeed, alterations in gut microbiome have been reported in depressive disorders (Horne and Foster, 2018; Liang et al., 2018; Liu et al., 2016), circadian and sleep disturbances (Li et al., 2018; Thompson et al., 2020; Voigt et al., 2014), and erectile dysfunction (Li et al., 2017; Okamoto et al., 2020; Osman, 2019; Tirandaz et al., 2018).

5.3. *Observations in the animal models*

To further explore the effects of this drug on steroid levels, adult male rats were subcutaneously treated with finasteride at a dose of 3 mg/kg for 21 days. Neuroactive steroid levels were assessed in the plasma, CSF, and brain structures, such as the cerebral cortex, cerebellum, and hippocampus, 24 h after the last finasteride injection or one month after withdrawal, to mimic a chronic treatment and suspension phase, respectively (Giatti et al., 2016). After treatment, few alterations were observed. In plasma, an increase in ISOALLO and 17β-E levels, associated with a decrease DHT levels, were reported. In the CSF, PREG and 3β-diol levels were increased, whereas those of 3α-diol decreased. The situation is different in brain structures (Giatti et al., 2016). Indeed,

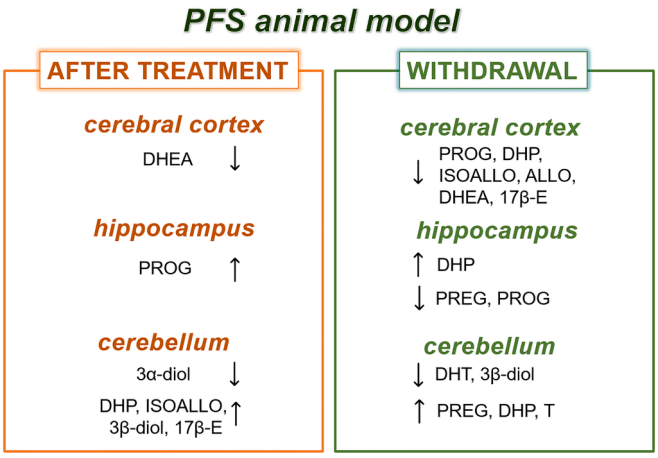

Fig. 5. Alterations in neuroactive steroid levels occurring in brain areas of finasteride-treated male rats: effects after treatment and at withdrawal.

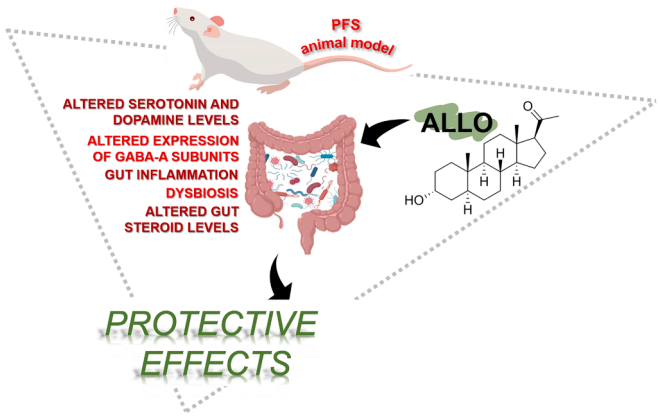

Fig. 6. Gastrointestinal parameters in PFS experimental model and local anti-inflammatory effect of allopregnanolone.

in the cerebral cortex, only a decrease in DHEA was detected, whereas in the hippocampus, an increased level of PROG was observed; in the cerebellum, only 3α-diol levels were decreased, whereas those of DHP, ISOALLO, 3β-diol, and 17β-E increased (Fig. 5). The situation after the withdrawal period was still different, with more alterations observed in comparison with those detected after subchronic treatment. In particular, in plasma, a reduction of the levels of PROG, ALLO, DHT, and 3α-diol was observed, whereas in the CSF, only DHT presented a decrease and DHEA, T, and 17β-E an increase. Thus, the animal model presents some similarities in the alterations of neuroactive steroid levels observed after suspension compared to patients, having a similar decrease in plasma levels of ALLO, and DHT in CSF, as well as an increase in the CSF levels of DHEA and T. Considering the brain structures at withdrawal, in the cerebral cortex, the levels of several neuroactive steroids (i.e., PROG, DHP, ISOALLO, ALLO, DHEA and 17β-E) were decreased (Fig. 5). In the cerebellum, a decrease in the levels of DHT and 3β-diol and an increase in those of PREG, DHP, and T were observed. Finally, in the hippocampus, increased levels of DHP coupled with decreased levels of PREG and PROG have been detected (Fig. 5) (Giatti et al., 2016).

The effect of finasteride treatment and its withdrawal was also evaluated on the gut steroid levels. As demonstrated, drug treatment not only decreased DHT levels but also increased its precursor (i.e., T) (Diviccaro et al., 2022b). Interestingly, even if no differences in PREG, PROG, DHP, ISOALLO, DHEA, and 17b-E were detected, a significant decrease in 3α-5α-reduced metabolites of PROG and T (i.e., ALLO and 3α-diol) was reported (Diviccaro et al., 2022b). A different pattern of gut steroids at finasteride withdrawal was observed. An increase in PREG levels associated with a persistent decrease in ALLO levels has been reported, suggesting a local relationship between these two molecules in gut inflammation (Diviccaro et al., 2022b). Indeed, in this context, it is important to highlight that analysis of gut microbiota at the withdrawal reported that, although α-diversity metrics were not modified, changes in β-diversity, based on weighted and unweighted UniFrac distances, observed during treatment, persist through time. Interestingly, the finasteride discontinuation leads to a decrease in the *Ruminococcaceae, Oscillospira*, and *Lachnospira* bacterial taxa in fecal samples (Diviccaro et al., 2019). A decrease in these taxa has been previously associated with inflammatory processes (Lo Presti et al., 2019; Qin et al., 2022; Vich Vila et al., 2018; Xu et al., 2021; Yilmaz et al., 2019a; Yilmaz et al., 2019b). In addition, *Oscillospira* is a class of microorganism capable of producing short-chain fatty acids such as butyrate, which is an important reference indicator for screening "next-generation probiotics"(Yang et al., 2021), thus, its decrease suggests a putative dysfunction in short-chain fatty acids production in the PFS model with possible harmful outcome. Interestingly, finasteride treatment affects depressive-like behavior in adult male rats associated with a decrease of adult hippocampal neurogenesis and an increase in neuroinflammation (Diviccaro et al., 2019). In both human and animal models, depressive symptoms are associated with reactive gliosis (Yirmiya et al., 2015) and altered hippocampal morphology (Stockmeier et al., 2004). Collectively, it is feasible that the neuroinflammatory environment, following microglia and astrocyte activation, together with depressive symptoms might also be exacerbated by a dysfunction of microbiota-brain communication.

In addition, we reported that, after therapy discontinuation, the phylum of *Firmicutes* decreased, whereas *Bacteroidetes* increased compared with basal values in rats (Diviccaro et al., 2019). *Bacteroidetes* phylum are often increased in inflammatory bowel disease and are associated with its progression and development (Stojanov et al., 2020). For instance, mucosal biopsies from inflamed and non-inflamed regions of the intestine from patients with inflammatory bowel disease and healthy individuals revealed increased *Bacteroidetes* and reduced *Firmicutes* abundance (Walker et al., 2011).

We recently further confirmed that, at finasteride withdrawal, gut inflammation may occur. Indeed, an increase in the proinflammatory cytokines interleukin-1 beta (IL-1β) and tumor necrosis factor alpha (TNF-α), as well as a decrease in dopamine levels and an increase in serotonin levels, were observed in the colon of adult male rats (Diviccaro et al., 2022b). These changes, as reported in other experimental conditions (Chen et al., 2022; Hamamah et al., 2022; Mawe and Hoffman, 2013; Yao et al., 2022), may suggest a local inflammation in PFS patients. For instance, in patients with irritable bowel syndrome, there is a decreased transcription of the serotonin transporter (SERT), resulting in elevated serotonin levels, which ultimately causes diarrhea and discomfort (Sikander et al., 2009; Vahora et al., 2020a, b). In addition, an increase in L-dopa levels and a decrease in dopamine levels have been reported in patients with inflammatory bowel disease, indicating low L-amino acid decarboxylase activity (Magro et al., 2002). Impairment of the dopaminergic system as a feature of inflammatory bowel disease pathogenesis is supported by the finding that dopamine agonists may rescue normal function (Tolstanova et al., 2015).

It is important to highlight that ALLO treatment, in agreement with its anti-inflammatory features observed in other experimental models (Diviccaro et al., 2021b; Fujii et al., 2021; Giatti et al., 2012; He et al., 2004; Yilmaz et al., 2019b), is protective against the alterations observed during finasteride withdrawal in adult male rat colon (Fig. 6). Indeed, at the drug suspension, the decrease in ALLO levels observed in the gut correlates with the increase in IL-1β and TNF-α, serotonin, and a decrease in dopamine. Treatment with this steroid significantly decreased the gene expression of these pro-inflammatory cytokines, and the levels of serotonin in the colon of adult male rats. These effects probably imply the capacity of this steroid to modulate GABA-A receptors. Indeed, GABA-A receptors are enriched within the enteric

nervous system (Seifi et al., 2014) and regulate stress-induced gastrointestinal inflammation (Auteri et al., 2015; Seifi et al., 2018). We have demonstrated that changes in the gene expression of some subunits of the GABA-A receptor in adult male rat colon occurred during finasteride withdrawal (i.e., α3, β2, β3, and δ) and that ALLO treatment counteracted some of these changes (i.e., β2, β3, and δ subunits).

A local relationship between ALLO and PREG has also been observed. Indeed, ALLO treatment was able to significantly counteract the increase in PREG levels occurring at finasteride withdrawal, and it was associated with a decrease in the gene expression of the enzyme converting cholesterol into PREG (i.e., P450scc). As we demonstrated, the increase in PREG levels at withdrawal was positively correlated with inflammation. Therefore, because of the anti-inflammatory features of this steroid (Murugan et al., 2019; Weng and Chung, 2016), it is possible to hypothesize that the observed PREG increase could be ascribed to a possible compensatory anti-inflammatory response, to cope with the negative pattern also induced by finasteride withdrawal.

Another important aspect still unexplored is the "GUSome", well-known as the β-glucuronidases (GUS) enzymes of intestinal bacteria, which can drastically alter the pharmacological properties of drugs (Biernat et al., 2019; Pollet et al., 2017), also affecting the levels of active deconjugated metabolites, such as free-steroids. In this context, is important to report that the microbiome also regulates the availability of sex steroids in the gut environment, especially for the metabolism of androgens (Collden et al., 2019; Jaggar et al., 2020). Sex steroids can be conjugated in the liver to increase their solubility and promote the enterohepatic cycle for their excretion; here microbiota can affect the mechanisms of deconjugation, thus altering steroid clearance and content. Indeed, dysbiosis is a crucial aspect to be considered, not only for their active metabolites but also for the microbiome-encoded enzymes essential to human health. Although, the causal relationship between sex steroid level alterations observed in the colon (Diviccaro et al., 2022b) and plasma (Giatti et al., 2016) with microbiome dysbiosis is not demonstrated, it should not be excluded.

Altogether, these observations suggest a crucial role of the gut-brain axis, and its signals (i.e., steroids, neurotransmitters and microbiota) in PFS. In particular, for the erectile dysfunction (ED) observed in PFS patients, it is important to highlight that sexual dysfunction may be related not only to altered levels of sex steroids and neurotransmitters (Andersson, 2011; de Souza et al., 2022) but also to alterations in gut microbiota (Li et al., 2021; Okamoto et al., 2020; Osman, 2019; Tirandaz et al., 2018). We have recently observed that finasteride treatment in male rats induces molecular alterations associated with ED, not only in plasma (i.e., decreased levels of DHT and epinephrine, and increased levels of norepinephrine), but also directly in the corpus cavernosum (i.e., increased levels of T and decreased levels of DHT, 5α-R type II, nitric oxide (NO) synthase activity, NO_2 levels, and ornithine transcarbamylase activity) (Diviccaro et al., 2023). Interestingly, these molecular alterations did not occur in the corpus cavernosum at withdrawal (Diviccaro et al., 2023). Therefore, these data suggest that the sexual side effects of PFS are more related to dysfunction in a sexual central control rather than a peripheral compromised condition. Indeed, observations obtained in PFS patients and in male rats after finasteride suspension show the nervous system as an important target, with alterations that could be associated with sexual dysfunction, such as depressive symptomatology and peripheral neuropathy (Basaria et al., 2016; Caruso et al., 2015; Diviccaro et al., 2019; Diviccaro et al., 2020a; Melcangi et al., 2019; Melcangi et al., 2017). Moreover, it is important to highlight that male sexual behavior (e.g., sexual motivation and reward to sexual performance) is controlled by complex neural circuits (Andersson, 2011; Argiolas and Melis, 2013). Therefore, future experiments will be important to explore whether finasteride withdrawal affects these circuits and their relationship in the context of the signals of the gut-brain axis.

5.4. Side-effects induced by antidepressants

Among antidepressants, SSRIs, like citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline, represent efficacious drugs with good tolerance. Therefore, they are frequently prescribed for depression, anxiety, obsessive–compulsive, panic and post-traumatic disorders, premenstrual syndrome, and premenstrual dysphoric disorder. In addition, several off-label applications, such as migraine, body dysmorphic disorder, inflammatory bowel disease, impulse-control disorder, paraphilias, hypersexuality, as well as premature ejaculation have been proposed for SSRIs (Jannini et al., 2022). However, these drugs also show a variety of side effects, where the most frequent are sleeping problems, weight gain, and sexual problems (Atmaca, 2020; Edinoff et al., 2021; Giatti et al., 2018b; Hirschfeld, 1998; Jannini et al., 2022; Piazza et al., 1997; Rosen et al., 1999; Segraves and Balon, 2014; Tanrikut et al., 2010). In particular, some studies reported a high incidence of SSRI-induced sexual side effects (about 59 %), especially in patients treated for depression (Atmaca, 2020; Haberfellner, 2007; Montejo et al., 2001; Montejo-Gonzalez et al., 1997; Williams et al., 2010).

The negative sexual symptomatology described after the use of this class of drugs affects both sexes. Indeed, some differences in the symptoms have been reported, with men suffering at a higher rate compared to women for sexual dysfunction, whereas in women this symptom is more intense (Montejo-Gonzalez et al., 1997). Moreover, women more frequently report sexual arousal dysfunction, while men have more likely deficits in sexual desire and orgasm (Serretti and Chiesa, 2009).

5.5. Post-SSRI sexual dysfunction (PSSD)

Side effects induced by SSRI treatment generally disappear after drug discontinuation. However, in some patients, this symptomatology may also persist after stopping the drug with the occurrence of the PSSD (Bahrick, 2008; Bala et al., 2018; Csoka et al., 2008; Csoka and Shipko, 2006; Gul et al., 2023; Healy, 2019; Klaas et al., 2023; Patacchini and Cosci, 2021; Peleg et al., 2022; Reisman, 2017; Rothmore, 2020). Sexual symptoms in PSSD include decreased libido and sex drive, weak or non-pleasurable orgasm, genital anesthesia, erectile dysfunction, as well as a lack of connection between the brain and penis (Fig. 3) (Ben-Sheetrit et al., 2015; Ben-Sheetrit et al., 2023; Giatti et al., 2018b Healy et al., 2022; Laumann and Waite, 2008; Rosen et al., 1999). This condition does not seem to be dependent on the SSRI used, on the dose, or on the indication for the prescription of the drug (Bala et al., 2018; Reisman, 2017).

It is noteworthy to highlight that literature reports describing PSSD symptoms are focused on male symptomatology. To our knowledge, very limited reports indicate the existence of this condition in women (Bala et al., 2018; Csoka et al., 2008; Ekhart and van Puijenbroek, 2014; Healy, 2018; Hogan et al., 2014). However, in online forums and blogs, many female patients report the presence of persistent sexual side effects. Thus, it would be important to improve the study of this issue also in women and female animal models.

5.6. What we know about the etiopathogenesis of SSRI-induced sexual dysfunction and its persistence (PSSD)

The mechanisms causing sexual dysfunction during SSRI treatment are still almost unknown, therefore different hypotheses have been proposed. For instance, one takes into consideration the serotoninergic inhibitory activity on mesolimbic dopamine release related to the control of sexual behavior. Indeed, dopamine facilitates sexual motivation and sexual behavior (Andersson, 2011; Hull et al., 2004). Imaging studies further support the hypothesis of a link between serotonin and dopamine to explain SSRI-induced sexual dysfunction. Indeed, fMRI and positron emission tomography reported that, in the treatment of depression, these drugs specifically modulate brain regions and circuits

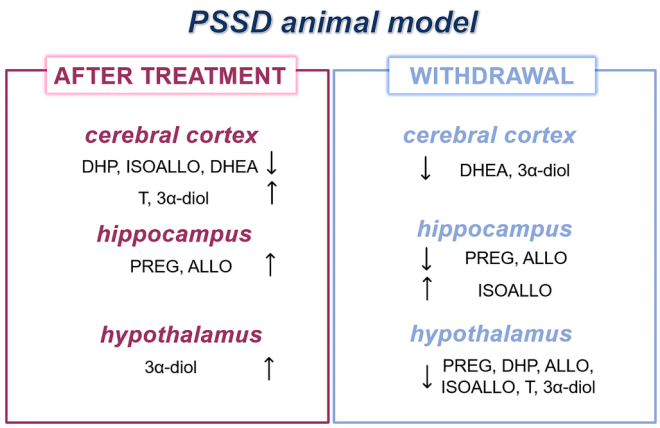

Fig. 7. Alterations in neuroactive steroid levels occurring in brain areas of paroxetine-treated male rats: effects after treatment and at withdrawal.

involved in sexual behavior (Graf et al., 2014). In agreement, cerebral activation in response to erotic video clips in healthy volunteers taking SSRIs showed that areas involved in different phases of sexual functioning and the reward system were affected (Abler et al., 2012; Abler et al., 2011). These latter studies, even if conducted on healthy subjects, strengthen the concept of dopamine and serotonin involvement in the development of sexual dysfunction under SSRI medications. In line with this hypothesis, results obtained in male rats, indicate that paroxetine treatment was associated with an important decrease in the activity of dopaminergic circuits present in cerebral areas associated with sexual performance (Santana et al., 2019). Another hypothesis took into consideration a personal predisposition, linked to genetic variants, to develop sexual dysfunction. Indeed, depressed patients treated with citalopram and reporting sexual problems presented polymorphisms in genes related to the glutamatergic system that correlate to decreased libido and difficulties in achieving erections and orgasms (Perlis et al., 2009). Serotonin neurotoxicity was also hypothesized. Indeed, ecstasy, which stimulates serotonin release and inhibits its reuptake, produces axonal damage leading to persistent sexual alterations (Ben-Sheetrit et al., 2015). Furthermore, endocrine abnormalities in the hypothalamic-pituitary-testis axis of depressed patients treated with SSRIs (i.e., low serum levels of gonadotropins and testosterone, and elevated levels of prolactin) were observed, with a worse profile in patients specifically reporting sexual problems (Safarinejad, 2008). Indeed, in vitro studies demonstrate that SSRIs may inhibit dopamine release through both serotonin-dependent and independent actions, thus in turn promoting prolactin secretion (Lyons et al., 2016). In addition, SSRI treatment, and in particular paroxetine, worsens spermatogenesis in male rats (Erdemir et al., 2014).

Furthermore, epigenetic mechanisms have been also proposed (Csoka and Szyf, 2009). Indeed, as demonstrated in cultured human cells (i.e., HEK-293), chronic exposure to citalopram, showed significant differential methylation (Kanherkar et al., 2018). Finally, a recent paper has reported that paroxetine treatment in adult male rats impaired testicular steroidogenesis (i.e., increasing estrogen/T ratio) and macrophage polarization. Interestingly these testicular changes were not recovered with the suspension of drug treatment (Beltrame et al., 2023).

Even if these theories seem to be plausible in the context of altered sexual function during SSRI treatment, it is not clear if they can account also for the persistence of sexual problems reported by PSSD patients. Clinical studies in PSSD patients addressing the reward system and the neurobiology of dopamine and serotonin circuits are urgently needed.

5.7. Steroid molecules, gut microbiota and PSSD

Data from the literature indicates that SSRI treatment (like for instance fluoxetine and paroxetine) affects steroid levels in the brain of depressed people and experimental models, and this could account, at least in part, for antidepressant therapeutic ability (Uzunov et al., 1996; Uzunova et al., 1998). To evaluate the potential effect of antidepressant treatment and its withdrawal on neuroactive steroid levels in a physiological setting, we treated adult male rats with paroxetine, 10 mg/kg *per os* for 14 days and neuroactive steroid levels after the last treatment and after a month of withdrawal were evaluated (Giatti et al., 2021a). Interestingly, after the subchronic treatment with paroxetine, we observed few alterations in the levels of neuroactive steroids compared to the withdrawal. Thus, after 14 days of paroxetine treatment, no alterations were detected in plasma, while only a decrease in 3α-diol and an increase in 17β-E levels were observed in the CSF. In the hippocampal region, increased levels of PREG and ALLO were observed, while in the hypothalamus, only 3α-diol was altered, with an increase in its levels (Fig. 7). The cerebral cortex is the brain region where the highest number of variations were identified (Fig. 7). Indeed, DHP, ISOALLO, and DHEA levels were decreased, while those of T and 3α-diol were increased (Giatti et al., 2021a). A different situation was observed at the withdrawal, where more alterations have been detected in brain regions (Fig. 7). Indeed, also at this time point, only a decrease in the levels of 17β-E was observed in the CSF while in plasma no alterations have been reported. In the hippocampus, a decrease in PREG and ALLO levels was coupled to an increase of those of the 3β-isomer of ALLO, ISOALLO. Interestingly, in the hypothalamus and the cerebral cortex, only decreased levels were detected. Thus, while the levels of the androgens (i.e., DHEA and 3α-diol) were altered in the cerebral cortex, in the hypothalamus we observed a variation in the levels of PREG, DHP, ALLO, ISOALLO, T, and 3α-diol (Fig. 7) (Giatti et al., 2021a).

Interestingly, the levels of PREG, the first steroid produced from cholesterol, were reduced in both the hippocampus and hypothalamus. However, the mechanism producing this alteration was different in the two brain areas considered. Indeed, hippocampal PREG levels were reduced because the treatment withdrawal produced an increase in its sulfate form, the PREG-S (Giatti et al., 2021a). This increase was confirmed by the increase in the expression levels of the enzymes deputed to the conversion in the sulfate form (sulfotransferase family 2B member 1 - SULT2β1) and by the decrease of the enzyme for the *retro*-conversion in the free-form (steroid sulfatase – STS) as well as by the increase in PREG-S levels detected by LC-MS/MS. In the hypothalamus, instead, PREG levels were reduced probably due to the increase in the levels of oxysterols observed in this tissue (Giatti et al., 2021a). Indeed, oxysterols represent the oxidized form of cholesterol and some of them, and the 27-hydroxy cholesterol in particular, are produced within the mitochondria, thus reducing the substrate (i.e., cholesterol) available to form the steroids.

Interestingly, off-label use of antidepressant drugs for functional gastrointestinal disorders is also highlighted (Gershon and Tack, 2007). In particular, serotonin is prevalently synthesized by the gastrointestinal tract rather than CNS as a neurotransmitter involved in the gut motility and visceral sensitivity. Despite this, the paroxetine-associated effect on gut steroids was still not investigated in male adult rats. Thus, in our animal model we reported that, collectively, two distinct patterns after treatment and at withdrawal were observed (Diviccaro et al., 2022c). Briefly, the levels of PREG were not affected by SSRI treatment although PROG and its metabolites and androgens as well were modified. Indeed, a significant reduction of PROG, followed by an increase in DHP and ISOALLO was observed. No differences in ALLO levels were detected in paroxetine-treated rats compared to controls. However, DHEA, androgen precursor, significantly increased after paroxetine treatment even if T levels were not modified. On the other hand, a significant decrease of the 5α-reduced metabolite of T, DHT was detected, followed by a decrease of 3α-diol. Moreover, no differences in the T metabolite, 17β-E, were reported. Interestingly, after one month of paroxetine withdrawal, the gut steroid levels were restored. However, a significant increase in PREG levels by SSRI withdrawal was observed.

Notably, a link between SSRIs with sex steroids (Ayala et al., 2018;

Munkboel et al., 2018) and microbiota (Dethloff et al., 2020; Sjostedt et al., 2021; Zhang et al., 2021) was already highlighted. However, no studies about paroxetine treatment and its suspension investigate the microbiota composition in correlation with gut steroid production. On this basis, the composition of gut microbiota in stool samples was also characterized in an experimental model of PSSD (Diviccaro et al., 2022c).

The gut microbiota composition analysis revealed that 14-day paroxetine treatment in male adult Sprague-Dawley rats changed β-diversity, based on unweighted but not weighted UniFrac distances. On the contrary, α-diversity metrics were not affected by SSRI treatment (Diviccaro et al., 2022c). As concerning the gut microbiota, the most relevant taxa reduced by paroxetine treatment were *Clostridia UCG-014* and *Clostridiales* families and *Gastranaerophilales* (belonging to *Vampirivibrionia* class). Interestingly, an opposite trend of these taxa can be associated with colitis experimental models (Wu et al., 2021) and gut epithelial inflammation (Wang et al., 2018), suggesting a putative microbiota-associated anti-inflammatory effect during the treatment. This effect is in line with the off-label indication for functional gastrointestinal disorders. On the other side, a different picture after the suspension was observed. In particular, a negative trend of *Actinobacteria* and *Bifidobacteriaceae* was detected. Interestingly, the same trend was also observed in patients PFS (Borgo et al., 2020), who experienced persistent sexual dysfunction, as PSSD patients. In agreement, a depletion of *Bifidobacterium* (belonging to *Actinobacteria*) observed in the PSSD experimental model was associated with an inflammatory environment, as reported in several studies in other models (Wu et al., 2021). To date, no study describes the situation of PSSD patients versus healthy subjects. However, based on the data obtained in the experimental model, this issue would be informative to confirm the possible presence of dysbiosis.

5.8. Common aspects between PFS and PSSD

As here reported, persistent sexual dysfunction is a feature shared by PFS and PSSD. This common aspect could be determined by similar etiopathogenetic mechanisms. In particular, sex steroids, neurotransmitters (i.e., serotonin and dopamine), and gut microbiota are variably interconnected with each other in PFS and PSSD. Indeed, dopamine is the neurotransmitter involved in the major pathways of sexual behavior (i.e., sexual motivation, erection and ejaculation, reward and motor functions) (Amalric and Koob, 1993; Hull et al., 1986; Hull et al., 2004; Moses et al., 1995; Peeters and Giuliano, 2008; Zeiss, 2005). The mesencephalic dopaminergic neurons are chiefly under the control of T via ARs or, to a minor extent, 17β-E via ERβ (Creutz and Kritzer, 2002; Kritzer, 1997), while the hypothalamic dopaminergic neurons are chiefly under the control of ERα (Simerly et al., 1997), and dopamine may cooperate with the kisspeptin system, but in a still unknown way (Clarkson and Herbison, 2011). As demonstrated by the use of agonists and antagonists of dopamine receptors (Dominguez and Hull, 2005), the action of dopamine on male sexual behavior can be mediated by the release of this neurotransmitter at the level of the medial preoptic area (MPOA). This release is regulated by the action of the enzyme nitric oxide synthase (NOS) (Hull and Dominguez, 2006). NOS-positive neurons of the MPOA can be directly regulated by sex steroids; indeed, both ERα and AR are present in these neurons (Sato et al., 2005). Accordingly, orchidectomy produces an increase in intracellular dopamine content coupled with a decrease in its release, due to the lack of NOS production mediated by the decrease in T levels (Hull et al., 2004).

Serotonin is generally considered an inhibitory factor for sexual behavior (Hull et al., 2004; Olivier et al., 2011), even if this may also depend on which receptor(s) and brain region is activated (Angoa-Perez and Kuhn, 2015). The dorsal part of the raphe nucleus (DRN) has been considered an important region to study the link among gonadal hormones, serotonin, and sexual behavior. As demonstrated, ERα and ERβ are expressed within the DRN serotoninergic neurons of both sexes, whereas the ARs are visible only in males in neurons adjacent to serotonin elements (Sheng et al., 2004). In male macaques, T and DHT stimulate the serotonin neurons in the DRN in an aromatase-independent way (Bethea et al., 2014). Sex steroid receptors distribution in macaques is similar to that observed in rodents, with about 40 % of serotonin cells of the DRN that contains ERα or ERβ, whereas ARs are expressed in neighboring neurons (Bethea et al., 2015). In conclusion, the serotonin action on sexual behavior can be mediated by the action of gonadal hormones at the level of DRN: direct action of estrogens is mediated by the presence of ERα and ERβ within the serotoninergic neurons, whereas the androgens are probably acting via local AR-dependent circuits of the DRN. Altogether, these observations indicate that dopamine is under the inhibitory tone of serotonin, whereas neuroactive steroids integrate, among others, peripheral and central stimuli to control dopamine circuits (through serotonin action). Therefore, perturbation of sex steroid levels induced by finasteride or SSRIs might be responsible for alterations of these neurotransmitters, thus producing the sexual dysfunction observed during the treatment, and possibly the persistent sexual dysfunction occurring in PFS and PSSD. However, in the context of neurotransmitters, it is important to highlight that finasteride itself or paroxetine may also affect the balance of the levels of norepinephrine and epinephrine, acting on the enzyme involved in their conversion. Indeed, as recently demonstrated, by a multidisciplinary approach (i.e., 3D proteome-wide scale *in silico* screening of a human and murine protein database using SPILLO-PBSS software, docking and molecular dynamics analysis and *in vitro* and *in vivo* assays) the enzyme phenylethanolamine N-methyltransferase (PNMT), responsible for the conversion of norepinephrine into epinephrine, is an off-target of finasteride (Giatti et al., 2021b) and paroxetine (Giatti et al., 2022). These drugs inhibit the PNMT enzymatic activity in the adrenal glands and consequently alter the levels of these neurotransmitters (Fig. 8). This is interesting because the balance of these two catecholamines is involved in the control of male sexual function, and in particular in the control of penile erection. Thus, norepinephrine released in the penis induces the flaccid state by contracting the trabecular smooth muscle (Andersson, 2011). Indeed, in healthy men, a reduction in norepinephrine levels is associated with penile tumescence and erection, whereas an increased level of this hormone is associated with the transition from rigidity to detumescence (Becker et al., 2002). Epinephrine levels are increased in the tumescence phase in relation to the flaccid condition and then decreased in the rigid and detumescence phases (Becker et al., 2002).

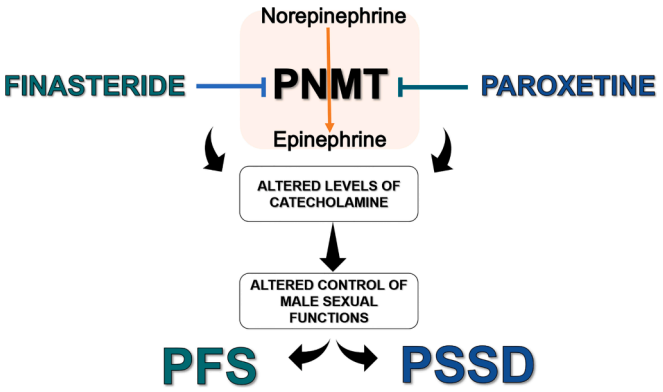

Fig. 8. Finasteride and paroxetine inhibition of PNMT enzymatic activity.

Finally, a possible component in the complex puzzle of PFS and PSSD is represented by the gut microbiota. Indeed, as reported in this review, gut microbiota populations are affected by the treatment with finasteride (Borgo et al., 2020; Diviccaro et al., 2019) and paroxetine (Diviccaro et al., 2022c). The observed changes in the microbiota populations support gut dysbiosis reported in both the experimental model of PFS (Diviccaro et al., 2022b) and PSSD (Diviccaro et al.,

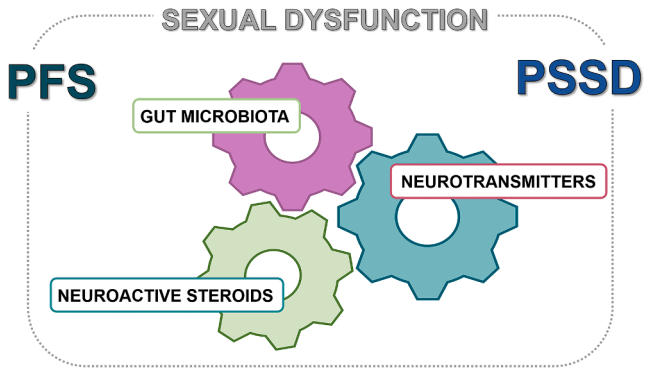

Fig. 9. A putative linkage between neurotransmitters, gut microbiota, and neuroactive steroids in the persistent sexual dysfunction induced by finasteride or SSRIs.

2022c). Moreover, these changes may also be related to depressive symptomatology observed in the PFS experimental model (Diviccaro et al., 2019). Interestingly, norepinephrine may also influence the gut microbiota. Indeed, this neurotransmitter promotes the growth of Gram-negative bacteria and, in general, increases virulence and facilitates bacterial invasion (Lyte et al., 1997). In addition, increased levels of norepinephrine reported in an experimental model of stroke, were associated with altered microbiota composition (Houlden et al., 2016).

6. Conclusions and perspectives

Observations here reported suggest a key role of steroid molecules, and their interactions with neurotransmitters and gut microbiota, in the context of PFS and PSSD (Fig. 9). Even though in recent years the attention of the scientific community has been raised also on these conditions, more work is needed. In particular, there is an urgent need to find diagnostic markers able to discriminate and categorize patients. In this context, the alteration in gut microbial populations and/or the identification of specific microbiota-derived bio-products might be proposed. Moreover, a deeper knowledge of the mechanisms leading to the appearance of the symptoms during but especially after treatment is necessary to propose efficient treatments. In this context, the recent evidence obtained in male rats, that treatment with ALLO can counteract gut inflammation induced by finasteride withdrawal (Diviccaro et al., 2022b), might represent an interesting background to designing steroid-based therapeutic strategy, not only for PFS but also for PSSD.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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