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Review

Patients treated for male pattern hair with finasteride show, after discontinuation of the drug, altered levels of neuroactive steroids in cerebrospinal fluid and plasma

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ABSTRACT

Observations performed in a subset of patients treated for male pattern hair loss indicate that persistent sexual side effects as well as anxious/depressive symptomatology have been reported even after discontinuation of finasteride treatment. Due to the capability of finasteride to block the metabolism of progesterone (PROG) and/or testosterone (T) we have evaluated, by liquid chromatography–tandem mass spectrometry, the levels of several neuroactive steroids in paired plasma and cerebrospinal fluid (CSF) samples obtained from post-finasteride patients and in healthy controls. At the examination, post-finasteride patients reported muscular stiffness, cramps, tremors and chronic fatigue in the absence of clinical evidence of any muscular disorder or strength reduction. Although severity of the anxious/depressive symptoms was quite variable in their frequency, overall all the subjects had a fairly complex and constant neuropsychiatric pattern. Assessment of neuroactive steroid levels in CSF showed a decrease of PROG and its metabolites, dihydroprogesterone (DHP) and tetrahydroprogesterone (THP), associated with an increase of its precursor pregnenolone (PREG). Altered levels were also observed for T and its metabolites. Thus, a significant decrease of dihydrotestosterone (DHT) associated with an increase of T as well as of 3α-diol was detected. Changes in neuroactive steroid levels also occurred in plasma. An increase of PREG, T, 3α-diol, 3β-diol and 17β-estradiol was associated with decreased levels of DHP and THP. The present observations show that altered levels of neuroactive steroids, associated with depression symptoms, are present in androgenic alopecia patients even after discontinuation of the finasteride treatment.

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Contents

Abbreviations: 3α-diol, 5α-androstane-3α,17β-diol; 3β-diol, 5α-androstane-3β,17β-diol; 17β-E, 17β-estradiol; AR, androgen receptor; CSF, cerebrospinal fluid; DHEA, dehydroepiandrosterone; DHP, dihydroprogesterone; DHT, dihydrotestosterone; IS, internal standards; LC-MS/MS, liquid chromatography tandem mass spectrometry; PREG, pregnenolone; PROG, progesterone; T, testosterone; THP, tetrahydroprogesterone.

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1. Introduction

Observations obtained in multiple double-blind randomized controlled trials for male pattern hair loss have indicated that finasteride (i.e., a 5α-reductase inhibitor used for the treatment of human benign prostatic hyperplasia and androgenic alopecia) treatment was associated with sexual dysfunction [1–3]. Similar side effects were also reported in patients treated for benign prostatic hyperplasia [4–7]. Very important, observations performed in a subset of patients for male pattern hair loss seem to indicate that persistent sexual side effects (e.g., low libido, erectile dysfunction, decreased arousal and difficulty in reaching orgasm) have been reported even after discontinuation of the treatment [8,9]. Patients also developed depression during finasteride treatment [10,11] that still persisted despite treatment withdrawal [12]. Depression after finasteride treatment might be due to impairment in the levels of neuroactive steroids. This steroid family, which includes both steroid hormones produced in peripheral glands and steroids directly synthesized in the nervous system (i.e., neurosteroids), has an important role in the control of nervous function, affecting mood, behavior, reproduction and cognition, as well as being protective agents in models of injury and neurodegenerative diseases [13–16]. Indeed, finasteride is not only able to block 5α-reductase (5α-R) enzyme, which converts testosterone (T) into dihydrotestosterone (DHT), but also the conversion of progesterone (PROG) into dihydroprogesterone (DHP) [16]. In this context, it is also important to highlight that these neuroactive steroids are then converted by the action of the 3α- or 3β-hydroxysteroid dehydrogenase into 5α-androstane-3α,17β-diol (3α-diol) or 5α-androstane-3β,17β diol (3β-diol) in case of DHT and into tetrahydroprogesterone (THP), also known as allopregnanolone, or into isopregnanolone in case of DHP [16]. It is interesting to note that THP, as well as the 3α-diol (i.e., a metabolite of DHT), are known as ligands of GABA-A receptor [17]. Moreover, isopregnanolone does not bind directly to the GABA-A receptor [18], but it antagonizes the effect of THP on the GABA-A receptor [19,20]. Changes in GABA as well as in neuroactive steroid levels in plasma and cerebrospinal fluid (CSF) are associated with depression in several human studies [21].

Interestingly, our recent preliminary observations obtained in three male patients who received finasteride for the treatment of androgenic alopecia and that after drug discontinuation still had long-term sexual side effects as well as anxious/depressive symptomatology showed altered neuroactive steroid levels in plasma and CSF vs. those assessed in 5 healthy patients [22]. A further link with neuroactive steroids may be supported by recent observations. Indeed, as reported in a subset of post-finasteride patients with persistent symptomatology, a decline in their alcohol consumption was also observed [23]. This is very interesting, because a relationship between GABAergic neuroactive steroids and ethanol consumption is well documented [24].

On the basis of this interesting finding, we here extend our observations analyzing by liquid chromatography–tandem mass spectrometry (LC–MS/MS) the levels of neuroactive steroids, such as pregnenolone (PREG), PROG and its derivatives, DHP, THP and isopregnanolone, dehydroepiandrosterone (DHEA), testosterone (T) and its derivatives, DHT, 3α-diol, 3β-diol and 17β-estradiol (17β-E), in paired plasma and CSF samples obtained from seven post-finasteride patients (i.e., patients who received the drug for the treatment of androgenic alopecia and resulting in long-term sexual side effects as well as anxious/depressive symptomatology after finasteride discontinuation) and comparing these levels vs. those assessed in twelve healthy controls.

2. Materials and methods

PREG, PROG, DHP, THP, isopregnanolone, T, DHT, 3α-diol, 3β-diol DHEA and 17β-E were purchased from Sigma Aldrich. 17,21,21,21-D_4-PREG (D_4-PREG) was kindly synthesized by Dr. P. Ferraboschi (Dept. of Med. Biotech. & Translational Medicine, University of Milano, Italy); 2,2,4,6,6-17α,21,21,21-D_9-PROG (D_9-PROG) was obtained from Medical Isotopes (Pelham, NH, USA); 2,3,4-$^{13}C_3$-17β-estradiol ($^{13}C_3$-17β-E) was obtained from Sigma-Aldrich, Italy. SPE cartridges (Discovery DS-C18 500 mg) were from Supelco, Italy. All solvents and reagents were HPLC grade (Sigma Aldrich, Italy).

2.1. Study design and sample preparation

Patients were recruited through the "Italian network finasteride side effects", where the possibility to undergo CSF and plasma examination in the context of an approved pilot study was made available. Given the exploratory nature of the study no exclusion criteria were established, except the use of drugs known to potentially interfere with neuroactive steroids levels. Symptoms reported by the patients were collected using a standardized questionnaire prepared after consensus among the members of the "Italian network on finasteride side effects" based on an extensive collection of the reported symptoms. The presence of a representative pattern of these symptoms was necessary to be eligible for neuroactive steroid assessment.

The questionnaire was used as a method to systematically collect information on patients conditions and not as a validated tool to assess the features of post-finasteride syndrome. In order to limit selection and recall bias it was filled in by patients only once before they were made aware of the possibility to undergo neuroactive steroid assessment.

The study procedure was approved by the Ethics Committee of the S. Gerardo Hospital, Monza-Italy and the participating subjects provided their written informed consent before enrollment.

In order to obtain reliable normal control values, CSF and plasma were collected from 12 subjects who underwent spinal anesthesia for orthopedic surgery at San Gerardo Hospital of Monza. These subjects were otherwise healthy, were carefully screened for the absence of any neurological or psychiatric disorder in their personal or family history and gave their written informed consent to the use for scientific purpose of the aliquot (approx 100–200 μl) of CFS drawn to verify the correct position of the spinal needle, according to the procedure approved by the Ethics Committee of the S. Gerardo Hospital in Monza.

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2.2. Quantitative analysis of neuroactive steroids by LC–MS/MS

Extraction and purification of the samples were performed according to Caruso et al. [25].

Briefly, samples were spiked with $^{13}C_3$-17β-E (1 ng/sample), D_9-PROG (0.2 ng/sample) and D_4-PREG (5 ng/sample), as internal standards (IS) and homogenized in MeOH/acetic acid (99:1 v/v) using a tissue lyser (Qiagen, Italy). After an overnight extraction at 4 °C, samples were centrifuged at 12,000 rpm for 5 min and the pellet was extracted twice with 1 ml of MeOH/acetic acid (99:1, v/v). The organic residues were resuspended with 3 ml of MeOH/H_2O (10:90, v/v) and passed through SPE cartridges, the steroids were eluted in MeOH, concentrated and transferred in autosampler vials before the LC-MS/MS analysis.

2.3. Calibration curves

Quantitative analysis was performed on the basis of calibration curves daily prepared and analyzed as previously described [25]. Linear least-square regression analysis was performed and in addition, a blank (non-spiked sample) and a zero sample (only spiked with IS) were run to demonstrate the absence of interferences at the retention times and m/z corresponding to all the analytes. Moreover, the precision of the assay, inter-assay accuracy, precision and reproducibility are calculated as described in [25] and are within tolerance range for all the neuroactive steroids.

2.4. Instrumental conditions

Positive atmospheric pressure chemical ionization (APCI+) experiments were performed with a linear ion trap – mass spectrometer (LTQ, ThermoElectron Co, San Jose, CA, USA) using nitrogen as sheath, auxiliary and sweep gas. The instrument was equipped with a Surveyor liquid chromatography (LC) Pump Plus and a Surveyor Autosampler Plus (ThermoElectron Co, San Jose, CA, USA). The mass spectrometer (MS) was employed in tandem mode (MS/MS) using helium as collision gas.

The LC mobile phases were described by Caruso et al. [25]. The Hypersil Gold column (100 mm × 3 mm, 3 μm; ThermoElectron Co., San Jose, CA, USA) was maintained at 40 °C. Peaks of the LC–MS/MS were evaluated using a Dell workstation by means of the software Excalibur® release 2.0 SR2 (ThermoElectron Co., San Jose, CA, USA). Samples were analyzed using the transitions previously reported [26].

2.5. Statistical analysis

The linearity of the standard curve (r^2) and all the validation parameters of the method were judged by GraphPad4 PRISM (version 5). Student *t* test was used to compare control subjects and MS patients. A *p*-value of less than 0.05 was considered significant.

3. Results

3.1. General data and self-reported frequency of the most symptoms reported by the patients at the moment of sampling

The seven post-finasteride patients we have considered in our study had taken Propecia (1 mg/day) in 5 cases and Proscar (1.25 mg/day) or Finasteride (1.25 mg/day) in 2 cases. Mean age of these patients was 38 years old; mean of treatment duration was 727 days. The interval between finasteride withdrawal and CSF sampling was very wide (range 171–5000 days, median 1635 days).

Although the severity of the anxious/depressive symptoms was quite variable in their frequency, overall all the subjects had a fairly complex and constant neuropsychiatric pattern. The most frequently reported symptoms were: reduction in self-confidence, decreased initiative and difficulty in concentration (71%), forgetfulness or loss of short-term memory (43%), irritability or easily flying into a rage (57%), depression and feelings of worthlessness (86%), suicidal thoughts (14%), anxiety (57%) panic attacks (14%) and sleep problems (86%). Loss of libido and sexual desire (86%), difficulty in achieving an erection (71%) and genital numbness or paresthesia (57%) were also reported. Furthermore, all these patients reported at the moment of clinical and laboratory assessment muscular stiffness and cramps (43%), tremors (57%), chronic fatigue (86%) as well as joint pain and muscular ache (86%) in the absence of clinical evidence of any muscular disorder or strength reduction. It is important to highlight that, with the exception of sleep problems already reported by two patients, all these symptoms were not present before treatment with finasteride. To perform a complete neurological assessment, before CSF drawing under sterile conditions after local anesthesia, the post-finasteride patients underwent brain magnetic resonance imaging, with normal results in all subjects. The standard examination of CSF (i.e. protein, glucose and cellular content) was normal in all cases.

3.2. Assessment of neuroactive steroids

The levels of neuroactive steroids in CSF and plasma of the seven post-finasteride patients were compared with those of twelve male, age-matched healthy controls. In comparison to the healthy controls, the post-finasteride patients presented a quite different neuroactive steroid pattern both in CSF and in plasma. Fig. 1 shows the levels of PREG, its metabolite PROG, and the levels of the further metabolites, DHP, THP and isopregnanolone. As reported, the levels of PREG were significantly increased in CSF and plasma of post-finasteride patients. On the contrary, PROG was significantly decreased in CSF but was unchanged in plasma. Its metabolites had a similar pattern. Indeed, DHP, THP and isopregnanolone were significantly decreased in CSF of post-finasteride patients with levels under detection limit. DHP and THP were also significantly decreased in plasma, with the levels of THP that were under detection limit. Fig. 2 shows the levels of DHEA, its metabolite T, and the levels of the further metabolites, DHT, 3α-diol, 3β-diol and 17β-E. As reported, DHEA levels were unchanged both in CSF and plasma; on the contrary, both in CSF and plasma of post-finasteride patients the levels of T were significantly increased. While the levels of the first metabolite of T, DHT, were significantly decreased in CSF but unchanged in plasma, the levels of the further metabolites, 3α-diol and 3β-diol were significantly increased in plasma. Similarly to what happened in plasma, the levels of 3α-diol in CSF were significantly increased. Levels of 17β-E were significantly increased in plasma and unchanged in CSF.

4. Discussion

The present results show that persistent sexual side effects as well as anxious/depressive symptoms are associated with changes of neuroactive steroid levels in CSF and plasma of seven male patients with male pattern hair loss despite discontinuation of finasteride. These results extend our previous preliminary observations that were obtained comparing three post-finasteride patients vs. five control subjects [22]. It is important to highlight that the controls used in our preliminary observations underwent a diagnostic lumbar puncture for a suspected neurological disease but proved to be negative. However, because in those control patients we cannot exclude a transitory inflammatory event, we have now compared a higher number of post-finasteride patients with twelve subjects who underwent spinal anesthesia for orthopedic surgery

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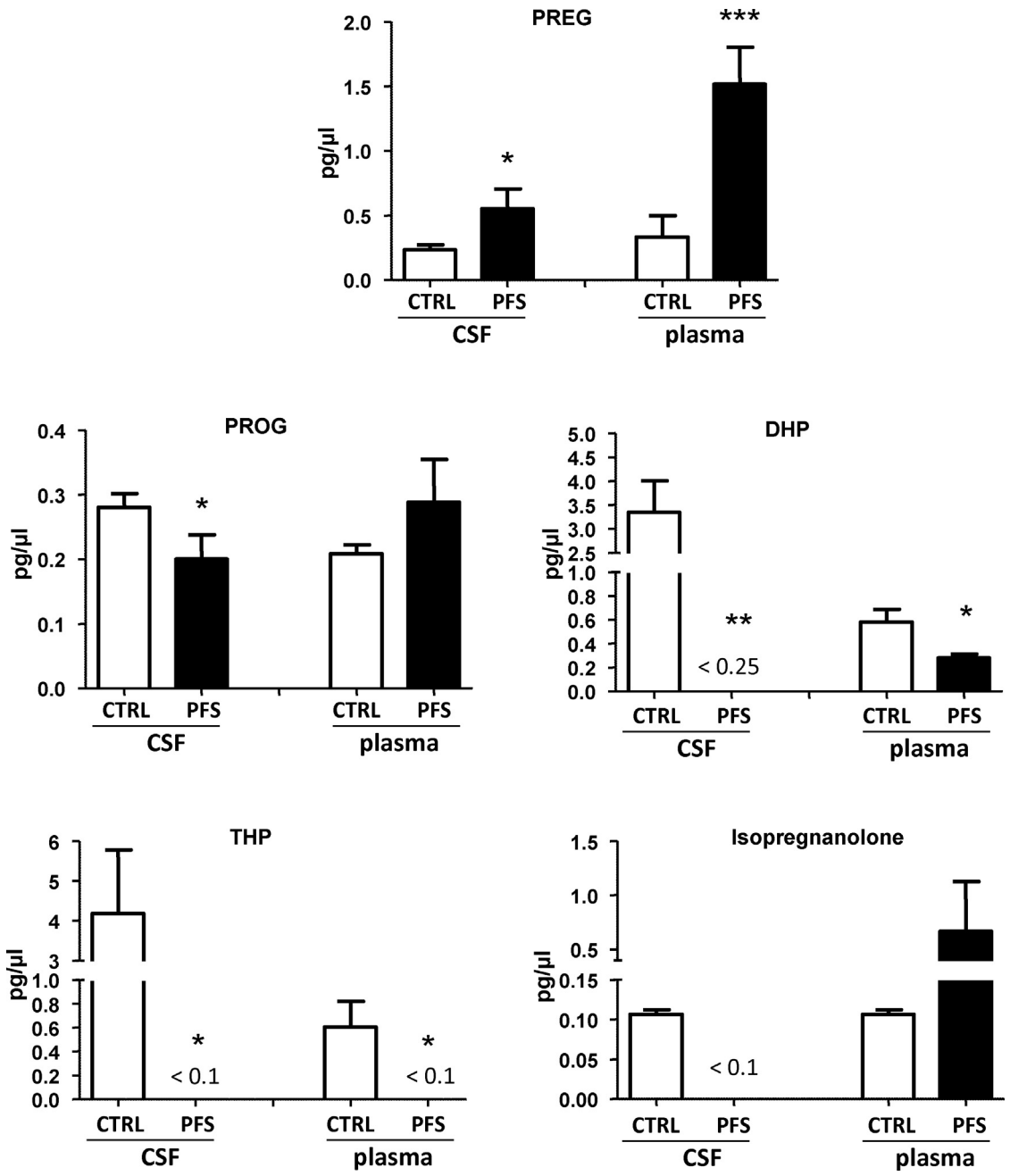

Fig. 1. Pregnenolone (PREG), progesterone (PROG), dihydroprogesterone (DHP), tetrahydroprogesterone (THP) and isopregnanolone levels in cerebrospinal fluid (CSF) and in plasma of controls (CTRL) and post-finasteride patients (PFS). Data ($n = 12$ for CTRL and 7 for PFS) are expressed as pg/µl ± SEM. $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$; the detection limit for DHP is <0.25 pg/µl, that for THP and isopregnanolone is <0.1 pg/µl.

and were carefully screened for the absence of any neurological or psychiatric disorder in their personal or family history.

In our preliminary observations we observed a decrease of metabolites of PROG and T, such as THP, isopregnanolone and DHT, associated with an increase of T and 17β-E in CSF. On the contrary, in plasma a decrease in DHP levels associated with an increase of 3α-diol and 17β-E levels was observed [22]. Observations here presented show in CSF a decrease of metabolites of PROG, such as DHP and THP, as well as of PROG itself. This finding was associated with an increase of its precursor PREG. Altered levels were also observed for T and its metabolites. Indeed, a significant decrease of DHT associated with an increase of T as well as of 3α-diol was detected. Changes in neuroactive steroid levels also occurred in plasma of post-finasteride patients. An increase of PREG levels was associated with decreased levels of DHP and THP. An increase of T also occurred in plasma and this was associated with increased levels of 3α-diol and 3β-diol as well as of 17β-E.

The few observations so far present in the literature have mainly focused the attention on the role of 3α-reduced metabolites of PROG and particularly of THP in anxious/depressive symptomatology. In particular, this neuroactive steroid was decreased in CSF as well as in plasma and this disequilibrium could be corrected with different antidepressants [21,27–30]. At least in plasma, as reported by others in patients suffering from depression, the decrease in the levels of THP [31] was associated with an increase of isopregnanolone [27]. Here we report, a tendency of an increase, which however did not reach the statistical significance, in plasma of post-finasteride patients.

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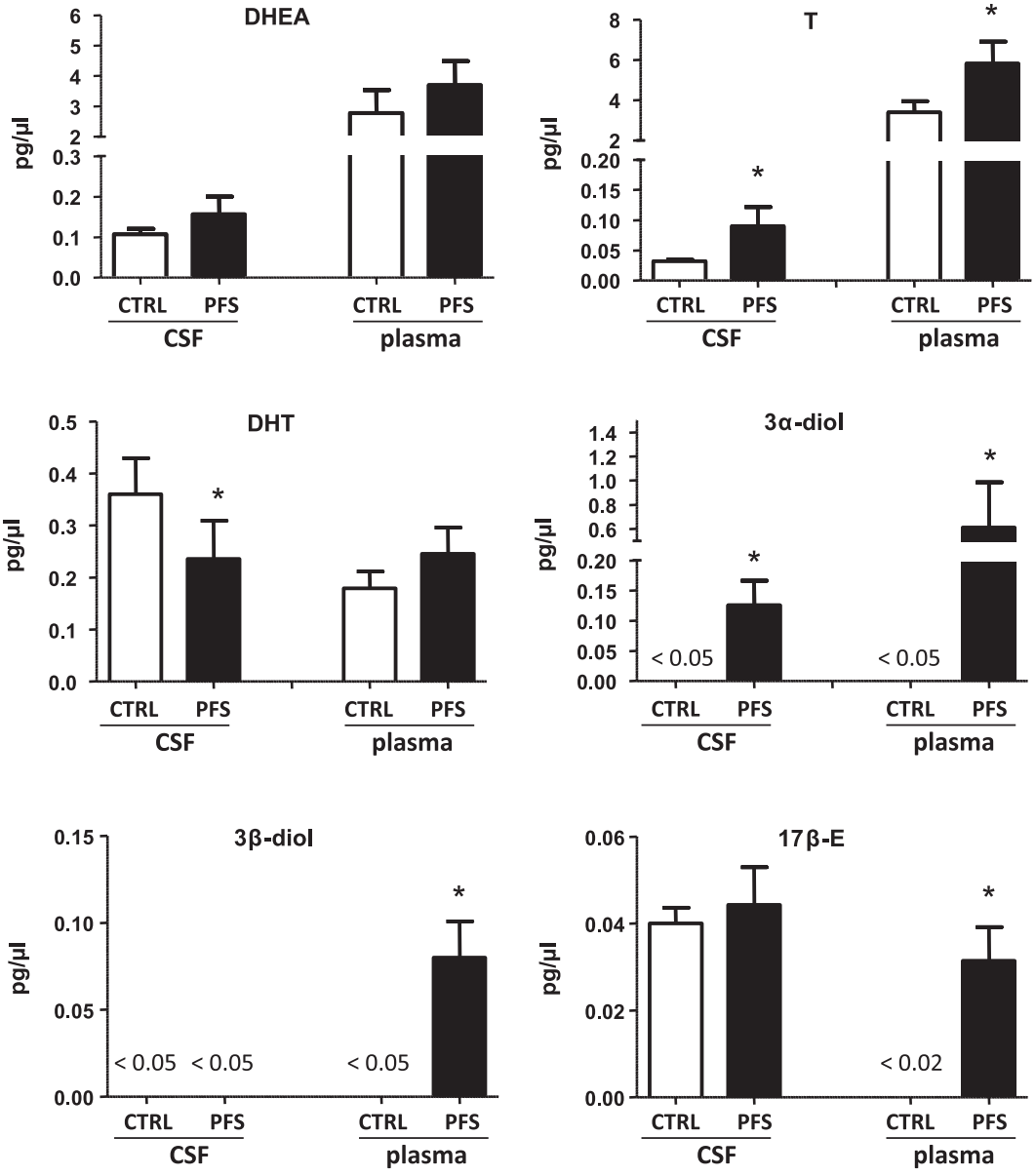

Fig. 2. Dehydroepiandrosterone (DHEA), testosterone (T), dihydrotestosterone (DHT), 5α-androstane-3α,17β-diol (3α-diol), 5α-androstane-3β,17β diol (3β-diol) and 17β-estradiol (17β-E) levels in cerebrospinal fluid (CSF) and in plasma of controls (CTRL) and post-finasteride patients (PFS). Data ($n = 12$ for CTRL and 7 for PFS) are expressed as pg/µl ± SEM. *$p < 0.05$; the detection limit for 3α-diol and 3β-diol is <0.05 pg/µl, that for 17β-E is <0.02 pg/µl.

A relationship between T levels and depression has also been demonstrated [32]. Indeed, young hypogonadal as well as aged men, showing decreased levels of T, exhibit a high prevalence of anxiety disorders and major depressive disorder [33–36]. In our study, we observed an increase in the CSF and plasma levels of T. However, the active metabolite of T, DHT was significantly decreased in CSF of post-finasteride patients. Indeed, finasteride blocks the conversion of T into DHT [37], which is able, in comparison to T, to interact with the androgen receptor with a higher affinity [16]. An intriguing finding of our study is represented by the prolonged duration of psychiatric symptoms and CSF changes after finasteride withdrawal, resembling the long-term/irreversible effects of phenothiazines in patients affected by schizophrenia [38].

Recently, it has been demonstrated that treatment with finasteride induces a decreased of DHT levels in brain of mice associated with a decrease of hippocampal neurogenesis [39,40]. Interestingly, adult neurogenesis has been related to depression [41]. Indeed, depressed patients show a reduced hippocampal volume related with a reduced dendritic complexity, decreased neuronal soma size, as well as reduced hippocampal neurogenesis [42,43]. In this context it is important to highlight that GABA has crucial roles in regulating different steps of adult neurogenesis, including proliferation of neural progenitors, migration and differentiation of neuroblasts, and synaptic integration of newborn neurons [44]. As here demonstrated the levels of PROG and T, and particularly those of their metabolites which, like for instance THP and 3α-diol are also to modulate GABA transmission through GABA-A receptors [17], are affected in post-finasteride patients and reported to modulate adult neurogenesis [41,45].

5. Conclusions

Data here reported clearly show that the blockade of 5α-reductase by finasteride induces not only as previously described [46,47] a decrease of PROG and T metabolite levels during the treatment, but it may also induce a persistent alteration of neuroactive

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steroid levels despite discontinuation of the drug. Indeed, as here demonstrated, after discontinuation of the finasteride treatment a subset of patients that was treated for male pattern hair loss show sexual dysfunction as well as anxious/depressive symptomatology associated with altered levels of PREG, PROG, DHP, THP T, DHT and 3α-diol in CSF and of PREG, DHP, THP, T, 3α-diol, 3β-diol and 17β-E in plasma.

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