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Physiopathological role of the enzymatic complex 5α-reductase and 3α/β-hydroxysteroid oxidoreductase in the generation of progesterone and testosterone neuroactive metabolites

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ABSTRACT

The enzymatic complex 5α-reductase (5α-R) and 3α/3β-hydroxysteroid oxidoreductase (HSOR) is expressed in the nervous system, where it transforms progesterone (PROG) and testosterone (T) into neuroactive metabolites. These metabolites regulate myelination, brain maturation, neurotransmission, reproductive behavior and the stress response. The expression of 5α-R and 3α-HSOR and the levels of PROG and T reduced metabolites show regional and sex differences in the nervous system and are affected by changing physiological conditions as well as by neurodegenerative and psychiatric disorders. A decrease in their nervous tissue levels may negatively impact the course and outcome of some pathological events. However, in other pathological conditions their increased levels may have a negative impact. Thus, the use of synthetic analogues of these steroids or 5α-R modulation have been proposed as therapeutic approaches for several nervous system pathologies. However, further research is needed to fully understand the consequences of these manipulations, in particular with 5α-R inhibitors.

1. Introduction

In addition to be a target for neuroactive steroids, the nervous system has all the necessary molecular machinery for steroid synthesis and metabolism. Thus, neural cells express the molecules involved in the first and rate-limiting step of steroidogenesis, i.e., the transport of cholesterol to the mitochondria. These molecules include steroidogenic acute regulatory protein and translocator protein of 18 kDa (TSPO) (Giatti et al., 2019d). Neural cells express also cytochrome P450 cholesterol side-chain cleavage enzyme, which transforms cholesterol in pregnenolone within the mitochondria. Then, several steroidogenic enzymes located in the endoplasmic reticulum of neurons and glial cells metabolize pregnenolone in a variety of steroids, such as progesterone (PROG) and testosterone (T) (Giatti et al., 2019d).

Among the steroidogenic proteins expressed by neural cells, the enzymatic complex formed by 5α-reductase (5α-R) and 3α- or 3β-hydroxysteroid oxidoreductase (HSOR), plays a key functional role by the generation of reduced metabolites of PROG and T that have a potent activity on neurons and glial cells, acting on a variety of steroid and neurotransmitter receptors and exerting a homeostatic regulation of neural function and behavior (Celotti et al., 1992; Melcangi et al., 2008).

This enzymatic complex is very versatile, being able to reduce and subsequently hydroxylate all steroids possessing the delta 4-3keto configuration. For instance, PROG can be metabolized into dihydroprogesterone (DHP) by the action of the enzyme 5α-R and subsequently into 3α, 5α-tetrahydroprogesterone (THP), also known as allopregnanolone, or into 3β, 5α-tetrahydroprogesterone (isopregnanolone), by the action of the enzyme 3α- or 3β-HSOR, respectively. Similarly, T can be converted into dihydrotestosterone (DHT) and subsequently into 5α-androstane-3α,17β-diol (3α-diol) or 5α-androstane-3β,17β-diol (3β-diol). In the reactions producing 3α,5α-reduced metabolites, the enzymatic reaction performed by 5α-R is the rate-limiting step (Dubrovsky, 2006). Although we will center here our attention exclusively on PROG and T metabolites, it is important to mention that these enzymes may also convert corticosterone and deoxycorticosterone (DOC) into dihydrocorticosterone and dihydrodeoxycorticosterone (DHDOC), respectively, and this latter metabolite can be then further converted into 3α,5α-tetrahydrodeoxycorticosterone (THDOC).

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To exert they regulatory functions, the levels of PROG and T metabolites generated by 5α-R and HSOR enzymes fluctuate in the nervous tissue of developing and adult animals depending on the changing physiological and endocrine conditions, with important differences between males and females. In addition to these physiological changes, the levels of PROG and T metabolites suffer also alterations in the nervous system under psychiatric and neurodegenerative disorders. The significance of these latter changes is still under debate and may either represent compensatory adaptations to the pathological conditions or reflect a pathological dysfunction in the activity of 5α-R and HSOR enzymes or, more probably, a combination of both.

To discuss these questions, we present in the next sections a review of our present knowledge on the expression and activity of 5α-R and 3α/3β-HSOR in the nervous tissue, focusing on the physiological functions of the PROG and T reduced metabolites generated by these enzymes. We also examine the modifications in the levels of these metabolites that occur in the central (CNS) and peripheral (PNS) nervous system, discussing the possible consequences of these changes under physiological and pathological conditions and their implications for the treatment of psychiatric and neurodegenerative disorders.

2. 5α-Reductase characteristics and distribution in the nervous system

To date, four genes have the *SRD5A* acronym in human genome (i.e. *SRD5A1*, *SRD5A2*, *SRD5A3* and *SRD5A2L2*), but only the first two encode for the enzyme 5α-R (i.e., called type 1 and type 2), able to generate the steroid metabolites mentioned above (Celotti et al., 1992; Normington and Russell, 1992; Russell and Wilson, 1994; Stiles and Russell, 2010). 5α-R type 3 is a polyprenol reductase with a crucial role in N-linked protein glycosylation (Cantagrel et al., 2010) and consequently seems not to be involved in steroid metabolism, with the exception of a cancer prostatic model, where it is also associated with DHT production and with maintenance of androgen signaling activation (Uemura et al., 2008).

5α-R type 1 is expressed with high levels in regions of the CNS that are particularly rich in white matter (i.e., midbrain, corpus callosum, anterior commissure, optic chiasm, pons and spinal cord) (Celotti et al., 1992; Melcangi et al., 1988a; Patte-Mensah et al., 2004). In agreement with this, the enzyme is present in elevated concentrations in purified myelin preparations obtained from the rat brain (Melcangi et al., 1989; Melcangi et al., 1988a; Melcangi et al., 1988b) and is expressed in oligodendrocytes, the myelin forming cells of the CNS, and in neurons (Melcangi et al., 1990a; Melcangi et al., 1993; Melcangi et al., 1994). In addition, 5α-R activity has been also detected in Schwann cells, the myelinating cells of the PNS (Melcangi et al., 1990b; Melcangi et al., 2001; Schaeffer et al., 2010; Yokoi et al., 1998). In particular, the 5α-R activity in Schwann cells is at least four times higher than in oligodendrocytes (Melcangi et al., 1998b).

5α-R type 1 is also present in microglia (Gottfried-Blackmore et al., 2008) and astrocytes (Melcangi et al., 1993; Melcangi et al., 1994). In particular, as reported in cell cultures, type 2 astrocytes, which probably correspond to fibrous astrocytes *in vivo*, express the enzyme. In contrast, type 1 astrocytes, which probably correspond to protoplasmatic astrocytes, do not express 5α-R type 1 (Melcangi et al., 1993; Melcangi et al., 1994). Interestingly, 5α-R activity present in type 1 astrocytes is stimulated by the simultaneous presence of neurons, indicating a possible interaction of the two populations of cells in the metabolism of neuroactive steroids (Melcangi et al., 1995).

5α-R type 1 mRNA has been also localized in cortical, hippocampal, and olfactory bulb glutamatergic neurons and in some output neurons of the amygdala and thalamus (Agis-Balboa et al., 2006). 5α-R type 2 is also widely expressed in most key regions of the adult rat brain, ranging from the forebrain to the brain stem and cerebellum (Castelli et al., 2013). However, its immunoreactivity is higher in the spinal cord (i.e., dorsal and ventral horn of the gray matter) and particularly in oligodendrocytes (Patte-Mensah et al., 2004). Finally, it should be mentioned that not only differentiated CNS cells but also stem cells originating from the mouse striatum express 5α-R (Melcangi et al., 1996).

3. 3α/β-Hydroxysteroid oxidoreductase characteristics and distribution in the nervous system

3α-HSOR is a member of the aldo-keto reductase superfamily which includes aldehyde reductase, aldo-reductase and dihydrodiol dehydrogenase (Jez et al., 1997; Jez and Penning, 2001). Up to now, four human 3α-HSOR isozymes, but only one isoform in rats, have been cloned (Penning et al., 2003).

The presence of 3α-HSOR and 3β-HSOR has been identified in the CNS (Melcangi et al., 2014). For instance, 3α-HSOR mRNA levels have been detected in the rat cerebral cortex and the cerebellum, with lower expression in the latter structure (Giatti et al., 2019a). In addition, the analysis of 3α-HSOR mRNA distribution in the mouse brain by in situ hybridization has shown that this enzyme is co-localized with 5α-R type 1 in neurons of the cerebral cortex, hippocampus, olfactory bulb, amygdala and thalamus (Agis-Balboa et al., 2006). Furthermore, in the spinal cord, 3α-HSOR immunoreactivity is largely distributed in both white and gray matters, even if the highest density is present in sensory regions of the dorsal horn (Patte-Mensah et al., 2004).

In addition to neurons, 3α-HSOR activity appears to be highly localized in glial cells, such as type 1 astrocytes in culture (Melcangi et al., 1993; Melcangi et al., 1994) and oligodendrocytes (Gago et al., 2001; Patte-Mensah et al., 2004), although, 3α-HSOR activity has not been detected in myelin membranes of the CNS (Melcangi et al., 1988a; Melcangi et al., 1988b). In oligodendrocytes 3α-HSOR activity is developmentally regulated. Indeed, as demonstrated by assessment of progesterone metabolism, the formation of DHP in fully differentiated oligodendrocytes is 5-fold higher than in oligodendrocyte pre-progenitors and in oligodendrocyte progenitors, while that of THP is the opposite (i.e., decrease with the differentiation of oligodendrocytes) (Gago et al., 2001).

4. Physiological actions of 5α-reductase and 3α/β-Hydroxysteroid oxidoreductase products of progesterone and testosterone in the nervous system

The metabolites of PROG and T formed by the action of the enzymatic complex 5α-R and 3α- or 3β-HSOR have a profound physiological impact in the nervous system, because they are also ligands for a variety of neuronal and glial receptors that are not directly modulated by PROG and T (Fig. 1). The 5α-reduced metabolites of PROG and T (i.e., DHP and DHT) are agonists of progesterone (PR) and androgen receptor (AR), respectively. The further 3α,5α-reduced metabolites interact with different receptors. For instance, in the case of DHP metabolites, THP is able to bind the GABA-A receptor, while isopregnanolone antagonizes the effect of THP on this receptor (Belelli and Lambert, 2005; Gee et al., 1988; Melcangi et al., 2008; Rupprecht, 2003). In the case of DHT metabolites, 3α-diol and 3β-diol are agonists of GABA-A receptor and ERβ, respectively (Handa et al., 2008; Melcangi et al., 2008).

4.1. Progesterone reduced metabolites

The physiological effects of progesterone metabolites have been summarized in table 1. In particular, in the mammalian brain, and specifically in the female one, the main role of PROG and its reduced metabolites is linked to the hypothalamic regulation of gonadotrophin release (Banks and Freeman, 1980; Barraclough et al., 1986) as

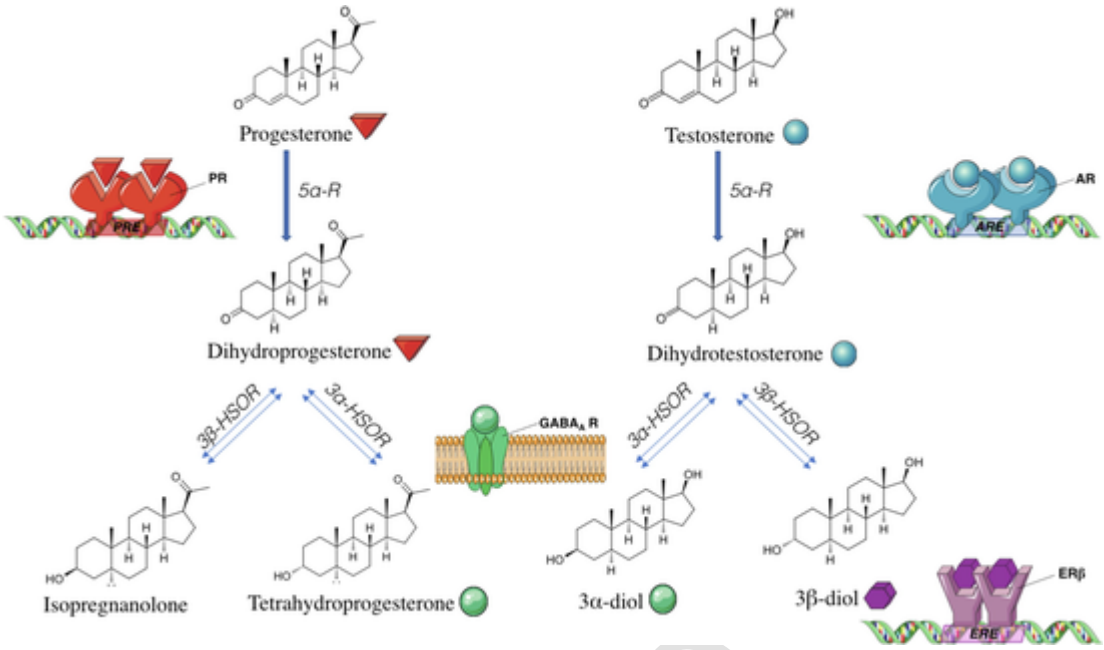

Fig. 1. Biosynthesis of progesterone and testosterone metabolites and their mechanism of action. Single and bidirectional arrows indicate the irreversible and reversible reactions, respectively. 3α-hydroxysteroid oxidoreductase: 3α-HSOR; 3β-hydroxysteroid oxidoreductase: 3β-HSOR; 5α-R: 5α-reductase; AR: androgen receptor; ARE: androgen responsive element; ER: estrogen receptor; PR: progesterone receptor; PRE: progesterone responsive element. See text for further details.

well as to the control of reproduction and related behaviors (Laconi and Cabrera, 2002; Levine et al., 2001; Mani and Portillo, 2010; Mani et al., 1994; Mani and Oyola, 2012). The peak in the levels of PROG observed during the estrous cycle, which is associated with an increased PR expression in the hypothalamus (McGinnis et al., 1981a; McGinnis et al., 1981b; Moguilewsky and Raynaud, 1979; Romano et al., 1989; Scott et al., 2002), is necessary for the lordosis response, a behavioral mechanism facilitating copulation (Blaustein and Feder, 1980; McGinnis et al., 1981a; McGinnis et al., 1981b; Parsons et al., 1980). The inhibition of the brain synthesis of THP reduces this behavioral response (Frye et al., 2008b; Petralia et al., 2005), indicating that THP is involved in the regulation of lordosis by PROG. THP induces lordosis in an experimental model lacking PR (Frye et al., 2006), suggesting that THP is acting in part through GABA-A receptor. Indeed, THP regulates lordosis and other motivated behaviors by its action on GABA-A receptors located in the midbrain ventral tegmental area (Frye, 2011; Frye et al., 2008b). In addition, THP also acts through PR to regulate lordosis, since the administration of mifepristone, a PR antagonist, inhibits the induction of this behavioral response by THP (Beyer et al., 1995; Gonzalez-Mariscal et al., 1989). This action of THP through PR can be explained based on the ability of THP to be *retro*-converted into DHP by 3α-HSOR (Belyaeva et al., 2007; Chetyrkin et al., 2001; Penning, 2011).

Beside reproductive effects, PROG metabolites are also crucial for mammalian brain maturation. Indeed, it is interesting to note that the enzymes 5α-R type 1 and 2, are strongly expressed in the brain of fetal and neonatal rodents (Martini et al., 1996). In agreement with this, a critical role for THP in brain maturation has been demonstrated. Indeed, the endogenous levels of this steroid fluctuate physiologically during rodent fetal life and after birth (Grobin and Morrow, 2001). These fluctuations may contribute to maintain the low level of arousal activity, characteristic of fetal brain (Nicol et al., 1998). Moreover, neonatal levels of THP promote the formation of neuronal circuitry and support the survival of developing neurons (Griffin et al., 2004). This neuroactive steroid is also involved in the structural formation of several brain regions, such as the cerebral cortex, thalamus and hippocampus (Cooper et al., 1999; Grobin et al., 2006). Furthermore, PROG and its metabolites are involved in oligodendrocyte differentiation (Ghoumari et al., 2005) and myelin formation (Chan et al., 1998; Chan et al., 2000; Ghoumari et al., 2003; Guennoun et al., 2001), other crucial events for brain maturation.

Besides being necessary for brain maturation of the fetus, THP is also important for the pregnant mother. Indeed, the higher levels of PROG during pregnancy are related to a subsequent increase of THP levels in the maternal peripheral circulation and in the maternal brain (Bicikova et al., 2002; Concas et al., 1998). In particular, in rats, the rise of this neuroactive steroid interferes with the hypothalamus-pituitary-adrenal axis, reducing the response to stress exposure of the mother, in particular during late pregnancy (Brunton et al., 2009; Brunton et al., 2005; Ma et al., 2005; Neumann et al., 1998).

DHP and THP exert crucial functions in the adult brain, where the enzymatic complex 5α-R and 3α-HSOR co-localizes in glutamatergic and GABAergic neurons of the cerebral cortex, hippocampus, amygdala and thalamus, suggesting that metabolites so formed are relevant for neurotransmitter synthesis and the modulation of their activity in these cells (Agis-Balboa et al., 2006). PROG metabolites are also active in the cerebellum, where they regulate the neuronal cytoskeleton. In particular, DHP or THP administration to ovariectomized animals decreases microtubule-associated protein Tau and glycogen synthase kinase 3beta expression in the cerebellum but not in the hypothalamus (Guerra-Araiza et al., 2007). In addition, protein content of glutamic acid decarboxylase is increased by THP administration in the olfactory bulb, suggesting that also this region is modulated by this PROG metabolite (Guerra-Araiza et al., 2008).

The reduced metabolites of PROG are also involved in mood regulation. In particular, THP acts in concert with glucocorticoids in the regulation of the stress response. Thus, increased levels of THP and 3α,5α-derivative of deoxycorticosterone (i.e., THDOC) have been observed in plasma and cerebral cortex of adult male rats after swim stress (Purdy et al., 1991). Interestingly, the expression of genes related to stress can be modulated by these molecules in both sexes (Patchev and Almeida, 1996; Patchev et al., 1994).

Table 1
Actions of progesterone and testosterone metabolites in physiological conditions.

Steroid	Central Nervous System	Peripheral Nervous System
DHP	Reproductive functions, lordosis response	P0 expression
	Glutamatergic and GABAergic neurotransmission	Krox-20 and Sox-10 expression
	Cytoskeleton regulation	
THP	Lordosis response	P0 and PMP22 expression
	Fetal brain maturation	Krox-20 expression
	Glutamatergic, GABAergic and dopaminergic neurotransmission	Glutamic acid decarboxylase and excitatory amino acid carrier 1 expression in Schwann cells
	HPA axis regulation	
	Cytoskeleton regulation	
	Norepinephrine levels	
DHT	Neuronal and glial cells differentiation	P0 expression
	Synaptic density and transmission	
3α-diol	GABAergic neurotransmission	P0 and PMP22 expression
3β-diol	HPA axis regulation	

THP also has a trophic effect on dopaminergic neurons (Wang, 2014) and is involved in the regulation of the dopaminergic system (Cabrera et al., 2002; Khisti et al., 2002; Mosher et al., 2019). In animals reared in social isolation, an experimental model in which dopaminergic signaling is altered, show a reduction in the protein expression of 5α-R type 1 and 2 in the nucleus accumbens and in the medial prefrontal cortex in comparison to animals subjected to social rearing. The decreased expression of these enzymes was associated with reduced levels of THP and THDOC in the brain but not in plasma (Bortolato et al., 2011). Further evidence for the action of THP on dopamine regulation was obtained using the foot shock stress, which induces extracellular dopamine release from cortical dopaminergic neurons. Reduction of THP levels by the administration of finasteride in this model produces an amplification of dopamine release in the prefrontal cortex (Dazzi et al., 2002), while THP treatment completely prevents the dopamine increase in the cerebral cortex and in the nucleus accumbens (Motzo et al., 1996). THP also modulates dopamine levels and dopamine metabolism during the estrous phase of the female ovarian cycle. Indeed, its administration decreases the levels of dopamine and the dopamine metabolite 3,4-dihydroxyphenylacetic acid in striatum (Laconi et al., 2007). Similarly, THP treatment decreases dopamine output in the nucleus accumbens and prefrontal cortex in freely moving rats (Motzo et al., 1996). On the other hand, in an *in vitro* system, such as the PC12 pheochromocytoma cell line, THP administration increases both dopamine and norepinephrine levels by regulating catecholamine synthesis and their vesicle trafficking (Charalampopoulos et al., 2005).

PROG metabolites also exert a physiological role in the PNS. Indeed, peripheral nerves as well as Schwann cells express PR and GABA-A receptors (Jung-Testas et al., 1996; Melcangi et al., 2011; Melcangi et al., 1999). One of the actions of THP on Schwann cells is to enhance GABA synthesis through an increased expression of glutamic acid decarboxylase (Magnaghi et al., 2010) and to promote glutamate uptake through an increase in the excitatory amino acid carrier 1 (Perego et al., 2011). In addition DHP and THP regulate the expression of myelin proteins, such as glycoprotein zero (P0), in peripheral nerves and Schwann cells. In cultured Schwann cells, mifepristone, a PR antagonist, blocks the stimulatory effects of PROG or DHP on P0. Furthermore, treatment with mifepristone on postnatal (PN) day 1 decreases P0 expression at PN day 20 in rats (Melcangi et al., 2003b). Taken together, these data suggest that PROG metabolites enhance P0 expression by acting through PR in a classic genomic mechanism of action. This is also implied by the fact that nuclear receptor coactivators are involved in this regulation. This is the case of steroid receptor coactivator-1 (SRC-1), also known as NcoA-1, one of the first nuclear receptor coactivators found to interact with hormone-bound steroid receptors, including PR (Oñate et al., 1995). Thus, the over-expression of SRC-1 potentiates the DHP-induced increase in P0 expression in MCS80 immortalized Schwann cells. On the contrary, SRC-1 silencing eliminates this increase in P0 expression (Cavarretta et al., 2004). In addition, putative PROG responsive elements have been identified on the P0 gene (Magnaghi et al., 1999), further supporting the idea that P0 is regulated by a classical steroid genomic mechanism. PROG metabolites also affect myelination in Schwann cells by regulating the expression of specific transcription factors. For instance, Krox-20 expression is stimulated by treatment with DHP or THP, while Sox-10 expression is enhanced by DHP (Magnaghi et al., 2007).

In contrast to P0, the expression of peripheral myelin protein 22 (PMP22) is regulated by THP, but not by DHP, suggesting that this effect may be mediated by the GABA-A receptor (Melcangi et al., 2005; Melcangi et al., 1999). Indeed, a GABA-A receptor antagonist (i.e., bicuculline) completely abolished the stimulatory effect exerted by THP on PMP22 in Schwann cell cultures, while a GABA-A receptor agonist (i.e., muscimol) had a stimulatory effect on PMP22 that was comparable to that of THP (Magnaghi et al., 2001). A further support for the idea that THP is acting on the GABA-A receptor to regulate PM22 expression in Schwann cells is the finding that isopregnanolone, which does not directly interact with GABA-A receptor, does not alter PMP22 expression either.

The effects of PROG metabolites on the expression of P0 and PMP22 are sexually dimorphic. Indeed, DHP treatment induces a stimulatory effect on P0 mRNA levels in primary Schwann cell cultures obtained from male rats, but not in the cultures obtained from females (Magnaghi et al., 2006). On the contrary, treatment with THP increases gene expression of P0 in female rat Schwann cells, but not in male cells. Similarly, the expression of PMP22 is stimulated by THP in female, but not in male Schwann cell cultures (Magnaghi et al., 2006).

4.2. Testosterone reduced metabolites

The physiological effects of testosterone metabolites have been summarized in table 1. DHT is a selective and potent agonist for AR, showing higher affinity for this receptor than its precursor T (Wilson and French, 1976). The binding of DHT to AR triggers molecular mechanisms involved in the regulation of neuronal, glial and synaptic differentiation and in the coordination of the appearance of typical male features in specific brain regions (Cooke et al., 1998; Morris et al., 2004). DHT regulates synaptic density and transmission in slice hip-

pocampal cultures from male rodents, but not from female animals. Furthermore, the inhibition of DHT synthesis with finasteride, reduces dendritic spine maturation and long-term potentiation (Brandt et al., 2019).

In contrast to the high affinity of DHT for AR, its metabolites 3α-diol and 3β-diol show a low affinity for this receptor. As mentioned above, 3α-diol binds to GABA-A receptor (Lambert et al., 1995; Majewska et al., 1986; Paul and Purdy, 1992; Puia et al., 1990). Indeed, this DHT metabolite has well known effects on behavior by the modification of GABA signaling (Frye, 2007; Rosellini et al., 2001). The other DHT metabolite, 3β-diol, binds ERβ (Kuiper et al., 1997) but not GABA-A receptor. ERβ is probably involved in the modulation exerted by 3α-diol on the stress response mediated by HPA axis (Handa et al., 2008). Thus, peripheral 3β-diol treatment is as effective as peripheral DHT administration in reducing corticosterone and ACTH increases in response to restraint stress (Lund et al., 2004a, b). These effects of 3β-diol are blocked by co-administration of the ER antagonist tamoxifen, but not by the AR antagonist flutamide, suggesting that 3β-diol mediates the effects of DHT on corticosterone and ACTH secretion by binding to ERβ (Lund et al., 2006; Lund et al., 2004a, b).

T reduced metabolites also exert physiological effects in the PNS. For instance, in adult male rats, orchidectomy decreases the expression of P0 mRNA in the sciatic nerve, while subsequent treatment with DHT or 3α-diol restores P0 mRNA to pre-castration levels (Magnaghi et al., 2004; Magnaghi et al., 1999). Orchidectomy also decreases PMP22 mRNA levels in the rat sciatic nerve, but only 3α-diol treatment restores PMP22 levels (Magnaghi et al., 2004). In agreement with these results, DHT and 3α-diol increase P0 and PMP22 mRNA levels, respectively, in cultures of rat Schwann cells (Magnaghi et al., 1999; Melcangi et al., 2000a).

5. Regulation of the levels of progesterone and testosterone reduced metabolites in the nervous system under physiological and pathological conditions

5.1. Physiological conditions

As revealed by liquid chromatography-tandem mass spectrometry analyses (Fig. 2), the levels of reduced metabolites of PROG and T show differences between the nervous system, plasma and cerebrospinal fluid (CSF), between the CNS and PNS and between males and females on diestrus day (Caruso et al., 2013b). In addition, the levels of DHP, THP and isopregnanolone are higher in the brain of pseudopregnant females than in the brain of males (Meffre et al., 2007).

Sex differences in the levels of 5α-reduced PROG and T metabolites may be due to a sex dimorphism of the steroidogenic enzymes synthesizing these molecules. For instance, in green anole lizards, there is a higher gene expression of 5α-R type 2 in the brain of females than in the male brain (Cohen and Wade, 2010). Sex differences in the brain expression of 5α-R have been also observed in rats, where the mRNA levels of this enzyme are significantly higher in the cerebellum of males. In contrast, the mRNA levels of 3α-HSOR are significantly higher in the cerebellum of proestrus females than in males. This sex dimorphism does not occur in the cerebral cortex (Giatti et al., 2019a).

RAT TISSUE	MALE	FEMALE (DIESTRUS)
Plasma	DHT; 3α-diol	DHP; THP; ISOPREG
CSF	DHT; THP	ISOPREG
Hippocampus	DHT; 3α-diol	DHP; THP
Cerebral Cortex	DHT; 3α-diol	DHP; THP; ISOPREG
Cerebellum	DHT; 3α-diol	DHP; ISOPREG
Spinal cord	DHT; 3α-diol	DHP; ISOPREG
Sciatic nerve	DHT; 3α-diol; ISOPREG	DHP; THP

Fig. 2. Levels of progesterone and testosterone reduced metabolites in physiological conditions. Levels in different compartments of male and female (on diestrus day) rats. Higher level in males or females with respect to the other sex. 3α-diol: 5α-androstane-3α,17β-diol; CSF: cerebrospinal fluid; DHP: dihydroprogesterone; DHT: dihydrotestosterone; ISOPREG: isopregnanolone (3β-5α-tetrahydroprogesterone); THP: 3α-5α-tetrahydroprogesterone.

Another important consideration is that the levels of PROG and T reduced metabolites in the nervous system are influenced by its circulating levels. Indeed, gonadectomy affects the levels of these molecules in the CNS and the PNS (Caruso et al., 2010b). Interestingly, the changes induced by gonadectomy present specific features in different regions of the nervous system, are different in the two sexes and depend on the duration of gonadal hormone deprivation (Caruso et al., 2010b). Recent results also indicate a sex specific effect of long-term gonadectomy on the enzymes involved in the production of these metabolites. Thus, a decrease of 3α-HSOR occurred in female, but not in male, cerebellum (Giatti et al., 2019a). Altogether these results indicate that the levels of the 5α-reduced metabolites of PROG and T present in the nervous system under physiological conditions, even if influenced by the steroid hormone environment, show specific patterns depending on sex and brain region.

The levels of PROG and T reduced metabolites in the nervous system are also affected by neurodegenerative and psychiatric disorders. In some cases, these changes have been shown to be different in males and females, in agreement with the fact that many neurodegenerative and psychiatric disorders show a sex difference in term of incidence and/or manifestations of the pathology. The main findings are discussed in the following subsections.

5.2. Mental disorders

5.2.1. Alterations in steroidogenic enzymes and steroid levels

Altered THP plasma and/or CSF levels are a common finding in stress-related disorders and psychiatric diseases (Bali and Jaggi, 2014; Dong et al., 2001; Guidotti et al., 2001), suggesting that PROG metabolism is altered under these pathological conditions. For instance, anxiety-like behavior and depression are associated with decreased plasma and/or CSF levels of THP (Frye et al., 2008a; Maguire, 2019; Romeo et al., 1998; Rupprecht and Holsboer, 1999; Rupprecht et al., 2010; Schule et al., 2014; Walf and Frye, 2012). Similar changes have been observed in women affected by post-partum depression (Osborne et al., 2017) or post-partum anxiety (Osborne et al., 2019). THP and 3α-diol plasma levels are also decreased in association with increased depression and anxiety symptoms in anorexic and overweight/obese women (Dichtel et al., 2018). In agreement with these changes in THP levels, the expression of 5α-R type 1 enzyme is downregulated in prefrontal cortex Brodmann's area 9 of depressed patients (Agis-Balboa et al., 2014).

Plasma levels of THP are decreased in human alcoholics during alcohol withdrawal and return to normal levels upon recovery (Romeo et al., 1996). Modifications in THP levels and in the expression of steroidogenic enzymes associated with alcohol consumption have been also observed in animal models. Thus, ethanol treatment results in an increase in the gene expression and protein levels of 5α-R type 1, 2 and 3 in the prefrontal cortex of adolescent male rats (Sanchez et al., 2014) and THP levels are altered in the cerebral cortex and hippocampus after ethanol withdrawal in mice (Jensen et al., 2017).

5.2.2. Functional implications

The decrease in 5α-R type 1 brain expression and in THP plasma levels in depressed patients probably reflect an impaired neuroactive steroid homeostasis that may contribute to the symptomatology or even

to the pathogenesis of depression. Indeed, THP levels show a negative correlation with the severity of depressive symptoms (Uzunova et al., 1998). Furthermore, effective antidepressant treatments improve the reduced levels of THP in depressed patients (Griffin and Mellon, 1999; Romeo et al., 1998; Strohle et al., 1999; Uzunova et al., 2006) and fluoxetine (i.e., a selective serotonin reuptake inhibitor), increases the brain levels of THP in rats (Fry et al., 2014), although this effect was only detected in female animals.

Changes in the levels of THP in plasma, observed in human patients with post-traumatic stress disorders (PTSD), probably also reflect an alteration in steroid metabolism contributing to the pathology. Thus, THP is decreased in association with PTSD re-experiencing and depressive symptoms in PTSD patients, as well as with enhanced contextual fear memory and impaired fear extinction in PTSD experimental models (Pinna, 2019).

Changes in PROG metabolism may also be implicated in pathological mechanisms in autism, since there is a significant association between single nucleotide polymorphisms rs523349 (Leu89Val) located in SRD5A2 gene encoding 5α-R type 2 and autism (Zettergren et al., 2013). In addition, knockout mice for 5α-R type 2 enzyme show reduced dominance-related behaviors, as well as deficits of novelty-seeking and risk-taking responses (Mosher et al., 2018). Polymorphic variations in the enzymes 5α-R type 1 and 3α-HSOR have been also associated with increased risk of alcohol dependence (Milivojevic et al., 2011).

Although THP levels are decreased in numerous affective and psychiatric disorders and THP treatment may alleviate depressive symptoms, it is important to consider that in some cases the changes in THP levels may represent a positive homeostatic mechanism to regulate GABA-A receptor activity and counterbalance the pathological alterations in synaptic activity caused by the disease. This is the case of premenstrual dysphoric disorder and Tourette syndrome, in which the treatment with isopregnanolone, which inhibits the effects of THP on GABA-A receptors (Belelli and Lambert, 2005; Gee et al., 1988; Melcangi et al., 2008; Rupprecht, 2003), ameliorates the behavioral alterations (Bixo et al., 2018; Mosher et al., 2017) (see also Section 6.1.).

5.2.3. Sex differences

The alterations in PROG metabolism in mood and anxiety disorders may be different in males and females. For instance, environmental stress in rats caused by artificial light, immobility in a small space and excessive heat, results in an increased expression of 5α-R type 2 enzyme in the brain of adult males, but in decreased expression in the brain of females (Sanchez et al., 2009). Furthermore, THP levels are decreased in the male, but not in the female brain in a mouse model of autism spectrum disorder-like behavior induced by an inhibitor of the enzyme 5α-R type 1 and 2 (i.e., SKF105111) (Ebihara et al., 2017). In the reeler mouse, another experimental model of autism, the levels of DHT are decreased at postnatal day 5 in male, but not in female cerebellum, a brain region that shows morphological alterations in autistic patients, although other brain regions were not explored in this study (Biamonte et al., 2009).

In human PTSD patients, decreased CSF levels of THP are associated with impairment of 3α-HSOR in females (Rasmusson et al., 2006) and of 5α-R in males (Rasmusson et al., 2019). In addition, THP levels are decreased in the medial orbital frontal cortex of male patients, but not in female patients with this pathology (Cruz et al., 2019). Changes in THP brain levels associated with alcohol abuse are also different in men and women. Thus, sex differences in THP immunoreactive levels, being higher in men than in women, are detected in the substantia nigra pars medialis in patients diagnosed with alcohol use disorder (Hasirci et al., 2017).

5.3. Alzheimer's disease

Changes in brain levels of PROG metabolites have been detected in Alzheimer's disease (AD) mouse models, such as the 3xTg-AD mouse. Indeed, the levels of DHP and its metabolite, isopregnanolone, are significantly increased in the limbic region of 3xTg-AD male mouse in comparison to what reported in wild type mice (Caruso et al., 2013a). Since DHP exerts neuroprotective actions in experimental models of neurodegeneration (see Section 6.3.), the increase in its levels in the 3xTg-AD mouse brain may represent an endogenous neuroprotective mechanism. However, the significance of this finding for human pathology is unclear, because the levels of its metabolite THP are not significantly affected by AD in the brain of human patients (Weill-Engerer et al., 2002). Furthermore, although the existence of sex differences in AD is well established (Mielke et al., 2014; Rahman et al., 2019), the influence of sex in the levels of PROG and T reduced metabolites in the brain of AD animal models and patients remains to be determined. Nevertheless, low plasma T levels are significantly associated with increased risk of AD in elderly men (Lv et al., 2016), while higher free T levels in women are associated with lower cerebral Aβ positivity (Lee et al., 2017). This is also confirmed by assessment in postmortem human brain tissue (Rosario et al., 2011).

5.4. Parkinsońs disease

Low DHP levels have been reported in the CSF of Parkinson's disease (PD) patients (di Michele et al., 2003). In agreement with this finding, the expression of the 5α-R type 1 enzyme is downregulated in the substantia nigra, while that of 3α-HSOR type 3 is upregulated in the caudate nucleus (Luchetti et al., 2010). The levels of PROG and T reduced metabolites are also altered in PD rodent models. Indeed, striatal levels of DHP are decreased and those of isopregnanolone increased, by injection with 6-hydroxydopamine to male rats (Melcangi et al., 2012), while 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine treatment increases the brain levels of DHT in male mice (Bourque et al., 2016). This increase in DHT levels in PD male mice may be an endogenous protective mechanism, because DHT is neuroprotective in PD animal models (Bourque et al., 2009; Khasnavis et al., 2013). In contrast the decreased levels of DHP in PD models may impair the endogenous protective environment provided by this PROG metabolite. However, it is still necessary to confirm these findings in humans. In addition, as mentioned for AD, there is still need of a comparative assessment of the levels of PROG and T reduced metabolites in the brain of male and female PD patients or experimental models, despite the higher incidence of the disease in males (Benito-Leon et al., 2003; de Lau et al., 2004; Van Den Eeden et al., 2003; Wooten et al., 2004) and the existence of sex differences in the pathological alterations (Haaxma et al., 2007) (Czlonkowska et al., 2006).

5.5. Multiple sclerosis

Altered levels of PROG and T reduced metabolites are detected in patients affected by multiple sclerosis (MS). For instance, increased levels of isopregnanolone and 3α-diol, and decreased levels of DHP, DHT and THP have been detected in the CSF of Relapsing-Remitting MS (RRMS) male adult patients (Caruso et al., 2014). THP levels are also significantly decreased in brain samples of male MS patients (Noorbakhsh et al., 2011).

In agreement with these observations in humans, 5α-R expression in the hippocampus and cerebral cortex is decreased in the mouse cuprizone demyelination model (Leicaj et al., 2018) and PROG and T reduced metabolites are affected in the CNS of experimental autoimmune encephalomyelitis (EAE) rat MS model (Caruso et al., 2010a; Giatti

et al., 2010). Interestingly, in this latter case, these changes depend on the pathological phase considered and on the protocol used to induce the pathology. For instance, the levels of DHP, DHT and 3α-diol are decreased in the spinal cord at the chronic phase of the disease after induction with guinea pig spinal cord tissue in complete Freund's adjuvant (Caruso et al., 2010a; Giatti et al., 2010), but not when the induction is made by syngeneic whole spinal cord homogenate suspended in incomplete Freund's adjuvant (Giatti et al., 2013).

PROG and T reduced metabolites are protective in MS models (Noorbakhsh et al., 2014; Noorbakhsh et al., 2011) (Bebo et al., 1999; Dalal et al., 1997; Giatti et al., 2015; Palaszynski et al., 2004). Therefore, the decrease in their levels may contribute to increase the manifestation of the pathological alterations and may contribute to sex differences in the pathology. Indeed, different levels of PROG and T reduced metabolites have been detected in male and female EAE animals, in agreement with the higher incidence of MS in females (Dooley and Hogan, 2003; Gleicher and Barad, 2007; Jacobson et al., 1997) and the existence of sex differences in MS symptomatology, course of the disease, age of onset and pathological alterations (Golden and Voskuhl, 2017). Interestingly, sex differences in PROG and T reduced metabolites in EAE animal models depend on the phase of pathology considered. Indeed, THP levels are increased, while DHT and 3α-diol levels are decreased, in the spinal cord of males, but not of females, at the acute phase of the disease (i.e., 14 days post-immunization) (Giatti et al., 2010). Furthermore, at the chronic phase (i.e., 40 days post-immunization), in addition to the decrease in DHT and 3α-diol levels observed in the acute phase (Giatti et al., 2010), there is also a decrease in the levels of DHP, also exclusively in males (Caruso et al., 2010a). In the cerebellum, the acute and chronic phases of the disease are associated with a significant decrease of isopregnanolone and 3α-diol levels in males (Caruso et al., 2010a; Giatti et al., 2010). In contrast, in the female cerebellum, THP levels are decreased at the acute phase of the disease (Giatti et al., 2010), while at the chronic phase the levels of isopregnanolone are increased and the levels of DHP and THP are decreased (Caruso et al., 2010a). In the male cerebral cortex, there is a decrease in the levels of DHP, DHT and 3α-diol and an increase in the levels of THP at the acute phase of the disease (Giatti et al., 2010). Then, the levels of DHP and DHT remain decreased at the chronic phase (Caruso et al., 2010a). However, none of these changes are detected in the cerebral cortex of females (Caruso et al., 2010a; Giatti et al., 2010).

Sex differences in PROG metabolites have been also detected in human RRMS patients. Thus, THP levels in the CSF are higher in male than in female patients (Orefice et al., 2016). However, this difference is observed in the active but not in the stable-phase, where the levels are comparable in the two sexes. In addition, while male and female RRMS patients with gadolinium-enhanced lesions showed comparable THP levels, in RRMS patients without gadolinium-enhanced lesions the levels of THP were lower in males than in females (Orefice et al., 2016).

5.6. Traumatic CNS injury and stroke

Brain levels of PROG metabolites (i.e., THP and isopregnanolone) and of T, such as DHT, are affected in experimental model of traumatic brain injury (TBI) (Lopez-Rodriguez et al., 2015; Lopez-Rodriguez et al., 2016; Meffre et al., 2007). Spinal cord transection also affects PROG metabolites, with an increase in DHP and THP levels (Labombarda et al., 2006). DHP levels are also increased six hours after middle cerebral artery occlusion in mice (Liu et al., 2012). These changes may reflect an endogenous protective response, given the therapeutic efficacy of the treatment with DHP or THP in experimental stroke (Sayeed et al., 2006) and TBI (Djebaili et al., 2005).

In agreement with the existence of sex differences in the incidence and outcome of TBI and stroke (Bushnell et al., 2018; Mollayeva et al., 2018), sex differences in PROG metabolites have been detected in animal models of these CNS injuries. For instance, TBI results in increased brain levels of isopregnanolone in pseudopregnant female rats (Meffre et al., 2007) and in decreased brain levels of THP and isopregnanolone in female mice (Lopez-Rodriguez et al., 2015). On the contrary, a decrease of DHT levels, associated with an increase in T levels, was observed by 2 weeks after TBI in the brain of male mice, but not in the female brain (Lopez-Rodriguez et al., 2016). Furthermore, cerebral levels of DHP are rapidly upregulated in male, but not in female mice in an experimental model of middle cerebral artery occlusion (i.e., ischemic stroke model) (Zhu et al., 2017).

5.7. Diabetic encephalopathy

Diabetes alters brain function (i.e., diabetic encephalopathy) as well as, as observed in animal models, the levels of PROG and T reduced metabolites in the nervous system (Calabrese et al., 2014; Giatti et al., 2018b; Pesaresi et al., 2010a; Pesaresi et al., 2010b; Romano et al., 2017; Romano et al., 2018). The specific alterations in the levels of these metabolites depend on the duration of pathology. For instance, the levels of 3α-diol are decreased in the spinal cord of male rats after long-, but not after short-term diabetes (Calabrese et al., 2014; Pesaresi et al., 2010b).

Sex differences in the outcome of diabetic encephalopathy in humans and in animal models (Giatti et al., 2019b) have been also reported and the observations obtained in streptozotocin (STZ) experimental model show that the nervous levels of PROG and T reduced metabolites are modified in a sex-dimorphic way and with regional differences. For instance, compared to control animals, the levels of THP are decreased in the spinal cord and those of DHT are decreased in the cerebral cortex, cerebellum and spinal cord of diabetic males but not of diabetic females (Pesaresi et al., 2010b). In contrast, the levels of DHP and isopregnanolone are decreased in the cerebellum of both long-term diabetic male and female rats (Pesaresi et al., 2010b). Although the consequence of these changes in PROG and T reduced metabolites in the brain of diabetic animals has not been fully explored yet, it is known that DHP exerts protective effects on myelin in the spinal cord of diabetic rats (Pesaresi et al., 2010a) and that THP, DHP, DHT and 3α-diol exert protective effects in the peripheral nerves of diabetic animals (Afrazi et al., 2014; Calabrese et al., 2014; Leonelli et al., 2007; Roglio et al., 2007; Veiga et al., 2006). Therefore, the alterations in the levels of these steroids in the brain of diabetic animals most probably will facilitate the progress of the pathological alterations associated to diabetic encephalopathy.

5.8. Peripheral neuropathy

Animal models of peripheral neuropathy also show alterations in the levels of PROG and T reduced metabolites (Caruso et al., 2008; Giatti et al., 2018b; Pesaresi et al., 2011; Pesaresi et al., 2010b; Roglio et al., 2008). For instance, alterations in PROG metabolites in the sciatic nerve have been detected in a mouse model of peripheral neuropathy, the sterol regulatory element binding protein-1C knockout mice (Cermenati et al., 2015). In the sciatic nerve of these animals, the levels of DHP and isopregnanolone are decreased at 2 months of age and the levels of isopregnanolone and THP are increased at 10 months of age, in comparison to those observed in wild type animals (Mitro et al., 2017). In another model of peripheral neuropathy, the crush injury of the sciatic nerve, a decrease in the levels of DHP and THP, associated with a decrease in the expression of enzyme 5α-R, is observed in the distal portion of the injured nerve in male rats (Roglio et al., 2008).

The decrease in the expression of 5α-R and in the levels of PROG and T reduced metabolites has probably a negative impact for functional recovery from peripheral neuropathy, because several studies in different animal models have shown that the treatment with these steroids improves the structure and function of the damaged peripheral nerves (see Section 6.4.). Thus, in this case, there is a clear potential application of steroid therapy. However, as for other pathological conditions, it is important to consider that sex specific changes in PROG and T metabolites also occur in peripheral neuropathy. For instance, in the sciatic nerve of male rats, but not in females, DHT levels are decreased and those of THP are increased after one month of diabetes (Pesaresi et al., 2018). Further sex differences are detected with longer duration of diabetes. Thus, by 3 months of diabetes a decrease in DHT and 3α-diol levels are detected in the male rat sciatic nerve, while in females there is a decrease in the levels of THP and isopregnanolone (Pesaresi et al., 2010b). In another animal model of inherited peripheral neuropathy (i.e., Charcot-Marie-Tooth disease type 1A), sexual differences in the levels of some PROG and T reduced metabolites have also been identified. Indeed, compared to control animals, the levels of isopregnanolone are decreased in the peripheral nerves of female rats and those of 3α-diol are decreased in the peripheral nerves of males (Caruso et al., 2008).

5.9. Neuropathic pain

Alterations in PROG metabolites are also associated with chronic neuropathic pain. For instance, in animals with neuropathic pain induced by peripheral nerve injury, the levels of THP are increased in the spinal cord, together with an increased expression and activity of 3α-HSOR (Gonzalez et al., 2019). In this case, the increase in the levels of THP and in the expression and activity of 3α-HSOR seem to be an adaptive response to control pain (Patte-Mensah et al., 2010; Patte-Mensah et al., 2014). In agreement with this interpretation, a decreased expression of 5α-R type 1 and type 2 in the dorsal spinal cord has been shown to be associated with the manifestation of allodynic behaviors in animals with spinal cord injury (Coronel et al., 2016). Furthermore, there is an increase in THP levels in the rat lateral thalamus (i.e., an important brain region for pain modulation) after spared nerve injury (Zhang et al., 2016). Interestingly, in this experimental model, THP levels are also increased in the hippocampus (Zhang et al., 2017b), suggesting that PROG metabolites may also participate in pain-associated emotions.

6. Therapeutic actions of the modulation of progesterone and testosterone reduced metabolites in psychiatric and neurodegenerative disorders

As mentioned above the levels of PROG and T metabolites are affected in many neurodegenerative and psychiatric disorders. In agreement, several therapeutic effects of the modulation of these metabolites have been reported, as summarized in table 2 and here discussed in detail.

6.1. Mental disorders

Anxiolytic and anti-stress actions of THP administration are well established (Barbaccia et al., 2001; Zorumski et al., 2019). These effects are probably mediated by activation of GABA-A receptors, since PROG administered to PR knockout mice is still able to exert anxiolytic effects (Reddy et al., 2005). However, the anti-depressive effect of THP, at least in the forced swimming model, seems to involve also the stimulation of dopamine D2-like receptors (D'Aquila et al., 2010).

Sex specific features are an important component of the actions of THP in mood and anxiety disorders. For instance, THP attenuates only in females the HPA axis responses to interleukin-1β in adult prenatally

Table 2
Neuroprotective actions of progesterone and testosterone metabolites in pathological situations.

Steroid	Central Nervous System	Peripheral Nervous System
DHP	Stroke, oxygen-glucose deprivation, traumatic brain injury, neurotoxicity induced by kainic acid or human immunodeficiency virus	Chemotherapy-induced peripheral neuropathy
	Diabetic spinal cord cell apoptosis	Diabetes-induced peripheral neuropathy
	High glucose level toxicity on DRG	Nerve transection and crush
	Myelin lipid profile alteration induced by diabetes	Ageing-induced myelin abnormalities
THP	Anxiety, depression and stress	Diabetes-induced peripheral neuropathy
	HPA axis activation induced by IL1β	Ageing-induced myelin abnormalities
	Stroke, seizures, traumatic brain injury, multiple sclerosis, Alzheimer's and Parkinson's diseases, fragile X-associated tremor/ataxia syndrome, ischemic stroke	Chemotherapy-induced peripheral neuropathy
	Diabetic spinal cord cell apoptosis	
	Oxygen-glucose deprivation, neurotoxicity induced by kainic acid or human immunodeficiency virus	
	Reinstatement of cocaine-seeking behavior induced by yohimbine	
Isopregnanolone	Premenstrual dysphoric disorder	
	Tourette syndrome	
DHT	Multiple sclerosis, Parkinson's diseases, traumatic brain injury	Diabetes-induced peripheral neuropathy

Table 2 (*Continued*)

Steroid	Central Nervous System	Peripheral Nervous System
	Apoptosis, neurotoxicity induced by kainic acid, by serum deprivation, or by glutamate, acute demyelination	Nerve injury-induced peripheral neuropathy
3α-diol	β-amyloid toxicity	Diabetes-induced peripheral neuropathy Chemotherapy-induced peripheral neuropathy
3β-diol	HPA axis activation induced by IL1β	

stressed rats, while 3β-diol normalized these responses in males (Brunton et al., 2015). THP also blocks in females, but not in males, the stress-induced reinstatement of cocaine-seeking behavior induced by yohimbine (Anker and Carroll, 2010). Furthermore, although THP has anxiolytic effects, women with premenstrual dysphoric disorder show an altered sensitivity to THP over the menstrual cycle in comparison to healthy controls, determined by recording the saccadic eye velocity as a measure of GABA-A receptor activity (Timby et al., 2016). Interestingly, THP effects are antagonized by the treatment in the premenstrual phase with isopregnanolone, reducing negative mood symptoms in premenstrual dysphoric disorder (Bixo et al., 2018). In agreement, isopregnanolone treatment has been also demonstrated to reduce the number of tic-like behaviors induced by stress in D1CT-7 mice (i.e., an experimental model of Tourette syndrome) (Cadeddu et al., 2019). Indeed, in the same experimental model, THP exacerbated the Tourette syndrome-symptoms (Mosher et al., 2017).

6.2. Analgesic actions

Studies by Mensah-Nyagan and his collaborators have demonstrated that 5α-R and 3α-HSOR are expressed in pain information processing centers of the CNS, such as the dorsal root ganglia and the dorsal horn of the spinal cord (Meyer et al., 2019; Patte-Mensah et al., 2010). In addition, substance P, one of the main neuropeptides involving in pain processing, regulates the synthesis of THP in the dorsal horn of the spinal cord (Patte-Mensah et al., 2005). This suggests that endogenous THP is involved in pain processing. Indeed, the silencing of 3α-HSOR and the consequent inhibition of the local synthesis of THP in the dorsal root ganglia or in the spinal cord enhances neuropathic pain induced by sciatic nerve injury (Patte-Mensah et al., 2010; Patte-Mensah et al., 2014), while the pharmacological administration of THP ameliorates diabetic-induced thermal hyperalgesia in the STZ model (Afrazi et al., 2014). The analgesic actions of THP are, at least in part, mediated by the potentiation of GABA-A receptor activity and the inhibition of T-type Ca^{2+} channels (Pathirathna et al., 2005a; Pathirathna et al., 2005b). In addition, not only THP, but also its precursor DHP, suppress neuropathic symptoms (allodynia/hyperalgesia) evoked by antineoplastic drugs such as vincristine (Meyer et al., 2010) and oxaliplatin (Meyer et al., 2011a).

T reduced metabolites also decrease neuropathic pain associated with diabetes mellitus. Indeed, DHT and 3α-diol treatments are effective on alterations of mechanical nociceptive threshold and tactile allodynia induced by diabetes, respectively (Calabrese et al., 2014). 3α-diol is also able to exert beneficial effects on painful symptoms occurring in paclitaxel-induced peripheral neuropathy (Meyer et al., 2013).

6.3. Neuroprotection in experimental models of neurodegeneration

Neuroprotective actions of PROG and T reduced metabolites have been characterized in a variety of *in vitro* and *in vivo* models of neurodegeneration. DHP and THP are protective against kainic acid-induced excitotoxicity in the hippocampus *in vivo* (Ciriza et al., 2006). In addition, THP treatment reduces seizures (Frye and Scalise, 2000), prevents cell apoptosis in the spinal cord of STZ diabetic rats (Afrazi et al., 2014) and protects against stroke (Sayeed et al., 2006), oxygen-glucose deprivation (Ardeshiri et al., 2006), TBI (Djebaili et al., 2005) and the neurotoxic effects exerted by human immunodeficiency virus (Paris et al., 2016). THP is also able to reduce axonal injury in EAE (Noorbakhsh et al., 2014; Noorbakhsh et al., 2011), and it is protective in AD models, inducing neurogenesis/oligodendrogenesis and reducing β-amyloid levels (Irwin and Brinton, 2014; Irwin et al., 2014) and bioenergetics deficits (Wang et al., 2019) as well as in an experimental model of amyotrophic lateral sclerosis (i.e., Wobbler mouse) (Meyer et al., 2017). In PD experimental models, THP is also able to improve cognitive dysfunction (Nezhadi et al., 2016) and motor performance (Adeosun et al., 2012). In addition, a pilot clinical study performed in patients affected by fragile X-associated tremor/ataxia syndrome also show that THP treatment improves cognitive function and some aspects of neurodegeneration (Napoli et al., 2019; Wang et al., 2017).

Reduced metabolites of T also exert neuroprotective actions. For instance, DHT is neuroprotective in experimental model of PD (Bourque et al., 2009; Khasnavis et al., 2013), in EAE models (Bebo et al., 1999; Dalal et al., 1997; Giatti et al., 2015; Palaszynski et al., 2004) and in an experimental model of TBI (Barreto et al., 2007). DHT is also able to protect hippocampal neurons from different damages, such as kainic acid injection (Ramsden et al., 2003), apoptosis (Nguyen et al., 2010; Zhang et al., 2004) and serum deprivation (Hammond et al., 2001). Moreover, it is also a protective agent for motoneurons (Huppenbauer et al., 2005). However, DHT effects on stroke are still unclear. Indeed, both protective and deleterious effects have been reported (Quillinan et al., 2014).

The further metabolite of DHT, 3α-diol, exerts neuroprotective effects in SH-SY5Y neuronal cells and in primary cortical neurons, inhibiting the phosphorylation of extracellular signal-regulated kinase induced by amyloid β peptide 1-42. Interestingly, this effect is mediated by both GABA-A receptor-dependent and independent mechanisms (Mendell et al., 2018).

Altogether, these observations indicate that the PROG and T reduced metabolites are neuroprotective agents. In this context, it is important to highlight that most of the studies present in the literature and discussed above have been conducted only in one sex. However, the protective effects exerted by the metabolites of PROG and T show sex specific features. For instance, in cultured hippocampal neurons, DHT shows protective effects for apoptosis induced by glutamate in males, but not in females (Zup et al., 2014). THP exerts dose-dependent sex-specific neuroprotective actions in ischemic models. For instance, a low dose of this DHP metabolite induces a higher neuroprotection from ischemic damage in females than in males (Kelley et al., 2011). In epilepsy animal model, THP shows greater antiseizure potency in females than in males and this effect seems to be associated with a greater abundance of extrasynaptic δ–subunit of GABA-A receptors in females (Reddy et al., 2019).

6.4. Neuroprotection in peripheral neuropathy

In the STZ experimental rat model of peripheral diabetic neuropathy, THP treatment improves nerve conduction velocity, thermal threshold and skin innervation density, while its precursor DHP, in addition to these effects, also improves alterations in Na^+,K^+-ATPase activity (Leonelli et al., 2007). Furthermore, DHP protects dorsal root ganglia cultures exposed to high levels of glucose (Giatti et al., 2018b). Neuroprotective effects of DHP have been also reported in other experimental models of peripheral nerve damage, such as transection (Melcangi et al., 2000a), crush (Roglio et al., 2008) and docetaxel-induced peripheral neurotoxicity (Roglio et al., 2009). Furthermore, DHP and THP are also able to counteract the damage on peripheral nerves induced by the aging process in rats (Azcoitia et al., 2003; Melcangi et al., 2003a).

DHT and 3α-diol are also protective in the PNS. For instance, DHT induces a faster regeneration and functional recovery of injured nerves (Huppenbauer et al., 2005; Jones et al., 2001; Tanzer and Jones, 2004; Vita et al., 1983; Yu, 1982). In the STZ experimental diabetic rat model, DHT stimulates the activity of Na^+,K^+-ATPase in the sciatic nerve and counteracts the impairment of nerve conduction velocity, thermal sensitivity and skin innervation density (Roglio et al., 2007). In this experimental model, also 3α-diol is able to reduce morphological alterations in the sciatic nerve (Mitro et al., 2014) and to improve nerve conduction velocity, thermal sensitivity and skin innervation density (Roglio et al., 2007).

6.5. Myelin protection

Myelin preservation is one of the protective actions of PROG metabolites in both peripheral nerves and CNS. Thus, DHP and THP increase the expression of myelin proteins, such as P0 and PMP22 (Melcangi et al., 2003a; Melcangi et al., 1998a; Melcangi et al., 2000b) and exert beneficial effects on the number and shape of myelinated fibers, reducing the frequency of myelin abnormalities (Azcoitia et al., 2003; Melcangi et al., 2003a) in aged rats. THP also decreases demyelination in EAE experimental model (Noorbakhsh et al., 2014; Noorbakhsh et al., 2011). In addition, DHP counteracts the decreased expression of P0 and PMP22 (Leonelli et al., 2007) and the increase in the number of fibers with myelin infoldings in the sciatic nerve of STZ diabetic rats (Veiga et al., 2006). This metabolite of PROG also increases the expression of myelin basic protein, in the spinal cord of STZ diabetic rats (Pesaresi et al., 2010a).

Not only myelin proteins but also lipid components of the myelin are targets for the protective effects of PROG metabolites. Indeed, by promoting fatty acid desaturation, which is altered in STZ experimental model, DHP reduces myelin structural alterations in peripheral nerve (Mitro et al., 2014) and restores to control levels the myelin lipid profile in the cerebral cortex (Cermenati et al., 2017) of diabetic animals.

T reduced metabolites also exert protective actions on myelin. Thus, in cerebellar organotypic cultures, DHT protects against acute demyelination (Hussain et al., 2013). In addition, in the STZ experimental model, DHT stimulates the expression of P0 (Roglio et al., 2007) and its metabolite 3α-diol reduces the accumulation of saturated fatty acids in the myelin of sciatic nerve (Mitro et al., 2014).

6.6. Control of neuroinflammation

Control of neuroinflammation, a common aspect in neurodegenerative and psychiatric diseases (Glass et al., 2010; Meyer et al., 2011b; Tansey, 2010; Tansey and Goldberg, 2010; Wee Yong, 2010; Wuwongse et al., 2010), is one of the crucial mechanisms of neuroprotection by PROG metabolites (Giatti et al., 2012; Giatti et al., 2019c). Indeed, THP reduces protein-protein interactions initiating the toll-like receptor 4-dependent signaling in immune cells and the brain (Balan et al., 2019). Thus, THP decreases microglia reactivity and lymphocyte infiltration in EAE experimental model (Noorbakhsh et al., 2014; Noorbakhsh et al., 2011) and neuroinflammatory burden in AD models (Irwin and Brinton, 2014; Irwin et al., 2014). In ischemic stroke, THP downregulates the production of pro-inflammatory cytokines, such as TNF-α and IL-6, protecting against BBB disruption and reducing infarct size (Ishrat et al., 2010). In addition, THP decreases the brain expression levels of IL-1β and TNF-α after TBI in rats (He et al., 2004) and increases the expression of CD55, a potent inhibitor of the complement convertases that are activators of the inflammatory cascade (VanLandingham et al., 2007). T reduced metabolites also regulate neuroinflammation and gliosis. For instance, in the EAE model, DHT reduces pro-inflammatory IFN-γ expression and gliosis in the spinal cord (Giatti et al., 2015) and increases the expression of anti-inflammatory IL-10 by autoantigen specific T lymphocytes (Dalal et al., 1997).

7. Limitations and alternatives for the use of progesterone and testosterone reduced metabolites as therapeutic agents for the nervous system

As reviewed in the previous section, PROG and T reduced metabolites exert a variety of protective actions in the nervous system. Therefore, it has been suggested that they may be used for neuroprotective pharmacological treatments. For instance, THP has been proposed as potential candidate for the treatment of mood and anxiety disorders (Wirth, 2011), neuropathic pain (Meyer et al., 2019), AD (Irwin et al., 2015), TBI (Reddy and Estes, 2016) or demyelinating diseases (Schumacher et al., 2014), among other nervous system pathologies. The main disadvantages of the treatment with natural steroid metabolites are represented by their rapid metabolism and their low oral bioavailability. For these reasons, an extensive research has been devoted to synthesize analogues of these molecules and particularly of THP (Carter et al., 1997; Hogenkamp et al., 2014; Rey and Coirini, 2015; Rey et al., 2015; Taleb et al., 2018).

Promising neuroprotective effects have been observed with some of these analogues (Althaus et al., 2017; Karout et al., 2016; Reddy and Estes, 2016; Rey et al., 2013; Zorumski et al., 2019). In particular, there is an extensive literature on the neuroprotective effects of two synthetic analogues of THP, such as ganaxolone and brexanolone. Ganaxolone is neuroprotective in an experimental model of Niemann-Pick Type-C, even if its effect is less robust than that exerted by THP (Mellon et al., 2008). Ganaxolone also improves dysfunctional emotional behavior in an animal model of PTSD (Pinna and Rasmusson, 2014), ameliorates behavioral abnormalities in Angelman syndrome (Ciarlone et al., 2017), reduces preterm-associated neurodevelopmental impairment following preterm birth (Shaw et al., 2019), regulates GABA transport and neuroinflammation in MS (Paul et al., 2014) and induces remyelination in focal demyelination of corpus callosum (Mouihate and Kalakh, 2019). In addition, ganaxolone is effective for the treatment of ethanol withdrawal-induced seizures (Nipper et al., 2019) and exerts therapeutic effects in animal models of epilepsy and related conditions (Chuang and Reddy, 2018; Saporito et al., 2019; Zolkowska et al., 2018), being now under assessment in clinical trials for the treatment of various seizure disorders (i.e., NCT03572933, NCT03865732 and NCT03350035).

Brexanolone, produced by Sage Therapeutics, has recently received the approval of US Food and Drug Administration for the specific treatment of post-partum depression (Meltzer-Brody et al., 2018; Zheng et al., 2019; Zorumski et al., 2019). However, even if this molecule may represent an important new treatment option, some concerns on

its use have been raised (Cristea and Naudet, 2019; Morrison et al., 2019).

An alternative to the use of synthetic steroids is to enhance the endogenous synthesis of PROG and T reduced metabolites. One option for this is the pharmacological activation of steroidogenesis with ligands of TSPO, a molecule that forms part of the macromolecular complex involved in the transfer of cholesterol into mitochondria (Papadopoulos et al., 1997). Some TSPO ligands stimulate steroidogenesis, including the synthesis of PROG and T reduced metabolites (Da Pozzo et al., 2016; Papadopoulos, 2014; Papadopoulos et al., 2018), and exert neuroprotective actions in animal models that depend on an increase in the levels of these neuroactive steroids. This is the case of etifoxine (Daugherty et al., 2013) and XBD173 (Leva et al., 2017) in EAE mice, midazolam (Miao et al., 2014) and YL-IPA08 in rat models of PTSD (Shang et al., 2019) and chronic stress-related depression (Zhang et al., 2017a), PK11195 in a rat *ex vivo* glaucoma model (Ishikawa et al., 2016) and Ro5-4864 and AC-5216 in diabetic rats (Mitro et al., 2012) (Giatti et al., 2009) (Qiu et al., 2016).

Activation of liver X receptors (LXRs) has been also shown to raise the levels of PROG and T reduced metabolites in the nervous system. For instance, the treatment with the LXR ligand GW3965 increases the levels of DHP, THP, isopregnanolone and 3α-diol in the spinal cord and the cerebral cortex and the levels of DHP and 3α-diol in the sciatic nerve of diabetic rats (Cermenati et al., 2010) (Mitro et al., 2012). Therefore, it is possible that PROG and T reduced metabolites mediate the neuroprotective effects of LXRs reported in animal models of cerebral ischemia (Cheng et al., 2010), MS, AD and PD (Paterniti et al., 2017; Xu et al., 2013). However, this has not been proved yet.

Interestingly, at least in the sciatic nerve, the protective effect of LXR ligands is associated with an increase in the expression of 5α-R, among other steroidogenic molecules (Cermenati et al., 2010). The modulation of 5α-R activity has been proposed as a therapeutic treatment for neuropsychiatric disorders in which excessive levels of PROG or T reduced metabolites may have a negative impact, like for instance Tourette syndrome and pathological gambling (Bortolato et al., 2008; Fanni et al., 2019; Frau and Bortolato, 2019; Paba et al., 2011). The 5α-R inhibitor dutasteride has been also shown to reduce alcohol consumption in adult men (Covault et al., 2014). In addition, a clinical study performed in women with premenstrual dysphoric disorder showed that dutasteride reduces irritability, sadness, anxiety, food cravings and bloating (Martinez et al., 2016).

Inhibitors of 5α-R have been reported to exert male-specific neuroprotective effects in experimental models of neurodegenerative diseases in rodents, like dutasteride in an experimental model of PD (Litim et al., 2015; Litim et al., 2017) or finasteride in ischemic brain injury induced in aged rats (Tanaka et al., 2019). These male-specific effects of 5α-R inhibition are in agreement with the previously discussed sex differences in the neuroprotective actions of PROG and T reduced metabolites. Indeed, the cellular and molecular consequences of the inhibition of 5α-R are different in the male and female injured brains (Golz et al., 2019), suggesting that the neuroprotective effects depend on a different balance of PROG and T reduced metabolites in each sex, which is also probably different for each pathological condition (Golz et al., 2019). However, we are still far from a fully understanding of this protective steroid balance and we have an incomplete knowledge on all the possible neurological and psychiatric consequences of 5α-R inhibition. Indeed, serious endocrine and neuropsychiatric side effects (i.e., erectile and ejaculatory dysfunctions, loss of libido, depression, anxiety, suicidal thoughts and sleep problems) have been reported in a subset of male patients treated with 5α-R inhibitors for androgenetic alopecia. Importantly, these effects may persist despite treatment suspension (Diviccaro et al., 2020; Giatti et al., 2018a; Irwig, 2012a, b; Traish et al., 2015), a situation that has received the name of post-finasteride syndrome. Interestingly, alterations in the methylation pattern of the gene encoding for 5α-R type 2 and in the levels of the reduced metabolites of PROG and T have been detected in the CSF of patients with this syndrome (Melcangi et al., 2019; Melcangi et al., 2017). These alterations further emphasize the need for an adequate understanding of the role of 5α-R for neural function.

8. Conclusions

The studies reviewed here indicate that the generation of PROG and T reduced metabolites in the nervous system has regional and cellular specificity, which is the result of the cell-specific expression of the enzymes 5α-R and 3α- and 3β-HSOR. In addition, the action of the enzymatic products of 5α-R and 3α/β-HSOR also shows cellular and regional specificity, since it depends on receptors that are not homogeneously distributed in the nervous tissue, such as AR, PR and ERβ, or that have a different regional and subcellular subunit composition that determines steroid actions, as is the case for the GABA-A receptor (Belelli and Lambert, 2005). The significance of this regional specificity of action is still unclear, but suggests that PROG and T reduced metabolites may act as neuromodulators, modifying neurotransmission or intracellular signaling in a specific cell to cell communication manner. Indeed, the neuromodulatory action of these neuroactive steroids has been ascertained in some cases, such as in the control of pain (Meyer et al., 2019). However, this possible neuromodulatory role remains to be ascertained for other functions of PROG and T reduced metabolites.

An important aspect that has been reviewed here is the existence of sex differences in the physiological effects exerted in the nervous system by PROG and T reduced metabolites. As we have seen, this is also associated with dissimilar levels of these steroids in males and females. The function of these differences is unclear, except for those that may be involved during development in the generation of a sex dimorphic brain differentiation. In the adult brain, dissimilar levels and actions of PROG and T reduced metabolites in males and females may be involved in the generation of sex dimorphic behaviors, but they may also represent a compensation for the sexually differentiated actions of sex steroids. This latter possibility has not been received enough attention yet.

Similar considerations may apply for the observed differences in the levels and actions of PROG and T reduced metabolites in neurodegenerative and psychiatric disorders in males and females. Here, in addition, it is unclear whether these differences are a cause or a consequence of the specific manifestation of the pathological alterations in each sex, because, in general, the available observations on steroid changes in nervous tissue under pathological conditions are mere correlations. However, it is clear that some PROG and T reduced metabolites exert neuroprotective actions, suggesting that a decrease in their levels may enhance the pathological alterations, while their increase under pathological conditions may represent an endogenous neuroprotective mechanism. In contrast, as we have discussed before, excessive levels of PROG or T reduced metabolites may have a negative impact in other pathological situations, such as in Tourette syndrome, pathological gambling and premenstrual dysphoric disorder. Of course, this information supports possible therapeutic interventions using synthetic steroid analogs to enhance steroid signaling or using inhibitors for 5α-R, the rate limiting step in the generation of PROG and T reduced metabolites, to decrease steroid signaling. While proofs of concept for such treatments are well established in animal models and good results have been also obtained in some human conditions, in particular with the use of synthetic steroids, further research is still necessary to determine the efficacy and safety of such treatments in humans, in particular considering their possible long-term effects and their different consequences in men and women.

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.

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