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Neurosteroids and the mesocorticolimbic system

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ABSTRACT

The mesocorticolimbic system coordinates executive functions, such as working memory and behavioral flexibility. This circuit includes dopaminergic projections from the ventral tegmental area to the nucleus accumbens and medial prefrontal cortex. In this review, we summarize evidence that cells in multiple nodes of the mesocorticolimbic system produce neurosteroids (steroids synthesized in the nervous system) and express steroid receptors. Here, we focus on neuroandrogens (androgens synthesized in the nervous system), neuroestrogens (estrogens synthesized in the nervous system), and androgen and estrogen receptors. We also summarize how (neuro)androgens and (neuro)estrogens affect dopamine signaling in the mesocorticolimbic system and regulate executive functions. Taken together, the data suggest that steroids produced in the gonads and locally in the brain modulate higher-order cognition and executive functions.

1. Introduction

Androgens and estrogens are secreted by the testes and ovaries, respectively, into the circulatory system and modulate brain functions (Celec et al., 2015; Luine and Frankfurt, 2020). Endogenous androgens include androstenedione, testosterone, and 5α-dihydrotestosterone, while endogenous estrogens include 17β-estradiol and estrone (Fig. 1). Baulieu and colleagues first demonstrated that the nervous system also synthesizes steroids (Baulieu, 1998; Corpéchot et al., 1981). Steroids that are synthesized in the brain are referred to as "neurosteroids" and include neuroandrogens and neuroestrogens. Historically, studies of neurosteroids have focused on two brain regions, the hypothalamus and hippocampus, and on a few corresponding behaviors, such as aggression, reproduction, and spatial memory (Hojo and Kawato, 2018; Micevych and Sinchak, 2008). Recent studies suggest that other brain regions, including nodes of the mesocorticolimbic system (Fig. 2), produce neuroandrogens and neuroestrogens, possibly to modulate motivation, higher-order cognition, and executive functions (Tobiansky et al., 2018).

In this review, we discuss neurosteroid synthesis and action within the mesocorticolimbic system and potential behavioral impacts. We provide an overview of the mesocorticolimbic system and its roles in executive functions. Next, we summarize recent work that indicates local synthesis of neuroandrogens and neuroestrogens within the mesocorticolimbic system, and we describe evidence for expression of androgen and estrogen receptors in the mesocorticolimbic system. We then highlight key mechanisms by which neuroandrogens, neuroestrogens, and other neurosteroids modulate dopamine signaling. Finally, we focus on neuroandrogens and gonadal androgens (i.e., produced in the testes or ovaries), and their effects on working memory and behavioral flexibility.

2. Executive functions and the mesocorticolimbic system

Executive functions are processes that facilitate selection and implementation of goal-directed behaviors. These include more basic operations such as selective attention, working memory, response inhibition, and action/outcome monitoring that work in concert to regulate more complex operations such as cognitive flexibility and cost-benefit decision making. Different regions of the prefrontal cortex (PFC) play integral roles in mediating these functions, and these areas regulate action selection in part through their interactions with striatal regions, including the dorsal caudate nucleus and the ventral nucleus accumbens (NAc).

Medial midbrain dopamine neurons originating in the ventral tegmental area (VTA) innervate both the medial PFC (mPFC) and NAc

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(Fig. 2), and dopamine transmission within the mPFC and NAc is critical for some of the functions mediated by these two regions. Early studies focused on dopamine facilitation of working memory, which is mediated primarily by the dopamine D_1 receptor (D_1R) (Brozoski et al., 1979; Floresco, 2013). Higher-order executive functions such as cognitive flexibility are also mediated by mPFC and striatal dopamine via complex mechanisms involving multiple neuromodulator and neurotransmitter actions, including glutamatergic, cholinergic, and dopaminergic systems (Jett et al., 2017; Prado et al., 2017). For example, to focus on dopamine, during shifts between goal-directed behavioral strategies, dopamine acts via the dopamine D_2 receptor (D_2R) in the mPFC to facilitate suppression of old strategies, whereas dopamine acts via D_1R in both the mPFC and NAc to facilitate establishment and maintenance of new strategies (Floresco, 2013; Haluk and Floresco, 2009; Ragozzino, 2002). Similarly, dopamine refines cost-benefit decision making, but the specific mechanisms vary across brain regions and are reliant on the specific costs and benefits (Cools, 2019; Floresco, 2013; Jenni et al., 2021; Larkin et al., 2016; Nowend et al., 2001; Schweimer and Hauber, 2006). The critical involvement of dopamine in various executive functions suggests that neurosteroids that influence dopamine signaling, such as neuroandrogens and neuroestrogens, may also influence these functions.

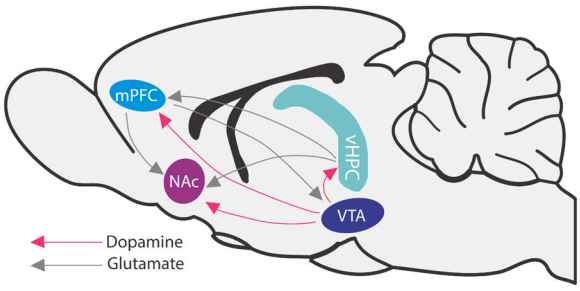

Fig. 2. Simplified sagittal view of projections in the mesocorticolimbic system. The VTA sends dopaminergic projections to the NAc, mPFC, and vHPC. Glutamatergic hippocampal efferents project to the NAc and mPFC, and glutamatergic mPFC efferents project to the NAc and VTA. mPFC, medial prefrontal cortex; NAc, nucleus accumbens; VTA, ventral tegmental area; vHPC, ventral hippocampus.

3. The mesocorticolimbic system is steroid-synthetic

The major nodes of the mesocorticolimbic system each contain all or many of the steroidogenic enzymes to synthesize bioactive steroids from cholesterol or steroid precursors (e.g., CYP11A1 (cytochrome P450 side chain cleavage), 3β-HSD (3β-hydroxysteroid dehydrogenase), CYP17A1

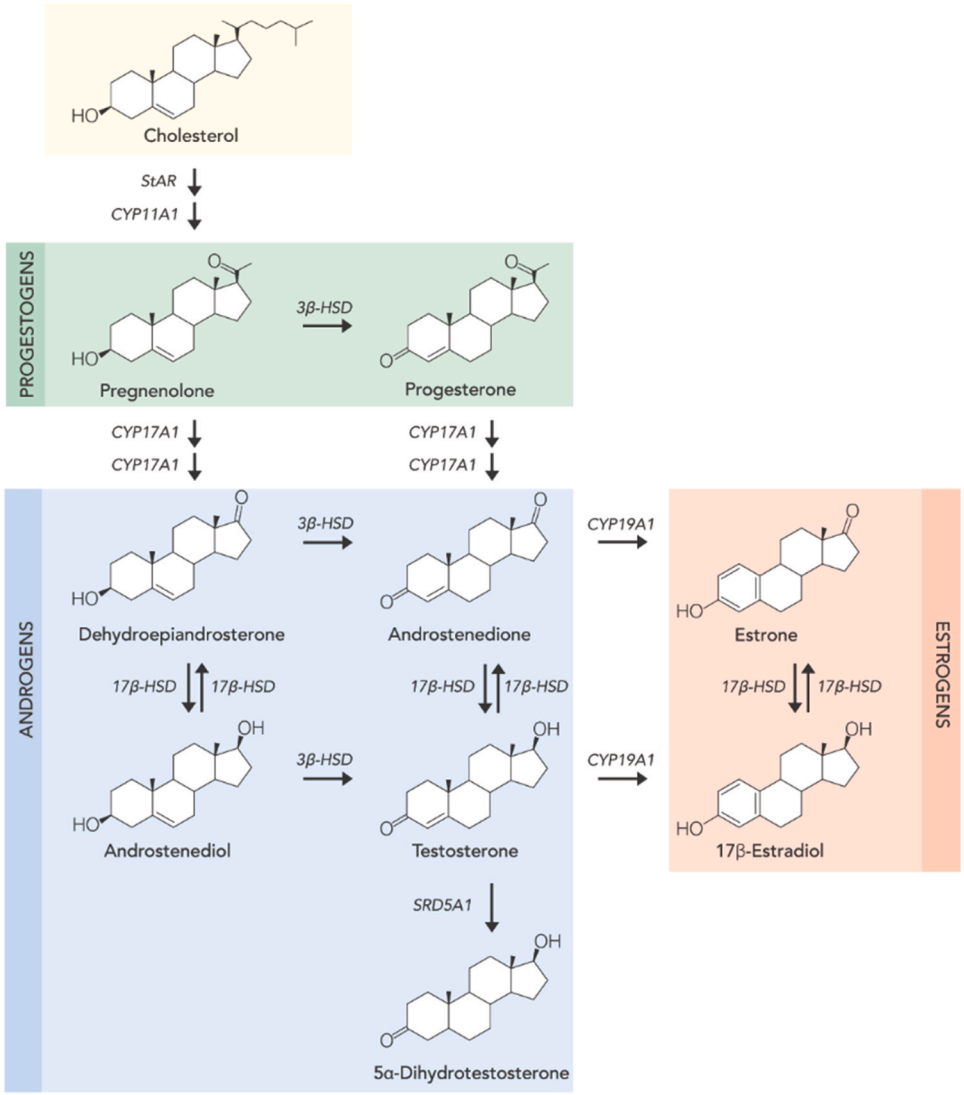

Fig. 1. Simplified steroidogenic pathway for progestogens, androgens, and estrogens. StAR (steroidogenic acute regulatory protein) is a transport protein that regulates cholesterol transport within mitochondria. This is the rate-limiting step in the production of steroid hormones. CYP11A1 (cytochrome P450 side chain cleavage) localizes to the mitochondrial inner membrane and catalyzes the conversion of cholesterol to pregnenolone. 3β-HSD (3β-hydroxysteroid dehydrogenase) is located in the mitochondria or endoplasmic reticulum and converts pregnenolone to progesterone (and DHEA to androstenedione). The enzyme CYP17A1 has 17α-hydroxylase and 17,20-lyase activities, is located in the endoplasmic reticulum, and is important for the production of androgens. 17β-HSD (17β-hydroxysteroid dehydrogenase) is necessary to produce testosterone and 17β-estradiol. CYP19A1 (aromatase) is necessary to synthesize estrogens from androgens. SRD5A1 (steroid 5α-reductase, 5αR) converts testosterone to 5α-dihydrotestosterone (DHT), a potent androgen.

(cytochrome P450c17), 17β-HSD (17β-hydroxysteroid dehydrogenase), CYP19A1 (aromatase); Fig. 1) in both males and females (Giatti et al., 2019; Tobiansky et al., 2021). For example, CYP17A1 is expressed in the mesocorticolimbic system and has 17α-hydroxylase and 17,20-lyase activities. These are needed for 2 important steps in the steroidogenic pathway: 1) conversion of pregnenolone to DHEA, and 2) conversion of progesterone to androstenedione. Thus, CYP17A1 is essential for production of androgens, including testosterone and thus DHT, as well as estradiol. Under specific circumstances, CYP17A1 also has squalene monooxygenase (epoxidase) activity that functions in cholesterol biosynthesis (Liu et al., 2005). Moreover, CYP17A1 is also critical for cortisol production in the adrenals in humans (Miller and Auchus, 2011). CYP19A1, or aromatase, is also present in the mesocorticolimbic system. It converts testosterone to 17β-estradiol or androstenedione to estrone (Fig. 1). CYP19A1 has also been suggested to metabolize estrogens into catechol estrogens, thereby inactivating estrogens (Balthazart et al., 1994; Balthazart and Ball, 1998; Osawa et al., 1993). Importantly, once a steroid is synthesized, it is released into the area where it was synthesized (Saldanha et al., 2011). The functions of further steroidogenic enzymes are described in detail in the legend of Fig. 1.

Studies have examined steroidogenic enzyme mRNA, protein, and activity in the mesocorticolimbic system. Using brain microdissection (Palkovits punch) and qPCR to assess mRNA, researchers have shown regional differences in *Cyp17a1*, *17β-HSD*, and *Cyp19a1* expression in male and female rats (Tobiansky et al., 2021). *Cyp19a1* mRNA is expressed in the PFC of both male and female rats (Hutson et al., 2019). *Cyp19a1* mRNA levels are lower in the VTA than the mPFC or NAc. In contrast, *Cyp17a1* mRNA levels are lower in the mPFC than the NAc or VTA (Tobiansky et al., 2021). The ontogeny of NAc CYP19A1 protein expression in male and female rats has been reported recently (Krentzel et al., 2021). Adult male mice (Foidart et al., 1995), and male and female rats, also express CYP19A1 protein in the NAc (Krentzel et al., 2021). CYP19A1 protein in NAc has not been assessed in female mice, to our knowledge. CYP17A1 protein has been detected in the VTA via immunohistochemistry (Nicola et al., 2021). Lastly, few studies have measured steroidogenic enzyme activity in the mesocorticolimbic system specifically, but CYP19A1 activity is detected in the PFC (MacLusky et al., 1986). In summary, there is ample evidence for CYP19A1 expression in the VTA, NAc and PFC, which indicates that the mesocorticolimbic system can produce neuroestrogens to influence neural function and behavior.

Steroidogenic enzymes in the mesocorticolimbic system are regulated by gonadal steroids and other factors. Here we provide three examples. First, in adult male rats, gonadectomy greatly decreases *Cyp17a1* mRNA levels in the VTA after 2 wk, but they rebound to control levels after 6 wk, suggesting a compensatory response to long-term gonadectomy (Tobiansky et al., 2018). However, gonadectomy does not affect *Hsd3b1* or *Cyp19a1* mRNA levels in the VTA or other nodes of the mesocorticolimbic system (Tobiansky et al., 2018). Second, rat maternal sucrose intake during pregnancy and lactation reduces *Cyp17a1* mRNA levels in the NAc of the adult male, but not female, offspring (Tobiansky et al., 2021). Expression of other steroidogenic enzymes in the mesocorticolimbic system was not affected. This indicates that levels of *Cyp17a1* mRNA in the mesocorticolimbic system, which might reflect production of neuroandrogens, are programmed by maternal diet in a sex-specific manner. Importantly, adult male, but not female, offspring of dams consuming sucrose show greater motivation to work for a sugar reward in a progressive ratio task and greater preference for palatable diets in a food preference task. This suggests that a reduction in NAc neuroandrogens might increase motivation for sugar and preference for palatable foods. Third, in adult male rats, long-term caloric restriction has no effects on *Cyp17a1*, *Hsd3b1* or *Cyp19a1* mRNA levels in the mesocorticolimbic system (Tobiansky et al., 2018). This is valuable data, as caloric restriction is often used to increase motivation to work for sugar rewards in operant conditioning paradigms (Jenni et al., 2021).

Little is known about which cell types express steroidogenic enzymes in the mesocorticolimbic system. Generally, neurosteroids can be produced by a variety of cell types, including neurons, astrocytes, oligodendrocytes, and microglia (Xu et al., 2022). The limited availability of suitable antibodies and the low steroidogenic enzyme protein levels in the brain make this area of research challenging. Some mesocorticolimbic regions, such as the mPFC that contains glutamatergic pyramidal neurons (Floresco, 2013), are largely unexplored in this regard. To our knowledge, it is not known whether mPFC neurons or glia express steroidogenic enzymes. This is an important area for future investigation.

In the VTA, tyrosine hydroxylase immunoreactive (TH-ir) neurons project to the NAc and mPFC (Fig. 2), and some of these TH-ir neurons co-express CYP17A1 (Nicola et al., 2021), which is necessary to synthesize androgens. TH is a key enzyme for dopamine synthesis and is regulated by gonadal steroids. The VTA also contains glutamatergic and GABAergic neurons, but it is not known whether these neurons express steroidogenic enzymes. VTA astrocytes [Glial Fibrillary Acidic Protein (GFAP)-immunoreactive cells] do not co-express CYP17A1 (Nicola et al., 2021).

Multiple steroidogenic enzymes are expressed in the NAc. GABAergic medium spiny neurons are the predominant projection neuron in the NAc and express dopamine, glutamate, and cholinergic receptors (Cao et al., 2018; Surmeier et al., 2007). These medium spiny neurons also co-express 5α-reductase (5αR) type I and 3α-hydroxysteroid dehydrogenase (3α-HSD), which are needed to synthesize allopregnanolone, in adult male mice (Agis-Balboa et al., 2006). However, 5αR type I and 3α-HSD are not expressed by NAc astrocytes in adult male mice (Agis--Balboa et al., 2006). In NAc core and shell, CYP19A1 protein is expressed in GABAergic medium spiny neurons neonatally, and their number increases until adulthood. The proportion of medium spiny neurons expressing CYP19A1 increases more quickly in the NAc core compared to the shell during prepubertal development. Overall, there are no sex differences in NAc CYP19A1 expression; however, as NAc core medium spiny neurons are sensitive to estrous cycle phase, (Proaño et al., 2020) and 17β-estradiol rapidly modulates glutamatergic and dopaminergic signaling in the NAc (Krentzel et al., 2019; Yoest et al., 2018), it would be useful to examine CYP19A1 expression throughout the estrous cycle. In conclusion, neurons in the VTA projecting to the NAc and PFC (Fig. 2), as well as medium spiny neurons in the NAc, express steroidogenic enzymes to produce neuroandrogens and neuroestrogens (Fig. 1).

Measurements of local steroid levels also suggest that the mesocorticolimbic system synthesizes steroids. Androgen levels are locally elevated in the mesocorticolimbic system relative to blood (Tobiansky et al., 2021), when measured with immunoassays or highly specific liquid chromatography tandem mass spectrometry (LC-MS/MS) assays. First, male and female rats have higher testosterone levels in the VTA (2–4 times higher) than in the blood (Tobiansky et al., 2018, 2021). Second, after long-term (6 wk) gonadectomy, male rats still contain testosterone in the mesocorticolimbic system, but not in the blood (Tobiansky et al., 2018). Third, caloric restriction (for 2 or 6 wk) decreases circulating and brain levels of testosterone in intact males, and caloric restriction also decreases mPFC testosterone levels in gonadectomized males, which lack detectable systemic testosterone. By contrast, caloric restriction tends to increase testosterone levels in the NAc and the VTA in gonadectomized males. These data suggest that caloric intake has region-specific effects on local testosterone synthesis within the mesocorticolimbic system (Tobiansky et al., 2018). Fourth, in adult male and female rats, testosterone and progestogen levels are higher in the mesocorticolimbic system compared to other brain regions (e.g. hippocampus) (Sze and Brunton, 2021; Tobiansky et al., 2018). Fifth, acute stress rapidly increases neurosteroid levels in the frontal cortex of rats (Sze and Brunton, 2021). These results indicate that the brain can locally and rapidly adjust neurosteroid levels.

4. Steroid receptors in the mesocorticolimbic system

Different nodes within the mesocorticolimbic system express multiple steroid receptors (Tobiansky and Fuxjager, 2021), but here we focus on androgen receptor (AR) and estrogen receptors (ERs) (Fig. 3). There are multiple types of ERs present in the mesocorticolimbic system, including those encoded by the *Esr1* gene (nuclear ERα and the post-transcriptionally modified membrane-associated ERα), the *Esr2* gene (nuclear ERβ and the post-transcriptionally modified membrane-associated ERβ), and the *Gper1* gene (the membrane-associated G-protein coupled estrogen receptor-1 or GPER1) (Gross and Mermelstein, 2020). In the brain, AR and ERs are expressed by neurons and glia (Xu et al., 2022). For decades, researchers failed to find many AR and ERs in the mesocorticolimbic circuit (Quigley et al., 2021). However, with more sensitive techniques, inclusion of females and developing animals, and examination of non-nuclear steroid receptors, recent studies have detected substantial levels of nuclear and membrane-associated AR and ERs within mesocorticolimbic regions (Becker and Chartoff, 2019; Krentzel et al., 2022; Low et al., 2020, 2017).

The AR is present in several regions within the mesocorticolimbic system. *Ar* mRNA is present in the VTA, NAc, and mPFC of male and female rats, with high expression in the NAc (Tobiansky et al., 2021; Fig. 3), consistent with the observation that androgens reduce dendritic spine density of NAc medium spiny neurons (Gross et al., 2018; Huijgens et al., 2021; Wallin-Miller et al., 2016). In adult male rats, short-term (2 wk) and long-term (6 wk) gonadectomy decrease *Ar* mRNA in the hypothalamus, but interestingly do not affect *Ar* mRNA in the mesocorticolimbic system. By contrast, chronic caloric restriction increases *Ar* mRNA in the NAc but not in the hypothalamus (Tobiansky et al., 2018). Using a very sensitive immunohistochemical technique, Low and colleagues were able to detect AR protein in the VTA, NAc, mPFC and orbitofrontal cortex (OFC), with subregional differences (e.g., NAc shell > NAc core) (Low et al., 2020). Moreover, AR-ir cells decrease with age in the mPFC but not in the VTA or NAc (Low et al., 2020). In the mPFC, neurons express AR, but not astrocytes (Low et al., 2017). In addition, AR-ir cells in the mPFC could be detected in intact males, but not gonadectomized males or intact females, even though AR-ir cells could be detected in other brain regions in gonadectomized males and intact females (Low et al., 2017). It remains unclear whether the membrane-associated androgen receptor ZIP9 (Thomas et al., 2018) is present in the mesocorticolimbic system.

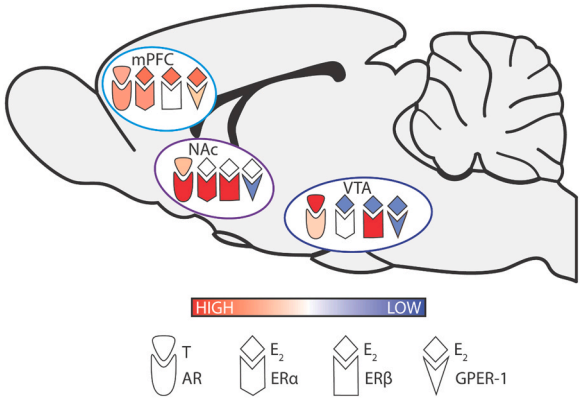

Fig. 3. Steroids and steroid receptors in the mesocorticolimbic system of adult rats. The illustration shows the ligands testosterone (T) and 17β-estradiol (E2) and their levels, as well as their receptor levels in the mesocorticolimbic system. Symbols of ligands and receptors are explained at the bottom of the figure. High expression is indicated in red, low expression is indicated in blue. Levels of T are highest in the VTA, lower in the mPFC, and lowest in the NAc. Levels of E2 are highest in the mPFC, lower in the NAc, and lowest in the VTA. ERα levels are highest in the NAc, lower in the mPFC, and lowest in the VTA. ERβ levels are high in the VTA and NAc, and lower in the mPFC. GPER-1 levels are high in the mPFC and lower in the NAc and VTA. mPFC, medial prefrontal cortex; NAc, nucleus accumbens; VTA, ventral tegmental area; AR, androgen receptor; ERα, estrogen receptor alpha; ERβ, estrogen receptor beta; GPER-1, G-Protein associated Estrogen Receptor 1; T, testosterone; E2, 17β-estradiol.

Several types of ERs are present in multiple nodes of the mesocorticolimbic system. *Esr1* mRNA is present in VTA, NAc, and mPFC of adult male and female rats (Tobiansky et al., 2018; Fig. 3) and is higher in the VTA and NAc than in the mPFC (Tobiansky et al., 2021). Nuclear ERs are present in the VTA and co-localize with TH (Becker and Chartoff, 2019), suggesting that estrogens modulate dopamine production. In the male and female rat NAc, nuclear ERα expression is age-dependent, with high levels in the perinatal period, decreasing levels in the prepubertal period, and very low levels in adulthood (Krentzel et al., 2021). NAc nuclear ERα expression decreases in a subregion- and sex-specific manner (Krentzel et al., 2021). In the NAc core, females express more nuclear ERα than males at PND3 and PND20. Overall expression of nuclear ERα is higher in perinatal and prepubertal NAc core compared to NAc shell. In the NAc shell, nuclear ERα expression did not differ by sex during development. In summary, the expression of nuclear ERs in the NAc during early development provides a route by which neuroestrogens can affect the mesocorticolimbic system (Harp et al., 2020). In the NAc of female rats, an electron microscopy study has localized membrane-associated ERα on GABAergic medium spiny neurons and on GABAergic and dopaminergic terminals (Almey et al., 2022). One outstanding issue is whether these ERs are expressed on glutamatergic and cholinergic terminals within the NAc. In the mPFC of both males and females, *Esr1* mRNA is highest perinatally and decreases with age (Westberry and Wilson, 2012).

Esr2 mRNA is very low perinatally and increases with age in the mPFC, with higher levels in females than in males (Westberry and Wilson, 2012). Thus, ERβ is the main ER in the juvenile mPFC. Interestingly, *Esr2* mRNA levels in the mPFC drop sharply with the onset of puberty in female rats (Drzewiecki et al., 2021). A change in *Esr2* mRNA during puberty in males has not been examined yet. Given the difficulties with assessing nuclear and membrane-associated ERβ using antibodies (Snyder et al., 2010), less is known regarding ERβ protein expression in the NAc; however, an electron microscopy study has identified ERβ in adult female rat NAc (Almey et al., 2015). Knockdown of *Esr2* (ERβ) mRNA in the NAc attenuates cocaine-seeking behavior, suggesting a role for ERβ in reward seeking (Satta et al., 2018). In the NAc, the very low levels of nuclear ERα and ERβ in adulthood are associated with the expression of membrane-associated ERα and ERβ (Almey et al., 2015; Krentzel et al., 2021). Overall, ERα and ERβ are present in the mesocorticolimbic system and positioned to influence glutamatergic, cholinergic, and dopamine signaling (Low et al., 2020; Quigley et al., 2021).

GPER1 is present in the NAc and VTA (Krentzel et al., 2021; Luo and Liu, 2020) of both male and female rats during development and adulthood. In the NAc, GPER1 expression is highest in the perinatal and prepubertal periods, and decreases during development to low levels in adulthood (Fig. 3). GPER1 expression is similar between males and females. An electron microscopy study of female rat NAc localized GPER1 expression in GABAergic medium spiny neurons, as well as in GABAergic and dopaminergic terminals (Almey et al., 2015), but glutamatergic and cholinergic terminals have not been assessed. The mPFC of adult male and female rats has relatively low levels of nuclear ERs, but higher levels of GPER1 (Hutson et al., 2019; Tobiansky et al., 2021). Overall, the localization of GPER1 in the NAc and mPFC indicates that these receptors are well-placed to modulate glutamatergic, dopaminergic, and cholinergic transmission within the mesocorticolimbic system (Oberlander and Woolley, 2016). In summary, AR and ERs are expressed in several critical regions of the mesocorticolimbic system, and steroid receptor levels are affected by sex, developmental stage, caloric intake, and gonadal hormones.

5. Androgens and estrogens modulate dopamine signaling

Dopaminergic signaling is robustly modulated by androgens and estrogens at multiple levels and in multiple brain regions (Kokane and Perrotti, 2020; Purves-Tyson et al., 2014; Quigley et al., 2021; Yoest et al., 2018), as well as glutamatergic (Brady et al., 2022; Maher et al., 2022) and possibly cholinergic signaling (Krentzel et al., 2022, 2019; Proaño et al., 2020; Proaño and Meitzen, 2020). Here we focus on dopaminergic signaling. Dopamine signaling is regulated by androgens and estrogens across multiple time frames, including short time frames (Becker, 1999; Song et al., 2019), which is consistent with non-genomic mechanisms of steroid action. While neurosteroids often act via non-genomic mechanisms, there is little known regarding neurosteroid modulation of dopamine signaling in the mesocorticolimbic system. Most studies focus on gonadal androgens and estrogens (e.g., effects of gonadectomy) or assume that the effects of exogenous androgens and estrogens reflect those of gonadal steroids. However, recent data from our laboratories demonstrate that both gonadal steroids and neurosteroids modulate dopaminergic signaling (Tomm et al., 2022).

5.1. Androgens regulate dopamine synthesis

First, we focus on studies that manipulated peripheral steroids and examined effects on dopamine synthesis in the mesocorticolimbic system, and second, we highlight studies that manipulated neurosteroids. In aged male rats with low circulating testosterone levels, TH-ir is reduced in the VTA and NAc core but is increased in the mPFC and medial orbitofrontal cortex (MOFC), relative to young male rats (Tomm et al., 2018). In young adult male rats, long-term gonadectomy (7 wk) does not affect TH-ir in the VTA, NAc, mPFC or lateral orbitofrontal cortex (LOFC) but reduces TH-ir in the MOFC (Tomm et al., 2022). In contrast, shorter-term gonadectomy (4 wk) increases TH-ir in the prelimbic and infralimbic portions of the mPFC (Kritzer, 2003; Fig. 4).

Inhibition of brain androgen synthesis or action also impacts TH. In gonadectomized and intact adult male rats, systemic treatment with the CYP17A1 inhibitor abiraterone acetate (for 1 wk) tends to decrease TH-ir in the VTA and NAc core (Tomm et al., 2022, Fig. 4) but increases TH-ir in the prelimbic mPFC (Tomm et al., 2022). These effects of abiraterone acetate in gonadectomized males suggest a neural site of action, as abiraterone acetate does cross the blood-brain barrier (Tomm et al., 2022). Thus, TH might be modulated by neuroandrogens in a region-specific manner (Fig. 4). In addition, the brain-penetrant AR antagonist enzalutamide reduces TH-ir in the VTA, although this study used intact males and thus cannot directly implicate neuroandrogens (Nicola et al., 2021, Fig. 4). These data complement the well-known findings that testosterone treatment or gonadectomy alter multiple aspects of dopaminergic signaling (Beatty et al., 1982; de Souza Silva et al., 2009; Dluzen and Ramirez, 1989; Purves-Tyson et al., 2014; Thiblin et al., 1999; Walker, 2001).

The CYP19A1 (aromatase) knockout mouse model that is unable to produce estrogens shows changes in NAc gene expression compared to control animals (Shay et al., 2020). In detail, *Pts*, which encodes an enzyme necessary for catecholamine biosynthesis, is down-regulated in male and female CYP19A1 knockout mice compared to wild-type controls. Other neurosteroids might also regulate TH, particularly progesterone or allopregnanolone, a bioactive neurosteroid derived from progesterone. For example, a maternal high-sucrose diet increases progesterone levels in the brain and reduces TH-ir in the NAc and mPFC (Tobiansky et al., 2020).

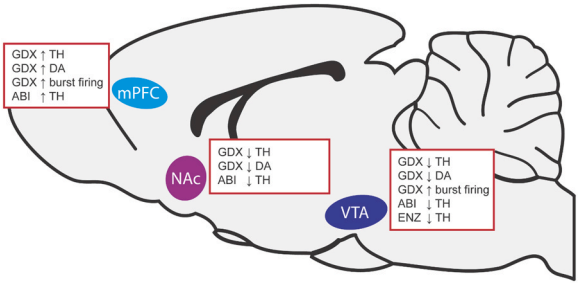

Fig. 4. Experimental effects of gonadal steroids and neurosteroids on dopamine signaling in the mesocorticolimbic system. Gonadectomy alters dopamine signaling in the mPFC by increasing TH, DA, and burst firing. ABI treatment also increases TH in the mPFC. TH in the NAc is reduced by gonadectomy and ABI treatment. Gonadectomy also reduces DA in the NAc. Reduced testosterone signaling in the VTA by gonadectomy, ABI and ENZ reduces TH-immunoreactivity. Gonadectomy reduces DA in the VTA but increases burst firing. mPFC, medial prefrontal cortex; NAc, nucleus accumbens; VTA, ventral tegmental area; GDX, gonadectomy; TH, tyrosine hydroxylase; DA, dopamine; ABI, abiraterone acetate (CYP17A1 inhibitor); ENZ, enzalutamide (androgen receptor antagonist).

5.2. Androgens and estrogens regulate dopamine receptors

Androgens, estrogens, and glucocorticoids regulate dopamine receptor subtypes D_1R, D_2R and D_3R depending on age and sex (Andersen et al., 1997; Kopec et al., 2018). We are not aware of research that specifically manipulated neurosteroids and examined dopamine receptors, and thus we focus on sex differences, manipulation of peripheral steroids, and the effects of early-life stress. During development, early-life stress, which alters maternal and offspring steroids, affects dopamine receptor expression and binding affinity (Berger et al., 2002; Pallarés et al., 2013). During adulthood, dopamine receptor expression and binding affinity are modulated by androgens, estrogens, and glucocorticoids (Kaasinen et al., 2001; Lévesque and Di Paolo, 1990; Cabib et al., 1998), as detailed below.

Prenatal and perinatal alterations in steroids program dopamine receptor expression in adulthood. Prenatal stress increases D_2R protein in the mPFC and NAc core but decreases D_3R in the NAc core and shell in adult male rats (Berger et al., 2002; Henry et al., 1995). Perinatal maternal separation has enduring effects on D_3R regulation in the mPFC and NAc of male but not female rats (Hill et al., 2014). Perinatal exposure to androgens or estrogens also alters dopamine receptors. For example, in adult rats, D_1R levels in the NAc are higher in males than females, but postnatal testosterone treatment reverses this sex difference (Elgueta-Reyes et al., 2021). Moreover, the ontogeny of D_1R in the NAc is different in males and females (Kopec et al., 2018).

Androgens and estrogens also modulate dopamine receptor distribution and affinity in adulthood. Male rats have higher D_1R (but not D_2R) levels in the NAc than females (Andersen et al., 1997; Hasbi et al., 2020), and D_1R levels in the NAc are modulated by androgens (Elgueta-Reyes et al., 2021). In female rats, D_2R levels in the NAc fluctuate across the estrous cycle (Yoest et al., 2018), ovariectomy increases D_2R levels in the NAc, and estradiol treatment reduces D_2R levels in the NAc (Chavez et al., 2010). By contrast, levels of D_1R in the NAc are not altered by these treatments in females (Chavez et al., 2010). The ratio of D_1R to D_2R and levels of dopamine receptor homodimers and heterodimers also differ between the sexes, impacting dopamine signaling (Cullity et al., 2019; Hasbi et al., 2020). The D_1R:D_2R ratios in the mPFC and ventral striatum are higher in females than in males (Cullity et al., 2019). In addition, female rats have more D_1R-D_2R heterodimers compared to males (Hasbi et al., 2020). In summary, in the adult brain, androgens and estrogens affect dopamine receptor expression, the D_1R:D_2R ratio, receptor dimerization, and receptor binding affinity.

5.3. Androgens and estrogens modulate dopamine release and extracellular dopamine levels

In this section, we focus on how gonadectomy and manipulation of peripheral steroids affect extracellular dopamine levels, as we are not aware of any data specifically on the effects of neurosteroids.

Testosterone regulates dopamine release and extracellular dopamine levels. Postnatal testosterone treatment in males and females, and postnatal 17β-estradiol treatment in females, increases dopamine release in the NAc in adulthood (Elgueta-Reyes et al., 2021). Increased dopamine release also occurs after gonadectomy in adult male rats. In detail, brief and phasic bursts of TH-ir cells in the VTA cause dopamine release in the NAc and mPFC (Lohani et al., 2018). Gonadectomy increases burst firing in VTA cells in a androgen-sensitive and estrogen-insensitive manner (Locklear et al., 2017). Furthermore, long-term gonadectomy increases PFC extracellular dopamine levels (Aubele and Kritzer, 2011). Gonadectomy also increases burst firing in PFC cells that project to the VTA, consequently increasing extracellular dopamine in the VTA (Aubele and Kritzer, 2012; Locklear et al., 2017). In the PFC, extracellular dopamine levels are similar in male and female rats at baseline. In addition, the AR antagonist enzalutamide reduces dopamine release from the VTA in the ventral hippocampus (Nicola et al., 2021). Estrogens in other regions of the brain can also increase stimulant-induced dopamine in the NAc (Tobiansky et al., 2016). For example, treatment of ovariectomized female rats with estradiol rapidly increases cocaine-induced dopamine release in the NAc shell. This effect was mediated by ERβ but not ERα and could not be observed in gonadectomized males treated with estradiol (Yoest et al., 2019).

Allopregnanolone (3α,5α-3-hydroxy-5-pregnan-20-one), a positive allosteric modulator of $GABA_A$ receptors, also modulates dopamine release and extracellular dopamine levels. A recent study using fast scan cyclic voltammetry reported that allopregnanolone differentially decreases dopamine levels in the NAc in male and female rats in response to VTA stimulation (Dornellas et al., 2021). Moreover, i.c.v. allopregnanolone administration to male rats increases dopamine release in response to morphine in the NAc (Rougé-Pont et al., 2002).

5.4. Androgens and estrogens affect dopamine reuptake and metabolism

Dopamine transporter (DAT) levels are also modulated by androgens and estrogens. Here we again focus on the effects of gonadectomy and peripheral steroid manipulations. Females have higher DAT levels in the NAc than males, and female DAT levels vary across the estrous cycle (Yoest et al., 2018). The density of DAT in the NAc is reduced by ovariectomy and could be rescued by 17β-estradiol treatment (Chavez et al., 2010). In females that were exposed to testosterone at postnatal day 1 (PND1), DAT expression in the NAc is reduced in adulthood, whereas males do not show this effect (Dib et al., 2018). Gonadectomy increases extracellular dopamine in the NAc in response to amphetamine, suggesting that gonadal steroids decrease DAT expression or function (Hernandez et al., 1994). In the mPFC, increasing the concentration of allopregnanolone and inhibiting 5α-R differentially modulates the expression of dopamine-metabolizing enzymes and dopamine concentrations, particularly in response to ethanol (Dazzi et al., 2002). Dopamine is metabolized by catechol O-methyltransferase (COMT), and COMT expression is sensitive to 5α-dihydrotestosterone and 17β-estradiol (Salih et al., 2008; Schendzielorz et al., 2011). In summary, neurosteroids and gonadal steroids can impact dopamine signaling in the mesocorticolimbic system at multiple levels in sex- and age-specific manners, although the specific effects of androgens and estrogens synthesized in the brain remain to be elucidated. Future work needs to address the specific impact of gonadal vs. neural steroids on dopamine synthesis and dopamine signaling.

6. Neuroandrogens and neuroestrogens modulate executive functions

Androgens and estrogens affect dopamine-sensitive executive functions mediated by the mesocorticolimbic system (Hynes et al., 2020; Kritzer et al., 2007; Orsini et al., 2015; Wallin et al., 2015). Here, we focus on working memory and behavioral flexibility, both of which are critically-dependent on the integrity of different regions of the rodent PFC. Studies examining working memory reveal that gonadectomy in males impairs the acquisition of a T-maze delayed alternation paradigm in a testosterone-sensitive, estradiol-insensitive manner (Kritzer et al., 2001). Similarly, gonadectomy in male rats impairs working memory in an operant response alternation task in a manner that is also testosterone-sensitive and estradiol-insensitive, and this negative effect on working memory in gonadectomized male rats is correlated with increased TH-ir in the mPFC (Kritzer et al., 2007). The effect of gonadectomy on working memory parallels its effects on more fundamental recognition memory processes, in that this manipulation perturbs learning on a novel object recognition task in adult male rats, and again this effect is rescued by testosterone but not estradiol (Aubele et al., 2008). Furthermore, male gonadectomy in rats impairs working memory but not reference memory in the radial arm maze (Spritzer et al., 2008). In postmenopausal women, estrogen replacement therapy is associated with increased working memory performance in spatial and verbal tasks (Duff and Hampson, 2000). In men, the use of anabolic androgenic steroids is associated with reduced working memory, suggesting that very high androgen signaling also disrupts working memory (Hauger et al., 2020).

With respect to behavioral flexibility, an initial study reported that testosterone treatment increases persistence in chicks (Andrew and Rogers, 1972). More recently, researchers have shown that chronic high testosterone treatment in male rats impairs behavioral flexibility in set-shifting and reversal learning tasks (Wallin and Wood, 2015). Moreover, chronic high testosterone treatment in male rats impairs behavioral flexibility in a rodent version of the Stroop task (test for cognitive control of contextual decision-making) (Wood and Serpa, 2020). In men, usage of anabolic androgenic steroids is associated with poorer cognitive flexibility (Hauger et al., 2020). By contrast, most studies examining the effects of reduced testosterone levels on behavioral flexibility use gonadectomy and report little to no effects (Kritzer et al., 2007; Tomm et al., 2022). However, one study used the antiandrogen cyproterone acetate in male rats and found increased behavioral flexibility in a set-shifting task (Thompson and Wright, 1979). Local synthesis of testosterone in the mesocorticolimbic system might explain why gonadectomy has no or weak effects on behavioral flexibility but cyproterone acetate has an effect (Tobiansky et al., 2018).

We recently showed that abiraterone acetate, which inhibits CYP17A1 activity and thus androgen synthesis in the testes and brain, increases behavioral flexibility of male rats in set-shifting and reversal learning tasks (Tomm et al., 2022). Importantly, long-term (7 wk) gonadectomy has no effects on behavioral flexibility. By contrast, abiraterone acetate increases behavioral flexibility, even in gonadectomized animals. In the set-shifting task, animals have to disengage from a previously learned strategy and adopt a new strategy, in order to keep earning sugar rewards. Abiraterone acetate reduces the number of total errors that rats made during the shift to the new strategy (Fig. 5**A**). More specifically, abiraterone acetate tends to reduce the number of perseverative errors (Fig. 5**B**). In the reversal learning task, abiraterone acetate treatment also reduces persistence in a spatial reversal learning operant task. Here, total errors during the shift are not affected by abiraterone acetate, but perseverative errors are reduced. These effects of systemic abiraterone acetate treatment are present in intact and gonadectomized male rats (Tomm et al., 2022), suggesting that abiraterone acetate reduces neuroandrogens. A decrease in brain testosterone levels would lead to decreases in brain DHT and estradiol levels. These behavioral effects are associated with an increase in TH-ir in the mPFC. To get a better understanding of how neuroandrogens affect these higher-order functions, future studies should deliver an AR antagonist or CYP17A1 inhibitor to specific brain regions in intact and gonadectomized males, and then assess behavioral flexibility. In the future, more studies are needed that dissect the effects of gonadal androgens and estrogens vs. neuroandrogens and neuroestrogens on behavioral flexibility and other executive functions.

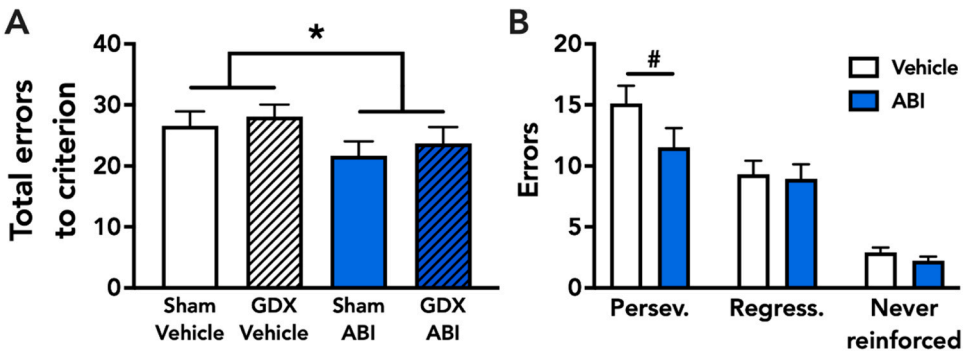

Fig. 5. Androgen synthesis inhibition increases behavioral flexibility. A, The CYP17A1 inhibitor abiraterone acetate increases behavioral flexibility in sham-operated and gonadectomized male rats and reduces the number of total errors to successfully adopt a new strategy in an operant set-shifting task. B, Abiraterone acetate treatment, independent of gonadectomy, tends to specifically reduce perseverative errors, suggesting reduced persistence when task contingencies change and animals have to adopt a new strategy. Sham, sham surgery; GDX, gonadectomy; ABI, abiraterone acetate; persev., perseverative errors; regress., regressive errors; $^{*}p \leq 0.05$; $^{\#}p \leq 0.1$.
Adapted from Tomm et al. (2022).

7. Conclusions

The concepts presented in this review have broad implications for understanding the sites of neurosteroid synthesis and action, as well as the behavioral functions of neurosteroids. Most studies of neurosteroids have focused on steroid synthesis in the hypothalamus and hippocampus, and neurosteroid effects on reproduction, aggression and spatial learning and memory. However, several recent studies suggest that neurosteroids are also produced and act in the mesocorticolimbic system, including the VTA, NAc and PFC. These data include expression of steroidogenic enzyme transcripts and proteins in the mesocorticolimbic system, as well as high local steroid levels in the mesocorticolimbic system relative to systemic steroid levels in the blood. Moreover, steroid receptors (including membrane-associated steroid receptors) are expressed in the mesocorticolimbic system. These lines of evidence raise the prospect that neurosteroids modulate behaviors mediated by the mesocorticolimbic system, such as higher-order cognition and executive functions. Recent experiments have focused on how gonadally- vs. neurally-produced steroids affect executive functions, such as behavioral flexibility, and the emerging data suggest that neurally-produced androgens reduce behavioral flexibility in a rat model. These studies raise the intriguing possibility of brain-targeted steroid treatments for neuropsychiatric diseases characterized by dysregulated dopamine signaling or impaired executive functions.

Declarations of interest

None

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