



Expanding the therapeutic potential of neuro(active)steroids: a promising strategy for hyperdopaminergic behavioral phenotypes

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ABSTRACT

Imbalances in dopamine activity significantly contribute to the pathophysiology of several neuropsychiatric disorders, including addiction, ADHD, schizophrenia, impulse control disorders, and Parkinson's Disease. Neuro (active)steroids, comprising endogenous steroids that finely modulate neuronal activity, are considered crucial regulators of brain function and behavior, with implications in various physiological processes and pathological conditions. Specifically, subclasses of Neuro(active)steroids belonging to the 5 α reductase pathway are prominently involved in brain disorders characterized by dopaminergic signaling imbalances. This review highlights the neuromodulatory effects of Neuro(active)steroids on the dopamine system and related aberrant behavioral phenotypes. We critically appraise the role of pregnenolone, progesterone, and allopregnanolone on dopamine signaling. Additionally, we discuss the impact of pharmacological interventions targeting 5 α reductase activity in neuropsychiatric conditions characterized by excessive activation of the dopaminergic system, ranging from psychotic (endo)phenotypes and motor complications to decision-making problems and addiction.

1. Introduction

1.1. Neuro(active)steroids as neuromodulators of synaptic function

Neuro(active)steroids (NaS) constitute a broad category of endogenous steroids exerting their effects within the central nervous system (CNS), irrespective of their site of synthesis. Originating from cholesterol, these lipid mediators can be locally synthesized in various brain regions, such as the cortex, striatum, hippocampus, and hypothalamus, or can arise from peripheral sources, including adrenal glands, gonads, and placenta (Baulieu, 1998; Giatti et al., 2019; Melcangi and Panzica, 2006; Paul and Purdy, 1992; Porcu et al., 2016). Their lipophilicity

enables them to readily cross the blood-brain barrier (BBB) and modulate neuronal function through interactions at multiple cellular sites. By engaging with a variety of ligand-gated ion channels, membrane and intracellular receptors, NaS act through both rapid and non-rapid signaling pathways, participating in canonical G protein-coupled receptors (GPCR) membrane signaling and/or nuclear genomic cell responses. Two of the main non-genomic targets of NaS are γ -aminobutyric acid (GABA_A) and N-methyl-D-aspartate (NMDA) receptors. NaS, such as allopregnanolone (AP) and allotetrahydrocorticosterone (THDOC), are potent endogenous positive allosteric modulators (PAM) of the inhibitory neurotransmitter GABA at both synaptic and extrasynaptic GABA_A receptors, which binding enhances

Abbreviations: 3 α -HSOR, 3 α -Hydroxysteroid Oxidoreductase; 5 α -DHP, 5 α -Dihydroprogesterone; 5 α r, 5 α -Reductase; ADHD, Attention Deficit Hyperactivity Disorder; AP, Allopregnanolone; BBB, Blood-Brain Barrier; CNS, Central Nervous System; Cryo-EM, Cryo-Electron Microscopy; CYP450_{sec}, Cytochrome P450 Side-Chain Cleavage; DAT, Dopamine Transporter; DHEAS, Dehydroepiandrosterone Sulfate; DHT, Dihydrotestosterone; GABA, Γ -Aminobutyric Acid; GD, Gambling Disorder; GPCR, G Protein-Coupled Receptors; IMM, Inner Mitochondrial Membrane; LID, L-DOPA-Induced Dyskinesias; NAC, Nucleus Accumbens; NAM, Negative Allosteric Modulators; NaS, Neuroactive Steroids; NMDA, N-Methyl-D-Aspartate; OMM, Outer Mitochondrial Membrane; ORT, Object Recognition Test; PAM, Endogenous Positive Allosteric Modulators; PCE, Prenatal Cannabis Exposure; PD, Parkinson's Disease; PFC, Prefrontal Cortex; PME, Pregnenolone-Methyl-Ether; PPD, Postpartum Depression; PPI, Prepulse Inhibition; PREG, Pregnenolone; Pregs, Pregnenolone Sulfate; PTSD, Post-Traumatic Stress Disorder; Star, Steroidogenic Acute Regulatory Protein; THC, Δ 9-Tetrahydrocannabinol; THDOC, Allotetrahydrocorticosterone; THP, 3 α , 5 α -Tetrahydroprogesterone; TM, D, Transmembrane Domain; TS, Tourette's Syndrome; VTA, Ventral Tegmental Area; σ 1, Sigma-1 Receptor.

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channel activation by GABA (Akk et al., 2007; Belelli and Lambert, 2005; Bitran et al., 1991). Behavioral and electrophysiological studies demonstrate that AP and THDOC have a particular affinity for extrasynaptically located GABA_A receptors incorporating the δ-subunit, which contribute to maintaining an inhibitory tonic current in response to ambient levels of GABA. Additionally, the sulfation process, catalyzed by sulfotransferase enzymes on NaS with comparable structures, confers opposing actions on GABA_A and NMDA receptors via different binding sites (Bowlby, 1993; Gibbs et al., 2006; Malayev et al., 2002; Mienville and Vicini, 1989; Park-Chung et al., 1997; Spivak, 1994). For instance, a recent study combines cryo-electron microscopy (cryo-EM) assays with electrophysiology and molecular dynamics simulations to explore GABA_A receptor binding sites and allosteric mechanisms for AP versus sulfated NaS. Legesse and collaborators (2023) corroborate earlier findings on the mechanism of action of PAM NaS, revealing that AP increases sensitivity to GABA and ion channel width binding at the β-α interfaces in the transmembrane domain subunit interface site on the GABA_A receptor. Contrary to earlier assumptions, Negative Allosteric Modulators (NAM)-NaS, such as pregnenolone (PREG) and dehydroepiandrosterone sulfate (DHEAs), primarily target the ion channel to exert inhibitory effects on GABA_A receptors. This stands in contrast to

the previously proposed notion that their action occurred at sites along the receptor-lipid interface. In fact, unlike AP, which can easily diffuse through the membrane and reach its binding site in the transmembrane domain (TMD), the charged sulfate groups of these NAMs do not allow inhibition of GABA_A receptors from the cytosolic side of the cell membrane, as they can only access their binding site externally. Sulfated NaS also modulate both the inhibition and excitation of NMDARs. These effects are contingent upon both the subunit composition and the structure of NaS, wherein pregnane sulfates primarily induce NMDAR inhibition, while pregnenolone sulfate (PREGs) elicits potentiation (Korinek et al., 2011; Malayev et al., 2002; Park-Chung et al., 1997, 1994). However, differently from GABA_A receptors, the precise binding site of sulfated NaS on NMDA receptors remains elusive. Initially, it was assumed to be extracellular (Park-Chung et al., 1997), with the M3-M4 extracellular loop of GluN2 subunits implicated in sulfated steroid action (Horak et al., 2006). Recent studies, however, have demonstrated the involvement of both the ligand-binding and transmembrane domains of GluN subunits (Hrcka Krausova et al., 2020; Wilding et al., 2016).

Within the CNS, both neuronal and glial cells participate in NaS synthesis (Akwa et al., 1991; Robel and Baulieu, 1995). NaS operate in a

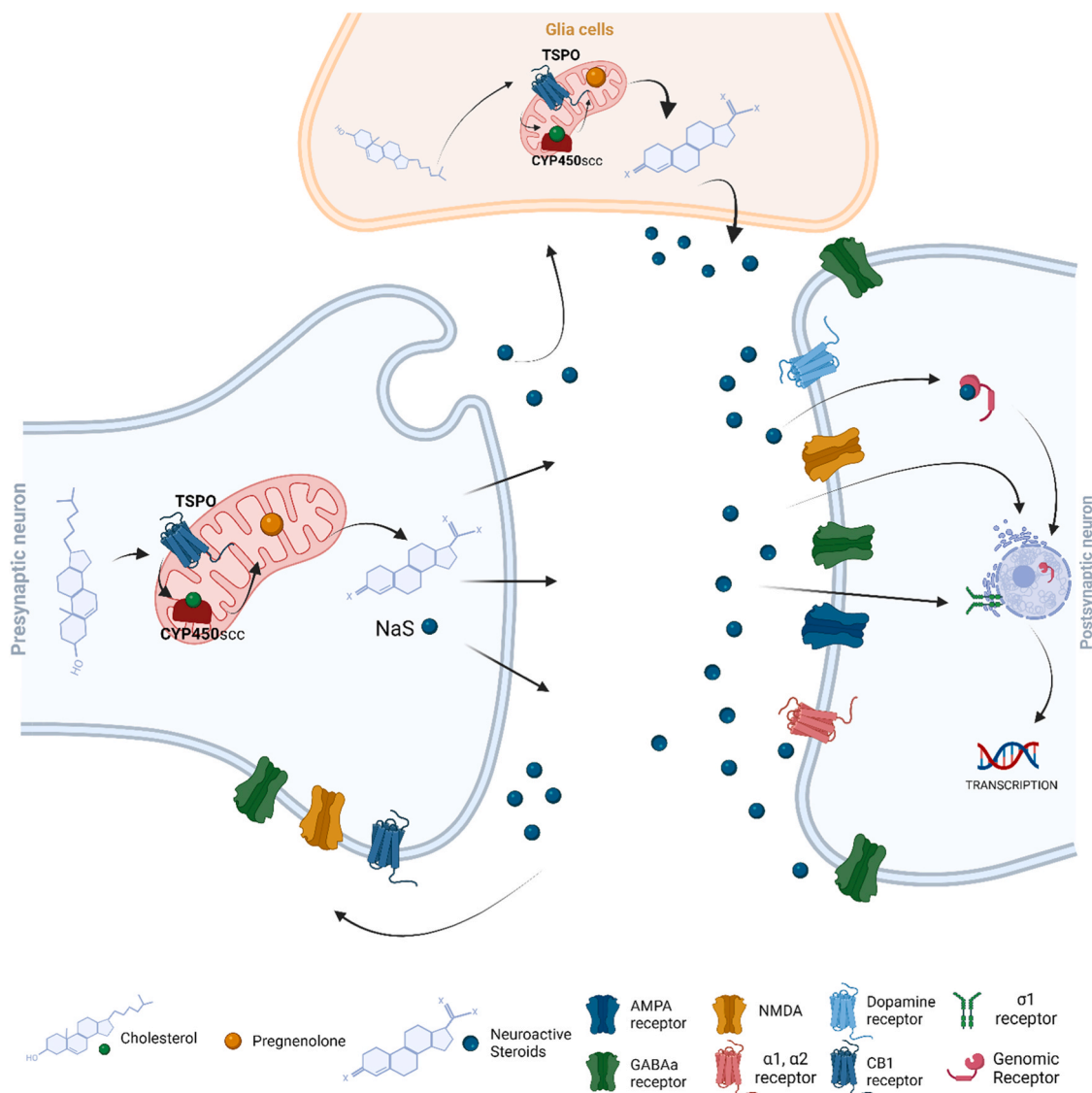


Fig. 1. Genomic and nongenomic mechanisms of neuro(active)steroids. Abbreviations: NaS, neuro(active)steroids; TSPO, Translocator protein; P450scc, cytochrome P450 side-chain cleavage (created with BioRender.com).

paracrine and/or autocrine manner to finely modulate neuronal activity. As autocrine and paracrine messengers, NaS can modulate the excitability of the same or neighboring cells through fast-acting activity, facilitating local communication between cells and synaptic components. In neurons, NaS can be synthesized by both pre- and post-synaptic terminals. Presynaptic synthesis involves their release into the synaptic cleft upon neuronal activation, where they influence synaptic transmission and neuronal excitability. Through postsynaptic release, NaS may act locally on postsynaptic receptors or diffuse back to presynaptic terminals, thereby influencing neurotransmitter release and participating in synaptic plasticity and neuronal responses to neurotransmitter signaling. Thus, NaS encompass all the core features of neuromodulators capable of modifying diverse neurotransmitter systems, including GABA (Lambert et al., 2009), glutamate (Irwin et al., 1994; Sedláček et al., 2008), and dopamine (Dornellas et al., 2020; Motzo et al., 1996; Rougé-Pont et al., 2002), among others. NaS can both enhance and inhibit synaptic transmission mediated by these neurotransmitters, thereby adjusting the balance of excitatory and inhibitory neurotransmission in key regions involved in behavioral regulation (Fig. 1).

The ability of NaS to modulate neuronal activity of the main excitatory and inhibitory neurotransmitters makes them crucial regulators of brain function and behavior, with implications in various physiological processes and pathological conditions. For instance, their levels follow profound dynamic changes in response to acute and prolonged stress exposures; whereas acute stress increases NaS concentrations in brain and plasma, chronic stress exposures typically reduce neurosteroidogenesis (Barbaccia et al., 2001; Biggio et al., 2014; Pisu et al., 2022; Serra et al., 2000). Additionally, NaS fluctuate throughout all the reproductive phases, including pregnancy, puberty and the ovarian cycle, contributing to emotional regulation and behavioral changes observed during these critical biological processes (Concas et al., 1998; Fadalti et al., 1999; Kimball et al., 2020; Luisi et al., 2000; Mellon and Vaudry, 2001; Pisu et al., 2022; Stomati et al., 1998; Wang et al., 1996).

Dysregulations of neurosteroidogenic pathways have been documented across a spectrum of neurological and psychiatric disorders, spanning from Parkinson's and Alzheimer's disease to depression, anxiety disorders, and schizophrenia (Bourque et al., 2024; Crowley and Girdler, 2014; di Michele et al., 2013; Dubrovsky, 2005; Eser et al., 2008; Heydari and Le Mellédo, 2002; Luchetti et al., 2023, 2011; Luscher et al., 2011; MacKenzie et al., 2007; Marx et al., 2006; Weill-Engerer et al., 2002). Noteworthy, compelling preclinical and clinical evidence suggests that specific subclasses of NaS, i.e. those belonging to the 5 α reductase pathway, are prominently involved in brain disorders characterized by dopaminergic signaling imbalances (Table 1). Dopamine plays a pivotal role in fundamental neuro-behavioral functions such as cognition, motivation, and motor control. Alterations of dopamine neurotransmission contribute to numerous neuropsychiatric disorders including addiction, attention deficit hyperactivity disorder (ADHD), schizophrenia, impulse control disorders, and Parkinson's disease (PD) (Cardinal et al., 2001; Castellanos and Tannock, 2002; Howes et al., 2017; Klein et al., 2019; Peters et al., 2020; Viggiano et al., 2002; Wang et al., 2017). Pathological imbalances in NaS synthesis and metabolism have been consistently observed in the abovementioned conditions. Although the precise mechanisms driving these changes remain elusive, the available evidence suggests that brain NaS dysregulation may be either the result of compensatory protective mechanisms, direct causal or contributing factor exacerbating pre-existing pathophysiological processes. Therefore, gaining insight into how NaS participate in the etiopathogenesis of dopamine-relevant brain disorders may potentially unveil novel therapeutic interventions based on neurosteroidogenic pathways. In this context, the specific classes of NaS associated with the 5 α reductase (5 α R) pathways (as detailed in the next paragraphs) have been shown to exert beneficial effects on aberrant behavioral phenotypes driven by hyperdopaminergic states. Preclinical studies suggest that NaS rescue properties appear to be mediated at different levels of dopamine neurotransmission, and engage

multiple dopaminergic receptors and the regulation of pre- and post-synaptic events.

To the best of our knowledge, this review represents the first comprehensive examination of NaS neuromodulatory effects on dysfunctional dopamine system and related aberrant behavioral phenotypes, with a particular emphasis on the subclass synthesized via the 5 α reductase pathway. Recent preclinical and clinical investigations suggest that these 5 α R-related NaS exhibit notable efficacy in ameliorating behavioral outcomes associated with hyperactivation of the mesostriatal dopamine system. In this review, we delve into how their modulatory actions on dopamine signaling may offer advantages over conventional pharmacotherapies, which primarily act through dopamine receptor blockade, and often lead to pronounced side effects and patients' nonadherence. We also discuss the potential therapeutic implications and limitations of NaS-based therapies targeting dopamine-related neuropsychiatric disorders. Lastly, we emphasize how understanding the precise neurobiological mechanisms underlying NaS-mediated modulation of dopamine signaling and associated behaviors is crucial for realizing clinical applications for these specific subclasses of NaS.

1.2. From cholesterol to allopregnanolone: the 5 α reductase pathways

The first step of steroidogenesis is the transfer of cholesterol from the outer (OMM) to the inner mitochondrial membrane (IMM), (Papadopoulos and Miller, 2012). Cholesterol, sourced from endogenous synthesis or from lipoprotein breakdown, serves the rate-limiting step in synthesizing all the class of steroids. Its transport across mitochondrial membranes is mediated by the cooperation of two crucial importer proteins, namely steroidogenic acute regulatory (StAR) protein and translocator protein (18 kDa, TSPO). While the mechanism involved in this process has not been fully elucidated yet, StAR appears to initiate cholesterol transfer into mitochondria (Stocco, 2000). It is located in the cytoplasm and acts as a shuttle protein binding to cholesterol molecules, and facilitating their movement from the OMM to the IMM. To efficiently anchor cholesterol to the OMM and to promote its translocation towards the IMM, StAR necessitates to interact with TSPO, a high-affinity cholesterol-binding protein located on the OMM. The role of TSPO is to facilitate the movement of cholesterol across the OMM, serving as a binding site for StAR and assisting the initial steps of cholesterol transfer into mitochondria (Miller and Bose, 2011).

Within the mitochondria, cholesterol undergoes a series of enzymatic conversions catalyzed by cytochrome P450 side-chain cleavage (CYP11A1, CYP450sc), leading to the formation of PREG, the precursor for the synthesis of all NaS. PREG is then converted to progesterone within the cytosol by 3 β -hydroxysteroid dehydrogenase enzyme. Subsequently, progesterone undergoes enzymatic modifications by 5 α reductase (5 α R), whose reaction is the rate-limiting step in the synthesis of 3 α , 5 α steroid derivatives (Bortolato et al., 2013). Among the five 5 α R isoenzymes, only the first two, namely 5 α R1 and 5 α R2, play major roles in neurosteroidogenesis. While the expression of both isoenzymes is widely distributed across most key regions of the adult rat brain (Castelli et al., 2013; Torres and Ortega, 2003), they differ in expression patterns and cellular localization. In rodents, the 5 α R1 is present in the majority of forebrain regions, and is localized in neurons oligodendrocytes, microglia, type 1 astrocytes, and Schwann cells (Celotti et al., 1992; Normington and Russell, 1992). The type 2 isoform is widely expressed throughout the brain, spanning from the forebrain to the brainstem and cerebellum of the adult rat, and is localized in neurons, but not in glial cells (Castelli et al., 2013). Although with different affinity, 5 α R1 and 5 α R2 convert progesterone into the 5 α -dihydro-derivatives, 5 α -dihydroprogesterone (5 α -DHP). The product of this 5 α R reaction serves as a substrate for 3 α -hydroxysteroid oxidoreductase (3 α -HSOR), enzymes that transform 5 α -DHP to 3 α , 5 α -tetrahydroprogesterone (THP; also known as allopregnanolone, AP) (Fig. 2). Thus, AP acts as the final product of the 5 α , 3 α metabolic pathway, originating from PREG and

Table 1Clinical and preclinical evidence reporting beneficial effects of 5 α R-related neuro(active)steroids on hyperdopaminergic-associated brain disorders/(endo)phenotypes.

Brain disorders	NaS-based drug	Patients	Treatment	Results	Adverse Events	References
Bipolar Disorders	Pregnenolone	Men and Women	50 mg/day or 100 mg/day for 8 weeks	Significant beneficial effects on depression and mania but not on cognition in unipolar and bipolar depressed patients with a history of substance abuse	Well-tolerated with minimal adverse events	(Osuji et al., 2010)
	Pregnenolone	Women	100 mg/day, titrated to 300 mg/day at week 2, and 500 mg/day at week 4	Depression remission rates significantly higher after pregnenolone treatment (61 % vs 37 %)	Well-tolerated with minimal adverse events	(Brown et al., 2014)
Cocaine use disorder	Pregnenolone	Men and Women	300 mg/day or 500 mg/day	Reduction of cocaine craving and anxiety	Not mentioned	(Milivojevic et al., 2022)
		Progesterone	Men and Women	400 mg/day	Reduction of negative emotion in women, but not men, following exposure to stress	Well-tolerated, with mild levels of transient side effects
Gambling disorder	Finasteride	Men	5 mg/day for 2 weeks	Reduction in interest in gambling corroborated by Y-BOCS score	Well tolerated	(Bortolato et al., 2012)
Major Depressive disorder	Dutasteride	Men	0.5 mg/day for 1–49 months	Increase in depressive symptoms at all intervals excluded >48 months	No mentioned	(Garcia-Argibay et al., 2022)
	Finasteride	Men	1 mg/day for 1–49 months	Increase in depressive symptoms at all time intervals investigated	No mentioned	
Zuranolone		Men and Women	30 mg/day for 14 days or 20 mg /day after adverse effects or reported sedation	Significant improvement in depressive symptoms	No serious adverse events	(Gunduz-Bruce et al., 2019)
		Men and Women	30 mg/day for 2 weeks	Significant improvement in depressive symptoms	No serious adverse events	(Suthoff et al., 2022)
		Men and Women	30 mg/day for 2 weeks	Significant improvement in depressive symptoms	No serious adverse events	(Arnaud et al., 2021)
Parkinson disease	Zuranolone	Men and Women	20 mg (I/II days), 30 mg (III day) for 1 week	Improvement of tremor and motor symptoms	Well-tolerated	(Bullock et al., 2021)
Post-Partum Depression	Brexanolone (Zulresso)	Women	I.V. infusion (60 h)	Improvement in depressive symptoms at the end of the first infusion	Sleepiness, dry mouth, loss of consciousness and flushing	Approved on March 19, 2019 (Epperson et al., 2023; S. Kanes et al., 2017; S. J. Kanes et al., 2017, 2017)
	Zuranolone (Zurzuvae)	Women	50 mg/day for 14 days	Improvement in the core symptoms of depression	Drowsiness, dizziness, diarrhea, fatigue, nasopharyngitis, and urinary tract infection	Approved on August 04, 2023 (Deligiannidis et al., 2023)
Schizophrenia	Pregnenolone	Men and Women	100 mg/day for 2 weeks, 300/day for 2 weeks, 500 mg/day for 4 weeks	Significant reduction in negative symptoms	Well-tolerated with minimal adverse events	(Marx et al., 2009)
		Men and Women	100 mg/day for 2 weeks, 300/day for 2 weeks, 500 mg/day for 4 weeks	Improvements in functional capacity but not in cognitive symptoms	Well-tolerated	(Marx et al., 2014)
		Men and Women	50 mg/day for 8 weeks	Reduction of PANSS negative scale and SANS domain scores	Well-tolerated without clinically significant changes	(Kreinin et al., 2017; Ritsner et al., 2014)
Tourette Syndrome	Finasteride	Men	5 mg/day for 24 days	Improvement in psychotic symptoms, general and negative symptoms.	No significant side effects	(Koethe et al., 2008)
		Men	5 mg/day for 28 weeks	Reduction in Y-GTSS and Y-BOCS score	Well-tolerated	(Bortolato et al., 2007)
Animal models Cannabis use disorder	NaS-based drug Pregnenolone	Men	5 mg/day for 18 weeks	Reduction in global severity, total, motor, and phonic tics. Significant reduction in Y-BOCS total and compulsion in patients with obsessive-compulsive comorbid symptoms	Two patients complained of a reduction in libido and occasional difficulty in achieving erection.No neuropsychiatric, metabolic, or endocrine side effects	(Muroni et al., 2011)
				Treatment 2–6 mg/kg S.C.	Results Rescue of THC-induced food-intake and memory impairments in Wistar rats and C57BL/6 N mice.	References Vallée et al., (2014))

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Table 1 (continued)

Brain disorders	NaS-based drug	Patients	Treatment	Results	Adverse Events	References
				6 mg/kg, S.C.	Rescue of psychotic-like effects and related endophenotypes in mice	(Busquets-Garcia et al., 2017)
				6 mg/kg S.C.	Rescue of synaptic defects and dopaminergic activity and behavior in PCE offspring	(Frau et al., 2019)
Cocaine use disorders	Progesterone			2 /kg mg0.5 mg/kg S.C. for 3 days	Reduction of cocaine-primed reinstatement in female, but not male rats	(Anker et al., 2009)
	Allopregnanolone			15 or 30 mg/kg S.C. for 3 days	Reduction of cocaine-primed reinstatement in female, but not in male rats	(Anker et al., 2009)
Depression	Allopregnanolone			5 µg/rat I.C.V. 0.5 or 0.05 µg/side 2 µg/0.3 µl	Reduction of immobility in Forced Swim Test Increase in latency to first immobility and reduction in total immobility time in the forced swim test	(Almeida et al., 2018) (Rodriguez-Landa et al., 2007)
	Progesterone			0.001, 0.01 and 0.1 M	Reduction of both time of immobility and number of immobility periods	(Estrada-Camarena et al., 2002)
Gambling disorder	Finasteride			25–50 mg/kg I.P.	countered the elevation in probability-discounting in reserpine-pramipexole model of pathological gambling	(Floris et al., 2022)
Opioid use disorder	Ganaxolone			10 mg/Kg S.C.	Reduction of contextual fear on SI mice	(Pinna and Rasmusson, 2014)
	Finasteride			5 nM in zebrafish, 50 mg/kg, IP in rats	Reduction in opioid intake in zebrafish and rat self-administration paradigms	(Bosse et al., 2021)
Parkinson disease	Pregnenolone			6, 18, 36 mg/kg, S.C. or 3 weeks	Pregnenolone counteracts LIDs development in 6-OHDA-lesioned rats without affecting the therapeutic efficacy of L-DOPA	(Corsi et al., 2023)
	Allopregnanolone			10 mg/kg S.C., once a week for 2 weeks	Normalization of the MPTP lesion-induced effects on motor performance, number of TH-expressing neurons in the SN, expression of TH protein, and levels of NE in the SN and midbrain.	(Adeosun et al., 2012)
				5,20 mg/kg S.C. for 2 months	AP enhances learning and memory in 6-OHDA model of Parkinson's disease in rats.	(Nezhadi et al., 2016)
	Finasteride			30 or 60 mg/kg, IP	Finasteride significantly reduces development and expression of dyskinesia induced by l-DOPA in 6-OHDA-lesioned rats without impacting the therapeutic effects of L-DOPA	(Frau et al., 2017)
	Dutasteride			15 or 30 mg/kg, IP	Dutasteride counteract dyskinesia without impacting the therapeutic effects of L-DOPA	(Fanni et al. 2019)
Schizophrenia	Pregnenolone			60 mg/kg for 2 weeks	Reduction of positive schizophrenia-like phenotypes and cognitive deficits in DAT-KO mice	(Wong et al., 2012)
	Pregnenolone sulfate			20 mg/kg or 40 mg/kg or 80 mg/kg S.C. for 10 days	Suppression of hyperlocomotion and behavioral stereotypes, and rescue of PPI deficits in DAT-KO mice. Long-term administration of 40 mg kg ⁻¹ PREGs alleviated the cognitive deficits of DAT-KO mice in the novel object recognition and social transmission of food preference paradigms	(Wong et al., 2015)
	Progesterone			10 mg/kg, S.C.	Progesterone dampens the hyperactivity, anxiety-like behaviors and PPI deficits in DAT-KO mice.	(Frye and Sora, 2010)

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Table 1 (continued)

Brain disorders	NaS-based drug	Patients	Treatment	Results	Adverse Events	References
Tourette syndrome	Allopregnanolone			5–15 mg/kg, I.P.	Exacerbation of TS-like manifestations in D1CT–7, but not wild-type littermates; these effects are countered by haloperidol	(Mosher et al., 2017)
	Finasteride			25–50 mg/kg, I.P.	Reduction of TS-like manifestations in D1CT–7	(Mosher et al., 2017)
	Isoallopregnanolone			5–10 mg/kg, S.C.	Reduction of tic-like behaviours induced by stress in D1CT–7 mice, akin to haloperidol and finasteride; IsoAP rescues the enhancement of tic-like behaviours induced by AP	(Cadeddu et al., 2020)
Sensory gating disorders	Abiraterone			10,25,50 mg/kg, I.P. 1 µg/µl I.C.V.	Normalization of the PPI deficits induced by the DA receptor agonist apomorphine	(Frau et al., 2014)
	Finasteride			10 µg/1 µl I.C.V., 0.5 µg/0.5 µl/ side (multiple brain regions)	Prevention of the apomorphine-mediated PPI deficits by finasteride I.C.V and accumbens (shell and core) infusions; finasteride prevents PPI deficits produced by amphetamine and apomorphine in gonadectomized rats	(Devoto et al., 2012)
				25–50 mg/kg, I.P.	Finasteride rescues PPI deficits induced by the full D(1)-like receptor agonist SKF–82958 but not apomorphine in C57BL/6 mice	(Frau et al., 2013)

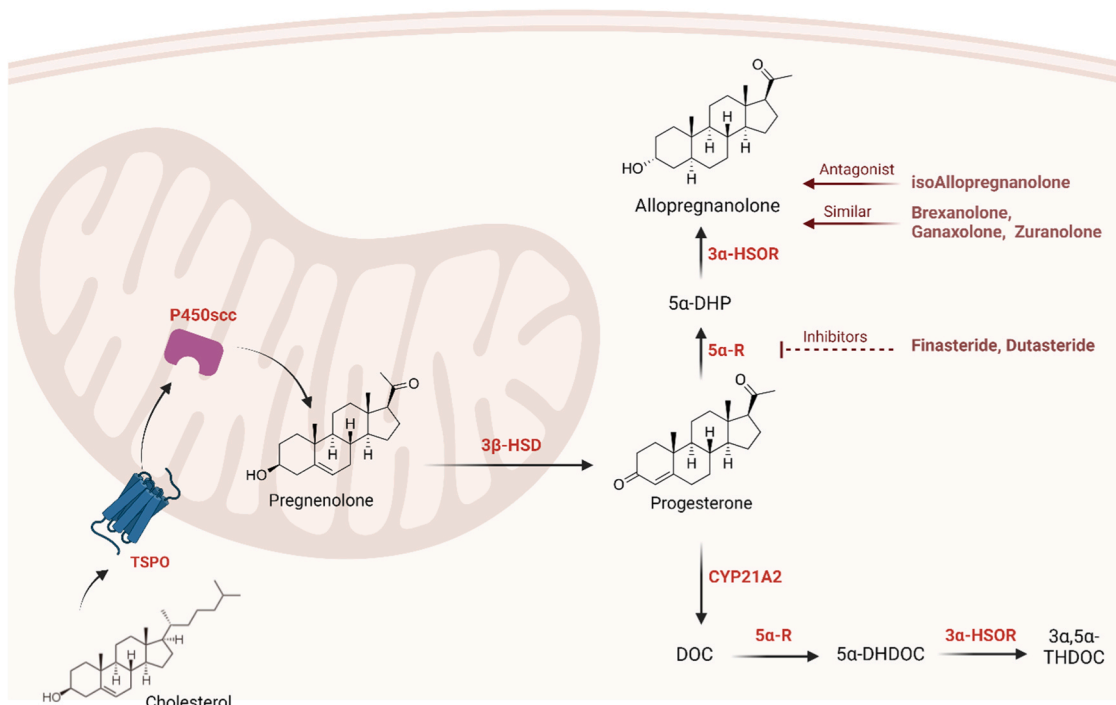


Fig. 2. Biosynthesis of neuro(active)steroids mediated by 5 α reductase pathway, from pregnenolone to allopregnanolone. Abbreviations: TSPO, Translocator protein; P450scc, cytochrome P450 side-chain cleavage; 3 β -HSD, 3 β -hydroxysteroid dehydrogenase; 5 α R, 5 α reductase; 3 α -HSOR, 3 α -hydroxysteroid oxidoreductase; CYP21A2, steroid 21-hydroxylase; DOC, deoxycorticosterone; 5 α -DHDOC, 5 α -dihydro deoxycorticosterone; 3 α ,5 α -THDOC, 3 α ,5 α -tetrahydrodeoxycorticosterone; 5 α -DHP, 5 α -dihydroprogesterone; Allopregnanolone, 3 α ,5 α -tetrahydroprogesterone (created with BioRender.com).

progressing through progesterone.

AP is mainly synthesized in the brain, although other tissues, including the ovaries (Cáceres et al., 2024), the placenta (Vacher et al., 2021) and adrenal glands (Almeida et al., 2018) have been

demonstrated to have steroidogenic capacity. AP is synthesized in the corpus luteum throughout the menstrual cycle, reaching its peak levels during the luteal phase under the influence of the luteinizing hormone (LH). During the second half of gestation, the placenta produces

significant amounts of AP to support neurodevelopmental processes in the fetus, to stabilize maternal mood, and to regulate maternal stress response. After birth, maternal AP levels can drop abruptly, thereby leading to a postpartum depression (PPD) in susceptible mothers, as well as long-term adverse neurobehavioral outcomes in offspring (Pinna et al., 2022). Similarly, in individuals with low resilience, persistent stress exposures may disrupt the responsiveness of the hypothalamic-pituitary-adrenal (HPA) axis, resulting in blunted synthesis of AP from the adrenal glands and onset of psychiatric conditions, such as major depressive disorder (MDD) and post-traumatic stress disorder (PTSD) (Almeida et al., 2021).

In addition to the conversion of progesterone into DHP, it is important to underline that 5 α R isoenzymes also catalyzes other important processes, including the conversion of testosterone into the potent androgen dihydrotestosterone (DHT) and the degradation of cortisol and corticosterone into their 5 α -reduced metabolites, which are less potent glucocorticoid receptor agonists (McInnes et al., 2004). For these properties in reducing DHT, the 5 α R inhibitors finasteride and dutasteride are currently prescribed for the treatment of benign prostatic hyperplasia as well as androgenic alopecia (Nickel et al., 2008). In humans, Finasteride has a much higher affinity for 5 α R2 than 5 α R1, while dutasteride inhibits both isoenzymes; importantly, such inhibition is a nearly irreversible process, with a slow rate of dissociation and long-lasting effects in humans (Traish, 2020). In terms of clinical application in the treatment of benign prostatic hyperplasia, both of these drugs induce DHT suppression, which ultimately leads to the reduction of prostate volume and a general improvement of urinary symptoms. Compared to finasteride, dutasteride therapeutic effects seems to be more rapid and to result in a greater and long-term improvement of urinary retention (Nickel, 2004; Nickel et al., 2008).

In parallel with the therapeutic indications of 5 α R inhibitors, the 5 α reductase pathways, alongside its substrates and metabolites, is increasingly recognized as particularly relevant in diverse stress- and dopamine-related brain disorders. A specific disruption of 5 α R enzymatic pathway, along with associated imbalances of NaS, has been consistently observed in patients with schizophrenia, Tourette's syndrome (TS), Post-Traumatic Stress Disorder (PTSD), and cannabis use disorders (Bortolato et al., 2022, 2022; Cai et al., 2018; Marx et al., 2006; Pineles et al., 2018; Rasmussen et al., 2006; Tomaselli and Vallée, 2019). Of note, these diseases are etiologically characterized by hyperdopaminergic states. In the next sections, we will present the most relevant preclinical and clinical evidence showing how targeting neurosteroidogenesis within the 5 α , 3 α pathway and/or exogenous administration of their associated NaS, can significantly modulate dopamine transmission in brain regions and circuitry strictly involved in these psychiatric conditions.

1.3. The modulatory effects of 5 α related NaS on dopamine system

The mesolimbic dopamine system is central to modulating various processes across neurobehavioral domains, including decision-making, motivation, information and reward processing, and emotional responses (Salamone and Correa, 2012; Zald and Treadway, 2017). Consequently, dysfunction or dysregulation of the mesolimbic dopamine pathway is widely recognized as a key etiological factor in major psychiatric disorders such as addiction, mood disorders, and schizophrenia. The primary approach of marketed drugs for these disorders is to target this pathway in order to restore physiological dopamine balance and/or to regulate dopamine receptor signaling. Examples of currently used therapeutics that modulate dopamine system include dopamine receptor antagonists for schizophrenia and bipolar disorders, dopamine agonists for PD, dopamine releasers (i.e. amphetamine-like drugs) for ADHD, and dopamine reuptake inhibitors for depression. However, due to dopamine involvement in several physiological processes, directly targeting dopamine synaptic function, and/or single or multiple dopamine receptors often leads to undesirable, and sometimes severe, side effects. An

alternative and promising approach may, therefore, involve an indirect neuromodulation of this system to potentially achieve similar neurobiological outcomes while minimizing adverse effects on behavioral regulation. From this standpoint, compelling evidence indicates that NaS play a modulatory role on midbrain dopamine system (Di Paolo, 1994; Sánchez et al., 2010). Among the subclasses of NaS, it is noteworthy that all the substrates and metabolites of the 5 α reductase pathways, namely PREG, progesterone, 5 α -DHP and AP, demonstrated disparate and multifold modulatory actions on dopamine transmission and signaling. For example, PREG administration has been shown to modulate dopamine release in the rodent PFC, thus suggesting a role in cognitive functions and a potential avenue in disorders where dopamine dysregulation is implicated. Consistent with this evidence, it dose-dependently rescues schizophrenia-like behavior phenotypes in dopamine transporter (DAT) knockout mice (Wong et al., 2012). Exogenous PREG administration significantly counteract a spectrum of hyperdopaminergic behavioral phenotypes due to deletion of DAT in the brain, including psychomotor agitation, stereotypy, and cognitive deficits in the prepulse inhibition (PPI) and object recognition tests (ORT) (Vallée et al., 2014; Wong et al., 2012). In partial agreement with these findings, the largest randomized clinical trials reported that exogenous PREG supplementation improved functional capacity in patients with schizophrenia compared to placebo, but failed to significantly improve cognitive symptoms (Marx et al., 2014). Activation of ventral tegmental area (VTA) dopaminergic neurons and an increase in dopamine extracellular levels in the NAc are hallmark effects of most drugs of abuse and have been implicated in drug addiction. Accordingly, Δ 9-tetrahydrocannabinol (THC) elicits a robust increase in extracellular NAc dopamine levels alongside firing activity of VTA neurons. Remarkably, not only PREG dampens these neurochemical and electrophysiological outcomes, but also reverses the reinforcing effects assessed in an intravenous self-administration model, suggesting potential therapeutic applicability for cannabis intoxication and further dopamine-dependent addictive behaviors (Vallée et al., 2014).

By influencing the expression and the activity of dopamine receptors, progesterone also regulate dopamine function. At physiological doses, it can rapidly increase striatal dopamine release in rats of both sexes, and independently from estradiol actions (Di Paolo et al., 1986; Ringuet et al., 1994). However, at higher doses, the changes in dopaminergic signaling within the dorsal and ventral striatum are time-dependent, with rapid increases in dopamine release immediately after acute hormone administration followed by later inhibition (Dluzen and Ramirez, 1984; Yoest et al., 2018). Of interest, the fluctuations of progesterone (and estradiol) levels across the menstrual cycle differently affect cognitive performance by modifying baseline dopamine levels in the PFC (Hidalgo-Lopez and Pletzer, 2017). However, data regarding dopamine receptor expression in response to progesterone administration appear controversial, with no changes or time-dependent effects on expression of striatal dopaminergic D2 receptors (Fernández-Ruiz et al., 1989; Lévesque and Di Paolo, 1993; Paden et al., 1982; Saigusa et al., 1997). The direct metabolite of progesterone, 5 α -DHP, has been less investigated in the context of dopamine regulation. However, previous evidence suggests that it may exert modulatory effects on dopamine transmission. For instance, a study by (Frye et al., 2006) demonstrated that 5 α -DHP administration affects dopamine release in the NAc, implicating its involvement in reward-related behaviors mediated by the dopaminergic system.

AP is the 5 α R-related NaS has received major attention with regard to its neuromodulatory effects on dopamine neurotransmission. The impact of AP on dopamine function in the rodent brain appears to exhibit narrow dose ranges and a hormetic dose response curves. For instance, at estimated physiological levels, AP enhances mesolimbic dopamine transmission and potentiates the dopamine response to morphine in the NAc, suggesting an important role in reward and motivation (Rougé-Pont et al., 2002). Consistent with these findings, AP facilitates reward-related behavior (Fish et al., 2014; Frye et al., 2011)

and reinstates ethanol-seeking behavior (Finn et al., 2008, 2004). AP also modulates the behavioral effects of D1 receptor activation (Frye et al., 2006) and affects the phosphorylation of DARPP-32 (Frye and Walf, 2010; Mani et al., 2000), a key molecule in dopamine D1 receptor signaling cascade (Scheggi et al., 2018; Svenningsson et al., 2004). Conversely, at supraphysiological concentrations (micromolar range), AP dose-dependently blocks hyperlocomotion and hyperactivity induced by amphetamine (Khisti et al., 2002), reduces sexual receptivity in female rats (Laconi and Cabrera, 2002), and produces place aversion (Beauchamp et al., 2000), akin to dopamine antagonists. Additionally, *in vitro* studies have shown that AP significantly decreases the amount of dopamine release in stimulated neurons, an effect attenuated by the GABA_A antagonist bicuculline (Knight et al., 2012). Since AP preferentially activates extrasynaptic GABA_A receptors, it may affect GABA tonic currents on VTA dopamine neurons, thereby inhibiting dopamine transmission (Vashchinkina et al., 2014). Consistent with this idea, AP administered intraperitoneally at escalating doses reduced evoked dopamine release in the NAc. This suggests that AP is able to blunt the phasic increase in NAc dopamine levels induced by electrical stimulation of VTA (Dornellas et al., 2020). Thus, collectively, these data support the notion that AP regulates mesolimbic dopamine transmission via specific GABA_A receptor subtypes, in a dose-dependent manner. This interpretation is indeed strengthened by other studies showing that several GABA_A agonists reduce dopaminergic transmission in the striatal regions (Brodnik et al., 2019; Smolders et al., 1995), and bicuculline, GABA_A receptor antagonist, prevents dopamine increase induced by AP in stimulated striatal neurons (Knight et al., 2012).

The effects of AP on dopamine signaling also show a state-dependent modulation, especially in the context of stress response. Acting as a positive allosteric modulator of GABA_A receptors, AP may regulate emotional behavior and exert anti-anxiety, anti-conflict and antinociceptive effects (Pinna et al., 2003). When subjected to acute stress paradigms, such as foot shock experiments, rodents exhibit increased dopamine release in several brain regions, including the PFC (Abercrombie et al., 1989; Deutch and Roth, 1990). Concomitantly, acute stress exposures triggers rapid increases in cortical and plasma concentrations of AP (Barbaccia et al., 1997, 1996; Cadeddu et al., 2022). Moreover, AP robustly reduces the extracellular concentration of dopamine in rat NAc and cerebral cortex, both at baseline and after its increase in response to stress (Motzo et al., 1996). Conversely, depletion of cortical AP enhances dopamine release induced by acute stress exposure (Dazzi et al., 2002), suggesting that AP contributes to the physiological regulation of basal and stress-induced dopamine release in the rat brain. AP influence extends to modulating dopaminergic neurotransmission under chronic stress conditions. For instance, in rats, the post-weaning isolation-rearing model of chronic stress elicits imbalances of AP and dopamine levels within the NAc and medial PFC, thus reflecting the complex interplay between AP signaling and chronic stress-induced neuroadaptations (Bortolato et al., 2011). This underscores the intricate and multifaceted role of AP in shaping dopaminergic neurotransmission under both acute and chronic stress conditions, shedding light on its therapeutic potential in mitigating stress-related neuropsychiatric disorders.

Typically, AP is posited to promote resilience and mitigate adverse outcomes of acute and short-term acute stress. However, its prolonged level elevation beyond physiological norms shifts brain homeostasis towards pathological behavioral changes. Consequently, numerous preclinical and clinical investigations indicate that exogenous or intracerebral AP infusions lead to impairments across multiple neuro-behavioral domains, including cognition, impulse control and information processing. For instance, AP elicits learning and memory deficits in various cognitive tasks in rodents (Johansson et al., 2002; Johansson et al., 2016; Cushman et al., 2011; Rabinowitz et al., 2014); in healthy women, an acute AP administration with a dose inducing tenfold plasma endogenous concentrations produces a small but significant deterioration of episodic memory scores without interfering with

semantic or working memory (Kask et al., 2008). Similar cognitive deficits are observed following the administration of the further PAM-steroid, THDOC (Schwabe et al., 2007). In light of this evidence, human conditions characterized by intrinsic supraphysiological AP levels, namely hepatic encephalopathy (Montagnese et al., 2021; Riggio et al., 2011) and primary biliary cholangitis (Wetten et al., 2022), show impairments in cognitive functions. Additionally, AP exposures may also exacerbate preexisting behavioral phenotypes with relevance to neurological and psychiatric conditions. Continuous AP exposures through implanted Alzet® osmotic pump impairs learning and memory in mice models of Alzheimer's disease (Bengtsson et al., 2013, 2012). Moreover, in relation to stress exposure, AP may contribute to maladaptive processes in vulnerable subjects. For example, AP dose-dependently exacerbates TS-like manifestations induced by stress in D1CT-7 mice, one of the best-characterized animal models of Tourette's syndrome; interestingly, the same AP doses failed to affect wild-type littermates (Mosher et al., 2017). Sleep deprivation, a further stressful situation, which is known to precipitate tic expression, produced sensorimotor deficits in rats by enhancing AP biosynthesis in the PFC (Cadeddu et al., 2023, 2022). Consistently, the exogenous administration of AP worsens sensorimotor gating function deficits in sleep deprived rats (Frau et al., 2017). Notably, the administration of finasteride reversed both the TS- and psychotic-like manifestations of D1CT-7 mice and sleep deprived rats, respectively, by recovering AP physiological levels. Accordingly, PAM-steroids alike AP produce paradoxical responses, characterized by irritability, aggression, and dysphoria, similar to those observed in premenstrual syndrome during the luteal phase and in treatments involving post-menopausal hormone replacement therapy (Bäckström et al., 2015).

1.4. 5 α reductase enzyme as a therapeutic target for hyperdopaminergic phenotypes

As previously discussed, 5 α R acts as a crucial enzyme in the biosynthesis of NaS, which exhibit distinctive modulatory effects on the dopaminergic system. Extensive literature indicates that pharmacological or environmental modulation of this enzyme leads to substantial alterations in its related neuroactive substrates and metabolites across cortical and limbic brain regions. Consequently, these alterations give rise to a diverse array of effects on emotional and cognitive regulation, as observed in both rodent models and humans. Numerous preclinical studies have demonstrated that, under baseline conditions, the selective inhibition of 5 α R results in two distinct neurochemical outcomes in the brain: (i) depletion of its products, especially AP; (ii) elevation of its substrates, primarily progesterone and PREG (Bortolato et al., 2011; Dazzi et al., 2002; Frau et al., 2016; Griffin and Mellon, 1999). Finasteride and dutasteride – two clinically approved drugs for the treatment of benign prostatic hyperplasia and androgenetic alopecia – are the most used 5 α R inhibitors in the preclinical setting to manipulate the levels of these NaS and explore their effects on brain function and behavior.

In light of this, our research group focused on investigating the impact of the pharmacological modulation of 5 α R pathway in animal models relevant to major psychiatric disorders characterized by dysregulation of NaS and dopamine system. Initially, we evaluated the effect of 5 α R inhibitors in ameliorating abnormal behaviors induced by psychotomimetic agents, including the dopaminergic agonists apomorphine and d-amphetamine, as well as the NMDA receptor antagonist dizocilpine. Notably, the antipsychotic-like properties of 5 α R blockade were assessed on behavioral phenotypes isomorphic to preattentive, motor, and cognitive abnormalities observed in schizophrenia and other psychiatric disorders (Geyer et al., 2001), whose symptoms are mitigated by antipsychotic drugs (Geyer et al., 2001; Hoffman et al., 1993). Alongside hyperlocomotion and stereotyped behavior – two well-established assays for measuring hyperdopaminergic-relevant phenotypes with high predictive validity for typical and atypical antipsychotics – we focused our investigations on the PPI of the acoustic startle reflex and its deficits

mediated by dopamine agonists and NMDA antagonists (Mansbach and Geyer, 1989). PPI refers to the normal reduction in startle amplitude occurring when a startling stimulus is preceded by a weaker prepulse and serves as a measure of preattentive sensorimotor gating. This endophenotype has been extensively used to mimic the documented gating deficits observed in schizophrenia and other dopamine-dependent psychiatric conditions (Swerdlow et al., 1994). The high face, construct and predictive validity of PPI for these disorders is underscored by the observation that administration of major psychotomimetic agents significantly disrupts the PPI index in both animals and humans, and in a manner sensitive to typical and atypical antipsychotic drugs (Geyer et al., 2001). Moreover, aside from schizophrenia, the loss of PPI has also been documented in other neuropsychiatric disorders associated with dopamine dysregulation, such as mania (Perry et al., 2001), TS (Swerdlow et al., 2001), thereby revealing itself as a transdiagnostic endophenotype for gating- and dopamine-dependent disorders (Frau and Melis, 2023; Geyer, 2006).

Our initial findings show that 5 α R inhibitors efficiently prevented PPI deficits along with other dopamine-relevant behavioral alterations (Bortolato et al., 2008). Importantly, their antidopaminergic properties were not associated with extrapyramidal symptoms typically exerted by neuroleptic drugs, even at the highest doses tested (Bortolato et al., 2008). Moreover, the rapid onset of all the behavioral effects observed after acute finasteride administration and other 5 α R inhibitors, suggests that the neuromodulatory actions of NaS of the dopamine system likely operate through non-genomic signaling.

In our endeavor to elucidate how finasteride modulates the dopamine system, we uncovered that the therapeutic effects prompted by 5 α R inhibition entail the involvement of two key target areas of the mesolimbic and mesocortical dopaminergic pathways, the NAc and the medial PFC (Devoto et al., 2012). These brain regions are prominent in the dopaminergic regulation of sensorimotor gating, and are implicated in the pathophysiology of schizophrenia and various other psychiatric disorders. Moreover, the influence of 5 α R inhibition on the dopaminergic regulation of sensorimotor gating function exhibits regional specificity, as evidenced by the absence of contribution from other forebrain regions, including the dorsal caudate, basolateral amygdala, and ventral hippocampus (Devoto et al., 2012; Frau et al., 2023). While our prior investigations suggest that systemic administration of finasteride leads to heightened dopamine levels in the Nac and medial PFC (Bortolato et al., 2011), our subsequent research revealed that its intracerebral infusion failed to elicit any alterations in extracellular dopamine contents within these regions (Devoto et al., 2012; Frau et al., 2016). These findings suggest that the antipsychotic-like effects of finasteride primarily stem from postsynaptic mechanisms and are functionally distinct from time-dependent fluctuations in cortical and striatal dopamine levels that follow systemic administration of 5 α R inhibitors.

We next investigated which receptor(s) might be involved in the antipsychotic-like effects of 5 α R inhibitors. To address this question, we employed different strains and rodent species known to be susceptible to the PPI-disrupting effects of selective D1, D2, and D3 dopaminergic agonists, such as C57BL/6 mice and Long Evans rats. Across two consecutive studies, we discerned that the antidopaminergic properties of finasteride are mediated through the negative modulation of D1 and D3 receptors, while D2 receptors remained unaffected (Frau et al., 2016, 2013). Considering that 5 α R inhibitors do not directly bind to dopamine receptors and the observed postsynaptic mechanism of action of finasteride on PPI regulation (Devoto et al., 2012), it is conceivable that the NaS changes produced by 5 α R inhibition may interfere with downstream signaling pathways associated with D1 and D3 receptors. While the quantification of brain regional changes in 5 α R-related NaS accompanying the antipsychotic-like effects of finasteride was not conducted across the aforementioned investigations, our recent steroidomic analysis show that the PPI-disrupting effect induced by selective D1 receptor agonist was concomitant with elevated levels of progesterone and some of its metabolites in the medial PFC (Frau et al., 2023). This

finding suggests that the D1 receptor activation results in an upsurge of progesterone levels that may ultimately lead to increased AP concentrations, possibly attributable to heightened 5 α R expression and/or activity. Notably, in the same study we showed that medial PFC levels of AP are necessary and sufficient to confer sensitivity to the PPI-disruptive effects of D1 receptor agonists in rodents (Frau et al., 2023; Cadeddu et al., 2022). Consistent with our results, other groups have shown that progesterone and AP modulate the behavioral effects of D1 receptor activation (Apostolakis et al., 1996; Frye et al., 2006; Petralia and Frye, 2006) as well as its signaling, such as the phosphorylation of DARPP-32 (Frye and Walf, 2010; Mani et al., 2000), a key molecule in the D1 receptor downstream cascade (Svenningsson et al., 2004). Moreover, both NaS affect σ 1 receptors, a protein chaperone known to enhance D1 receptor signaling (Fu et al., 2010) and to form heteromers with this receptor in the brain (Navarro et al., 2010). This aligns with findings suggesting that D1/D3 receptor blockers might prove useful in treating TS and schizophrenia, respectively (Gilbert et al., 2014; Sokoloff et al., 2013). Noteworthy, our preclinical findings have been substantiated by clinical investigations showing how finasteride exerted beneficial properties in patients suffering from these psychiatric conditions (see next sections) (Bortolato et al., 2007; Koethe et al., 2008; Muroi et al., 2011).

1.5. Targeting 5 α reductase pathway for L-DOPA-induced dyskinesia

Prompted by our experimental results on the antidopaminergic effects elicited by 5 α R inhibitors in psychotic-like phenotypes, we hypothesized similar therapeutic efficacy against L-DOPA-induced dyskinesias (LID), as this condition is also characterized by dopamine receptor signaling disruption. Indeed, LID is a serious side effect of chronic L-DOPA administration, which limits therapeutic efficacy and management of motor symptoms in advanced PD patients. Given that amantadine, the only current treatment option, exhibits limited efficacy and is associated with side effects, there is an urgent need to identify novel and more effective drugs. This aberrant motor behavior can be readily reproduced and studied in preclinical models of PD upon chronic L-DOPA treatment, which is associated with an increased phosphorylation of striatal cell modulators downstream to D1 receptors, such as pERK1/2 and pDARPP32 (Pavón et al., 2006; Santini et al., 2007).

In line with our hypothesis, in a first study we found that finasteride dampened the development of LID in 6-OHDA-lesioned male rats as well as in dyskinetic animals upon L-DOPA administration. The latter effect was also extended to female animals, albeit only with the higher tested dose. Most importantly, this effect was achieved without compromising the therapeutic efficacy of L-DOPA in ameliorating motor disability (Frau et al., 2017). The latter finding is pivotal for the translation of preclinical results to clinical applications. The antidyskinetic effect appeared to be mediated through post-synaptic neurons, as evidenced by finasteride ability to reduce dyskinesias induced by direct dopamine receptor agonists, thereby ruling out modulatory effects on L-DOPA-derived dopamine release (Frau et al., 2017).

In a subsequent study, we compared the antidyskinetic effect of finasteride with the one of its analog, namely dutasteride. This 5 α R inhibitor was found as effective as finasteride but at half of the dose, again without reduction of the therapeutic efficacy of L-DOPA on rescuing of motor deficits induced by the dopaminergic denervation (Fanni et al., 2019). Remarkably, the effect of 5 α R inhibitors was accompanied by the normalization of striatal signaling molecules that are upregulated upon chronic L-DOPA, such as pERK1/2, pDARPP-32, and G α_{olf} .

Whereas the precise mechanism by which 5 α R inhibitors exerts their antidyskinetic effect is not known, it may involve inhibition of D1-D3 receptor interaction. Indeed, chronic L-DOPA has been shown to produce upregulation of striatal D3 receptors that are otherwise expressed at low levels in physiological conditions (Aubert et al., 2005; Bézard et al., 2003; Bordet et al., 2000; Guillin et al., 2001). This event may yield to the formation of heteromeric complexes that display different

functional properties compared to homomeric receptors. In fact, it has been hypothesized that the bond of D3R to D1R prevents D1R internalization and potentiates its signaling cascade at striatal neurons (Fiorentini et al., 2008; Marcellino et al., 2008; Solís et al., 2017). According to this scenario, the antidyskinetic effect of 5 α R inhibitors was paralleled by decreased D1-D3 receptor coimmunoprecipitation in striatal homogenates. Of note, the ability of 5 α R inhibitors to interfere with D1R-D3R heteromer formation was restricted to the lesioned striatum, suggesting that dopamine depletion and pulsatile stimulation of its receptors are mandatory for dysregulated D1-D3 receptor interaction and prevention of thereof by dutasteride or finasteride. Thus, it is conceivable to posit that these heteromeric complexes primarily contribute to the upregulation of striatal signaling molecules, such as pERK1/2, pDARPP-32, and G α olf, thereby exacerbating both the behavioral and biochemical outcomes in response to dopaminomimetics.

In the effort to advance our understanding of the mechanisms underlying the antidyskinetic effects observed with finasteride and dutasteride, we investigated which NaS may be responsible for the antidyskinetic effect of 5 α R inhibitors. Interestingly, striatal PREG levels were reported to be specifically decreased following 6-OHDA lesion (Melcangi et al., 2012). Conversely, as mentioned earlier, pharmacological 5 α R inhibition results in increased levels of its NaS substrates, especially PREG (Frau et al., 2017). Therefore, we explored whether direct administrations of PREG to 6-OHDA-lesioned male rats might impact response to L-DOPA (Corsi et al., 2023). Results showed that concomitant treatment with PREG and L-DOPA reduced LID in a dose-dependent manner, akin to the effects observed with dutasteride. Once again, the therapeutic effect of L-DOPA was not affected by either treatment. Moreover, similar to dutasteride, the effect of PREG was associated with significant reduction of expression of dyskinesia markers expression, including pERK1/2, pDARPP-32, as well as D1-D3 receptors coimmunoprecipitation (Corsi et al., 2023). Interestingly, D1-D3 receptor coimmunoprecipitates showed a significant correlation with striatal BDNF levels. In fact, previous work has shown that L-DOPA treatment can induce BDNF expression, which in turn, can exacerbate maladaptive responses to L-DOPA (Guillin et al., 2001; Rylander et al., 2010). Accordingly, we found that striatal BDNF overexpression achieved through the delivery of a viral vector encoding the human BDNF gene, precipitated dyskinesia induced by both L-DOPA and direct D1 receptor agonists in 6-OHDA-lesioned rats (Scheggi et al., 2020; Tronci et al., 2017). Of note, this effect was paralleled by increased D1-D3 receptor coimmunoprecipitation. Indeed, previous work has shown that D3 receptor expression is under control of the BDNF gene (Guillin et al., 2001). Thus, by increasing D3 expression, BDNF would promote formation of dopamine receptor heterodimers, thus altering D1 receptor signaling cascade (Corsi et al., 2023). It is worth noting that, in our study, BDNF overexpression *per se* did not modify the levels of striatal D1-D3 receptor complexes, despite the increased availability of D3 receptors. By contrast, D1 receptor activation appeared essential to trigger heteromer formation, possibly by recruiting D3 receptors to the synaptic membrane (Scheggi et al., 2020). Taken together, these results suggest that PREG effect may be mediated through inhibition of L-DOPA-induced BDNF upregulation, prevention and D1-D3 heterodimer formation and consequent inhibition of the phosphorylation of key striatal signaling molecules that drive the exaggerated motor response to L-DOPA.

Although multiple NaS could potentially contribute to the antidyskinetic effect of PREG and 5 α R inhibitors, a specific increase of striatal PREG levels was observed following its exogenous administration, with no changes in the levels of other NaS. Similarly, elevated PREG levels were measured after 5 α R inhibitors treatment (Frau et al., 2015; Corsi et al., 2023). Although other steroids were not investigated in these studies, they could potentially contribute to the observed antidyskinetic effect through parallel mechanisms, such as mitigating inflammation, as demonstrated by corticosterone administration

(Barnum et al., 2008). A direct involvement of progesterone appears to be unlikely since its acute administration has been shown to increase dopamine release (Di Paolo et al., 1986), and no improvement of dyskinesia was observed in non-human primates lesioned with MPTP (Gomez-Mancilla and Bédard, 1992) or in clinical settings (Nicoletti et al., 2007). On the other hand, medroxyprogesterone in combination with other estrogens significantly improved dyskinesia in post-menopausal women (Nicoletti et al., 2007).

Despite additional studies are required to deepen our understanding of the contribution of multiple NaS to the pathophysiology of LID, the existing evidence strongly suggests the ability of these mediators to interfere with the maladaptive response to chronic L-DOPA after dopaminergic denervation.

1.6. Targeting 5 α reductase pathway in probability-discounting phenotypes produced by pramipexole

Neurosteroid modulation could be also a promising treatment option for iatrogenic complications caused by dopaminergic agonists, particularly gambling disorder (GD). Over the last few decades GD has become a serious recognized complication in PD, occurring in approximately 6 % of PD patients upon dopamine agonist medications. In particular, the dopaminergic agonists pramipexole and ropinirole, used in the therapy of PD, are associated with increased risk of developing hypersexuality, compulsive shopping, binge eating and pathologic gambling as adverse effects (Dodd et al., 2005; Weintraub et al., 2010; Weintraub and Mamikonyan, 2019). Despite growing attention and alarm on the impact of gambling on public health, therapeutic options are still inadequate (gradual reductions in dopaminergic agonists, antidepressants, antipsychotic medications, see (Jeon and Bortolato, 2020) and (Debove et al., 2024) for a detailed description) and efforts are urgently needed to clarify pathway strategies for high quality evidence.

In order to study the neurobiological mechanisms underlying GD, translational constructs have been developed to investigate impulsivity and risky decision making. By using these tasks, acute pramipexole was able to increase rat impulsive behavior (Madden et al., 2010) and to impair the ability to discriminate between advantageous and disadvantageous options (Pes et al., 2017).

To specifically model what happens in a subset of PD patients treated with pramipexole, our group has developed a model of iatrogenic gambling: using low doses of reserpine to mimic the dopamine deficit typical of PD without inducing motor alterations, pramipexole did not simply increase impulsive behavior but specifically reduced the ability to differentiate between distinct reward-associated choices (Orriù et al., 2020). Dysfunctional activation of reward and reinforcement systems in the brain, and possibly in dopamine function, has been proposed as one of the neurobiological underpinnings of GD (Balodis and Potenza, 2020). Neuroimaging studies have indeed showed a prominent involvement of frontal cortex and striatal regions (Hammes et al., 2019) and enhanced dopamine release in ventral striatum in PD patients with GD during the execution of gambling task (Steeves et al., 2009); reviewed by (Clark et al., 2019).

Thus, in searching novel therapies for GD, and consistently with the observation that the 5 α R inhibitor finasteride is endowed with anti-dopaminergic effects on several different paradigms (as reviewed in Frau and Bortolato, 2019) and elicited anti-dyskinetic properties in rodent models of PD (Fanni et al., 2019; Frau et al., 2017), NaS modulation may have some efficacy in attenuating risky behavior. Regarding the possible efficacy of 5 α R inhibitors in gambling disorder induced by dopamine agonists, the case report of Bortolato et al., 2012 is particularly remarkable. A 65-year old man with a history of PD received cabergoline or pramipexole in addition to his L-DOPA regimen and then developed gambling and compulsive habits, rapidly escalating. Since the patient was then diagnosed with benign prostatic hyperplasia, he was administered with finasteride and reported a subsequent attenuation of gambling behaviors and urge to play (Bortolato et al., 2012). However,

when the patient was surgically exposed to a prostatectomy and finasteride was discontinued, the patient within 3 weeks resumed his gambling habits; interestingly, when finasteride was reinstated, gambling habits were attenuated within 2 weeks (Bortolato et al., 2012). This case report led us to hypothesize that 5 α R inhibitors may effectively attenuate impulsivity, risk taking behavior and delay discounting, which are a common feature of behavioral addiction and predict gambling severity (Ciccarelli et al., 2020). In line with data of the case report, our group has demonstrated that in the reserpine-pramipexole model of pathological gambling, finasteride countered the elevation in probability-discounting (Floris et al., 2022). Several studies suggest that the pathological over-activation of reward dopaminergic system may be one of the potential mechanisms for dopamine agonists/modulators to induce GD, leading to a condition of sensitization of striatal circuits with abnormal activation of dopamine D2/D3 receptors, particularly in the NAc (Barras and Winstanley, 2016; Murray et al., 1994; Steeves et al., 2009). Our studies suggest that finasteride contrasts the D3-upregulation in the NAc induced by pramipexole (Floris et al., 2022). It is possible that finasteride, reducing the biosynthesis of AP and inducing an accumulation of steroid precursors like PREG and progesterone (Frau et al., 2017, 2015) or dehydroepiandrosterone (Bosse et al., 2021) change mRNA levels of dopamine of D2/D3 receptors (Purves-Tyson et al., 2014) or dysregulate the intracellular trafficking of D3 receptors (Laurine et al., 2003; Murakami et al., 2000). It is also worth noting that finasteride may reduce the reactivity to incentive stimuli that play a central role in the neurobiology of addiction and substance abuse disorders. Indeed, finasteride reduces the response to both stressful and rewarding stimuli (Godar et al., 2019) and the self-administration of different opioids like morphine and fentanyl without affecting their antinociceptive properties (Bosse et al., 2021), suggesting that it may be useful in different conditions characterized by compulsive and maladaptive features comparable to drug addiction.

1.7. Effects of pregnenolone (PREG) on the hyperdopaminergic phenotypes produced by prenatal cannabis exposure

Exposure to environmental risk factors during crucial periods of brain development can profoundly affect multiple neuronal pathways governing cognitive, emotional, and behavioral functions, ultimately heightening the vulnerability to neuropsychiatric disorders. Within this context, growing preclinical and clinical literature suggests that prenatal cannabis exposure (PCE) is associated with a spectrum of neuro-behavioral complications that could be ascribed to hyperdopaminergic etiologies. In fact, longitudinal studies investigating the impact of PCE on the major neurobehavioral domains in offspring have reported increased impulsivity, heightened incidence of risk-taking behaviors, and greater susceptibility to psychotic-like experiences and substance abuse (Corsi et al., 2019; Fine et al., 2019; Morris et al., 2011; Paul et al., 2021). Importantly, these investigations emphasize that such dopamine-related psychopathologies typically emerge during childhood and preadolescence, a period when the developing brain has not yet achieved complete maturation.

According to human studies, preadolescent PCE rat offspring displays a behavioral phenotype highly isomorphic with neurobehavioral disturbances observed in children. Moreover, rodent studies have uncovered two significant pieces of evidence yet to be extensively explored in humans: (i) the aberrant behavioral outcomes emerge only in males (Frau et al., 2019; Traccis et al., 2021); (ii) the psychopathological phenotypes of PCE offspring manifest only in response to an environmental challenge especially during preadolescence, namely THC –the major psychoactive component of cannabis– or acute stress exposure (Frau et al., 2019; Sagheddu et al., 2021; Traccis et al., 2021).

Thus, PCE has emerged as a viable rodent model for exploring the well-established "two-hit" hypothesis of mental illness. According to this conceptualization, an environmental insult acting as a "first hit," disrupts neurodevelopment thereby leading to increased susceptibility to a

"second hit" later in life, which ultimately triggers the manifestation of psychiatric symptoms (Frau and Melis, 2023; Mandy and Nyirenda, 2018). In this framework, the sustained and supraphysiological activation of the endocannabinoid signaling during intrauterine life biases the neurodevelopmental trajectories that are under its intricate regulatory control. Importantly, among these neurodevelopmental pathways, the endocannabinoid system exhibits a critical tropism for dopaminergic structures and circuits within the mesocorticolimbic system, which are relevant to emotional and cognitive processes (Harkany et al., 2007; Hurd et al., 2019)

Consequently, one of the neurobiological consequences of PCE-dependent disruption of endocannabinoid signaling is the impairments of mesolimbic dopamine signaling and the increased susceptibility to aberrant dopamine-relevant behavioral phenotypes. Indeed, the psychopathological phenotypes of preadolescent PCE progeny are associated with heightened excitability of VTA dopamine neurons alongside larger THC-induced dopamine release in the ventral striatum (Frau et al., 2019; Luján et al., 2024). Additionally, PCE disrupts the excitatory/inhibitory balance onto VTA dopamine cells, and elicits a polarity shift at excitatory synapses, from long-term depression to long-term potentiation (Frau et al., 2019). Aligned with clinical observations indicating the onset of neuropsychiatric symptoms as early as infancy in maternally exposed offspring, it is noteworthy that PCE rats manifest sensorimotor gating deficits, and paradoxically exaggerated locomotor responses only upon exposures to acute THC challenge (or stress) during the preadolescence period (Frau et al., 2019; Sagheddu et al., 2021). Notably, PCE female offspring do not exhibit either spontaneous or THC-induced psychopathological phenotypes, but rather adaptive coping strategies to acute stress (Traccis et al., 2021), which are most likely implicated in the protection from stress-induced PPI deficits (M. Melis, personal communication). Hence, the biological variable sex may serve as a protective factor against harmful environmental insults across neurodevelopment.

The (endo)phenotype unveiled by PCE is thus instrumental for exploring potential therapeutic tools aimed at preventing the transition of individual psychiatric susceptibility into late-onset mental disease. As abovementioned, PREG has promising actions on a number of behavioral manifestations associated to aberrant hyperdopaminergic signaling in humans and rodent models. Remarkably, PREG also rescues psychotic-like states in rodents through an endogenous allosteric negative modulation of the CB1 receptor (Vallée, 2016; Vallée et al., 2014). Given these findings, we hypothesized that it could mitigate PCE-induced alterations in the properties of mesolimbic dopamine neurons and associated behavioral readouts. Thus, we repeatedly administered PREG to PCE offspring and conducted a meso- to macro-scale analysis at least 24 after the final administration, in order to ensure a complete clearance of PREG from the body (Frau et al., 2019). Notably, PREG reversed both the intrinsic and synaptic hyperactive properties of dopamine neurons as well as their aberrant plasticity at excitatory synapses. It normalized the physiological responsiveness of mesolimbic transmission to acute THC administration and prevented THC-induced deficits in PPI. Additionally, PREG rescued the deterioration of PPI induced by acute stress in male PCE progeny (M. Melis, personal communication). Importantly, these remarkable antidopaminergic effects were attributed solely to PREG and not to its downstream neuroactive metabolites (e.g., progesterone, 5 α -DHP, AP), as pharmacological inhibition of the enzyme responsible for its metabolism, 3- β -hydroxysteroid dehydrogenase, failed to antagonize its protective effects (Frau et al., 2019).

While the molecular mechanisms underlying PREG effects on multiscale phenotypes altered by PCE remain largely unexplored, the existing literature suggests that its therapeutic properties may be attributed to interactions with multiple molecular targets. For instance, PREG binds to the sigma-1 (σ 1) receptor, a chaperone predominantly found in the endoplasmic reticulum and highly expressed in dopaminergic regions. This receptor is notably present in midbrain

dopaminergic neurons, where it plays a role in modulating dopamine function and release. Despite some contradictory findings regarding the effects of σ_1 receptor activation on the dopamine system, its ligands, including PREG, have demonstrated the ability to mitigate dysregulated dopamine signaling induced by psychostimulant drugs (Monnet and Maurice, 2006; Romieu et al., 2006, 2003). Accordingly, prolonged administration of supraphysiological amounts of PREG (500 mg/day) has been shown to decrease cravings triggered by both stress and cocaine cues in individuals diagnosed with cocaine use disorder (Milivojevic et al., 2022).

Beyond its biological targets, PREG levels and related metabolites have been found to be altered in patients with dopamine-relevant psychiatric conditions, including schizophrenia, mood disorders, and substance abuse. In two clinical trials investigating the adjunctive use of PREG in chronic schizophrenia patients, Marx et al., (2014), (2011), (2009) reported significant improvements in SANS scores (Scale for the Assessment of Negative Symptoms) when this neurosteroid was added to second-generation antipsychotics, compared to a placebo group. Subsequent research expanded these findings by further assessing schizophrenia symptoms in a larger patient cohort, under two different doses of PREG (low and high dose) added to the same antipsychotic medications. The low dose of PREG, but not the high dose, significantly reduced positive and extrapyramidal symptoms, as well as improved attention and working memory performance. Overall, PREG supplementation was well tolerated, with circulating levels of this neurosteroid significantly elevated in treated patients compared to their placebo counterparts (Ritsner, 2010).

Moreover, the prototypical antipsychotic clozapine has been found to markedly elevate PREG levels both in schizophrenia patients and rodent models, thus corroborating the involvement of this neurosteroid in the neurobiology of schizophrenia and the response to treatment. Accordingly, an increase in PREG/pregnanolone ratio has also been found in a cohort of bipolar depressed individuals with a history of cannabis use disorders, and PREG supplementation results in higher rates of depression remission compared to placebo. While there is currently no study documenting changes in PREG levels in individuals exposed to cannabis during pregnancy, it is significant to emphasize that animal models strongly suggest the potential therapeutic role of this neurosteroid in mitigating the negative impact of PCE (first hit) on dopamine system function. As such, it may contribute to fostering resilience against "second hits," such as acute exposure to THC or stress, which often lead to the development of dopamine-dependent psychiatric disorders.

1.8. Clinical relevance and limitations of 5 α R-related NaS in managing hyperdopaminergic-associated brain disorders

The recent approval of the synthetic analogue of AP, brexanolone, for the treatment of postpartum depression (PPD) has sparked renewed interest and momentum in the field of NaS, underscoring their clinical relevance and expanding their potential applications for psychiatric conditions. Marketed under the brand name ZULRESSO®, brexanolone stands as the first FDA-approved drug for PPD, offering a novel treatment option for women who do not respond adequately to conventional therapeutic interventions. Brexanolone exhaustively exemplifies both the risks and opportunities associated with NaS-based therapies in the clinical realm, as well as the need for careful consideration to attain optimal safety and efficacy profiles through this therapeutic strategy. For instance, brexanolone formulation requires intravenous administration over an extended period, typically ranging from approximately 60 to 90 hours, necessitating hospital admission and continuous patient monitoring to ensure the safe and effective delivery of the infusion. However, the desired rapid and enduring antidepressant properties of brexanolone are offset by its adverse effects, which include sedation, mental alterations, and the potential for loss of consciousness. Moreover, its administration may impact renal function, rendering it

contraindicated in patients with severe renal disease. Additionally, the cost of brexanolone treatment in the US may be prohibitively expensive, thus limiting access to this therapy for many individuals.

In response to these challenges, the development of a further FDA-approved drug in 2023, namely zuranolone, has been pursued. Zuranolone, an analogue drug built upon an orally available formulation, offers similar rapid antidepressant effects and longer duration of efficacy compared to brexanolone (30 days vs. up to 45 days) (Nashwan et al., 2024). Notably, zuranolone demonstrates superior efficacy, a more favorable safety profile, and fewer side effects compared to brexanolone, indicating that the oral administration route for NaS may maintain an optimal pharmacokinetic profile and therapeutic efficacy (Clayton et al., 2024; Deligiannidis et al., 2021). The dosing regimen of zuranolone involves a single daily oral dose, eliminating the need for 60 hours of infusions and hospital admission, thereby reducing patient non-adherence to treatment.

The rapid mechanisms of action of brexanolone and zuranolone align with those highlighted in this review regarding 5 α R-related NaS, thereby strongly suggesting that the exogenous administration of this class of NaS readily passes the BBB and immediately affects neuronal signaling. As mentioned earlier, the 5 α R-associated NaS AP and PREG exert negligible effects on canonical intracellular steroid receptors. However, the persisting effects observed in PDD patients under brexanolone and zuranolone treatment, well beyond the presence of these drugs in the brain, cannot rule out the contribution of genomic actions. Alternatively, the sustained activation of GABA_A receptor may mediate enduring structural and functional changes in neuronal plasticity through that are not yet fully understood. Likewise, in the hyperdopaminergic model of PCE, PREG rescues synaptic plasticity, mitigates deficits in dopamine neuron activity and restores behavioral phenotypes also 72 hours after the last administration, highlighting its potential to reprogram the mesolimbic dopamine system influenced by in utero THC exposure. Therefore, their ability to modulate dopaminergic signaling, along with their broader neuroprotective and neuroplastic effects, suggests they could have a unique multifaceted impact on psychiatric disorders characterized by acute symptomatic manifestations alongside underlying chronic pathophysiological processes (e.g. L-DOPA-induced dyskinesia in PD patients, tic manifestations in TS patients, and uncontrollable urges to gamble in impulse control disorders). However, further research is warranted to fully elucidate the mechanisms of action of this class of NaS to maximize their clinical application in treating dopamine-dependent psychiatric conditions.

The long-lasting effects shared by 5 α R-related NaS may overcome their well-known limitations stemming from poor bioavailability, short biological half-life, and rapid in vivo metabolism, which historically have hindered their clinical application. For instance, upon oral administration of PREG, high levels of this NaS can be detected in human samples, along with multiple related metabolites, including AP and its sulfated derivatives (Brown et al., 2014; Marx et al., 2014, 2009; Sripada et al., 2013). To address these limitations, synthetic PREG analogues have been developed with improved bioavailability and safer profiles compared to their parent molecule. One such analogue is pregnenolone-methyl-ether (PME, 3 β -methoxy-pregnenolone), which features a methylation at position 3 conferring resistance to conversion back to PREG or into other steroids and metabolites, both peripherally and centrally (Bianchi and Baulieu, 2012). Notably, PME readily crosses the rodent BBB following a single injection. Intriguingly, this compound seems to not have off-targets as it does not bind to several different neurotransmitter receptors (including NMDA and GABA-A) or transporters. Instead, it exerts biological activity on MAP2 and CLIP170, microtubule-associated proteins pivotal in microtubule dynamics and neuronal plasticity. Moreover, other PREG analogues have been developed in recent years. For instance, C3-C17 PREG analogs acting as CB1 signaling-specific inhibitors have been developed by INSERM and *Aelis Farma Biotech* (patent n. WO2014083068 A1) and are currently under investigation for CB1-related disorders (Haney et al., 2023), and for

other pathological conditions associated with aberrant endocannabinoid signaling (Vallée, 2016).

As previously discussed, a complementary approach to modify NaS signaling in the brain is offered by pharmacological modulation of the enzymatic machinery responsible for their synthesis and metabolism. Within the PREG to AP pathway, three critical enzymes, 3 α - and 3 β -HSD and 5 α R, can be targeted by indomethacin and trilostane, and finasteride (or dutasteride) respectively. While all these drugs efficiently inhibit their corresponding enzymes with various modes of competition against the endogenous substrate, only finasteride (and dutasteride) exhibit significant antidopaminergic activity in rodent models (Bortolato et al., 2008; Devoto et al., 2012; Frau et al., 2014, 2013). The robust preclinical findings obtained through these inhibitors were supported by human studies (Table 1). In the first investigation, finasteride demonstrated efficacy in reversing severe positive symptoms (delusions and florid hallucinations) and negative symptoms, as well as cognitive deficits in a male patient with chronic schizophrenia who did not respond to standard antipsychotic therapies (Koethe et al., 2008). Importantly, finasteride did not induce significant adverse effects, and upon discontinuation of the medication, the patient experienced a recurrence of psychotic symptoms, prompting him to request continuation of finasteride regimen (Nickel et al., 2008). However, placebo-controlled trials with adequate sample sizes are necessary to fully assess the potential therapeutic value of finasteride in patients with schizophrenia. Given the role of androgens and AP in the pathophysiology and clinical course of TS, 5 α R inhibitors might provide a therapeutic tool for this condition. Moreover, excess of dopamine in the striatum is thought to disrupt thalamo-cortical circuits in TS, resulting in physical and vocal tics that significantly affect patients' life quality (Branca and Bortolato, 2024). Interestingly, tic disorders are more predominant in males and exacerbated by external stressors, strongly suggesting the involvement of 5 α R-related NaS in their etiology. Moreover, dopamine agonists worsen tics, while dopaminergic antagonists dampen their severity (Sandor, 2003), especially through D1 receptor blockade (Gilbert et al., 2003). Considering these premises, finasteride was tested in adult male patients with TS. In two subsequent studies (Bortolato et al., 2007; Muroli et al., 2011), the administration of 5 mg/day of finasteride resulted in significant reductions of tic severity, as assessed by the Yale Tic Severity Scale. Importantly, finasteride showed limited side effects and good tolerability. Similar to what observed with schizophrenia patients, discontinuation of finasteride led to dramatic exacerbation of symptoms, which was mitigated by reinstating the 5 α R inhibitor (Bortolato et al., 2013).

In spite of the limited side effects and favorable tolerability profile of finasteride, clinical applicability of 5 α R inhibitors remains restricted. For instance, it is not feasible to use a drug that significantly interferes with androgen biosynthesis in TS patients, most of whom are children. Accordingly, concerns about the risk of reduced libido and sexual dysfunction have been raised in subsets of adult individuals undergoing finasteride treatment (Traish et al., 2015a, 2015b). Usually, sexual adverse events in patients taking finasteride may resolve either with continued treatment or upon discontinuation of the medication. However, recent reports highlight cases where symptoms such as reduced libido, erectile dysfunction, and orgasmic dysfunction, as well as psychological issues like depression, anxiety, and suicidal thoughts, persist even after finasteride therapy cessation (Giatti et al., 2024; Irwig, 2012; Traish, 2020; Traish et al., 2014). These persistent symptoms have been collectively termed as postfinasteride syndrome. The increased recognition of these issues prompted regulatory agencies, including the FDA, to update the labeling of finasteride and to include both the risks of depression and persistent sexual dysfunction.

Consequently, to be considered viable therapeutic options for psychiatric disorders, it is imperative to thoroughly investigate the neurobiological mechanisms underlying the actions of finasteride and other 5 α R inhibitors.

A very promising NaS-based therapeutic approach for mental

disorders involves the use of GABAA receptor modulating steroid antagonists (GAMSA). Notably, GABAA receptor activating compounds, such as AP and its analogs, can induce paradoxical negative psychiatric effects in susceptible individuals. These adverse effects may result from increased sensitivity to AP and/or significant fluctuations in its levels under various physiological and pathological conditions, including the menstrual cycle, pregnancy, postpartum periods, and hepatic encephalopathy (Bäckström et al., 2015). For example, in premenstrual dysphoric disorder (PMDD), a subgroup of women exhibits a spectrum of psychiatric symptoms (irritability, depressed mood, aggression, and emotional lability) correlating with AP level rise following ovulation at the beginning of the luteal phase. The effects of AP can be specifically blocked by its isomer, isoallopregnanolone (Sepranolone; UC1010, 3 β -OH-5 α -pregnan-20-one), as this GAMSA does not interfere with the actions of endogenous GABA or other GABAA agonists, such as benzodiazepines and barbiturates (Lundgren et al., 2003). In two subsequent clinical trials, Sepranolone has shown promising results in reducing PMDD symptoms compared to placebo (Bäckström et al., 2021; Bixo et al., 2017), including improvements in mood symptoms, distress, irritability, and physical symptoms. Notably, the timing of administration appears to be crucial, as its efficacy is most pronounced when AP levels reach their peak in the brain. Therefore, since Sepranolone has demonstrated good safety and tolerability in women, GAMSA can be a potential alternative or a complementary medication to 5 α R inhibitors for managing psychiatric disorders characterized by supraphysiological brain AP levels.

1.9. Conclusions: are NaS on the route to personalized neuropsychiatric therapy?

The growing interest in precision medicine strategies and the effort to integrate biological markers within the neuropsychiatric field reflects a fundamental shift in our approach to understanding and treating mental diseases. This shift stems from a deepening recognition of the intricate complexity and heterogeneity inherent in these conditions. As such, there is an urgent need to tailor treatments targeting unique (epi) genetic and neurobiological profiles of each individual. Presently, psychiatric diagnosis and treatment primarily rely on symptomatic presentation, often overlooking the underlying psychobiological mechanisms and the intricate interplay between genetic predispositions and environmental influences on the trajectory of these disorders.

To overcome these limitations, the National Institute of Mental Health has proposed a novel translational framework (Research Domain Criteria, RDoC) aimed at circumventing the challenges posed by symptom-based diagnostic classifications in neuropsychiatric disorders. This framework posits a complementary approach that integrates observable and measurable behavioral (endo)phenotypes within the functional domains of emotion and cognition, underpinned by related neurobiological mechanisms. In this context, some of the findings outlined herein collectively highlight how NaS associated with the 5 α R pathway are particularly suited for addressing hyperactivity of the mesolimbic dopamine system (neurobiology) that typically manifests by information processing deficit, recently recognized as endophenotype of RDoC sensorimotor domain. Notably, impairments in sensorimotor gating are consistently observed across various psychiatric conditions underpinned by aberrant function of mesolimbic dopamine signaling. Moreover, insights from animal models suggest that both the neurobiological underpinnings and behavioral outcomes that characterize these disorders are influenced by environmental perturbations, emphasizing the need for a comprehensive understanding of the complex interplay among genetic, neurobiological, and environmental factors. Once again, the PCE animal model provides by maternal cannabis exposure unveils in offspring an endophenotype of sensory information processing deficits arising from hyperdopaminergic states—an intermediate phenotype that can be ameliorated through PREG administration during preadolescence.

Consequently, the integration of NaS into this framework is particularly intriguing due to their involvement in modulating neurobiological pathways implicated in major psychiatric conditions, and evidence suggesting that they may address specific endophenotypes associated with hyperactivity of the mesolimbic dopamine system might be promising. Nonetheless, while the potential of NaS in personalized therapy is exciting, it is noteworthy to acknowledge that further research is needed to understand their mechanisms of action, optimize treatment protocols, and establish their utility as complementary biomarkers for patient stratification and monitoring. Overcoming these challenges is paramount to fully utilize NaS in clinical practice with safety and effectiveness.

Search strategies

The present review employed two primary databases (PubMed and Elsevier Embase) to thoroughly investigate the most pertinent preclinical and clinical literature regarding the impact of NaS on dopamine-related neuropsychiatric disorders through the involvement of 5 α reductase pathway. The systematic analysis of the international literature was conducted in accordance with PRISMA guidelines, with adaptations for preclinical investigations. The databases were used to search articles published between 1982 and 2024, using the following keywords: “neurosteroids”, “neuroactive steroids”, “allopregnanolone”, “progesterone”, “pregnenolone”, “pregnanolone”, “sulphated neurosteroids”, “sulphated neuroactive steroids”, “steroid-PAMs”, “GAMSA” AND “dopamine”, AND “rodents”, AND “mouse”, AND “rat” AND “human” AND “patient”. 239 were included in the present work, and duplicates and unrelated manuscripts were excluded.

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