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Stress and drug abuse-related disorders: The promising therapeutic value of neurosteroids focus on pregnenolone-progesterone-allopregnanolone pathway

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ABSTRACT

The pregnenolone-progesterone-allopregnanolone pathway is receiving increasing attention in research on the role of neurosteroids in pathophysiology, particularly in stress-related and drug use disorders. These disorders involve an allostatic change that may result from deficiencies in allostasis or adaptive responses, and may be downregulated by adjustments in neurotransmission by neurosteroids. The following is an overview of findings that assess how pregnenolone and/or allopregnanolone concentrations are altered in animal models of stress and after consumption of alcohol or cannabis-type drugs, as well as in patients with depression, anxiety, post-traumatic stress disorder or psychosis and/or in those diagnosed with alcohol or cannabis use disorders. Preclinical and clinical evidence shows that pregnenolone and allopregnanolone, operating according to a different or common pharmacological profile involving GABAergic and/or endocannabinoid system, may be relevant biomarkers of psychiatric disorders for therapeutic purposes. Hence, ongoing clinical trials implicate synthetic analogs of pregnenolone or allopregnanolone, and also modulators of neurosteroidogenesis.

1. Introduction: 20-years overview and new insights

1.1. Neurosteroids, neuroactive steroids, and neuromodulators concepts

The innovative premise that steroids might be synthesized *de novo* "within the brain for the brain" (and so-called neurosteroids) (Baulieu, 1997) has been demonstrated long over the 20 last years. As well, the term neuroactive steroids, coined by Paul and Purdy (Paul and Purdy, 1992), referred to steroids that can be synthesized in the brain, or by endocrine glands, and then reach the brain through the bloodstream and act rapidly on brain excitability at membrane level (McEwen, 1991; Rupprecht, 2003; Rupprecht and Holsboer, 1999). Evidence of neurosteroidogenesis has been provided by experimental research in non-mammalian and mammalian brain, as well as in the human brain and CSF. Moreover, synthesis of steroids occurs in the spinal cord and peripheral nervous system (Giatti et al., 2015; Melcangi et al., 2011; Mensah-Nyagan et al., 2008; Patte-Mensah et al., 2006) and new sites of steroidogenesis in muscle, adipocytes, intestine, and retina have been most recently revealed (Bélanger et al., 2002; Bouguen et al., 2015; Li et al., 2014; MacKenzie et al., 2008; Tchernof et al., 2015).

Besides, the common postulate of the action of steroid with classical steroid nuclear receptors was reconsidered, and several non-genomic targets were discovered. Evidences have shown that neurons and glia can produce neurosteroids which locally and differentially modulate neuronal activity by binding with various membrane neurotransmitter receptors, mainly γ-aminobutyric acid ($GABA_A$) (Belelli and Lambert, 2005; Lambert et al., 2009) and the glutamate N-methyl D aspartate (NMDA) (Irwin et al., 1994; Sedlácek et al., 2008), and hence state those steroids as autocrine-paracrine neuromodulators of synaptic signal transduction (Compagnone and Mellon, 2000; Shibuya et al., 2003). Two families of steroids emerged with a balance between inhibitory and excitatory brain inputs (Lambert et al., 2009; Paul and Purdy, 1992; Rupprecht, 2003). Amongst the inhibitory neuromodulators, the most studied remains allopregnanolone, since it is a potent positive allosteric modulator of $GABA_A$ receptor that acts with high potency at known binding sites of $GABA_A$ receptors (Hosie et al., 2006), resulting in a rapid and physiological relevant neuromodulatory control on brain excitability. For a long time and even now some neurosteroids have been considered as *pro*neurosteroids, such as pregnenolone and dehydroepiandrosterone (DHEA), given that they do not modulate $GABA_A$ or NMDA receptors, and in contrast, can be metabolized in active downstream steroids.

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1.2. From inactive to active steroid concepts using metabolic profile analysis

The development of steroid research incorporates the idea of analyzing metabolites and not focusing solely on one steroid of interest. The concept that individuals might have a “metabolic profile” in their biological fluids was first introduced in the '40s, and then revealed in the '70s using gas chromatography-mass spectrometry by measuring compounds present in human urine and tissue extracts (Novotny et al., 2008). Advanced methods of quantification, like the state-of-the-art mass spectrometry coupled to chromatography methods (Griffiths and Wang, 2009) allow to measure -with high sensitivity, reproducibility and precision- low concentrations of numerous steroids within individual biological samples extracted from small rodent brain regions (Concas et al., 2000; Griffiths et al., 1999; Higashi et al., 2009, 2005; Liere et al., 2017, 2000; Liu et al., 2003; Maldonado-Devincci et al., 2014b, 2014a; Marx et al., 2006b, 2006a, 2003; O'Dell et al., 2004; Park et al., 2017; Porcu et al., 2003; Uzunov et al., 1996; Vallée et al., 2014, 2010, 2000) and in human plasma, serum or cerebrospinal fluid (Caruso et al., 2015; George et al., 1994; Marx et al., 2006c; Melcangi et al., 2013; Nordström et al., 2006; Rasmusson et al., 2006; Ritsner et al., 2007; Romeo et al., 1996; Uzunova et al., 1998; Weill-Engerer et al., 2002). Determination of steroids metabolome may, therefore, serve for laboratory diagnosis of psychiatric disorders (Bicikova et al., 2013; Melcangi and Mensah-Nyagan, 2008). Indeed, comparative profiling analyses between health and disease states can reveal biomarkers as indicators of alterations in the biological process resulting from a disease or its progression.

This innovative approach made possible to establish new insights for the steroids previously defined as inactive. One of the most obvious examples is illustrated with pregnenolone, synthesized from cholesterol, and the precursor of all other steroids.

1.3. Focus on Pregnenolone-Progesterone-Allopregnanolone (PPA) pathway

Here we review preclinical and clinical evidence supporting a role for neurosteroids as potential biomarkers and therapeutic targets in both stress and drug abuse disorders. According to the most commonly published data and the new insights in neurosteroid research, this review will focus on Pregnenolone-Progesterone-Allopregnanolone (PPA) pathway. Pregnenolone is metabolized directly to progesterone, which includes allopregnanolone as one of its active metabolites. The intermediate metabolite 5α-dihydroprogesterone can be reversibly converted in 3α, 5α or 3β, 5α pregnanolone (Fig. 1). The main molecular targets of pregnenolone, progesterone and allopregnanolone involve the CB1 cannabinoid, progesterone and $GABA_A$ receptors, respectively. Although treatment with a high dose of pregnenolone induced an increased in allopregnanolone levels (Sripada et al., 2013), a specific role for pregnenolone will be as well highlighted in the pathophysiology of stress and drug abuse disorders. Preclinical and clinical data, along with the underlying mechanisms will focus on stress-related disorders involving anxiety, major and post-partum depression, premenstrual syndrome and post-traumatic stress disorders. Data on disorders related to alcohol and cannabis abuse, including psychoses such as schizophrenia, will also be highlighted. Finally, we will emphasize a new biomarker axis described, the interactions between neurosteroids and endocannabinoids.

2. Stress and drug abuse-related disorders

2.1. Stress-related disorders

The concept of stress response has evolved from the mechanistic view of homeostatic feedback regulation to dynamic models of adaptive feed-forward regulatory processes (Tonhajzerova and Mestanik, 2017). Then, the current model of stress response involved the concepts of allostasis and allostatic load, including the behavioral and physiological responses to the stressor, which promote adaptation (allostasis) but also contribute to pathophysiology (allostatic load/overload) when overused and dysregulated (McEwen, 2017). The concept of allostasis includes an adaptive or coping strategy with a feed-forward regulation, like an anticipatory stress response. Coping strategies include the possibility to control the stressor in case of acute stress condition or to habituate and predict the occurrence of repeated stress. Repeated stressors, especially when stress frequency is random, leading to unpredictable stress, constitute a substantial risk factor for the subsequent onset of stress-related disorders (Adler and Rehkopf, 2008; Kendler et al., 1999; Kessler, 1997; Southwick et al., 2005). Among them, one can have a non-exhaustive list of negative impacts on the body, the mind, emotions including anxiety and depression, and behaviors that can lead to substance abuse (Cox and Olatunji, 2016; Eser et al., 2006; Gradus, 2017; McEwen et al., 2015; Richter-Levin and Xu, 2018).

Detailed knowledge of the organism's regulatory pathways to stress may offer new targets for therapy of stress-related diseases. Physiological responses to stress comprise a cascade of adaptive neuroendocrine events mediated by stress systems that are designed to counteract stress and restore homeostasis or establish allostasis. Although the hypothalamic-pituitaryadrenal (HPA) system has been well described amongst the stress mediators, growing evidence suggests a role for neurosteroids as essential modulators of the nervous system functioning, especially for homeostasis and/or allostasis stability and regulatory stress-related functions (Barbaccia et al., 2001; Girdler and Klatzkin, 2007; Gunn et al., 2015; Longone et al., 2008).

2.2. Drugs abuse related disorder

2.2.1. Common substance abuse features

Substance abuse or addiction is described in the Diagnostic and statistical manual of mental disorders (American Psychiatric Association, DSM-5 2013) through several stages, including acute intoxication, harmful use, dependence syndrome, withdrawal state (with or without delirium), amnesic syndrome, residual and late-onset psychotic disorders, other mental and behavioral disorders. The development of drug addiction progresses along a continuum from acute drug use to compulsive use, and drug-seeking behavior and addiction may be defined as a chronic illness characterized by compulsive drug seeking and use, despite the continued presence of negative personal health and social consequences. The use of psychoactive substances affects brain functions resulting in alterations of a broad spectrum of life-being senses, including the vision, hearing, taste and smell, as well as other sensory modalities such as temperature, proprioception, pain, balance and equilibrioception, sensation of hunger and sexual stimulation. Moreover, it may be associated with neuropsychological deficits in mechanisms related to motivation, emotion, memory and executive functions (Fernández-Serrano et al., 2010). Then, alterations of these functions might interfere with the daily cognitive performance impacting on the quality of life, but also affect the core feature of addiction processes. Addiction occurs because drugs of abuse can take control of normal brain reward circuits, including the mesolimbic dopamine system that provides reinforcement of behaviors related to survival (Le Moal and Simon, 1991). Hence, dopamine (DA) neurons located in the ventral tegmental (VTA), projecting mainly to the nucleus accumbens (NAc) and also to the prefrontal cortex are involved in rewarding properties and reinforcing processes of natural stimuli (such as food) as well as of drugs of abuse (Di Chiara and Imperato, 1988). All addictive drugs trigger dopamine release from VTA neurons, indicating a shared, common brain mechanism by which multiple different drugs of abuse may shape behavior (Di Chiara and Bassareo, 2007; Nestler, 2005).

Like in stress-related disorders, allostasis and allostatic load are taking place in drug abuse and are important features involved in substance use disorders, such as cannabis use disorders (CUD) and alcohol use disorders (AUC) (George et al., 2012; Koob and Schulkin, 2018).

2.3. Cannabis use disorders (CUD)

Cannabis is one of the most increasing illicit (or legalized in some countries) drugs used and in Europe, and it is the most widely reported

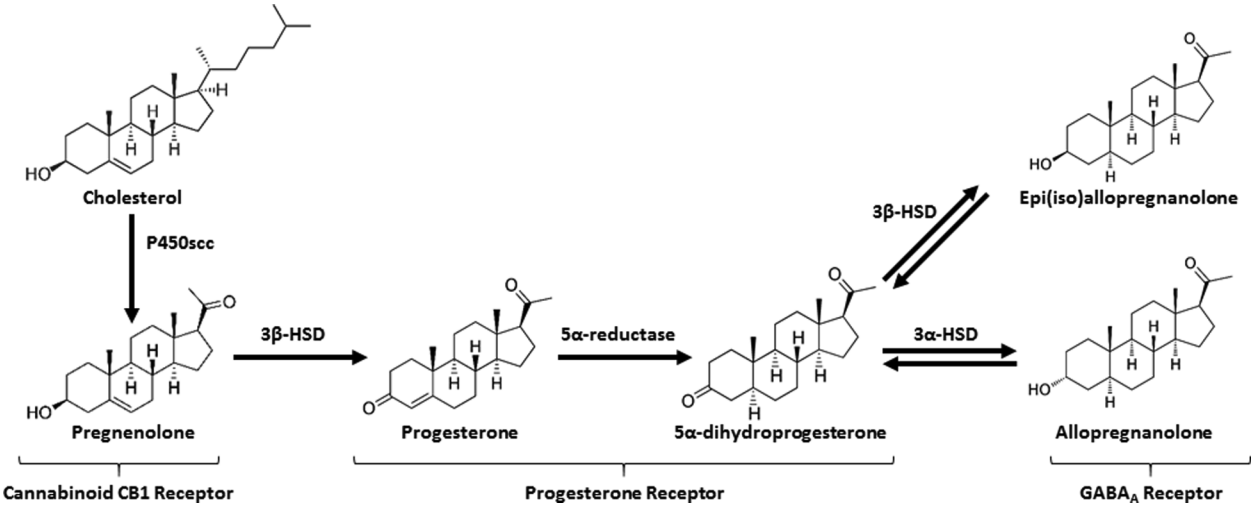

Fig. 1. Biosynthesis and molecular targets of the PPA pathway. The cholesterol, inside the mitochondrion is converted in pregnenolone by the cytochrome P450scc. The 3β-hydroxysteroid dehydrogenase (3β-HSD) and 5α-reductase enzymes convert pregnenolone in progesterone and 5α-dihydroprogesterone, respectively. The 3α-hydroxysteroid dehydrogenase (3α-HSD) and 3β-hydroxysteroid dehydrogenase (3β-HSD) enzymes regulate the chemical equilibrium of the conversion of 5α-dihydroprogesterone in allopregnanolone (3α,5α-tetrahydroprogesterone) and epiallopregnanolone (or isoallopregnanolone; 3 β,5α-tetrahydroprogesterone), respectively. The main molecular targets involve membrane receptors for pregnenolone and allopregnanolone, and the intracellular progesterone receptor for progesterone and 5α-dihydroprogesterone, as well as for allopregnanolone when converted back to 5α-dihydroprogesterone (Rupprecht et al., 1993). Pregnenolone can bind to a specific allosteric site and modulate the cannabinoid CB1 receptor signaling (Vallée et al., 2014), and allopregnanolone can bind the GABA$_A$ receptor on two different transmembrane sites (Hosie et al., 2006), modulating its activity.

illegal drug used amongst people entering in specialist addiction services (EMCDDA|European Drug Report, 2015). Approximately 9% of those who initiate cannabis use develop cannabis use disorders (CUD). Over the past two decades, the increased occurrence and severity of symptoms are mirroring the rising cannabis potency, and hence induced an increased demand for treatment for CUD (Freeman et al., 2018). Moreover, patterns of cannabis use are changing and expanding due to legalization, the availability of synthetic analogs mix (often with high potency) and cannavaping, as well as an emphasis on the potential therapeutic effect of the nonpsychotic ingredients of cannabis.

Cannabis produces its psychoactive effects in the brain, via its main component Δ^9-tetrahydrocannabinol (THC), which binds to the type-1 cannabinoid (CB1) receptors. CB1 localization in the brain is mainly related to motor and reward systems (Herkenham, 1992). Also, evidence showed a large distribution of CB1 in many brain areas, including the cortex, hippocampus, amygdala, basal ganglia outflow tracts, and cerebellum, that corresponds to the most prominent behavioral effects of cannabis and THC (Mackie, 2005). Acute reinforcing effects of THC involving CB1 have been reported in studies of brain stimulation reward, place preference, and intravenous self-administration (Gardner et al., 1988; Lepore et al., 1996, 1995). Moreover, studies in mice and rats have shown intravenous self-administration of a synthetic THC analog and highly potent CB1 agonist (Lefever et al., 2014; Martellotta et al., 1998; Mendizábal et al., 2006; Vallée et al., 2014) and intravenous self-administration of THC in monkeys (Tanda et al., 2000). Finally, selective CB1 antagonists precipitate a withdrawal syndrome in cannabinoid dependent animals (Fattore et al., 2001; Maldonado and Rodríguez de Fonseca, 2002). The overstimulation of CB1 receptors by THC switches them from their physiological roles, such as regulating food intake, metabolism, cognitive processes, and pleasure, and hence triggers a reduction in memory abilities, motivation and gradually leads to dependence. Therefore, heavy long-term cannabis use is associated with an increased risk of mental disorder, including psychosis, addiction, depression, suicidality, cognitive impairment, and motivation (Di Forti et al., 2014; Volkow et al., 2016).

Many of the reinforcing effects of THC are mediated by the mesocorticolimbic dopamine system (Maldonado and Rodríguez de Fonseca, 2002; Manzanares et al., 2018). Supporting the addictive effects of cannabis and THC, animal studies have shown that the distribution of CB1 receptors in the brain parallels the dopaminergic receptors, with high concentrations in the basal ganglia and hippocampus, although the highest concentrations of cannabinoid receptor are found in the cerebellum. Also, human imaging techniques have shown high densities receptors in the frontal cortical areas (Burns et al., 2007). Cannabis use induced the production of DA in the NAc and cell firing in the VTA through the action of THC on CB1 receptors in glutamatergic and GABAergic neurons associated with the NAc and VTA (Robbe et al., 2001). Also, in vivo microdialysis shows that acute THC or CB1 agonist increases dopamine efflux in the prefrontal cortex, striatum, and NAc (Bloomfield et al., 2016; Fadda et al., 2006; Lecca et al., 2006; Vallée et al., 2014). Moreover, THC exposure in rats reduces the medial prefrontal cortex dopamine turnover, involved in reward learning and decision-making (Verrico et al., 2003).

2.4. Alcohol use disorders (AUD)

The National Institute on Alcohol Abuse and Alcoholism (NIAAA) defines alcohol use disorders (AUD) as a chronic relapsing brain disease characterized by compulsive alcohol use, loss of control over alcohol intake, and a negative emotional state when not using. An estimated 15 million people in the United States had AUD in 2015, including a proportion of 75% men and 25% women. Adolescents can be diagnosed with AUD as well, and in 2015, an estimated 623,000 adolescents ages 12–17 had AUD in the United States. The prevalence of AUD has been estimated at 3.4% among people 18–64 years of age in Europe (women 1.7%, men 5.2%), resulting in close to 11 million affected people (Rehm et al., 2015).

To be diagnosed with AUD, individuals must meet certain criteria outlined in the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 2013). DSM-5 defined AUD as a maladaptive pattern of substance use leading to clinically significant impairment or distress, as manifested, depending on the severity, by 2 or more out of 11 of the DSM-5 criteria, occurring at any time in the same 12-month period. The DSM-5 criteria include a large amount of alcohol taken, unsuccessful efforts to control alcohol use, as well as a continuous alcohol intake despite adverse effects. Illustrations of negative effects are a failure in work, school or home obligations, a reduction in social, occupational, or recreational activities, and persistent or recurrent physical or psychological problems. Evidence have implicated dopamine contribution in the mediation of alcohol reinforcing actions (Koob and Le Moal, 2001), as well as the GABAergic system.

Indeed, at low intoxicating and high anesthetic doses alcohol can bind with GABA receptors (Frye and Breese, 1982; Gravielle, 2018; Olsen, 2018). Accordingly, GABAergic antagonists reverse many of the behavioral effects of alcohol that are associated with intoxication. Therefore, medications that act on GABA receptors are one of the potential pharmacological options for AUD (Farokhnia et al., 2019).

2.5. Stress and drugs abuse interplay

The interactions between stress and vulnerability to addiction have been extensively described, and a schematic model of stress effects on addiction has been illustrated (Sinha, 2008). Apart from genetic and familial factors, vulnerability factors for drugs abuse may include adverse events such as trauma and chronic stress combined with negative emotionality, poor executive function, and trait impulsivity. In line, evidence has shown that stressful life experiences and traumatic stress may be associated with increased substance abuse and comorbidity has been reported between stress-related disorders and substance use disorders (Koob and Kreek, 2007; Koob and Schulkin, 2018). For instance, stress-related factors increase cannabis or alcohol use (Bremner et al., 1996; Lipschitz et al., 2003; Schiff et al., 2007; Vlahov et al., 2004; Wills et al., 2001; Windle and Wiesner, 2004), and it has been reported the co-occurrence of cannabis or alcohol use with symptoms of psychiatric disorders, such as anxiety, depression, and schizophrenia (Bonn-Miller et al., 2007; Eser et al., 2008; Lev-Ran et al., 2012; Vujanovic et al., 2019). Accordingly, amongst the several pharmacotherapies for the treatment of AUD, antidepressant medications, such as the selective serotonin reuptake inhibitors (SSRIs), are considered as first-line pharmacologic treatments (DeVido and Weiss, 2012). Moreover, a high risk for the development of affective disorders is associated with a high risk for substance use disorders, suggesting common substrates for both disorders (Polter and Kauer, 2014). As an illustration, the mesolimbic dopamine system is a crucial player in the brain's reward system, and dysregulation of this system is involved in both depression and addiction (Koob and Kreek, 2007; Nestler and Carlezon, 2006; Piazza and Le Moal, 1996; Polter and Kauer, 2014).

Animal models have validated the interaction between stress and drug abuse. Acute and chronic stress can increase self-administration of drugs and reinstate drug-seeking, including alcohol; and early life stress can as well impact on drug intake later in life (Roman and Nylander, 2005). Furthermore, stress can increase drug craving for cannabis (Hyman and Sinha, 2009; McRae-Clark et al., 2011) and alcohol (Clay et al., 2018) in humans, although discrepancies have been reported for alcohol (Thomas et al., 2011).

3. Preclinical evidence between the pregnenolone-progesterone-allopregnanolone pathway and stress-related disorders

Changes in neurosteroids brain content play an important role in the modulation of the emotional state as well as in the homeostatic and/or allostatic mechanisms that counteract the alteration of neuronal activity elicited by stress. One of the most reported neurosteroids involved the potent positive modulator of $GABA_A$ receptors, allopregnanolone since GABAergic signaling plays a critical role in the neurobiological effects of stress (Bains, 2014; Maguire, 2019; Purdy et al., 1991). Moreover, chronic stress can modulate the subunits combination of $GABA_A$ receptors, hence increasing the efficacy of allopregnanolone on $GABA_A$ receptors leading to an amplified inhibition of GABA response by allopregnanolone (Locci and Pinna, 2017). Then, alterations in allopregnanolone and GABAergic signaling are potential contributing factors to neuroendocrine dysfunction and vulnerability to stress and stress-related disorders (Gunn et al., 2011). Accordingly, preclinical evidence showed that acute and chronic stress modulate neurosteroid levels, including pregnenolone-progesterone-allopregnanolone (PPA) pathway, and that alterations in pregnenolone and allopregnanolone concentrations may impact stress responses and stress-related disorders.

From the pioneer study of Purdy and collaborators in the 90's, a bunch of studies have described an increase in allopregnanolone levels in plasma and brain of rodents following various acute stress (forced swimming, CO2 inhalation, footshock, fixation, restraint stress) (Barbaccia et al., 1994, 1996a, 1996b, 1997; Biggio et al., 2007; Maldonado-Devincci et al., 2014a; Park et al., 2017; Purdy et al., 1991; Vallée et al., 2014, 2000), and fewer studies have reported an increase in pregnenolone levels in brain of rodents (Barbaccia et al., 1996a; Park et al., 2017; Vallée et al., 2014, 2000). Furthermore, mild to severe chronic stress paradigms, such as repeated restraint stress, forced swimming test or social isolation, decreased allopregnanolone (Guidotti et al., 2001; Khisti et al., 2000; Serra et al., 2007; Vallée et al., 2014) and pregnenolone (Vallée et al., 2014) levels. Furthermore, an acute stress challenge in chronically stressed animals increases pregnenolone brain levels (Vallée et al., 2014). It should be noted that the alterations in pregnenolone were specific to brain rodents and were almost unaltered or less altered in plasma and that the brain-to-plasma ratio was much higher for pregnenolone than for allopregnanolone (Park et al., 2017; Vallée et al., 2014), suggesting a role in neurosteroidogenesis, and in particular in brain pregnenolone in stress responses. Simultaneously, acute swim stress in rats did not induce changes in circulating concentrations of pregnenolone, which were significantly higher in the brain and more pronounced in females than in males, further suggesting gender-specific expression of neurosteroid enzymes in the brain in response to stress (Sze et al., 2018).

In addition, the major brain alterations involving pregnenolone were found in an animal model of unpredictable chronic stress that reached validity for the depression-like pattern suggesting that endogenous brain pregnenolone may be a significant endogenous substrate involved in the depression phenotype (Vallée, 2014). Similarly, a parallel has been established between the increase in pregnenolone levels in the hippocampus and frontal cortex of mice and the antidepressant effect of the systemic treatment with the competitive 3β-hydroxysteroid dehydrogenase (3β-HSD) inhibitor trilostane (Espallergues et al., 2012). As well, the administration of the antipsychotic neuroleptics (olanzapine, haloperidol or clozapine) in combination or not with antidepressants (such as selective serotonin reuptake inhibitors, SSRIs), clinically effective in bipolar depression (Tohen et al., 2003), produce elevations in hippocampal and cortical levels of pregnenolone and allopregnanolone in rats (Higashi et al., 2009; Khisti et al., 2002; Marx et al., 2006a, 2006b, 2003, 2000). Hence, one mechanism of action of SSRIs may involve both an enhanced sensitivity of $GABA_A$ receptors and the formation of allopregnanolone.

These data support the antipsychotic-like and antidepressant-like profile of allopregnanolone (Khisti et al., 2002; Shirayama et al., 2011; Ugale et al., 2004). Allopregnanolone can increase the GABAergic tone by its action at the $GABA_A$ receptors, leading to a behavioral profile similar to that of dopamine receptor antagonists, such as the neuroleptic haloperidol (Khisti et al., 2002). Furthermore, allopregnanolone administration can reduce stress response and triggers anxiolytic-like effects in several animal models (Akwa et al., 1999; Engin and Treit, 2007; Frye and Rhodes, 2006; Martín-García and Pallarès, 2005; Picazo and Fernández-Guasti, 1995; Reddy and Kulkarni, 1997; Rodgers and Johnson, 1998; Wieland et al., 1995). Moreover, 3β-methylated analog of allopregnanolone can counteract PTSD-like behavior induced by social isolation in mice (Pibiri et al., 2008; Pinna and Rasmusson, 2014). Animal studies have also reported that treatment with pregnenolone modulates anxiety and depression-like behaviors (Eser et al., 2008; Melchior and Ritzmann, 1994; Vallée et al., 2014). Moreover, pregnenolone administration can rescue cognitive impairments in the dopamine transporter knockout mouse model that mirrors certain symptoms of patients with schizophrenia (Wong et al., 2012).

Overall, preclinical studies have demonstrated that the pregnenolone-progesterone-allopregnanolone pathway is part of a key cerebral steroidogenesis pathway involved that mediates the allostasis mechanisms of stress response as well as the allostatic load that occurs in stress-related disorders. Although allopregnanolone remains the primary target, the evidence points to a role for pregnenolone as well.

Table 1
Brief overview of animal research evidence on the role of the PPA pathway in stress related disorders, alcohol intake and cannabis intoxication.

Disorder	Biomarker	Treatment	Effect on PPA	Behavioral response
Stress related disorders				
Acute stress	↑$ALLO_{brain}$[1]; ↑$PREG_{brain}$[1]; ↑$PROG_{brain}$[1]			
Mild to severe chronic stress	↓$ALLO_{brain}$[2]; ↓$PREG_{brain}$[2]			
Depression-like behaviors	↓$PREG_{brain}$[3]	Trilostane[4]	↑PREG[4]	antidepressant[4]
		SSRIs[5]	↑PREG[5]	antidepressant[5]
		ALLO[6]	N.R.	antidepressant[6]
Anxiety-like behaviors	↓$PREG_{brain}$[6,8]; ↓$ALLO_{brain}$[6,8]	ALLO[6]	N.R.	anxiolytic[7]
		PREG[8]	N.R.	anxiolytic[8]
Alcohol intake				
Acute intake	↑$ALLO_{brain,\ plasma}$[9]; ↑$PREG_{brain,\ plasma}$[10]			
Chronic intake	↓$ALLO_{brain,\ plasma}$[11]; ↑$ALLO_{CSF,\ brain}$[12]	ALLO[13]	N.R.	↓low doses; ↑high doses alcohol intake[13]
	↓$PREG_{brain,\ plasma}$[11]	3-methoxy PREG[14]	N.R.	↓alcohol intake[14]
Cannabis intoxication				
THC acute intake	↑$PREG_{brain}$[15]	PREG[15]	↑PREG[15]	rescue of THC-induced behaviors[15]
WIN self-administration	↑$PREG_{brain}$[15]	PREG[15]	↑PREG[15]	↓WIN seeking[15]
Psychotic-like behavior	N.R.	PREG[16]	N.R.	rescue of psychotic-like behaviors[16]

N.R., Not Reported; ↑ increase; ↓ decrease.
References: [1]Barbaccia et al., 1994, 1996a, 1997; Vallée et al., 2000; [2]Guidotti et al., 2001; Khisti et al., 2000; Serra et al., 2007; Vallée et al., 2014; [3]Vallée et al., 2014; [4]Espallergues et al., 2012; [5]Tohen et al., 2003; [6]Khisti et al., 2002; Shirayama et al., 2011; Ugale et al., 2004; [7]Akwa et al., 1999; Engin and Treit, 2007; Frye and Rhodes, 2006; Martín-García and Pallarès, 2005; Picazo and Fernández-Guasti, 1995; Reddy and Kulkarni, 1997; Rodgers and Johnson, 1998; Wieland et al., 1995; [8]Eser et al., 2008; Melchior and Ritzmann, 1994; Vallée, 2016; [9]Biggio et al., 2007; O'Dell et al., 2004; Sanna et al., 2004; VanDoren et al., 2000; Sanna et al., 2004; Tokuda et al., 2011; [10]O'Dell et al., 2004; [11] Beattie et al., 2017; [12]Maldonado-Devincci et al., 2016; Serra et al., 2006; [13]Ford et al., 2005b; Morrow et al., 2001; [14]Koob et al., 2018; [15]Vallée et al., 2014; [16]Busquets-Garcia et al., 2017.

4. Preclinical evidence for PPA pathway and drug abuse-related disorders

The main findings described in this review on animal research are summarized in Table 1.

4.1. Interactions between alcohol and PPA pathway of neurosteroids

Most animal studies on alcohol-induced alterations of neurosteroids have focused on allopregnanolone based on their common neurobiological substrate, $GABA_A$ receptors, but some studies have also reported alterations in pregnenolone. For instance, in rats, acute alcohol intake can increase allopregnanolone (Biggio et al., 2007; O'Dell et al., 2004; Sanna et al., 2004; VanDoren et al., 2000) and pregnenolone (O'Dell et al., 2004) levels. However, in mice, some studies have not shown an alteration of allopregnanolone with acute alcohol (Gabriel et al., 2004; Porcu et al., 2014), indicating some discrepancies depending on the animal model studied. Although some studies have failed to find an effect of alcohol on brain neurosteroids in adrenalectomized and gonadectomized rats (O'Dell et al., 2004), others have still detected an increase of allopregnanolone in the hippocampus (Sanna et al., 2004; Tokuda et al., 2011). Moreover, alcohol can affect cellular immunostaining of allopregnanolone within the brain of rats (Cook et al., 2014a), further illustrating a specific effect of alcohol on neurosteroidogenesis independently of peripheral sources of steroid. In chronic ethanol exposure conditions, long-term voluntary ethanol consumption differentially modulated allopregnanolone immunoreactivity in monkey brain, with decreased immunoreactivity in the amygdala (Beattie et al., 2017), and increased immunoreactivity in the hippocampus (Beattie et al., 2018). Additionally, chronic intermittent ethanol exposure and withdrawal alter allopregnanolone in cortical and limbic brain regions of mice (Maldonado-Devincci et al., 2014b).

It has been established that the effects of alcohol on neurosteroids may be related to stress. Chronic ethanol exposure and withdrawal can indeed be considered as potent stressors that can have an impact on subsequent reaction to alcohol and stress (Heilig et al., 2010). For instance, repeated ethanol exposure and withdrawal induced persistent adaptations of stress response in a rat model of ethanol dependence. Also, severe chronic stress, such as social isolation, can enhance the effect of ethanol on allopregnanolone (Biggio et al., 2007) and chronic intermittent ethanol exposure can modulate stress effects on allopregnanolone in mice (Maldonado-Devincci et al., 2016). In accordance with these data, modulating the composition of $GABA_A$ subunits by stress in a social isolation model in rats can lead both to improved allopregnanolone synthesis in the brain and to greater alcohol effectiveness on $GABA_A$ receptor functions and associated behaviors (Serra et al., 2006).

In addition, anxiolytic effects of voluntary ethanol consumption were observed after intrahippocampal allopregnanolone administration in rats (Martin-García et al., 2007), confirming that allopregnanolone-induced positive modulation of hippocampal $GABA_A$ receptors can be an important neurobiological target for reducing chronic alcohol consumption. In support of that, *in vitro* experiments showed that the increase in $GABA_A$ receptor-mediated mIPSCs in CA1 pyramidal neurons in hippocampal slices by ethanol was reversed by finasteride, an inhibitor of the synthesis of allopregnanolone. The mesolimbic dopamine system could also be a brain target for allopregnanolone to modulate the action of alcohol, as demonstrated by the potentiation of the biphasic effect of acute ethanol on mesocortical dopamine content in rats following an increase of the cortical content of allopregnanolone by progesterone administration (Dazzi et al., 2002).

The influence of neurosteroids on alcohol intake is quite complex. Low doses of allopregnanolone increase, while higher doses decrease ethanol self-administration in rodents (Ford et al., 2005b; Morrow et al., 2001). Moreover, intracerebroventricular administration of allopregnanolone can increase ethanol drinking in mice, suggesting a specific central effect of allopregnanolone (Ford et al., 2007). Allopregnanolone can reinstate ethanol-seeking behavior in mice, facilitating the consummatory phase underlying self-administration of ethanol (Finn et al., 2008) and produce subjective effects that are similar to ethanol in ethanol-like discriminative test in monkeys (Grant et al., 2008). Decreasing allopregnanolone levels with finasteride reduced the severity of chronic ethanol withdrawal (Ford et al., 2005a), and allopregnanolone levels were reduced in withdrawal seizure-prone mice (Snelling et al., 2014), suggesting a combined decrease in allopregnanolone and $GABA_A$ receptor sensitivity during the stress response related to ethanol withdrawal. In addition, increased allopregnanolone levels by the systemic administration of pregnenolone or by the overexpression of the steroidogenic enzyme cytochrome P450 side-chain

cleavage in the VTA was shown to decrease ethanol self-administration in alcohol-preferring P rats (Besheer et al., 2010; Cook et al., 2014b).

4.2. Interactions between THC and PPA pathway of neurosteroids

Apart from alcohol, other drugs of abuse can affect neurosteroid levels in rodents. For example, an increase in pregnenolone, progesterone and/or allopregnanolone has been observed in the brain after acute exposure to nicotine, cocaine, amphetamine, morphine or caffeine (Concas et al., 2006, 2000; Porcu et al., 2003; Vallée et al., 2014) and gamma-hydroxybutyric acid (GHB) administration increased brain and plasma levels of pregnenolone, progesterone and allopregnanolone in male rats (Barbaccia et al., 2002; Porcu et al., 2004). Furthermore, by comparing the acute effects of several drugs of abuse at doses corresponding to the median effective dose (ED50), we found a dramatic effect of THC, the main psychoactive component of cannabis, on pregnenolone levels within several brain areas of rats, that was reproduced in mice (Vallée et al., 2014) (Fig. 2). This effect was almost not observed for allopregnanolone and was much higher in the brain than in plasma. This increased brain concentration of pregnenolone was associated with an increase in brain expression of the enzymes involved in the synthesis of pregnenolone from cholesterol. The increase in pregnenolone in the nucleus accumbens (NAc) has also been observed with other CB1 receptor agonists but not with those of the CB2 receptor, whereas this effect was abolished with a CB1 antagonist.

Moreover, THC failed to increase pregnenolone levels in the NAc in full CB1 knock-out mice and in mice lacking CB1 receptors in striatal spiny neurons, supporting a CB1-dependent effect of THC on pregnenolone levels. In turn, pregnenolone was able to bind to a specific binding pocket on CB1 receptor, distinct from the orthosteric binding site, and to act as a negative allosteric modulator, leading to inhibition of the main behavioral and somatic effects of THC (Vallée et al., 2014), as well as a decrease in schizophrenia-like behaviors (Busquets-Garcia et al., 2017) in mice. Furthermore, pregnenolone reduced the effects of THC on dopamine neurons firing in the ventral tegmental area and on dopamine release into the NAc in rats (Vallée et al., 2014), supporting a role for pregnenolone in regulating the mesolimbic dopamine system involved in CB1-related drug addiction. As well, pregnenolone was able to modulate the self-administration of a CB1 agonist in mice by decreasing both drug intake and motivation to take the drug (Vallée et al., 2014). Overall, the above data support the idea that during THC intoxication, an endogenous regulatory mechanism involves a negative-feedback loop of pregnenolone on CB1 receptors that will counter THC addiction processes (Welberg, 2014). Thus, pregnenolone can compensate for some mechanisms of THC addiction, including the reduction in GABA release by THC's action on CB1 receptors of GABA neurons and in the inhibition of dopaminergic neurons by GABA resulting in increased release of dopamine in the NAc (Fig. 3).

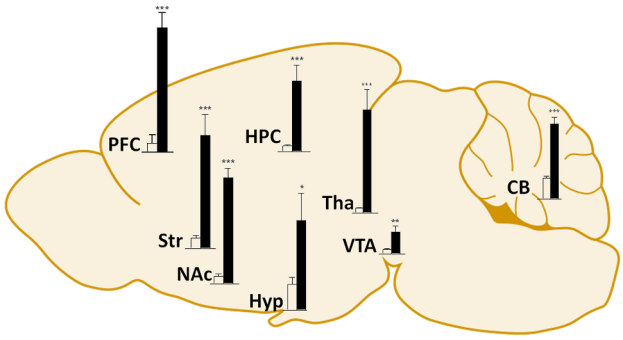

Fig. 2. Schematic representation of THC-induced brain increase of pregnenolone (adapted from Vallée et al., 2014). In comparison to vehicle-treated animals (white bars), systemic administration of THC (black bars) raised pregnenolone levels mainly in rodent brain regions rich in CB1 receptors. *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$ compared to animals that did not receive THC. PFC, prefrontal cortex; Str, dorsal striatum; NAc, nucleus accumbens; Hyp, hypothalamus; HPC, hippocampus; Tha, Thalamus; VTA, ventral tegmental area; CB, cerebellum.

5. Clinical evidence for PPA pathway and stress and/or drug abuse-related disorders

The main findings described in this review on human research are summarized in Table 2.

In support of the preclinical evidence, clinical data have reported dysregulation of the homeostasis of neurosteroidogenesis in neuropsychiatric disorders. An extensive review has been recently published (Porcu et al., 2016). We will describe here several stress-related clinical models in which neurosteroid impacts (mainly allopregnanolone and pregnenolone) have been reported. These models include anxiety, major and post-partum depression, panic disorder, premenstrual symptoms (PMS) in women and its severe dysphoric form, the premenstrual dysphoric disorder (PMMD), which is characterized by recurrent negative mood symptoms, such as irritability, depression, anxiety and emotional lability during the luteal phase of the menstrual cycle (Bixo et al., 2018). Other models include post-traumatic stress disorder (PTSD) (Pinna, 2018) and psychoses, such as schizophrenia (Cai et al., 2018a, 2018b), which onset can be related to cannabis abuse. Schizophrenia is one of the most frequently reported cannabis use disorders (CUD) for which new therapies involved the use of neurosteroids. Studies on alcohol use disorders and neurosteroids have also been reported.

Alterations in serum, plasma, cerebrospinal fluid (CSF) and/or postmortem brain tissues of allopregnanolone and pregnenolone levels have been associated with symptoms of several stress-related diseases, while few studies have yet examined these alterations in drug-related disorders.

A decrease in allopregnanolone has been found in plasma and CSF of patients diagnosed with major depression (Girdler et al., 2012; Romeo et al., 1998; Uzunova et al., 1998) and in of women in late pregnancy with concurrent self-rated symptoms of depression (Hellgren et al., 2014). Also, low allopregnanolone concentrations have been reported in the serum of women with PMS (Bicíková et al., 1998; Rapkin et al., 1997), in CSF of humans with PTSD (Rasmusson et al., 2006), in serum and parietal cortex of patients with schizophrenia (Marx et al., 2011, 2009, 2006c) and serum of individuals exhibiting bipolar disorder with a history of CUD (Mason et al., 2017). A decrease in allopregnanolone concentrations may lead to an inability to enhance GABA-mediated inhibition during states of altered excitability of the central nervous system, such as physiologic or psychological stress, which may contribute to the genesis of various mood disorder symptoms. Thus, increasing serum allopregnanolone levels, by treatment with different antidepressants, can protect against depressed mood (Romeo et al., 1998). In contrast, an increase in allopregnanolone has been reported in patients with bipolar disorder or major depressive disorder (Hardoy et al., 2006). Moreover, allopregnanolone was increased while its 3β isomer was decreased in patients suffering from panic disorder (Ströhle et al., 2002) or PMDD (Bixo et al., 2018, 2017). These findings suggest that alterations in 3α and 3β isomers of pregnanolone could synergistically lead to an imbalanced GABA response. Nevertheless, other studies failed to find a change in allopregnanolone concentrations in patients with generalized anxiety disorders or mixed anxiety-depression disorder (Schüle et al., 2014).

For pregnenolone, lower CSF levels were found in patients experiencing a depressive episode, either unipolar or bipolar type, compared to healthy controls (George et al., 1994). Moreover, studies have described a decrease in serum concentrations associated with some symptoms of schizophrenia (Marx et al., 2009; Ritsner et al., 2007), while others reported an increase in plasma (Cai et al., 2018b) and in postmortem brain tissue (Marx et al., 2006c) of patients with schizophrenia compared to control subjects.

Overall, the clinical studies suggest that neurosteroids changes may play a role in the neurobiology of stress-related disorders and/or their

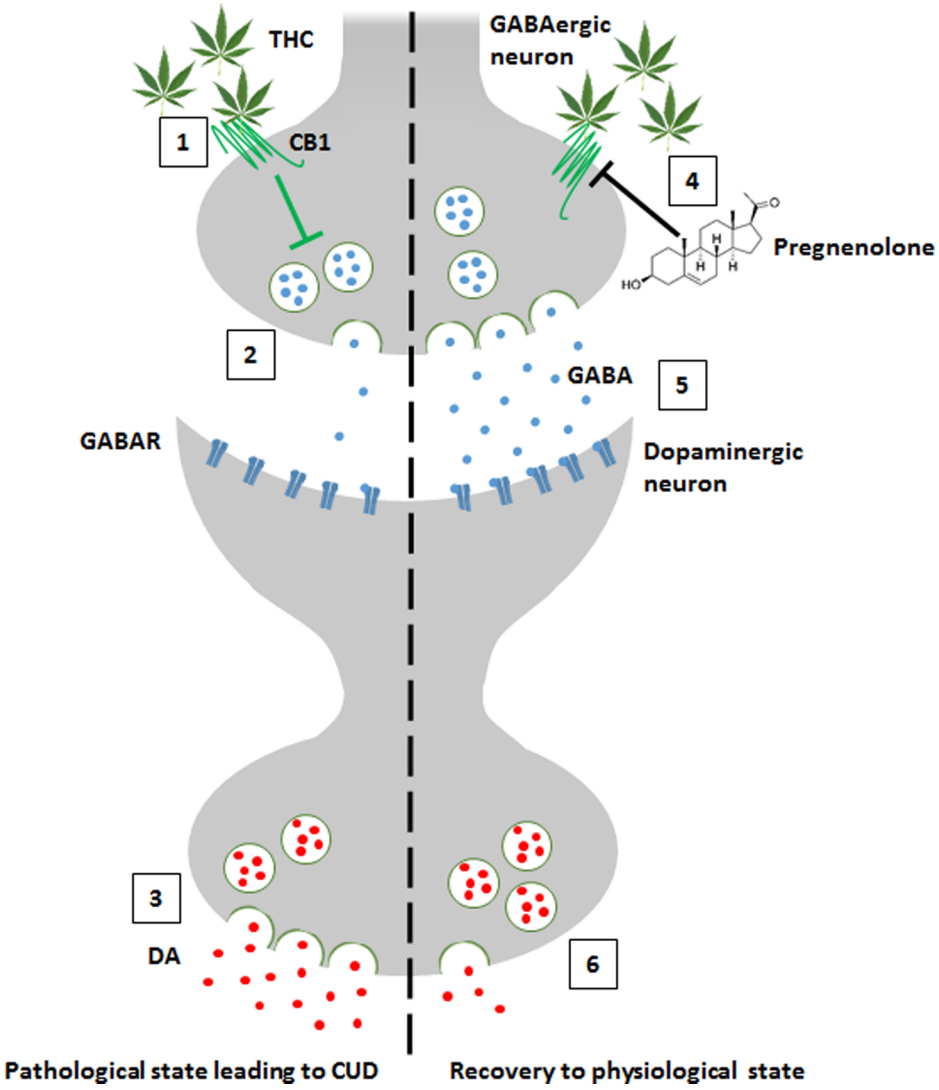

Fig. 3. THC effect on GABAergic and dopaminergic signaling involved in cannabis addiction (left), and pregnenolone mechanism of action via the cannabinoid CB1 receptor (right). THC binds to the CB1 receptor of the presynaptic GABAergic neuron[1]. CB1 is a G protein coupled receptor most often associated with a G_i protein, and the activation of CB1 by THC can block the entry of calcium into the cell and the release of the neurotransmitter GABA[2]. THC can then decrease the inhibition of post-synaptic dopaminergic neuron by GABA and increase the release of DA[3], which mediates cannabis addiction and can lead to cannabis use disorders (CUD). Excessive THC will increase pregnenolone levels, and pregnenolone will bind to an allosteric binding site of the CB1 receptor[4]. Pregnenolone may inhibit the effects of THC by restoring the inhibition of DA release[6] possibly via increasing GABA release[5]; leading to physiological recovery and potential protection against CUD.

treatment. Although there is evidence of a role for allopregnanolone in the pathophysiology of mood disorders, a beneficial role in some of them has been challenged (Rupprecht, 2014). Some discrepancies can indeed emerge between allopregnanolone levels and some physiopathological symptoms. For example, negative mood symptoms may occur in women with PMDD during the luteal phase of the menstrual cycle when progesterone and allopregnanolone usually are high (Bixo et al., 2018), while moderate to high levels of allopregnanolone have been shown to have anxiolytics effects. In that specific case a role for the 3β-isomer of allopregnanolone (3β,5α-pregnanolone, also named isopregnanolone or epiallopregnanolone) has been emphasized in the pathophysiology of PMMD and panic attacks, through a decrease in GABAergic tone. Accordingly, treatment with 3β,5α-pregnanolone, defined as GAMSA (GABA Modulation Steroid Antagonist) and also named sepranolone, reduces negative mood score in women with PMDD (Bixo et al., 2017). Other inconsistencies have been described for schizophrenia. Clinical trials challenging pregnenolone treatment reported decreased negative or positive symptoms and extrapyramidal side effects in patients with schizophrenia, with the resultant elevations in pregnenolone and allopregnanolone post-treatment being correlated with cognitive improvements (Kreinin et al., 2017; Marx et al., 2014, 2009; Ritsner et al., 2014, 2010). Treatment with pregnenolone that induces an increase in allopregnanolone concentration may also improve depressive symptoms in patients with bipolar disorder (Brown et al., 2014) and may improve the activation of mood and emotionally relevant neurocircuits (Sripada et al., 2013). In the other hand, antipsychotic treatments could improve symptomatology of schizophrenia and restore normal concentrations of pregnenolone and allopregnanolone by decreasing pregnenolone and increasing allopregnanolone (Cai et al., 2018b).

With respect to substance abuse disorders, higher plasma levels of allopregnanolone have been reported in adolescents after alcohol intoxication (Torres and Ortega, 2004), while a decrease has been observed during alcohol withdrawal (Romeo et al., 1996). Acute alcohol also induced high concentrations of pregnenolone, but low concentrations of allopregnanolone. In healthy men with no prior history of alcohol, the change in pregnenolone concentration after alcohol consumption was significantly correlated with alcohol liking, and the alcohol-induced change in allopregnanolone concentration was significantly correlated with both alcohol liking and the desire to drink more (Pierucci-Lagha et al., 2006). To date, the few studies that assessed the neurosteroidogenic effects of ethanol in humans used different doses of ethanol and/or different methods of steroid measurements that could lead to these inconsistent results (Porcu et al., 2016). The findings that the subjective effects of ethanol are diminished by prior administration of finasteride in healthy subjects with no history of substance use disorders (Pierucci-Lagha et al., 2005) or dutasteride in moderate-heavy drinkers (Covault et al., 2014), both allopregnanolone biosynthesis inhibitors, strongly suggest that allopregnanolone may play a role in ethanol's actions in humans.

Table 2
Brief overview of human research evidence on the role of the PPA pathway in stress related disorders, cannabis use disorder and alcohol use disorder.

Disorder	Biomarker	Treatment	Effect on PPA	Clinical response
Stress related disorders				
Depression	↓$ALLO_{plasma}$[1]; ↑$ALLO_{plasma}$[2]	ganaxolone[4]	none[4]	↓depressive symptoms[4]
	↓$PREG_{CSF}$[3]	3-methoxy PREG[5]	none[5]	↓depressive symptoms[5]
Post-partum depression	↓$ALLO_{serum}$[6]	brexanolone[7]	none[7]	↓depressive symptoms[7]
Panic disorder	↑$ALLO_{CSF}$[8]			
Premestrual symtoms	↓$ALLO_{serum}$[9]; ↑$ALLO_{plasma}$[10]	3β,5α-pregnanolone[10]	N.R.	↑mood[10]
Post-traumatic stress disorder	↓$ALLO_{CSF}$[11]	ganaxolone[12]	none[12]	↑stress[12]
Alcohol use disorders				
Alcohol abuse	↑$PREG_{plasma}$[13]; ↓$ALLO_{serum}$[13]	finasteride[15]; dutasteride[16]	↓ALLO[15,16]	↓ethanol effects[15,16]
Alcohol withdrawal	↑$ALLO_{plasma}$[14]			
	↓$ALLO_{plasma}$[19]			
Cannabis use disorders				
Cannabis dependence	N.R.	PREG analog[18]	none[18]	↓intake, craving, addiction[18]
Schizophrenia	↓$ALLO_{brain,\ serum}$[19]; ↓$PREG_{brain}$[20]	PREG[22]	↑PREG[22]; ↑ALLO[22]	↓negative and positive symptoms[22]
	↑$PREG_{plasma}$[21]	antipsychotics[11]	↓PREG[11]; ↑ALLO[11]	
Bipolar disorder	↓$ALLO_{serum}$[23]; ↑$ALLO_{plasma}$[2]	PREG[24]	N.R.	ameliorate symptoms[11]
				↓depressive symptoms[24]

N.R., Not Reported; ↑ increase; ↓ decrease.
References: [1]Girdler et al., 2012; Romeo et al., 1998; Uzunova et al., 1998; [2]Hardoy et al., 2006; [3]George et al., 1994; [4]Ligsay et al., 2017; [5]Baulieu et al., 2004; Bianchi et al., 2017; [6]Hellgren et al., 2014; [7]Frieder et al., 2019; Kanes et al., 2017; Meltzer-Brody et al., 2018; [8]Schüle et al., 2014; [9]Bicíková et al., 1998; Rapkin et al., 1997; [10]Bixo et al., 2018, 2017; [11]Rasmusson et al., 2006; [12]Rasmusson et al., 2017; [13]Pierucci-Lagha et al., 2006; [14]Torres and Ortega, 2004; [15]Pierucci-Lagha et al., 2005; [16]Covault et al., 2014; [17]Romeo et al., 1996; [18]Piazza et al., 2018, 2014, 2012; [19]Marx et al., 2011, 2009, 2006c; [20]Marx et al., 2009; Ritsner et al., 2007; [21]Cai et al., 2018b; Marx et al., 2006c; [22]Kreinin et al., 2017; Marx et al., 2014, 2009; Ritsner et al., 2014, 2010; [23]Mason et al., 2017; [24]Brown et al., 2014.

Research on the role of neurosteroids, in particular pregnenolone in cannabis use disorders (CUD) is currently underway using a well-established human laboratory model of cannabis withdrawal and self-administration (Haney, 2009; Herrmann et al., 2016).

Overall, based on all the clinical data described, pregnenolone and allopregnanolone are potential therapeutic targets for neuropsychiatric disorders related to stress and/or drug abuse.

6. Therapeutic opportunities for PPA pathway: proof-of-concept trials

Although endogenous steroids, such as pregnenolone and allopregnanolone, have a safe pharmacological profile, alternatives to their therapeutic use in humans have been outlined in order to compensate for their poor bioavailability and short biological half-life due to theirs rapid in vivo metabolism in downstream steroids (Vallée, 2016). Hence, strategies have been developed using modulators of their synthesis and other approaches have emerged by manipulating drug formulations and/or generating synthetic steroid analogs that can improve the absorption and pharmacokinetic profile.

An attractive research emerged with the use of neurosteroidogenic compounds to promote endogenous neurosteroidogenesis. This is the case for SSRIs (selective serotonin reuptake inhibitors) (Rasmusson et al., 2006; Schüle et al., 2014) and ligands of the translocator protein 18 kDa (TSPO) (Rupprecht et al., 2010). TSPO, formerly called peripheral or mitochondrial benzodiazepine receptor, is mainly located in the outer mitochondrial membrane and favors the transport of cholesterol to the inner mitochondrial membrane, ultimately promoting neurosteroid synthesis (Papadopoulos et al., 2006). TSPO ligands have been shown to enhance neurosteroidogenesis in the brain (Liere et al., 2017; Verleye et al., 2005) and to exert acute anxiolytic activity in rodent models (Kita et al., 2004; Verleye et al., 2005). In humans, TSPO ligands are promising candidates for fast-acting anxiolytic drugs with less severe side effects than one of the most prescribed anxiolytics, benzodiazepines (Rupprecht et al., 2010, 2009). As such, TSPO ligands, like etifoxine, can work as anxiolytics in clinical studies with a relatively favorable side effect profile (Poisbeau et al., 2018).

A significant and increasing body of evidence supports the therapeutic effectiveness of the development of synthetic steroid analogs. As a first example, Brexanolone, a proprietary soluble intravenous preparation of synthetic allopregnanolone, has been developed and a recent series of clinical trials on postpartum depression has shown a rapid reduction in depressive symptoms (Frieder et al., 2019; Kanes et al., 2017; Meltzer-Brody et al., 2018). Brexanolone then became the first drug specifically approved for the treatment of postpartum depression in adult women (Food and Drug Administration (FDA) approval in March 2019) (Scott, 2019). The following are models based on the stereochemical and structure-activity characteristics of steroids (Vallée, 2014; Vallée et al., 2014). Actually, 3α-OH configuration is required for binding and activity, and C3 and C17 positions are the primary targets for metabolism enzymes of steroids. As an example, the change in structural isomerism of the hydroxyl group at the C3 position of allopregnanolone can modulate its action on $GABA_A$ receptors. The 3β-epimer of allopregnanolone (3β,5α-pregnanolone) is a GABA Modulation Steroid Antagonist (GAMSA) compound, which reduced the negative mood score in women with PMDD (Bixo et al., 2018, 2017). This compound has been developed by the *Asarina Pharma* biotech (Sweden) and phase IIb clinical trial is ongoing (ClinicalTrials.gov; Identifier NCT03697265; *A Study Investigating Efficacy and Safety of Sepranolone (UC1010) in Patients With Premenstrual Dysphoric Disorder (PMDD)*).

Also, the substitution of the hydroxyl group at the C3 position by another chemical group associated or not with modifications at C17 position has been used to improve the metabolic stability of allopregnanolone or pregnenolone. For instance, a 3β-methylated synthetic analog of allopregnanolone, ganaxolone, has been tested in phase II clinical studies in severe postpartum depression (Frieder et al., 2019), as well as for mood disorders (anxiety, depression) associated with Fragile X syndrome in children and adolescents (Ligsay et al., 2017). However, in contrast of what was reported in animal model of PTSD (Pibiri et al., 2008; Pinna and Rasmusson, 2014), negative data have been reported regarding the effect of ganaxolone in patients with PTSD (Rasmusson et al., 2017), although some concerns have been expressed about this clinical study (Kawada, 2018).

Moreover, a 3-methoxy pregnenolone (MAP4343) has been developed by Baulieu and collaborators and *MAPREG (microtubule-associated protein/neurosteroidal pregnenolone)* biotech (France) (Baulieu et al., 2004; Bianchi et al., 2017). This analog of pregnenolone presents preclinical antidepressant efficacy in rats (Baulieu et al., 2012a, 2012b)

and is under phase II clinical trial (ClinicalTrials.gov; Identifier NCT03870776; *RESIST: Administration of MAP4343 in Antidepressant Non-Responders Patients Experiencing a Major Depressive Episode*). MAP4343 produced significant reduction of excessive alcohol drinking specifically in alcohol dependent rats and not in non-dependent rats (Koob et al., 2018). Furthermore, based on the allosteric negative modulation of pregnenolone on CB1 receptors and the consequential protection in rodent towards the brain intoxication to THC, the main psychoactive component of marijuana (Vallée et al., 2014), C3-C17 Non Metabolized Pregnenolone Derivatives have been developed by INSERM and *Aelis Farma* biotech (France) (Piazza et al., 2018, 2014, 2012) and a C3-C17 analog of pregnenolone is currently in phase II clinical trial for CUD indication (ClinicalTrials.gov; Identifier NCT03717272; *Effect of AEF0117 on Subjective Effects of Cannabis in CUD Subjects*).

7. Conclusions

Preclinical and clinical studies strongly suggest that a disruption of homeostatic stress mechanisms involving neurosteroids may play a pathogenic role in some psychiatric disorders. Therefore, allopregnanolone and/or pregnenolone can be used as novel biomarkers of these disorders. The role of allopregnanolone has been widely described through its action on the GABAergic system, showing correlations between allopregnanolone concentrations and certain symptoms. The frequently reported decrease in allopregnanolone can be rescued by pregnenolone treatment, for instance in schizophrenia, with the resulting improvement in symptoms. Consequently, the pregnenolone-progesterone-allopregnanolone pathway often indicates a final physiological role for allopregnanolone. However, pregnenolone has also been shown to have a specific role, particularly on the endocannabinoid system, by acting as a negative allosteric modulator of CB1 receptors, leading to a down-regulation of CB1 over-activation and related disorders.

Hence, the open questions “what is the role of pregnenolone and allopregnanolone” and “are they acting in concert with a different pharmacological profile?” (Rupprecht, 2014) is still relevant and ongoing. As an illustration, a common axis of biomarkers, including neurosteroids and endocannabinoids, has been proposed for post-traumatic stress disorder (Pinna, 2018). In this case, stress can modulate both the action of allopregnanolone on GABAergic system and on the endocannabinoid system, which could down-regulate allopregnanolone concentrations. Such a model can be validated for other psychiatric or drug-related disorders. Furthermore, a specific action for pregnenolone on the endocannabinoid system may complete this scheme, including negative allosteric modulation of CB1 receptors by pregnenolone (Vallée et al., 2014) and a possible activation of the FAAH enzyme that will disrupt the endocannabinoid tone (Sabatucci et al., 2019). Further investigations in animal models and humans would be required to validate these statements.

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