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Allopregnanolone (1938–2019): A trajectory of 80 years of outstanding scientific achievements

Eighty years of outstanding research by many talented neurosteroid scientists all over the world have contributed to the development of allopregnanolone as a psychotherapeutic drug, beginning with the discovery of allopregnanolone in the adrenal gland in 1938 and culminating in the 2019 FDA approval of intravenous allopregnanolone, best known as brexanolone and marketed as Zulresso™, as a fast-acting, short-course, long-lasting treatment for post-partum depression (PPD). This phenomenon now stands as a superb model of translational drug development in neuropsychopharmacology.

In 1981, Baulieu and colleagues suggested that allopregnanolone is produced directly by the brain (Corpéchot et al., 1981). These investigators proposed the term "*neurosteroid*" for "those steroids that are both synthesized in the nervous system, either de novo from cholesterol or from steroid hormone precursors like progesterone that accumulate in the nervous system" (Robel and Baulieu, 1994). Paul and Purdy (1992) suggested the term "neuroactive steroid" to define "any natural or synthetic steroid that rapidly alters neuronal excitability via non-genomic mechanisms." Indeed, studies unveiled the fundamental observation that allopregnanolone is a potent modulator of GABA effects at $GABA_A$ receptors (Majewska et al., 1986). This discovery was followed by the finding that levels of allopregnanolone in brain are susceptible to acute stress and persist even after adrenalectomy and ovariectomy (Purdy et al., 1991). The laboratories of Costa and Guidotti thereafter contributed the discovery, cloning and function of the peripheral benzodiazepine receptor, now renamed as 18 kDa translocator protein (TSPO) (Sprengel et al., 1989). They also observed that allopregnanolone synthesizing enzymes are absent in glia but highly expressed by principal glutamatergic neurons and long-projecting GABAergic neurons —suggesting that allopregnanolone might play a role in the coordination of brain circuit activity (Agis Balboa et al., 2006). A better understanding of stress effects on allopregnanolone biosynthesis and the role of allopregnanolone in the stress response was instrumental in building models of the state-dependent actions of allopregnanolone in regulating brain circuits underlying stress-related behaviors (Pibiri et al., 2008). Uzunova and Romeo and respective colleagues independently contributed to the first observation that allopregnanolone levels are downregulated in patients with major unipolar depression (Uzunova et al., 1998; Romeo et al., 1998). Evidence obtained on allopregnanolone pharmacology in rodent stress models and from depressed patients then suggested allopregnanolone's potential suitability as a treatment to improve mood symptoms (Pinna et al., 2003; Schüle et al., 2011). Thus, decades of studies led to the clinical trials that showed brexanolone's efficacy for PPD (Kanes et al., 2017; Meltzer-Brody et al., 2018).

This special issue is a collection of original investigations, as well as reviews of preclinical and clinical findings focused on the pleiotropic neurobiologic effects of allopregnanolone (Fig. 1). Several of these papers highlight the capacity of allopregnanolone to promote improvement in neuropsychiatric disorders ranging from PPD and posttraumatic stress disorder (PTSD) to premenstrual dysphoric disorder (PMDD) and Alzheimer's disease (AD). Others papers highlight the pharmacological potential of allopregnanolone as a general anesthetic or analgesic and even for local neuroprotective response following viral infection.

Two pioneers who have contributed groundbreaking discoveries in the field of neurosteroid research, Steven Paul and Alessandro Guidotti contributed a "*Pioneer Paper*" that describes, in a historical perspective, the trajectory of allopregnanolone research in 25 milestones from its discovery until the FDA approval on March 19, 2019 for PPD treatment (Paul et al., 2020). They discuss the findings that led to the discovery of allopregnanolone synthesis in the central nervous system and the direct and rapid, non-genomic actions of allopregnanolone and its derivatives via $GABA_A$ receptors. They discuss changes in brain levels of allopregnanolone during pregnancy and in the postpartum period or during exposure to protracted stress and its crucial role in the pathophysiology of mood disorders. The discovery that allopregnanolone induces marked anxiolytic, anti-stress and antidepressant effects and how this has provided new perspectives for development of novel drugs useful for the treatment of mood disorders and specifically for PPD is analyzed. PPD is a unique subtype of major depressive disorder and a substantial contributor to maternal morbidity and mortality. In addition to affecting the mother, PPD can have short- and long-term consequences for the infant and partner. Meltzer-Brody and Kanes (2020) discuss proposed mechanisms of PPD etiology, including altered regulation of stress response and dysfunctional GABA signaling. Their report focuses on the potential role of GABAergic signaling and allopregnanolone in PPD and discusses data implicating allopregnanolone in PPD in the context of the development of brexanolone injection for the treatment of adult women with PPD. Walton and Maguire (2019) discuss allopregnanolone-based treatment as an exciting development for patients and families impacted by PPD, but also as an opportunity that allows us to start asking questions about how and why this compound works. The authors thus examine the clinical and preclinical evidence supporting a role for allopregnanolone in the underlying neurobiology of PPD. However, the persistent antidepressant effects of allopregnanolone for PPD are not easily explained by known mechanisms of action of such steroids as positive allosteric modulators (PAMs) at $GABA_A$ receptors. Future work potentially elucidating a novel antidepressant mechanism of action thus may provide useful information for the next generation of antidepressant drug development. Indeed, several mechanisms appear to be involved in the pathogenesis of PPD, including neuroendocrine dysfunction, neuroinflammation, genetic and epigenetic modifications.

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Recent evidence highlights the higher risk for PPD in mothers exposed to unhealthy diets that increase inflammation. Matrisciano and Pinna (2020) discuss the role of bioactive micronutrients found in the so-called functional foods in preventing neuroinflammation and depression. An intriguing molecular substrate linking functional foods with improvement of mood is represented by the PPAR pathway, which can regulate allopregnanolone biosynthesis and brain-derived neurotropic factor (BDNF). Healthy diets by targeting the PPAR-neurosteroid axis and by decreasing low-grade inflammation may offer a suitable functional strategy to prevent and safely alleviate mood symptoms during the perinatal period. Zorumski et al. (2019) discuss opportunities to overcome mood disorders by treating men and women affected by major depressive disorder with neurosteroid-based treatments as a new era in treating mood and anxiety disorders based on the potential of these new therapeutics as modulators of brain function. They consider additional potential mechanisms contributing to antidepressant and anxiolytic effects but also the role as endogenous "stress" modulators of allopregnanolone and other GABAergic neurosteroids. Furthermore, they argue that a better understanding of the molecular, cellular, network and psychiatric effects of neurosteroids offers the hope of further advances in the treatment of mood and anxiety disorders. Pineles and colleagues (2020) demonstrate the contribution of deficits in allopregnanolone and pregnanolone (Allo + PA) to deficits in extinction retention demonstrated by women with PTSD in the mid-luteal but not follicular phase of the menstrual cycle. These findings align with preclinical research in male rodents and provide preliminary support for testing allopregnanolone as an adjunct to exposure-based treatments for PTSD. These findings also suggest a potential general role for allopregnanolone in memory consolidation. Kim and colleagues (2020) examine the collective, as well as separate effects of various neurobiological systems to PTSD severity in trauma-exposed unmedicated, tobacco-free, fasting males with and without chronic PTSD. A multiple regression model revealed substantial composite contributions of cerebrospinal fluid Allo + PA, neuropeptide Y, and interleukin-6 to total PTSD symptoms —together accounting for 76% of the variance in severity. This study also demonstrates the individual heterogeneity of PTSD biological endophenotypes, suggesting the need for integrated assessments to inform individualized treatment targeting in the clinic. Almeida and colleagues (2020) show how stress-induced rodent models of depression recapitulate to a decrease in allopregnanolone brain concentrations, and treatment strategies that upregulate allopregnanolone brain content or its direct administration reduces depressive-like behavior. They discuss evidence connecting the antidepressant effects of allopregnanolone to increased neurogenesis in crucial brain areas, including the hippocampus. They conclude that a possible interaction between changes in the $GABA_A$ receptor neurotrasmission and neurotrophic mechanisms induced by neurosteroids warrants further investigation. Pleiotropic actions of allopregnanolone account for its ability to promote recovery in a wide variety of neuropsychiatric illnesses. In this regard, Boero and colleagues (2020) discuss allopregnanolone and its precursors, pregnenolone and progesterone, which share many therapeutic actions of allopregnanolone probably after these compounds are converted to allopregnanolone in vivo. They present a theoretical framework for understanding how endogenous neurosteroids that regulate $GABA_A$ receptors, corticotropin releasing factor (CRF) and pro-inflammatory signaling in the innate immune system and brain could play a key role in both the prevention and treatment of stress-related disease. They further discuss cautions and limitations of allopregnanolone or precursor therapy. Belelli and colleagues (2020) suggest that the recent approval of allopregnanolone for treatment of PPD has reinvigorated interest in exploring the therapeutic potential of neuroactive steroids. They focus on the influence of such steroids on GABAergic signaling and the challenges faced in expanding their clinical utility including as general anesthetics, sedatives, analgesics, anticonvulsants, and antidepressants. Preclinical studies have highlighted $GABA_A$ receptor isoforms incorporating the δ subunit (δ-$GABA_A$Rs) as an important neuroactive steroid target. In their contribution, consideration is given to the potential of developing non-steroidal, selective positive allosteric modulators of δ-$GABA_A$Rs as future medicines. Allopregnanolone also plays a pivotal role in neurodevelopment. Bartolomé and colleagues (2020) discuss how altering its levels can affect brain maturation and behavior, as well as vulnerability to psychiatric disorders, including drug abuse. Intriguingly, manipulation of early postnatal allopregnanolone levels induces novelty seeking and increases ethanol intake in adult age. This can be explained by a mechanism related to a decrease in ventral striatal dopamine and serotonin levels and the alteration of $GABA_A$ and 5HT3 receptors. Bengtsson and colleagues (2020) discuss the unmet therapeutic need for cognitive dysfunction, dementia and Alzheimer's disease (AD). They focus on allopregnanolone's role in cognition and AD and suggest that allopregnanolone given intermittently promotes neurogenesis, decreases AD-related pathology and improves cognition. However, continuous exposure impairs cognition and deteriorates AD pathology. The disparity between these two outcomes depends on allopregnanolone administration pattern and provides insights for the therapeutic development of allopregnanolone and its antagonists for AD through clinical trials. Diviccaro and colleagues (2020) focused on adverse events using finasteride and dutasteride, approved for the treatment of benign prostatic hyperplasia and androgenetic alopecia. Adverse effects in men during treatment, such as sexual dysfunction and mood alteration are part of post-finasteride syndrome (PFS) symptoms

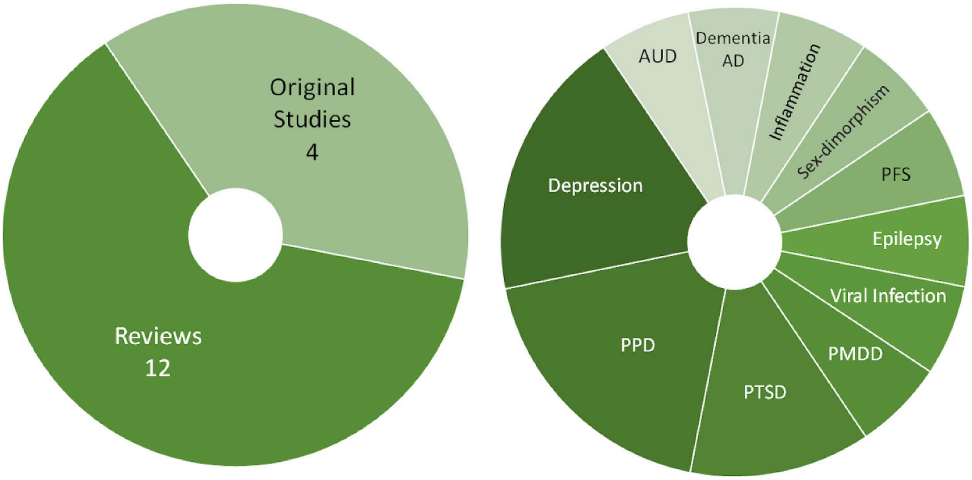

Fig. 1. Special issue content overview. Post-partum depression (PPD); posttraumatic stress disorder (PTSD); premenstrual dysphoric disorder (PMDD); post-finasteride syndrome (PFS); Alzheimer's disease (AD); alcohol use disorder (AUD).

that persist despite drug withdrawal. They argue on the need of clinical investigations to study this syndrome and understand better the underlying neurobiology. Molecular mechanisms and/or genetic determinants behind 5α-reductase inhibition-induced adverse effects should be explored both in patients and animal models in face of the emerging clinical problem caused by PFS. Even virological stressors are observed to enhance allopregnanolone synthesis in the brain. The report by Paris and colleagues (2020) demonstrates for the first time that exposure to the neurotoxic HIV protein, Tat, elevates allopregnanolone content in the brain (but not plasma) of male mice. In this case, allopregnanolone synthesis may be part of a local neuroprotective response given that allopregnanolone was able to attenuate Tat-potentiated mitochondrial membrane depolarization, neuronal death, and morphine-mediated psycho stimulation when administered in physiological concentrations to primary neurons or male mice. Prenatal stress (PNS) can influence behaviors associated with cognition, reward and emotional regulation. Torgersen and colleagues (2020) discuss how allopregnanolone in these regions modulates behavioral and parasympathetic effects. They tested whether exposing pregnant dams to resident-intruder stress on prenatal days 15–20 altered the levels of allopregnanolone in brain areas of male and female juvenile offspring. In cortex, hypothalamus, and midbrain of male rats exposed to PNS, levels of allopregnanolone were significantly lower, while in the hippocampus and cerebellum were higher among females. These differences in allopregnanolone levels varying by PNS, sex and brain regions provide insight in potential mechanism of sex-dimorphic stress regulation. Premenstrual dysphoric disorder (PMDD) is a severe mood disorder with core symptoms and increased sensitivity to stress occurring in the luteal phase of the menstrual cycle and a disorder of suboptimal sensitivity to neuroactive steroids. Hantsoo and Epperson (2020) describe the role of allopregnanolone in PMDD's pathophysiology and discuss evidence of increased luteal phase stress sensitivity in poor allopregnanolone-GABA control of the HPA axis. They discuss the hypothesis that PMDD pathophysiology is rooted in impaired $GABA_A$ receptor response to dynamic allopregnanolone fluctuations across the menstrual cycle, manifesting in affective symptoms and poor regulation of physiologic stress response. Selective serotonin reuptake inhibitors (SSRIs) and new drugs targeting $GABA_A$ receptors are treatments discussed for impaired allopregnanolone-GABA function in PMDD.

Hence, this special issue devoted to allopregnanolone recalls many significant discoveries related to allopregnanolone over the past many years while evaluating current perspectives and setting future directions in neurosteroid research. The need for clinical studies to examine a new generation of neurosteroid-based treatments in neuropsychiatry as well as a better understanding of the mechanisms associated with neurosteroid-related neuropathology is suggested in several contributions. One intriguing unmet achievement in neuropsychopharmacology, and generally in psychiatry, regards establishing predictive and diagnostic biomarkers that may facilitate successful clinical trials through patient stratification and enable more efficient and effective treatments for individualized patients. The strategy of looking at a *biomarker axis* rather than focusing on isolated neurobiological deficits may provide a more refined approach (Locci and Pinna, 2017). Having valid biomarkers will optimize rates of drug response and also decrease the incidence of drug-induced side effects. The identification of neurosteroidogenic targets also will stimulate development of novel drugs. Among alternative treatment strategies, the possibility of increasing allopregnanolone and other neurosteroid levels to improve symptoms or decrease susceptibility to mood disorders via physical exercise or diet may promote health in novel and more natural ways. The role of allopregnanolone in regulating immune reactions and inflammation is another emerging field that promises to impact our understanding and treatment of many pathophysiological conditions including depression, PTSD, alcohol use disorder, traumatic brain injury, and neurodegenerative diseases such as Parkinson's disease.

This Special Issue is dedicated to Erminio Costa (Cagliari, Italy, 1924 – Washington, DC, USA, 2009), a true pioneer of the field of neurosteroids and a mentor for many researchers who greatly contributed to this exciting field of neuroscience. I had the unique privilege of learning from him over a period of ten years during which he introduced me to the neurophysiology and pharmacology of neurosteroids. I greatly treasure his humor, leadership, mentorship, and more generally his passion for the field —a long-lasting and important legacy to be perpetuated by those of us remaining and yet to come.

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