Neurobiology of Stress 21 (2022) 100502

Contents lists available at ScienceDirect

Neurobiology of Stress

journal homepage: www.elsevier.com/locate/ynstr

Allopregnanolone: Regenerative therapeutic to restore neurological health

Gerson D. Hernandez, Roberta D. Brinton *

Center for Innovation in Brain Science, University of Arizona, Tucson, AZ, USA

ARTICLE INFO

Keywords:
Neurosteroids
Allopregnanolone
Regenerative therapeutic
Neurogenesis

ABSTRACT

Chronic stress has been proposed as a driver of altered brain structure and function, including the pathogenesis of neurodegenerative diseases and a driver of disease progression. A key outcome of stress in the brain is structural remodeling of neural architecture, which may be a sign of successful adaptation, whereas persistence of these changes when stress ends indicate failed resilience. Neuroendocrine homeostasis and stress response are mainly dependent upon the functioning of the hypothalamic–pituitary–adrenal axis. Neurosteroids will fluctuate depending on whether the stress is acute or chronic. Advancements in neurosteroid research have led to the identification of multiple targets for drug development, but the most promising innovative target may be neurogenesis, given its potential impact in neurodegenerative disorders like Alzheimer's disease. Allopregnanolone is an endogenous pregnane neurosteroid and a reduced metabolite of progesterone, which acts as a potent allosteric modulator and direct activator of the GABA-chloride channel complex. Perhaps the most intriguing finding related to the potential therapeutic effects of allopregnanolone is its potential to promote neuroregeneration.

Prelude by Dr. Brinton: In honor of and gratitude for Bruce McEwen, Ph.D, my post-doctoral mentor whose innovative, bold and expansive approach to science provided the launch pad for me to ultimately address the challenge that in the 21st century, there is not a single cure for a single neurodegenerative disease. Bruce's integrative genius preceded the age of omics and systems biology. His insights were the result of a deep understanding and appreciation of the complexities of organismic function from the molecular to the systems level.

While this special issue is published in Neurobiology of Stress, I should disclose that my first and only study of stress was when I initially joined Bruce's laboratory in 1984. My singular stress study with Bruce was an expansion of my earlier analyses that began with my predoctoral mentor Dr. Hank Yamaura and Dr. Kelvin Gee when we mapped allopregnanolone sites of action in brain. This project formed the perfect platform to connect with Bruce's interest in stress biology (Gee, 1988; Gee, Bolger, Brinton, Coirini and McEwen, 1988; Gee, Chang, Brinton and McEwen, 1987). At the time, evidence for neurosteroids in brain was just emerging and we had detected allopregnanolone binding sites in the hippocampus. With Bruce, we proceeded to determine whether allopregnanolone would modulate the stress response, and as reviewed below, it does indeed.

Thanks to Bruce's integrative approach, my career as a scientist was transformed. Bruce's laboratory was a vibrant world of discovery at every level from the molecular to the clinical. A case in point was the opportunity to be a blind observer of a clinical trial of estrogen in women with Alzheimer's disease conducted by Howard Fillit, M.D. It was that experience in Bruce's laboratory that transformed my career and expanded my horizon from mechanistic discovery science to translational science and ultimately to clinical science. Outcomes of these analyses have illuminated the bioenergetic crisis in brain following the decline of estrogen during midlife which sets into motion a cascade of events that ultimately can increase the risk of Alzheimer's disease (R. D. Brinton, 2013). Based on several decades of mechanistic, translational, and clinical science, we have developed an estrogen receptor beta selective formulation to prevent Alzheimer's prodromal pathology (G. Hernandez et al., 2018; Schneider et al., 2019; Y. Wang et al., 2020) that will now be tested in a phase 2 clinical trial. Bruce was a steadfast supporter of our endeavors at every step in this long journey.

And those allopregnanolone sites in the hippocampus …. some are on neural stem cells where they promote neurogenesis and oligogenesis. Based on our mechanistic science (R. D. Brinton, 2013), translational research and phase 1b/2a clinical trial (G. D. Hernandez et al., 2020; Raikes et al., 2022), we are now conducting a phase 2 clinical trial of allopregnanolone in persons with Alzheimer's disease, to regenerate the

Abbreviations: Allo, Allopregnanolone.

* Corresponding author. 1230 N. Cherry Avenue PO Box 210242, Tucson, AZ, 85721-0242, USA.
E-mail address: rbrinton@arizona.edu (R.D. Brinton).

https://doi.org/10.1016/j.ynstr.2022.100502
Received 21 July 2022; Received in revised form 31 October 2022; Accepted 4 November 2022
Available online 5 November 2022

degenerated brain (ClinicalTrials.gov ID: NCT04838301).

The arc of Bruce's integrative scientific genius is both expansive and impactful leading to discoveries that illuminate mechanistic insights with clinical translational opportunities. The legacy of Bruce S. McEwen, Ph.D. is alive and well in those he mentored, in the generations of scientists to come and in those, worldwide, who will benefit from his invaluable contributions.

1. Introduction

The central role of the brain in the neurobiology of stress and adaptation has been well documented by Bruce McEwen over many years (B. S. McEwen, 2006, 2007, 2016; Bruce S. McEwen et al., 2015; B. S. McEwen and Gianaros, 2010, 2011). Moreover, the relationship between stress, chronic inflammation and neurodegenerative disease is well established. Chronic stress has been proposed as a driver of altered brain structure and function, including the pathogenesis of neurodegenerative diseases and a driver of disease progression (Heneka et al., 2015; Herrera et al., 2015; Hiller, Quinn and Schmidt, 2017; Holmes, 2013; Justice, 2018; Madore, Yin, Leibowitz and Butovsky, 2020; Mishra and Brinton, 2018; Swaab, Bao and Lucassen, 2005; Vyas et al., 2016). According to McEwen and colleagues, a key outcome of stress in the brain is structural remodeling of neural architecture, which may be a sign of successful adaptation, whereas persistence of these changes when stress ends indicate failed resilience. The underlying mechanisms of plasticity and vulnerability of the brain provide the basis for understanding the efficacy of interventions for anxiety and depressive disorders as well as age-related cognitive decline. (Bruce S. McEwen et al., 2015).

2. Neurosteroids and stress

Neuroendocrine homeostasis and stress response are mainly dependent upon the functioning of the hypothalamic–pituitary–adrenal (HPA) axis. An essential regulator of the HPA axis is the corticotropin-releasing hormone (CRH) secreted by the hypothalamus, which promotes the secretion of adrenocorticotropic hormone (ACTH) by the anterior pituitary gland, which in turn promotes the secretion of corticosteroids by the adrenal glands (Taylor and Fishman, 1988). The main glucocorticoid, cortisol, acts on many organs and brain regions, mainly exerting negative feedback on the hypothalamus, pituitary, and hippocampus. The dysregulation of the HPA axis as a result of chronic stress has been implicated in the etiology of affective disorders such as anxiety and depression (De Kloet, Vreugdenhil, Oitzl and Joëls, 1997; Holsboer and Barden, 1996; Swaab et al., 2005), and various neuropsychiatric disorders have been characterized by fluctuations in the levels of neurosteroids (Engel and Grant, 2001; Miczek, Fish and De Bold, 2003; Paul and Purdy, 1992; Zorumski, Paul, Izumi, Covey and Mennerick, 2013).

"Neurosteroids" were first described several decades ago when an endogenous steroid was identified in the brains of adult rats and mice (Baulieu, 1981). Further research demonstrated that neurosteroids are synthesized *de novo* in the brain and nervous system from cholesterol and are potent modulators of glutamate and γ-aminobutyric acid (GABA) neurotransmitter receptors (Baulieu and Robel, 1990; Corpéchot et al., 1983; Gee, 1988; Gee et al., 1988; Gee et al., 1987; Hu, Bourreau, Jung-Testas, Robel and Baulieu, 1987; Paul and Purdy, 1992; Purdy, Morrow, Moore and Paul, 1991). The term "neuroactive steroids" was then used to define both natural steroids produced peripherally or in brain and synthetic steroids that rapidly alter the excitability of neurons (Paul and Purdy, 1992).

3. Allopregnanolone and stress

Allopregnanolone (3α-hydroxy-5α-pregnan-20-one) is an endogenous pregnane neurosteroid and a reduced metabolite of progesterone (Fig. 1), which acts as a potent allosteric modulator and direct activator of the GABA-chloride channel complex (Baulieu, Robel and Schumacher, 2001; R. Brinton, 1994). Neurosteroids bind to $GABA_A$ receptor at sites that differ from GABA, benzodiazepines, ethanol, and barbiturate binding sites and can act as positive or negative modulators of $GABA_A$ receptor function (Irwin and Brinton, 2014). Allopregnanolone (Allo) has high affinity to $GABA_A$ receptors and therefore, has shown to have anxiolytic, anticonvulsant, and hypnotic effects, which were first described in animals (Belelli, Bolger and Gee, 1989; Crawley, Glowa, Majewska and Paul, 1986; Mendelson et al., 1987).

It was demonstrated decades ago that neurosteroids increase acutely after various applied stressors in animal models (Barbaccia et al., 1996). Allo, in particular, has been shown to increase in animals following multiple stressors and seems to be involved in a negative feedback mechanism that reduces CRH, ACTH and corticosterone (Barbaccia et al., 1997; Guo et al., 1995; Patchev, Shoaib, Holsboer and Almeida, 1994; Purdy et al., 1991). Increases in neurosteroid levels have also been documented after acute stress exposure in humans and are suggested to be neuroprotective. Physiological stressors that demonstrate changes in allopregnanolone levels are pregnancy and parturition (Luisi et al., 2000a). During their reproductive years, women are chronically exposed to Allo concentrations ranging from less than 1 nmol/l (0.32 ng/ml) to over 4 nmol/l (1.27 ng/ml) during the luteal phase (Genazzani et al., 1998). During pregnancy, the increase in plasma progesterone results in a production rate of Allo that can reach 100 mg per day. The highest concentrations of Allo are reached during the third trimester of pregnancy at levels up to 157 nmol/l (50 ng/ml), which are not associated with adverse effects for either mother or fetus (Dombroski, Casey and MacDonald, 1997; Gago et al., 2004; Luisi et al., 2000b; Jun Ming Wang, Patrick B Johnston, Bret Gene Ball, & Roberta Diaz Brinton, 2005). Allo concentrations subsequently fall after parturition, a finding that has led to its correlation with post-partum behavioral disorders (Osborne, Betz, Yenokyan, Standeven and Payne, 2019). Moreover, allopregnanolone concentrations in the fetal brain are markedly increased in response to acute hypoxic stress caused by umbilical cord constriction, which indicates that a stressor such as prenatal hypoxemia initiates a neurosteroid response that may protect the fetal brain cells from hypoxia (Hirst, Yawno, Nguyen and Walker, 2006). In obstetrics, transient compression of the umbilical cord or uteroplacental insufficiency can be detected in electronic fetal heart monitor tracing as heart decelerations, which are related to interruption of fetal oxygenation (Lee

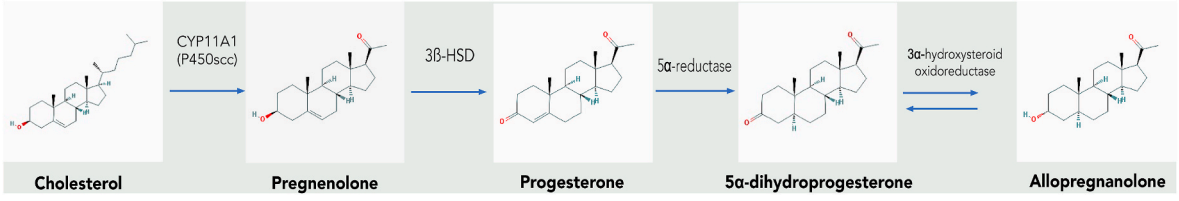

Fig. 1. Allopregnanolone biosynthetic pathway. Steroidogenesis of allopregnanolone starting from cholesterol metabolism. The brain must synthesize its own cholesterol from acetyl-CoA of peripherally circulating cholesterol. In the mitochondria it is converted into pregnenolone by the cytochrome P450 side-chain cleavage enzyme. It is then converted in the cytosol to progesterone. Allo is a reduced metabolite of progesterone synthesized in the adrenal cortex, gonads and central nervous system.

and Hon, 1963; Macones, Hankins, Spong, Hauth and Moore, 2008). In the case of impaired uteroplacental perfusion, decelerations result from chemoreceptor responses to hypoxia, which in mild cases typically leads to decreased fetal movements or sleeping. It has been postulated that the reason for such a fetal response is to reduce oxygen consumption, but perhaps it is also due to increased levels of allopregnanolone which consequently causes sedation. Lastly, increased levels of Allo have been associated with one behavioral condition known as premenstrual dysphoric disorder, in which symptoms are related to a women's menstrual cycle. (Girdler, Straneva, Light, Pedersen and Morrow, 2001). A significant increase in Allo is seen especially during the luteal phase, however symptom severity is not positively correlated with Allo levels, but rather exhibits a biphasic response considering that women with greater mood symptoms have lower levels of allopregnanolone (T. Bäckström et al., 2011; Girdler et al., 2001).

Contrary to what is observed in acute stress, allopregnanolone levels seem to be decreased in chronic stress, which has been attributed to compensatory changes to regain the reduced hypersensitivity of $GABA_A$ receptors (Bali and Jaggi, 2014; Matsumoto, Puia, Dong and Pinna, 2007; Serra, Pisu, Mostallino, Sanna and Biggio, 2008). Neurosteroid reduction in relation to disease-associated stressors has been demonstrated in persons with depression (Elena Romeo et al., 1998; Uzunova et al., 1998), migraines (Rustichelli et al., 2020), post-traumatic stress disorder (PTSD) (Rasmusson et al., 2006), and after blast-related traumatic brain injuries (TBI) (Marx et al., 2016). Patients with mood disorders, including major depression and PTSD, exhibit reduced levels of Allo, including its biosynthesis (Agis-Balboa, Guidotti and Pinna, 2014), in plasma, CSF and brain (Elena Romeo et al., 1998; Uzunova et al., 1998). Moreover, research has shown that treatment with selective serotonin reuptake inhibitors (SSRIs) increases Allo levels in the brain (Pinna, Costa and Guidotti, 2006) or reverses the stress induced decrease of Allo in both animal models and patients with depression (Elena Romeo et al., 1998; Uzunova et al., 1998). Interestingly, decreased neurosteroid levels was not detected in chronic stressors like work-related psychosocial stress and burnout (Torbjörn Bäckström, Bixo, Nyberg and Savic, 2013) perhaps because these are not necessarily disease associated stressors.

Collectively, the work cited above laid the foundation and prompted further research to develop neurosteroids as therapeutic agents. Consequently, a therapeutic development program recently yielded an exogenous formulation of allopregnanolone (Brexanolone) for affective disorders. Brexanolone has been granted a "breakthrough therapy designation" by the FDA for the treatment of post-partum depression (Azhar Y, 2020; Meltzer-Brody et al., 2018). Two separate clinical trials testing brexanolone in women with postpartum depression used a continuous intravenous (IV) titration infusion regimen for up to 60 hours, which resulted in significant and clinically meaningful reductions in Hamilton Rating Scale (HAM-D) for Depression scores compared to placebo (Meltzer-Brody et al., 2018). However, the pattern of adverse events leading to dose reductions or interruptions in the trials show that most were related to excessive sedation or loss of consciousness, which is expected with such a dosing regimen. Brexanolone has since been further developed as an oral formulation with early evidence for improving symptoms of depression, as measured by HAM-D scores, in a phase 3 clinical trial in women with postpartum depression (Kristina M. Deligiannidis et al., 2021).

4. Neurogenesis and allopregnanolone

Neurogenesis in the adult human hippocampus was demonstrated decades ago by Eriksson and colleagues (Eriksson et al., 1998) and others have confirmed that significant neurogenesis occurs in healthy, aging human brains (Boldrini et al., 2018; Spalding et al., 2013). The most prominent adult neurogenic niches are located in the hippocampal subgranular zone (SGZ) of the dentate gyrus and the subventricular zone (SVZ) of the lateral ventricles (Irwin and Brinton, 2014). In the hippocampal neurogenic niche, newborn dentate gyrus granule cells migrate to the granule cell layer and integrate into the adjacent molecular cell layer. As these cells mature, dendrites grow into the molecular cell layer to receive glutamatergic afferents from the entorhinal cortex and their axonal projections form mossy fiber synapses in the CA3 subfield to strengthen neural circuitry and function of the hippocampus (Irwin and Brinton, 2014). In addition to the classic neurogenic areas, newly born interneurons, most destined to be GABAergic, are dispersed throughout the relatively voluminous cortical space (Jurkowski et al., 2020; Lim, Mi, Llorca and Marín, 2018).

The adult neurogenic turnover rate in the neocortex is similar to that of the dentate gyrus, although with differences in cell type, function, and relative numeric ratios to surrounding mature cells (Heather A. Cameron and Dayer, 2008). The regenerative potential of these brain regions continues throughout the duration of life, but neuronal progenitor proliferation dramatically decreases with age in both animal models and humans (H. A. Cameron and McKay, 1999; Knoth et al., 2010; Kuhn, Dickinson-Anson and Gage, 1996). Impaired neurogenesis can result from factors that are associated with age-related degenerative diseases and dementia, such as HPA axis dysregulation, chronic inflammation and stress, and microglial activation (Becker, 2017).

Surget and Belzung reviewed previous theoretical and experimental work which supported the underlying role of adult hippocampal neurogenesis in stress response. Subsequently, they proposed that adult hippocampal neurogenesis, through its computational influences, is instrumental in shaping adaptation to environmental demands (Surget and Belzung, 2021). Neural networks require both plasticity and stability (Mermillod, Bugaiska, & BONIN, 2013). Thus, learning requires plasticity to be able to encode new knowledge and the stability to prevent previous knowledge from being forgotten. Hippocampal neurogenesis seems to influence specific functions of the hippocampus, specifically those that are related to cognitive processes like pattern separation, and those related to behavioral adaptation of stress (Anacker and Hen, 2017; Anacker et al., 2018; Clelland et al., 2009; Snyder, Soumier, Brewer, Pickel and Cameron, 2011). Interestingly, healthy aging has been associated with a decreasing ability of behavioral pattern separation that may be evidenced by episodic memory problems, and has been related to the aging dentate gyrus and concomitant CA3 subregion deficits (Yassa and Stark, 2011). This was demonstrated with diffusion tensor imaging of the perforant path fiber bundle during two behavioral pattern separation tasks, which showed an age-related decrease in diffusion signal (reduced fiber path integrity) (Yassa, Muftuler and Stark, 2010).

A great deal has been written about allopregnanolone's psychotherapeutic effects, but very little emphasis has been placed on allopregnanolone's regenerative effects (Fig. 2). Perhaps the most intriguing finding related to the effects of Allo was that allopregnanolone rapidly induced cytoarchitectural regression in cultured fetal hippocampal neurons, which later was shown to be a prelude to mitogenesis (R. Brinton, 1994; J. M. Wang, P. B. Johnston, B. G. Ball, & R. D. Brinton, 2005). Subsequently, Brinton and colleagues demonstrated that allopregnanolone, in a dose-dependent manner, induced a significant increase in proliferation of neuroprogenitor cells (NPCs) derived from the rat hippocampus and human neural stem cells (hNSCs) derived from the cerebral cortex (J. M. Wang et al., 2005). Based on those findings, they later demonstrated that a single administration of Allo reversed both neurogenic and cognitive deficits *in vivo* in male 3xTgAD mice prior to the appearance of Alzheimer's disease (AD) pathology (J. M. Wang et al., 2010). Important for therapeutic potential, Allo significantly increased neurogenesis and functionally reversed cognitive deficits in male 3xTgAD mice following the onset of AD pathology (Chen et al., 2011). In summary, Allo significantly increased the number of newly generated cells and increased their survival, restoring the regenerative potential of the brain to normal without exceeding normal (Singh et al., 2012; J. M. Wang et al., 2010). Such regenerative effect of Allo is dose-dependent and exhibits a classic U-shaped dose-response curve

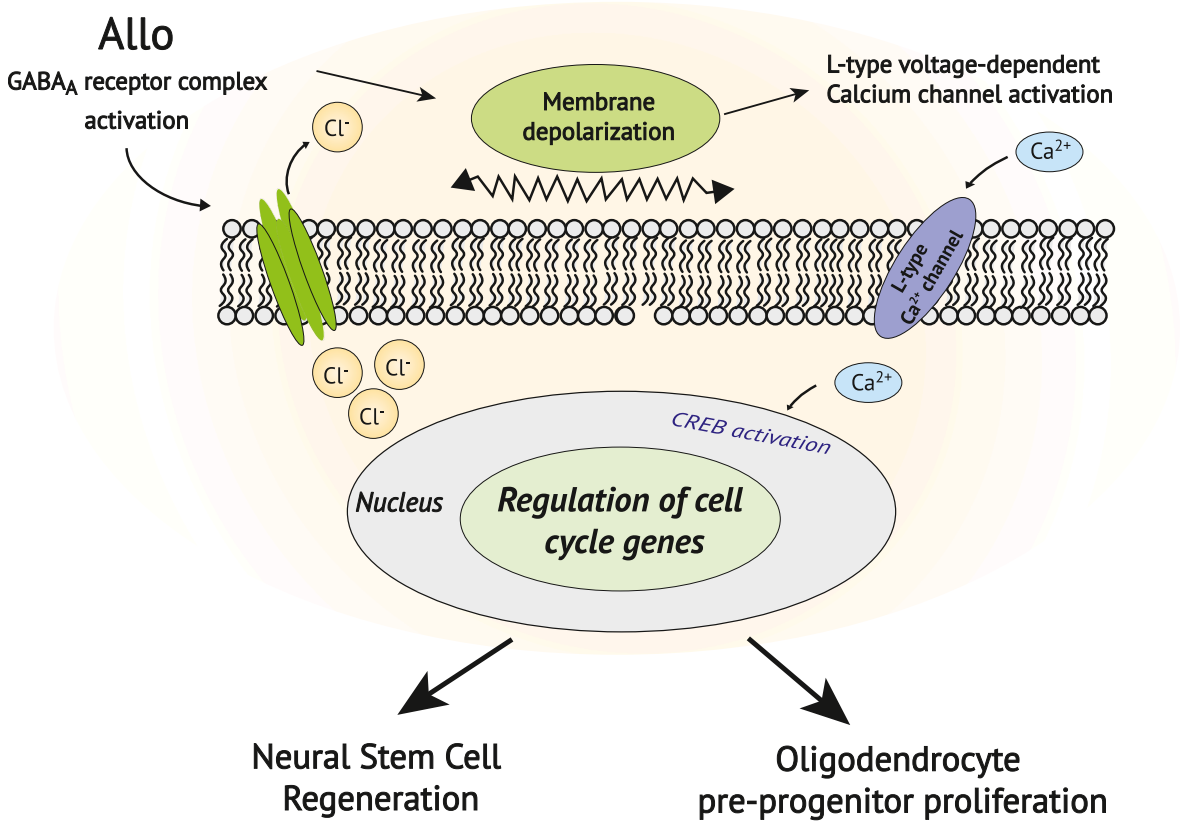

Fig. 2. Allopregnanolone regenerative mechanism of action. Allo activates the GABA$_A$ receptor complex promoting the efflux of chloride (Cl^-) ions from neural progenitor and neural stem cells. Extrusion of Cl^- from the intracellular compartment causes membrane depolarization and activation of voltage dependent L-type calcium (Ca^{2+}) channels. The resulting rise in intracellular Ca^{2+} activates calcium dependent kinases that will ultimately lead to regulation of gene expression and protein synthesis of cell cycle proteins.

indicating that more is not better. Based on that principle high doses of Allo, that induce a sedative response, do not promote neurogenesis. The inverted-U shaped dose response profile of Allo is particularly important from a safety perspective. Greater than normal concentrations of Allo or continuous unrelenting exposure to Allo inhibit neurogenesis thereby protecting against uncontrolled cell proliferation (Irwin and Brinton, 2014).

The aforementioned body of preclinical work has led to the clinical development of Allo as a novel regenerative therapeutic for Alzheimer's disease (Irwin and Brinton, 2014). Allo was administered for the first time in persons diagnosed with mild cognitive impairment due to AD or mild AD in a phase 1b/2a clinical trial (ClinicalTrials.gov Identifier: NCT02221622). Outcomes demonstrated that Allo was safe and well-tolerated after a single IV infusion and after weekly IV infusions for 12 weeks (G. D. Hernandez et al., 2020). A maximally tolerated dose of 6 mg was established using sedation as a threshold which interestingly demonstrated a sex difference in sedation tolerance. Women exhibited signs of sedation at doses $\geq$10 mg whereas men did at doses $\geq$ 6 mg. Therefore, to optimally target neurogenesis, the sub-sedative dose of 4 mg was chosen for the treatment regimen (G. D. Hernandez et al., 2020).

Exploratory analyses indicated that Allo has the potential to slow the rate of decline in hippocampal volume and may increase volume in participants who were APOE e4 carriers. Furthermore, multiple measures of white matter integrity indicated evidence of preserved or improved integrity. Allo significantly increased fiber tract fractional anisotropy and quantitative anisotropy, primarily in the corpus callosum, bilateral thalamic radiations, and bilateral corticospinal tracts. Lastly, consistent with structural changes in the brain, Allo increased local, interregional, and network-level functional connectivity in AD-vulnerable regions, including the precuneus and posterior cingulate, and network connections between the default mode network and limbic system.

Interestingly, women with postpartum depression and low levels of Allo have shown to have a reduced resting-state functional connectivity within corticolimbic regions such as anterior cingulate cortex, bilateral amygdala, hippocampus and dorsolateral prefrontal cortices (K. M. Deligiannidis et al., 2013).

Using surrogate imaging biomarkers as indicators of regeneration, we hypothesize that the regenerative effect of Allo has the potential to reverse the altered brain structure and function caused by chronic stress and seen in the progression of neurodegenerative diseases (Fig. 3). Based on the preclinical and early clinical evidence, we reasoned that if Allo exerts a regenerative effect in the brain then regeneration of the hippocampus could be evident in MRI detectable structural change: either as an increase in hippocampal volume relative to a participant's baseline and to placebo-treated participants, or a decrease in the magnitude of hippocampal atrophy relative to a participant's baseline and to placebo. Moreover, if Allo is promoting oligogenesis then indicators of white matter structural integrity could be detectable using diffusion tensor imaging. If Allo is improving or maintaining structural connectivity, we reasoned that functional connectivity could be an indicator of restored or regenerated synaptic neural networks. Lastly, if Allo is promoting neurogenesis and myelin-genesis then functional regeneration could be affected as indicated by an increase in local connectivity within functionally homogeneous regions (Raikes et al., 2022).

The development of Allo as a regenerative therapeutic (Fig. 4) continues with an upcoming phase 2, multi-center, double-blind, randomized, placebo-controlled, clinical trial assessing efficacy and further testing the safety of Allo (ClinicalTrials.gov Identifier: NCT04838301). This is a proof-of-concept trial of 18 months duration, with a parallel

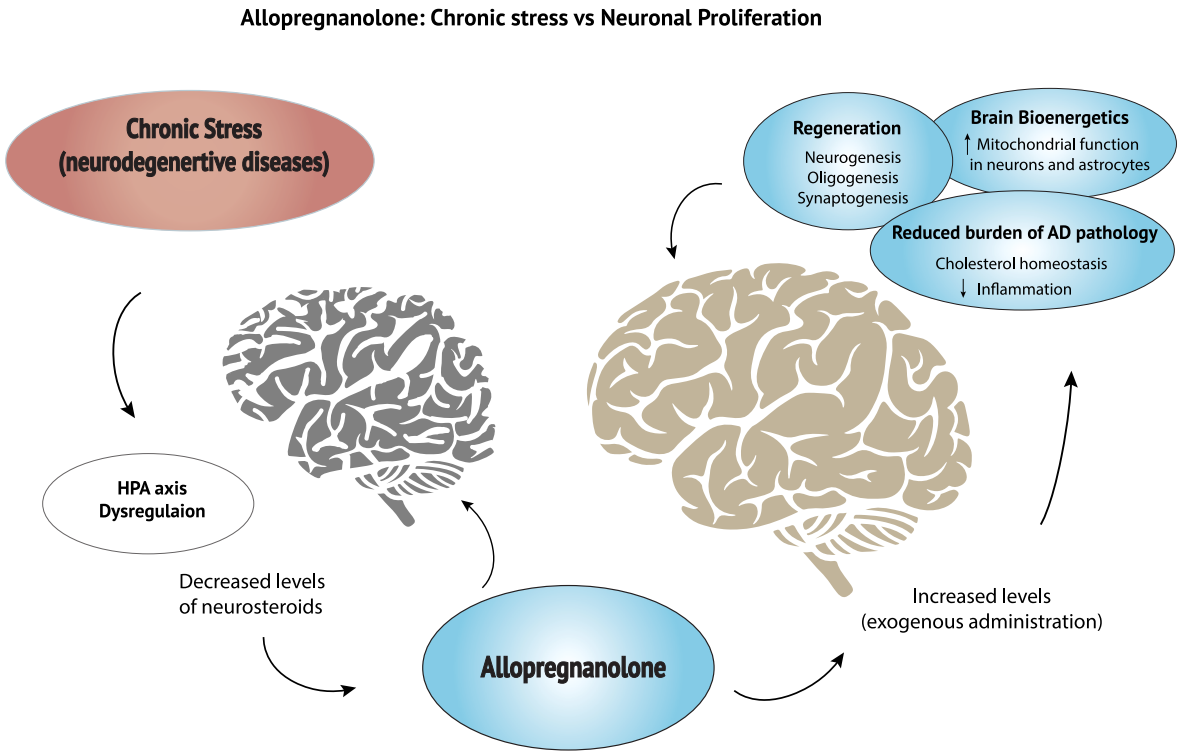

Fig. 3. Reversing altered brain structure and function. Chronic stress results in decreased levels of allopregnanolone which affects brain structure (i.e., brain atrophy) and function. Increased levels of allopregnanolone results in neural proliferation and improved brain structure and function.

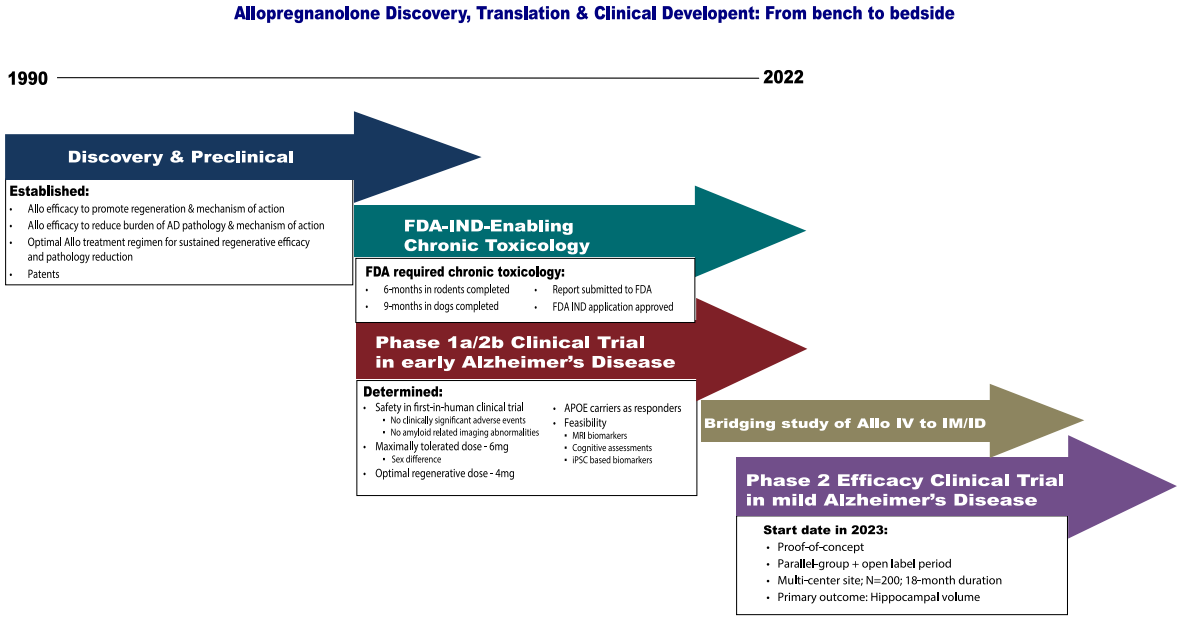

Fig. 4. Allopregnanolone's translational development progress: From early discovery to current clinical testing.

group design for the initial 12 months followed by an open-label period of 6 months, which will utilize an imaging endpoint as a surrogate biomarker of regeneration. Based on outcomes from the previous phase 1b/2a study, participants will be male and female, ranging in age from 55 to 80 years old, with an APOE e4-positive genotype and diagnosed with probable AD. Participants will receive weekly, 30-min intravenous infusions of Allo 4 mg or placebo.

5. Conclusions

The neurobiology of stress plays an important role in chronic inflammation and the development of neurodegenerative diseases. Advancements in neurosteroid research have led to the identification of multiple targets for drug development, but the most promising innovative target may be neurogenesis, given its potential impact in neurodegenerative disorders like Alzheimer's disease. This target has enabled the development of allopregnanolone as a regenerative therapeutic to restore neurological health.

CRediT authorship contribution statement

Gerson D. Hernandez: Writing – original draft, Visualization, Investigation, Conceptualization. **Roberta D. Brinton:** Writing – review & editing, Supervision, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Roberta Brinton reports a relationship with Neutherapeutics that includes: board membership. Gerson Hernandez reports a relationship with Neutherapeutics that includes: consulting or advisory. Roberta Brinton has patent #US8969329B2 issued to Roberta Brinton.

Acknowledgement

This research has been suppported by the National Institute on Aging, grant/award numbers: UF1AG046148, U01AG031115, U01AG047222, P50AG05142, R01AG063826; and, Alzheimer Drug Discovery Foundation grant 20150701.01.

References

Agis-Balboa, R.C., Guidotti, A., Pinna, G., 2014. 5α-reductase type I expression is downregulated in the prefrontal cortex/Brodmann's area 9 (BA9) of depressed patients. Psychopharmacology 231 (17), 3569–3580. https://doi.org/10.1007/s00213-014-3567-5.

Anacker, C., Hen, R., 2017. Adult hippocampal neurogenesis and cognitive flexibility - linking memory and mood. Nat. Rev. Neurosci. 18 (6), 335–346. https://doi.org/10.1038/nrn.2017.45.

Anacker, C., Luna, V.M., Stevens, G.S., Millette, A., Shores, R., Jimenez, J.C., Hen, R., 2018. Hippocampal neurogenesis confers stress resilience by inhibiting the ventral dentate gyrus. Nature 559 (7712), 98–102. https://doi.org/10.1038/s41586-018-0262-4.

Azhar Y, D.A., 2020. BrexanoloneStatPearls. Retrieved from. https://www.ncbi.nlm.nih.gov/books/NBK541054/.

Bäckström, T., Bixo, M., Nyberg, S., Savic, I., 2013. Increased neurosteroid sensitivity – an explanation to symptoms associated with chronic work related stress in women? Psychoneuroendocrinology 38 (7), 1078–1089. https://doi.org/10.1016/j.psyneuen.2012.10.014.

Bäckström, T., Haage, D., Löfgren, M., Johansson, I.M., Strömberg, J., Nyberg, S., Bengtsson, S.K., 2011. Paradoxical effects of GABA-A modulators may explain sex steroid induced negative mood symptoms in some persons. Neuroscience 191, 46–54. https://doi.org/10.1016/j.neuroscience.2011.03.061.

Bali, A., Jaggi, A.S., 2014. Multifunctional aspects of allopregnanolone in stress and related disorders. Prog. Neuro Psychopharmacol. Biol. Psychiatr. 48, 64–78. https://doi.org/10.1016/j.pnpbp.2013.09.005.

Barbaccia, M.L., Roscetti, G., Trabucchi, M., Mostallino, M.C., Concas, A., Purdy, R.H., Biggio, G., 1996. Time-dependent changes in rat brain neuroactive steroid concentrations and GABAA receptor function after acute stress. Neuroendocrinology 63 (2), 166–172. https://doi.org/10.1159/000126953.

Barbaccia, M.L., Roscetti, G., Trabucchi, M., Purdy, R.H., Mostallino, M.C., Concas, A., Biggio, G., 1997. The effects of inhibitors of GABAergic transmission and stress on brain and plasma allopregnanolone concentrations. Br. J. Pharmacol. 120 (8), 1582–1588. https://doi.org/10.1038/sj.bjp.0701046.

Baulieu, E.E., 1981. Steroid hormones in the brain: several mechanisms? In: Fuxe, K., Gustafsson, J.-Å., Wetterberg, L. (Eds.), Steroid Hormone Regulation of the Brain. Pergamon, pp. 3–14.

Baulieu, E.E., Robel, P., 1990. Neurosteroids: a new brain function? J. Steroid Biochem. Mol. Biol. 37 (3), 395–403. https://doi.org/10.1016/0960-0760(90)90490-c.

Baulieu, E.E., Robel, P., Schumacher, M., 2001. Neurosteroids: beginning of the story. In: International Review of Neurobiology, vol. 46. Academic Press, pp. 1–32.

Becker, S., 2017. Neurogenesis and pattern separation: time for a divorce. Wiley Interdiscip Rev Cogn Sci 8 (3). https://doi.org/10.1002/wcs.1427.

Belelli, D., Bolger, M.B., Gee, K.W., 1989. Anticonvulsant profile of the progesterone metabolite 5 alpha-pregnan-3 alpha-ol-20-one. Eur. J. Pharmacol. 166 (2), 325–329. https://doi.org/10.1016/0014-2999(89)90077-0.

Boldrini, M., Fulmore, C.A., Tartt, A.N., Simeon, L.R., Pavlova, I., Poposka, V., Mann, J. J., 2018. Human hippocampal neurogenesis persists throughout aging. Cell Stem Cell 22 (4), 589–599. https://doi.org/10.1016/j.stem.2018.03.015 e585.

Brinton, R., 1994. The neurosteroid 3 alpha-hydroxy-5 alpha-pregnan-20-one induces cytoarchitectural regression in cultured fetal hippocampal neurons. J. Neurosci. 14 (5), 2763–2774. https://doi.org/10.1523/jneurosci.14-05-02763.1994.

Brinton, R.D., 2013. Neurosteroids as regenerative agents in the brain: therapeutic implications. Nat. Rev. Endocrinol. 9 (4), 241–250. https://doi.org/10.1038/nrendo.2013.31.

Cameron, H.A., Dayer, A.G., 2008. New interneurons in the adult neocortex: small, sparse, but significant? Biol. Psychiatr. 63 (7), 650–655. https://doi.org/10.1016/j.biopsych.2007.09.023.

Cameron, H.A., McKay, R.D.G., 1999. Restoring production of hippocampal neurons in old age. Nat. Neurosci. 2 (10), 894–897. https://doi.org/10.1038/13197.

Chen, S., Wang, J.M., Irwin, R.W., Yao, J., Liu, L., Brinton, R.D., 2011. Allopregnanolone promotes regeneration and reduces β-amyloid burden in a preclinical model of alzheimer's disease. PLoS One 6 (8), e24293. https://doi.org/10.1371/journal.pone.0024293.

Clelland, C.D., Choi, M., Romberg, C., Clemenson Jr., G.D., Fragniere, A., Tyers, P., Bussey, T.J., 2009. A functional role for adult hippocampal neurogenesis in spatial pattern separation. Science 325 (5937), 210–213. https://doi.org/10.1126/science.1173215.

Corpéchot, C., Synguelakis, M., Talha, S., Axelson, M., Sjövall, J., Vihko, R., Robel, P., 1983. Pregnenolone and its sulfate ester in the rat brain. Brain Res. 270 (1), 119–125. https://doi.org/10.1016/0006-8993(83)90797-7.

Crawley, J.N., Glowa, J.R., Majewska, M.D., Paul, S.M., 1986. Anxiolytic activity of an endogenous adrenal steroid. Brain Res. 398 (2), 382–385. https://doi.org/10.1016/0006-8993(86)91500-3.

De Kloet, E.R., Vreugdenhil, E., Oitzl, M.S., Joëls, M., 1997. Glucocorticoid feedback resistance. Trends Endocrinol. Metabol. 8 (1), 26–33. https://doi.org/10.1016/S1043-2760(96)00205-6.

Deligiannidis, K.M., Meltzer-Brody, S., Gunduz-Bruce, H., Doherty, J., Jonas, J., Li, S., Lasser, R., 2021. Effect of zuranolone vs placebo in postpartum depression: a randomized clinical trial. JAMA Psychiatr. 78 (9), 951–959. https://doi.org/10.1001/jamapsychiatry.2021.1559.

Deligiannidis, K.M., Sikoglu, E.M., Shaffer, S.A., Frederick, B., Svenson, A.E., Kopoyan, A., Moore, C.M., 2013. GABAergic neuroactive steroids and resting-state functional connectivity in postpartum depression: a preliminary study. J. Psychiatr. Res. 47 (6), 816–828. https://doi.org/10.1016/j.jpsychires.2013.02.010.

Dombroski, R.A., Casey, M.L., MacDonald, P.C., 1997. 5-Alpha-dihydroprogesterone formation in human placenta from 5alpha-pregnan-3beta/alpha-ol-20-ones and 5-pregnan-3beta-yl-20-one sulfate. J. Steroid Biochem. Mol. Biol. 63 (1–3), 155–163. Retrieved from. https://www.ncbi.nlm.nih.gov/pubmed/9449217.

Romeo, Elena, Ströhle, Andreas, Spalletta, Gianfranco, Michele, Flavia di, Hermann, Bettina, Holsboer, Florian, Rupprecht, Rainer, 1998. Effects of antidepressant treatment on neuroactive steroids in major depression. Am. J. Psychiatr. 155 (7), 910–913. https://doi.org/10.1176/ajp.155.7.910.

Engel, S.R., Grant, K.A., 2001. Neurosteroids and behavior. Int. Rev. Neurobiol. 46, 321–348. https://doi.org/10.1016/s0074-7742(01)46067-3.

Eriksson, P.S., Perfilieva, E., Björk-Eriksson, T., Alborn, A.M., Nordborg, C., Peterson, D. A., Gage, F.H., 1998. Neurogenesis in the adult human hippocampus. Nat. Med. 4 (11), 1313–1317. https://doi.org/10.1038/3305.

Gago, N., El-Etr, M., Sananes, N., Cadepond, F., Samuel, D., Avellana-Adalid, V., Schumacher, M., 2004. 3α, 5α-tetrahydroprogesterone (allopregnanolone) and γ-aminobutyric acid: autocrine/paracrine interactions in the control of neonatal PSA-NCAM+ progenitor proliferation. J. Neurosci. Res. 78 (6), 770–783.

Gee, K.W., 1988. Steroid modulation of the GABA/benzodiazepine receptor-linked chloride ionophore. Mol. Neurobiol. 2 (4), 291–317. https://doi.org/10.1007/bf02935636.

Gee, K.W., Bolger, M.B., Brinton, R.E., Coirini, H., McEwen, B.S., 1988. Steroid modulation of the chloride ionophore in rat brain: structure-activity requirements, regional dependence and mechanism of action. J. Pharmacol. Exp. Therapeut. 246 (2), 803–812.

Gee, K.W., Chang, W.C., Brinton, R.E., McEwen, B.S., 1987. GABA-dependent modulation of the Cl- ionophore by steroids in rat brain. Eur. J. Pharmacol. 136 (3), 419–423. https://doi.org/10.1016/0014-2999(87)90317-7.

Genazzani, A.R., Petraglia, F., Bernardi, F., Casarosa, E., Salvestroni, C., Tonetti, A., Luisi, M., 1998. Circulating levels of allopregnanolone in humans: gender, age, and endocrine influences. J. Clin. Endocrinol. Metab. 83 (6), 2099–2103. https://doi.org/10.1210/jcem.83.6.4905.

Girdler, S.S., Straneva, P.A., Light, K.C., Pedersen, C.A., Morrow, A.L., 2001. Allopregnanolone levels and reactivity to mental stress in premenstrual dysphoric disorder. Biol. Psychiatr. 49 (9), 788–797. https://doi.org/10.1016/S0006-3223(00)01044-1.

Guo, A.L., Petraglia, F., Criscuolo, M., Ficarra, G., Nappi, R.E., Palumbo, M.A., Genazzani, A.R., 1995. Evidence for a role of neurosteroids in modulation of diurnal changes and acute stress-induced corticosterone secretion in rats. Gynecol. Endocrinol. 9 (1), 1–7. https://doi.org/10.3109/09513599509160184.

Heneka, M.T., Carson, M.J., El Khoury, J., Landreth, G.E., Brosseron, F., Feinstein, D.L., Kummer, M.P., 2015. Neuroinflammation in Alzheimer's disease. Lancet Neurol. 14 (4), 388–405. https://doi.org/10.1016/s1474-4422(15)70016-5.

Hernandez, G., Zhao, L., Franke, A.A., Chen, Y.-L., Mack, W.J., Brinton, R.D., Schneider, L.S., 2018. Pharmacokinetics and safety profile of single-dose administration of an estrogen receptor β-selective phytoestrogenic (phytoSERM) formulation in perimenopausal and postmenopausal women. Menopause 25 (2), 191–196. https://doi.org/10.1097/gme.0000000000000984.

Hernandez, G.D., Solinsky, C.M., Mack, W.J., Kono, N., Rodgers, K.E., Wu, C.Y., Brinton, R.D., 2020. Safety, tolerability, and pharmacokinetics of allopregnanolone as a regenerative therapeutic for Alzheimer's disease: a single and multiple ascending dose phase 1b/2a clinical trial. Alzheimers Dement (N Y) 6 (1), e12107. https://doi.org/10.1002/trc2.12107.

Herrera, A.J., Espinosa-Oliva, A.M., Carrillo-Jiménez, A., Oliva-Martín, M.J., García-Revilla, J., García-Quintanilla, A., Venero, J.L., 2015. Relevance of chronic stress and the two faces of microglia in Parkinson's disease. Front. Cell. Neurosci. 9 (312) https://doi.org/10.3389/fncel.2015.00312.

Hiller, A., Quinn, J., Schmidt, P., 2017. Does psychological stress affect the progression of Parkinson's disease (N5.002). Neurology 88 (16 Suppl. ment). N5.002. Retrieved from. http://n.neurology.org/content/88/16_Supplement/N5.002.abstract.
Hirst, J.J., Yawno, T., Nguyen, P., Walker, D.W., 2006. Stress in pregnancy activates neurosteroid production in the fetal brain. Neuroendocrinology 84 (4), 264–274. https://doi.org/10.1159/000097990.
Holmes, C., 2013. Review: systemic inflammation and Alzheimer's disease. Neuropathol. Appl. Neurobiol. 39 (1), 51–68. https://doi.org/10.1111/j.1365-2990.2012.01307.x.
Holsboer, F., Barden, N., 1996. Antidepressants and hypothalamic-pituitary-adrenocortical regulation. Endocr. Rev. 17 (2), 187–205. https://doi.org/10.1210/edrv-17-2-187.
Hu, Z.Y., Bourreau, E., Jung-Testas, I., Robel, P., Baulieu, E.E., 1987. Neurosteroids: oligodendrocyte mitochondria convert cholesterol to pregnenolone. Proc. Natl. Acad. Sci. U. S. A. 84 (23), 8215–8219. https://doi.org/10.1073/pnas.84.23.8215.
Irwin, R.W., Brinton, R.D., 2014. Allopregnanolone as regenerative therapeutic for Alzheimer's disease: translational development and clinical promise. Prog. Neurobiol. 113, 40–55. https://doi.org/10.1016/j.pneurobio.2013.08.004.
Jurkowski, M.P., Bettio, L., K. Woo, E., Patten, A., Yau, S.-Y., Gil-Mohapel, J., 2020. Beyond the Hippocampus and the SVZ: adult neurogenesis throughout the brain. Front. Cell. Neurosci. 14 https://doi.org/10.3389/fncel.2020.576444.
Justice, N.J., 2018. The relationship between stress and Alzheimer's disease. Neurobiology of stress 8, 127–133. https://doi.org/10.1016/j.ynstr.2018.04.002.
Knoth, R., Singec, I., Ditter, M., Pantazis, G., Capetian, P., Meyer, R.P., Kempermann, G., 2010. Murine features of neurogenesis in the human hippocampus across the lifespan from 0 to 100 years. PLoS One 5 (1). https://doi.org/10.1371/journal.pone.0008809.
Kuhn, H.G., Dickinson-Anson, H., Gage, F.H., 1996. Neurogenesis in the dentate gyrus of the adult rat: age-related decrease of neuronal progenitor proliferation. J. Neurosci. 16 (6), 2027–2033. https://doi.org/10.1523/jneurosci.16-06-02027.1996.
Lee, S.T., Hon, E.H., 1963. Fetal hemodynamic response to umbilical cord compression. Obstet. Gynecol. 22, 553–562.
Lim, L., Mi, D., Llorca, A., Marín, O., 2018. Development and functional diversification of cortical interneurons. Neuron 100 (2), 294–313. https://doi.org/10.1016/j.neuron.2018.10.009.
Luisi, S., Petraglia, F., Benedetto, C., Nappi, R.E., Bernardi, F., Fadalti, M., Genazzani, A. R., 2000a. Serum allopregnanolone levels in pregnant women: changes during pregnancy, at delivery, and in hypertensive patients. J. Clin. Endocrinol. Metab. 85 (7), 2429–2433. https://doi.org/10.1210/jcem.85.7.6675.
Luisi, S., Petraglia, F., Benedetto, C., Nappi, R.E., Bernardi, F., Fadalti, M., Genazzani, A. R., 2000b. Serum allopregnanolone levels in pregnant women: changes during pregnancy, at delivery, and in hypertensive patients. J. Clin. Endocrinol. Metab. 85 (7), 2429–2433. https://doi.org/10.1210/jcem.85.7.6675.
Macones, G.A., Hankins, G.D., Spong, C.Y., Hauth, J., Moore, T., 2008. The 2008 National Institute of Child Health and Human Development workshop report on electronic fetal monitoring: update on definitions, interpretation, and research guidelines. Obstet. Gynecol. 112 (3), 661–666. https://doi.org/10.1097/AOG.0b013e3181841395.
Madore, C., Yin, Z., Leibowitz, J., Butovsky, O., 2020. Microglia, lifestyle stress, and neurodegeneration. Immunity 52 (2), 222–240. https://doi.org/10.1016/j.immuni.2019.12.003.
Marx, C.E., Naylor, J.C., Kilts, J.D., Dunn, C.E., Tupler, L.A., Szabo, S.T., Acheson, S.K., 2016. Frontiers in neuroscience neurosteroids and traumatic brain injury: translating biomarkers to therapeutics; overview and pilot investigations in Iraq and Afghanistan era veterans. In: Laskowitz, D., Grant, G. (Eds.), Translational Research in Traumatic Brain Injury. CRC Press/Taylor and Francis Group, Boca Raton (FL.
Matsumoto, K., Puia, G., Dong, E., Pinna, G., 2007. GABAA receptor neurotransmission dysfunction in a mouse model of social isolation-induced stress: possible insights into a non-serotonergic mechanism of action of SSRIs in mood and anxiety disorders. Stress 10 (1), 3–12. https://doi.org/10.1080/10253890701200997.
McEwen, B.S., 2006. Protective and damaging effects of stress mediators: central role of the brain. Dialogues Clin. Neurosci. 8 (4), 367–381. https://doi.org/10.31887/DCNS.2006.8.4/bmcewen.
McEwen, B.S., 2007. Physiology and neurobiology of stress and adaptation: central role of the brain. Physiol. Rev. 87 (3), 873–904. https://doi.org/10.1152/physrev.00041.2006.
McEwen, B.S., 2016. In pursuit of resilience: stress, epigenetics, and brain plasticity. Ann. N. Y. Acad. Sci. 1373 (1), 56–64. https://doi.org/10.1111/nyas.13020.
McEwen, B.S., Bowles, N.P., Gray, J.D., Hill, M.N., Hunter, R.G., Karatsoreos, I.N., Nasca, C., 2015. Mechanisms of stress in the brain. Nat. Neurosci. 18 (10), 1353–1363. https://doi.org/10.1038/nn.4086.
McEwen, B.S., Gianaros, P.J., 2010. Central role of the brain in stress and adaptation: links to socioeconomic status, health, and disease. Ann. N. Y. Acad. Sci. 1186, 190–222. https://doi.org/10.1111/j.1749-6632.2009.05331.x.
McEwen, B.S., Gianaros, P.J., 2011. Stress- and allostasis-induced brain plasticity. Annu. Rev. Med. 62, 431–445. https://doi.org/10.1146/annurev-med-052209-100430.
Meltzer-Brody, S., Colquhoun, H., Riesenberg, R., Epperson, C.N., Deligiannidis, K.M., Rubinow, D.R., Kanes, S., 2018. Brexanolone injection in post-partum depression: two multicentre, double-blind, randomised, placebo-controlled, phase 3 trials. Lancet 392 (10152), 1058–1070. https://doi.org/10.1016/s0140-6736(18)31551-4.
Mendelson, W.B., Martin, J.V., Perlis, M., Wagner, R., Majewska, M.D., Paul, S.M., 1987. Sleep induction by an adrenal steroid in the rat. Psychopharmacology (Berl) 93 (2), 226–229. https://doi.org/10.1007/bf00179939.
Mermillod, M., Bugaiska, A., Bonin, P., 2013. The stability-plasticity dilemma: investigating the continuum from catastrophic forgetting to age-limited learning effects. Front. Psychol. 4 https://doi.org/10.3389/fpsyg.2013.00504.
Miczek, K.A., Fish, E.W., De Bold, J.F., 2003. Neurosteroids, GABAA receptors, and escalated aggressive behavior. Horm. Behav. 44 (3), 242–257. https://doi.org/10.1016/j.yhbeh.2003.04.002.
Mishra, A., Brinton, R.D., 2018. Inflammation: bridging age, menopause and APOEε4 genotype to Alzheimer's disease. Front. Aging Neurosci. 10 (312) https://doi.org/10.3389/fnagi.2018.00312.
Osborne, L.M., Betz, J.F., Yenokyan, G., Standeven, L.R., Payne, J.L., 2019. The role of allopregnanolone in pregnancy in predicting postpartum anxiety symptoms. Front. Psychol. 10 https://doi.org/10.3389/fpsyg.2019.01033.
Patchev, V.K., Shoaib, M., Holsboer, F., Almeida, O.F., 1994. The neurosteroid tetrahydroprogesterone counteracts corticotropin-releasing hormone-induced anxiety and alters the release and gene expression of corticotropin-releasing hormone in the rat hypothalamus. Neuroscience 62 (1), 265–271. https://doi.org/10.1016/0306-4522(94)90330-1.
Paul, S.M., Purdy, R.H., 1992. Neuroactive steroids. FASEB (Fed. Am. Soc. Exp. Biol.) J. 6 (6), 2311–2322. https://doi.org/10.1096/fasebj.6.6.1347506.
Pinna, G., Costa, E., Guidotti, A., 2006. Fluoxetine and norfluoxetine stereospecifically and selectively increase brain neurosteroid content at doses that are inactive on 5-HT reuptake. Psychopharmacology 186 (3), 362–372. https://doi.org/10.1007/s00213-005-0213-2.
Purdy, R.H., Morrow, A.L., Moore Jr., P.H., Paul, S.M., 1991. Stress-induced elevations of gamma-aminobutyric acid type A receptor-active steroids in the rat brain. Proc. Natl. Acad. Sci. U. S. A. 88 (10), 4553–4557. https://doi.org/10.1073/pnas.88.10.4553.
Raikes, A.C., Hernandez, G.D., Matthews, D.C., Lukic, A.S., Law, M., Shi, Y., Brinton, R. D., 2022. Exploratory imaging outcomes of a phase 1b/2a clinical trial of allopregnanolone as a regenerative therapeutic for Alzheimer's disease: structural effects and functional connectivity outcomes. Alzheimers Dement (N Y) 8 (1), e12258. https://doi.org/10.1002/trc2.12258.
Rasmusson, A.M., Pinna, G., Paliwal, P., Weisman, D., Gottschalk, C., Charney, D., Guidotti, A., 2006. Decreased cerebrospinal fluid allopregnanolone levels in women with posttraumatic stress disorder. Biol. Psychiatr. 60 (7), 704–713. https://doi.org/10.1016/j.biopsych.2006.03.026.
Rustichelli, C., Bellei, E., Bergamini, S., Monari, E., Baraldi, C., Castro, F.L., Ferrari, A., 2020. Serum levels of allopregnanolone, progesterone and testosterone in menstrually-related and postmenopausal migraine: a cross-sectional study. Cephalalgia 40 (12), 1355–1362. https://doi.org/10.1177/0333102420937742.
Schneider, L.S., Hernandez, G., Zhao, L., Franke, A.A., Chen, Y.L., Pawluczyk, S., Brinton, R.D., 2019. Safety and feasibility of estrogen receptor-β targeted phytoSERM formulation for menopausal symptoms: phase 1b/2a randomized clinical trial. Menopause 26 (8), 874–884. https://doi.org/10.1097/gme.0000000000001325.
Serra, M., Pisu, M.G., Mostallino, M.C., Sanna, E., Biggio, G., 2008. Changes in neuroactive steroid content during social isolation stress modulate GABAA receptor plasticity and function. Brain Res. Rev. 57 (2), 520–530. https://doi.org/10.1016/j.brainresrev.2007.06.029.
Singh, C., Liu, L., Wang, J.M., Irwin, R.W., Yao, J., Chen, S., Brinton, R.D., 2012. Allopregnanolone restores hippocampal-dependent learning and memory and neural progenitor survival in aging 3xTgAD and nonTg mice. Neurobiol. Aging 33 (8), 1493–1506. https://doi.org/10.1016/j.neurobiolaging.2011.06.008.
Snyder, J.S., Soumier, A., Brewer, M., Pickel, J., Cameron, H.A., 2011. Adult hippocampal neurogenesis buffers stress responses and depressive behaviour. Nature 476 (7361), 458–461. https://doi.org/10.1038/nature10287.
Spalding, K.L., Bergmann, O., Alkass, K., Bernard, S., Salehpour, M., Huttner, H.B., Frisén, J., 2013. Dynamics of hippocampal neurogenesis in adult humans. Cell 153 (6), 1219–1227. https://doi.org/10.1016/j.cell.2013.05.002.
Surget, A., Belzung, C., 2021. Adult hippocampal neurogenesis shapes adaptation and improves stress response: a mechanistic and integrative perspective. Mol. Psychiatr. https://doi.org/10.1038/s41380-021-01136-8.
Swaab, D.F., Bao, A.M., Lucassen, P.J., 2005. The stress system in the human brain in depression and neurodegeneration. Ageing Res. Rev. 4 (2), 141–194. https://doi.org/10.1016/j.arr.2005.03.003.
Taylor, A.L., Fishman, L.M., 1988. Corticotropin-releasing hormone. N. Engl. J. Med. 319 (4), 213–222. https://doi.org/10.1056/nejm198807283190405.
Uzunova, V., Sheline, Y., Davis, J.M., Rasmusson, A., Uzunov, D.P., Costa, E., Guidotti, A., 1998. Increase in the cerebrospinal fluid content of neurosteroids in patients with unipolar major depression who are receiving fluoxetine or fluvoxamine. Proc. Natl. Acad. Sci. U. S. A. 95 (6), 3239–3244. https://doi.org/10.1073/pnas.95.6.3239.
Vyas, S., Rodrigues, A.J., Silva, J.M., Tronche, F., Almeida, O.F.X., Sousa, N., Sotiropoulos, I., 2016. Chronic stress and glucocorticoids: from neuronal plasticity to neurodegeneration. Neural Plast. 2016, 6391686 https://doi.org/10.1155/2016/6391686.
Wang, J.M., Johnston, P.B., Ball, B.G., Brinton, R.D., 2005. The neurosteroid allopregnanolone promotes proliferation of rodent and human neural progenitor cells and regulates cell-cycle gene and protein expression. J. Neurosci. 25 (19), 4706–4718. Retrieved from. http://www.jneurosci.org/content/jneuro/25/19/4706.full.pdf.
Wang, J.M., Singh, C., Liu, L., Irwin, R.W., Chen, S., Chung, E.J., Brinton, R.D., 2010. Allopregnanolone reverses neurogenic and cognitive deficits in mouse model of Alzheimer's disease. Proc. Natl. Acad. Sci. USA 107 (14), 6498–6503. https://doi.org/10.1073/pnas.1001422107.
Wang, Y., Hernandez, G., Mack, W.J., Schneider, L.S., Yin, F., Brinton, R.D., 2020. Retrospective analysis of phytoSERM for management of menopause-associated vasomotor symptoms and cognitive decline: a pilot study on pharmacogenomic effects of mitochondrial haplogroup and APOE genotype on therapeutic efficacy. Menopause 27 (1), 57–65. https://doi.org/10.1097/gme.0000000000001418.

Yassa, M.A., Muftuler, L.T., Stark, C.E.L., 2010. Ultrahigh-resolution microstructural diffusion tensor imaging reveals perforant path degradation in aged humans in vivo. Proc. Natl. Acad. Sci. USA 107 (28), 12687–12691. https://doi.org/10.1073/pnas.1002113107.

Yassa, M.A., Stark, C.E.L., 2011. Pattern separation in the hippocampus. Trends Neurosci. 34 (10), 515–525. https://doi.org/10.1016/j.tins.2011.06.006.

Zorumski, C.F., Paul, S.M., Izumi, Y., Covey, D.F., Mennerick, S., 2013. Neurosteroids, stress and depression: potential therapeutic opportunities. Neurosci. Biobehav. Rev. 37 (1), 109–122. https://doi.org/10.1016/j.neubiorev.2012.10.005.