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Review article

Neuroactive steroids and PTSD treatment

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ABSTRACT

This review highlights early efforts to translate pre-clinical and clinical findings regarding the role of neuroactive steroids in stress adaptation and PTSD into new therapeutics for PTSD. Numerous studies have demonstrated PTSD-related alterations in resting levels or the reactivity of neuroactive steroids and their targets. These studies also have demonstrated substantial variability in the dysfunction of specific neuroactive steroid systems among PTSD subpopulations. These variabilities have been related to the developmental timing of trauma, severity and type of trauma, genetic background, sex, reproductive state, lifestyle influences such as substance use and exercise, and the presence of comorbid conditions such as depression and chronic pain. Nevertheless, large naturalistic studies and a small placebo-controlled interventional study have revealed generally positive effects of glucocorticoid administration in preventing PTSD after trauma, possibly mediated by glucocorticoid receptor-mediated effects on other targets that impact PTSD risk, including other neuroactive steroid systems. In addition, clinical and preclinical studies show that administration of glucocorticoids, 17β-estradiol, and GABAergic neuroactive steroids or agents that enhance their synthesis can facilitate extinction and extinction retention, depending on dose and timing of dose in relation to these complex PTSD-relevant recovery processes. This suggests that clinical trials designed to test neuroactive steroid therapeutics in PTSD may benefit from such considerations; typical continuous dosing regimens may not be optimal. In addition, validated and clinically accessible methods for identifying specific neuroactive steroid system abnormalities at the individual level are needed to optimize both clinical trial design and precision medicine based treatment targeting.

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1. Introduction

Numerous studies have demonstrated alterations in the resting levels and reactivity of a range of neuroactive steroids in humans with posttraumatic stress disorder (PTSD). In addition, animal models have established a role for such neuroactive steroids in the development and reversal of PTSD-like behavioral phenotypes. Neuroactive steroids implicated in the pathogenesis of PTSD are derived from the glucocorticoid, androgen, and more recently characterized gamma-amino-butyric acid (GABA)ergic pregnane steroid synthetic pathways (Fig. 1). Steroids from each of these pathways impact stress adaptation via effects on gene expression, as well as by rapid modulation of neuronal excitability and signaling. Changes in gene expression are induced by steroid binding to cognate membrane bound steroid receptors that traffic to the nucleus to engage steroid response elements on a range of genes. Rapid alterations in neuronal excitability and signaling are produced by the binding of these steroids to specific sites within classical neurotransmitter receptors embedded in external neuronal membranes or, in some cases, in the membranes of cytoplasmic organelles such as the endoplasmic reticulum. Efforts to translate pre-clinical and clinical findings regarding the role of such neuroactive steroids in PTSD pathogenesis into novel and specific therapeutics for PTSD are promising but nascent. The following review will highlight areas of potential for PTSD treatment development as well as identify gaps in our knowledge to be addressed by further work.

2. Dysregulated neuroactive steroid systems associated with PTSD: treatment implications

2.1. Glucocorticoids

Cortisol levels and dynamics vary across individuals and subpopulations with PTSD, and reflect the effects of multiple factors: genetic predisposition, cumulative and developmental timing of trauma, sex, reproductive status, comorbid conditions such as depression or chronic pain, use of exogenous agents such as nicotine, alcohol and a variety of pharmaceuticals, experimental design and study specific assay techniques [1,2]. In addition, some PTSD-associated alterations in glucocorticoid system function may compensate for other, sometimes uncharacterized, alterations in the system that serve to preserve effective glucocorticoid signaling overall. For example, decreases in cortisol reactivity resulting from chronic smoking, which is common in PTSD, or from genetic factors that reduce cortisol synthesis, which are common in some ethnic groups [3], may be offset by increases in glucocorticoid receptor number or sensitivity [4,5]. The variability of glucocorticoid system findings in PTSD does not, however, negate the importance of this system as a potential target for PTSD therapeutics. Logue et al. [6] found that most of the genes with decreased or increased expression in association with PTSD are normally upregulated or downregulated, respectively, by dexamethasone—highlighting a role for reduced glucocorticoid receptor signaling in PTSD pathogenesis.

For example, an FKBP5 gene polymorphism that confers risk for dissociation, depression and PTSD, along with increased and prolonged cortisol responses to hypothalamic-pituitary-adrenal (HPA) axis stimulation, renders the FKBP5 gene vulnerable to developmental stress-induced demethylation—resulting in increased FKBP5 protein expression and reduced glucocorticoid receptor signaling [7]. This, in turn, may reduce expression of resilience-related genes with promoter-based glucocorticoid response elements, such as the genes involved in brain-derived neurotrophic factor (BDNF) [8], neuropeptide Y (NPY) [9] and GABAergic neuroactive steroid synthesis [10]. Such underlying pathophysiological mechanisms may account for the efficacy of glucocorticoid administration in reducing fear-potentiated startle (e.g., [11]) and reducing PTSD risk after trauma [12,13], perhaps by enhancing extinction and extinction retention [14]. For example, the administration of low dose dexamethasone before extinction training increased amygdala FKBP5 gene methylation and enhanced extinction retention, presumably by enhancing glucocorticoid receptor signaling. High dose dexamethasone, which reduced amygdala FKBP5 gene methylation, enhanced extinction without affecting extinction retention [14]. A single dose of corticosterone injected *immediately after* reactivation of conditioned fear, or *30 min before each* fear reactivation trial conducted in series, facilitated extinction retention, apparently by consolidating extinction learning [15].

2.2. Estradiol and estradiol-Related systems

17β-estradiol synthesized by the ovaries, adrenal glands and brain has numerous effects that may contribute to the pathophysiology of PTSD. For example, 17β-estradiol exerts antidepressant effects [16] at the recently characterized non-nuclear, intracelluar, seven-transmembrane G-protein coupled estrogen receptor 1 (GPER), which induces changes in neuronal signaling as well as gene transcription [17]. Examination of this receptor in explicit animal models of PTSD has not yet been undertaken, however. 17β-Estradiol also exerts PTSD-relevant effects via its better known receptors embedded in external neuronal membranes that traffic estradiol to nuclear hormone response elements in the promoters of a variety of genes. 17β-Estradiol activation of estrogen receptor alpha (ERα), expressed in the amygdala, is anxiogenic. Activity of 17β-estradiol at ERβ, expressed at highest levels in the hippocampus, but also in the amygdala and prefrontal cortex (PFC), is anxiolytic and facilitates extinction consolidation and retention [18]. ERβ receptor signaling thus may contribute to the enhanced extinction retention observed in healthy women when estradiol levels are highest [18,19]. In contrast, women with PTSD show *deficits* in extinction retention during the mid-luteal phase when estradiol and progesterone are both high [19]. Several mechanisms may contribute to this phenomenon. It is possible that ERβ signaling is deficient in this population. PTSD risk and severity in women (only) also has been associated with a single nucleotide polymorphism in an ERα sensitive gene for the pituitary adenylate cyclase-activating polypeptide (PACAP) type I receptor (PAC1); this polymorphism conferred poor cue discrimination in a differential fear-conditioning paradigm [20]. A PTSD-related failure to metabolize progesterone into its potent GABAergic metabolites also may play a role in poor extinction retention during the luteal phase in women with PTSD [21]. In female rodents, 17β-estradiol has been shown to upregulate expression of hippocampal 3α-hydroxysteroid dehydrogenase (3α-HSD) [22], the enzyme step at which GABAergic neuroactive steroid synthesis appears to be blocked in women with PTSD [21; Pineles et al., manuscript in preparation].

17β-Estradiol may also interact with other neurobiological systems that impact PTSD risk and recovery. While testosterone upregulates the synthesis of NPY, 17β-estradiol decreases NPY synthesis [23]. Plasma and CSF levels of NPY are decreased in men with PTSD, and lower levels of NPY achieved during intense training stress among male military personnel are associated with increased dissociative symptoms and poorer military performance [2]. In addition, higher resting NPY levels have been associated with the capacity for PTSD recovery in predominantly male veteran populations [24,25], and enhanced extinction in male rodents [9]. NPY regulation has not yet been investigated in female rodent models of PTSD or specifically in women with PTSD.