Sleep and hypothalamic pituitary adrenal axis responses to metyrapone in posttraumatic stress disorder

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ABSTRACT

Disturbed sleep is a core feature of posttraumatic stress disorder (PTSD), characterized in part by decreased delta power sleep that may result from stress-related alterations in corticotropin releasing factor (CRF), hypothalamic pituitary adrenal axis (HPA) regulation and glucocorticoid signaling. Overnight HPA axis response mediating sleep disturbances in men and women with PTSD was examined using a metyrapone challenge. Metyrapone blocks cortisol synthesis, removing negative feedback, and increases the release of hypothalamic CRF and pituitary adrenocorticotropic hormone (ACTH). Laboratory-based polysomnography was used to monitor the sleep of 66 medically healthy, medication-free men and pre-menopausal follicular phase women including 33 with chronic PTSD (16 women and 17 men) and 33 age- and sex-matched controls (14 women and 19 men) over 3 consecutive nights. Participants completed an overnight metyrapone challenge after an adaptation and baseline night of sleep and ACTH was obtained by repeated blood sampling. Metyrapone resulted in a greater increase in ACTH and greater decreases in cortisol and delta spectral power sleep in PTSD subjects compared to controls, and a greater increase in ACTH in women compared to men. There was no sex difference in metyrapone effects on delta power sleep, and no significant metyrapone by PTSD by sex interactions with either ACTH or delta power sleep. Regression analyses indicated that a greater increase in ACTH response was associated with a greater decrease in delta power sleep response in PTSD subjects, but no such relationship was found in controls. The PTSD group difference was similar in men and women. These results suggest that stress-related alterations of the HPA axis in PTSD may contribute to sleep difficulties. Therapeutics that target the HPA axis may offer promise as a potential future treatment for PTSD and related sleep difficulties.

1. Introduction

Posttraumatic stress disorder (PTSD) is a disabling consequence of trauma, manifested by recurrent and distressing re-experiencing of the traumatic event, avoidance of trauma reminders, and hyperarousal symptoms, seen in increased startle reactivity and impaired sleep that result from central and autonomic nervous system alterations (American Psychiatric Association, 2013; Hendrickson and Raskind, 2016). Disturbed sleep is one of the most prevalent PTSD symptoms, with patients reporting difficulties with non-restorative sleep, frequent awakenings and nightmares, and a debilitating impact on many domains of functioning (Hoge et al., 2007). A meta-analysis of objective sleep studies reported alterations in sleep duration and patterns in PTSD, including increased Stage 1 sleep and decreased slow wave sleep (SWS) (Kobayashi et al., 2007). Studies using spectral analysis, a powerful method that examines quantitative sleep microarchitecture, have shown that delta band spectral power, which is most prominent in slow wave NREM sleep, is decreased in PTSD (Neylan et al., 2003; Otte et al., 2007; Richards et al., 2013). Delta power sleep is driven by thalamocortical oscillations and thought to both represent the bioenergetic recovery process of cortical wake activity and replay phenomenon in models of procedural memory consolidation (Genzel et al., 2014). Functions of delta power sleep include homeostatic recovery, glucose metabolism and other fundamental biological processes (Tasali

et al., 2008). Deficiencies in delta power sleep associated with PTSD may have important consequences for cognition and health.

Stress-related alterations in corticotropin releasing factor (CRF) and the hypothalamic-pituitary-adrenal (HPA) axis may account for alterations in delta power sleep in PTSD. CRF, which functions as a neurotransmitter in extrahypothalamic sites (e.g., amygdala, locus ceruleus (LC), bed nucleus of the stria terminalis (BNST)), has an arousing effect on the cortex (Reviewed in (Zorrilla and Koob, 2004)). CRF is also the primary hypothalamic neuropeptide involved in the control of adrenal secretion of cortisol. Pulsatile CRF release in the hypothalamus leads to adrenocorticotropic hormone (ACTH) release in the pituitary gland, which then stimulates adrenal cortisol release. CRF, ACTH and cortisol levels are lowest in the first few hours of sleep when delta power sleep activity is maximal (Friess et al., 1995). CRF pulses increase after 4–5 h of sleep and reach peak activity at the beginning of the wake period (Gallagher et al., 1973). The rise in overall activity of the HPA axis prepares the organism for food intake, regulates changes in energy metabolism, and promotes optimal neural activity required for initiating wakeful behavior (McEwen, 1995). Studies have found an inverse relationship between delta power sleep and pulsatile cortisol release (e.g., (Vgontzas et al., 1999)). The apparent relationship between peripheral cortisol levels and delta power sleep is likely to be driven by activity of hypothalamic CRF, supported by findings that exogenous cortisol infusion, which reduces CRF, increases delta power sleep (Friess et al., 1994).

PTSD is associated with increases in both hypothalamic and extrahypothalamic CRF activity. CRF mediates anxiety and fear behaviors via signaling with CRF1 receptors located in the amygdala, LC, BNST, and cerebral cortex (See (Zorrilla and Koob, 2004) for review). Several studies have found higher levels of CRF in cerebrospinal fluid (CSF) in PTSD, reflecting mainly extrahypothalamic sources (Baker et al., 1999; Bremner et al., 1997; Sautter et al., 2003). Elevated peripheral CRF measured in plasma was found in veterans with PTSD compared to combat-exposed veterans without PTSD and healthy controls (de Kloet et al., 2008). Increased CRF may explain the increased ACTH and cortisol response to psychological challenge observed in individuals with PTSD (Bremner et al., 2003). However, the findings have been mixed. For example, dexamethasone suppression-CRH stimulation resulted in a blunted ACTH response in PTSD, which was interpreted to indicate possible down-regulation of CRF receptors from chronically elevated hypothalamic CRF release (Strohle et al., 2008).

Metyrapone challenge remains the strongest stimulus for endogenous CRF release that exists in the field. Metyrapone, a medication used for the diagnosis of adrenal insufficiency, blocks cyp11B1 (11ß-hydroxylase) and hence blocks the conversion of 11-deoxycortisol to cortisol. This results in reduced cortisol synthesis and increased levels of 11-deoxycortisol (Fiad et al., 1994). Reduced cortisol concentrations result in removal of glucocorticoid negative feedback to the underlying drive of the paraventricular nucleus of the hypothalamus to release CRF, but has no impact on extrahypothalamic CRF (Kalin et al., 1987). Metyrapone causes a 12-fold amplification of secretory ACTH release and results in increased awakenings and reduced delta power sleep (Jahn et al., 2003).

In two previous studies, we found that the sleep and endocrine responses to metyrapone (i.e., decrease in delta power and increase in ACTH, respectively) were significantly diminished in PTSD compared to controls. Further, in the whole sample, greater decline in delta power sleep activity was significantly correlated with greater increases in 11-deoxycortisol and ACTH measured the morning before and after metyrapone administration (Neylan et al., 2003; Otte et al., 2007), providing initial evidence of alterations in the brain response to increased hypothalamic CRF. However, metyrapone blocks cortisol synthesis for approximately 4 h, and the endocrine response was assessed 9 h after metyrapone was administered. Although PTSD subjects had a significantly smaller increase in ACTH compared to controls, it is unclear whether the two groups had the same immediate peak and recovery of the ACTH response proximal to metyrapone administration. In order to better understand the effect of the neuroendocrine challenge on delta power sleep in PTSD, the present study examined the effects of metyrapone on ACTH using repeated sampling of nocturnal hormone activity during sleep recordings in men and women with chronic PTSD compared to healthy controls. We tested the hypothesis that the ACTH response to metyrapone would be associated with a decreased delta power sleep response and that the relationship between ACTH and delta power sleep responses would be moderated by having PTSD. Due to previous findings of sex differences in sleep architecture and in ACTH responses to metyrapone (Inslicht et al., 2014; Richards et al., 2013), we also examined sex differences in these relationships.

2. Materials and methods

The present study used a cross-sectional, 2×2 design (PTSD/control $\times$ female/male) involving 66 medically healthy, non-medicated adults aged 19–39 years in an inpatient sleep laboratory. The study sample was comprised of 33 individuals with current chronic PTSD (16 women and 17 men; 48% female) and 33 control subjects (14 women and 19 men; 42% female). This sample was drawn from a larger study of 93 participants. We excluded data from 10 participants due to side effects or an inadequate metyrapone dose and from 17 participants due to missing data related to difficulties in blood collection over the night or poor quality sleep EEG recordings. Chronic PTSD was defined by fulfillment of DSM-IV criteria for chronic PTSD on the Clinician-Administered PTSD Scale (CAPS) and a CAPS score > 40.

Female participants were premenopausal (having at least one menstrual period in past 12 months) as determined by medical screening interview, and were scheduled during the follicular phase of the menstrual cycle within 10 days following the onset of menses. Exclusion criteria included extreme morning or evening tendencies or irregular sleep wake schedules as documented by actigraphy and sleep diary; a diagnosis of sleep apnea; history of traumatic brain injury, presence of neurologic disorders or systemic illness; use of psychiatric, anticonvulsant, antihypertensive, sympathomimetic, steroidal, statin or other prescription medications; anemia, recent blood donation in the past 2 months, obesity (defined as BMI > 30); prominent suicidal or homicidal ideation; alcohol abuse or dependence in the prior 2 years; substance abuse or dependence in the previous year; any psychiatric disorder with psychotic features; bipolar disorder or obsessive compulsive disorder; and pregnancy. Exclusion criteria for control subjects also included a lifetime history of major depressive disorder (MDD) or panic disorder.

Nocturnal blood sampling was obtained as a part of a 3-night polysomnography sleep study (night 1 = adaptation, nights 2–3 = pre- and post-metyrapone administration) conducted in a Clinical Research Center (CRC). Habitual sleep onset time, calculated from the actigraphy and sleep diary data was used to determine the timing of procedures on the CRC. Subjects were instructed to maintain the same sleep onset time during the week of actigraphy monitoring as well as during the CRC admission. All subjects were alcohol and drug-free and restricted to having one optional cup of caffeinated coffee each morning. Two hours before habitual sleep onset, a catheter was inserted in an antecubital vein for repeated sampling of blood on nights 2 and 3 (5.5 ccs every 15 min providing 32 samples for each night). Assays for ACTH and cortisol were performed on every other sample, resulting in 16 pre- and 16 post-metyrapone measures. Blood was sampled for up to 8 h following the final dose of metyrapone (M = 6.5 h; SD = 1.9 h). A single additional blood sample was obtained in the morning, at habitual wake time, to measure ACTH, cortisol, and 11-deoxycortisol.

Subjects were allowed to walk on the CRC, but were instructed to avoid vigorous activity. They were allowed to watch TV, play games and talk to staff. All subjects were provided meals at 8:00 AM, 12:00 noon, and 5:30 PM. Prior to the 3rd night of polysomnography subjects were given metyrapone as described below. The timing of the doses