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Sympathetic activity and hypothalamo-pituitary—adrenal axis activity during sleep in post-traumatic stress disorder: A study assessing polysomnography with simultaneous blood sampling

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Summary
Background: Nightmares and insomnia in PTSD are hallmark symptoms, yet poorly understood in comparison to the advances toward a biological framework for the disorder. According to polysomnography (PSG), only minor changes in sleep architecture were described. This warrants alternative methods for assessing sleep regulation in PTSD.
Methods: After screening for obstructive sleep apnea and period limb movement disorder, veterans with PTSD ($n = 13$), trauma controls (TCs, $n = 17$) and healthy controls (HCs, $n = 15$) slept in our sleep laboratory on two consecutive nights with an IV catheter out of which blood was sampled every 20 min from 22:00 h to 08:00 h. Nocturnal levels of plasma adrenocorticotropic hormone (ACTH), cortisol, melatonin were assessed in conjunction with PSG registration, as well as subjective sleep parameters.
Results: PTSD patients showed a significant increase in awakenings during sleep in comparison to both control groups. These awakenings were correlated with ACTH levels during the night, and with the subjective perception of sleep depth. Also, heart rate (HR) was significantly increased in PTSD patients as compared with both control groups. The diurnal regulation of ACTH, cortisol and melatonin appeared undisturbed. PTSD patients exhibited lower cortisol levels at borderline

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significance ($p = 0.056$) during the first half of the night. ACTH levels and cortisol levels during the first half of the night were inversely related to slow wave sleep (SWS).
Conclusion: This study suggests that hypothalamo-pituitary—adrenal (HPA) axis activity is related to sleep fragmentation in PTSD. Also, activity of the sympathetic nervous system (SNS) is increased during sleep in PTSD. Further research is necessary to explore the potential causal relationship between sleep problems and the activity of the HPA-axis and SNS in PTSD.

1. Introduction

Patients with a post-traumatic stress disorder (PTSD) frequently suffer from sleep disturbances such as nightmares, frequent awakening, and sleep initiation and sleep maintenance insomnia (Neylan et al., 1998; Ohayon and Shapiro, 2000). Sleep disturbances are of clinical relevance in PTSD, as they are often therapy-resistant (Davidson et al., 2001; Zayfert and DeViva, 2004), and related to suicide risk (Ribeiro et al., 2012). Insomnia and nightmares may also exert a negative effect on daytime symptoms (Belleville et al., 2009). Recent studies show that sleep quality may even be directly related to hippocampus functioning and morphology (Van Der Werf et al., 2009; Neylan et al., 2010). Furthermore, sleep fragmentation is related to blunted growth hormone secretion in PTSD (van Liempt et al., 2011), which may be an underlying mechanism for compromised neuroplasticity and hippocampal functioning (Kim et al., 2010).

Restoring sleep disturbances in PTSD may hypothetically stimulate neuroplasticity and recovery. In order to be able to improve sleep, we need more knowledge of the characteristics and contributing factors of sleep disturbances in PTSD. A major difficulty in research into PTSD-related sleep disturbances is that despite very frequent complaints of insomnia and nightmares, objective sleep is only mildly disturbed, according to polysomnography (PSG), which is the golden standard in sleep research (Hurwitz et al., 1998; Pillar et al., 2000). Earlier PSG studies have shown a small increase in stage 1 non rapid eye movement sleep (NREM) and decrease in slow wave sleep (SWS) (Kobayashi et al., 2007). Objective measures of total sleep time (TST), waking after sleep onset (WASO), and sleep onset latency (SOL) were not related to the subjective estimates of TST, WASO and SOL (Woodward et al., 1996). Further research is needed to explain why PTSD patients suffer from insomnia and nightmares, while their sleep architecture is mostly undisturbed with normal amounts of TST and rapid eye movement (REM) sleep.

Some studies have found increased awakenings during sleep in PTSD (Mellman et al., 1995; Breslau et al., 2004; Habukawa et al., 2007). This type of sleep fragmentation may interrupt beneficial processes during sleep, and may induce alterations in stress hormones (Steiger, 2007).

To date, little is known about the biological systems that are involved in sleep dysregulation in PTSD. The hypothalamo-pituitary—adrenal (HPA) axis and the sympathetic nervous system (SNS) are well characterized in PTSD, and have been associated with sleep regulation as well (Saper et al., 2005). Furthermore, a relationship between nightmares and delayed sleep phase has been suggested (Nielsen, 2010). The onset of melatonin secretion, which commences about 2 h before sleep onset, is a well-established method for determining circadian rhythm disturbances such as delayed sleep phase syndrome. To the best of our knowledge, melatonin secretion and circadian rhythm disturbance have not been studied in PTSD.

In order to further unravel the profile and underlying mechanisms of sleep alteration in PTSD, we undertook a sleep study in PTSD patients that assessed three sets of parameters: 1. HPA-axis activity and melatonin secretion; 2. objective sleep structure according to PSG, including awakenings and heart rate (HR); 3. subjective perception of sleep. Most previously conducted PSG studies used either trauma controls (TCs), or healthy controls (HCs), or a mixed group in their study design. However, studies have shown that alterations in HPA-axis functioning have also been described in trauma exposed mentally healthy individuals (de Kloet et al., 2007; Klaassens et al., 2010). We therefore included two control groups: one group of veterans with similar deployment-related exposure to combat, and one group of non-combat-exposed military personnel and non-trauma-exposed civilians. In line with earlier research we expected increased sleep fragmentation and increased HR in PTSD patients (Habukawa et al., 2007; Woodward et al., 2009). Furthermore, decreased cortisol levels and increased ACTH levels in PTSD patients were expected, which is in agreement with increased CRH levels in PTSD (Baker et al., 1999; de Kloet et al., 2008a,b). Lastly, we hypothesized that the onset of melatonin secretion would be delayed in PTSD patients.

2. Materials and methods

2.1. Participants

Veterans with PTSD were recruited through the outpatient clinic of the Military Mental Healthcare (MMH), Utrecht, the Netherlands. TCs were veterans without PTSD. HCs were civilians or service members who had never been deployed. All control subjects were recruited through advertisements. Controls were matched with the PTSD group for age, year of deployment (TC) and region of deployment (TC). After a verbal and written description of the study, written informed consent was obtained. All participants were screened for psychiatric illness using the Structured Clinical Interview for DSM-IV axis I disorders (SCID-I) (Spitzer et al., 1992). The diagnosis of PTSD was confirmed by the Clinician Administered PTSD Scale (CAPS) (Blake et al., 1995), and consensus by two clinicians (SvL, EV). PTSD patients were included when they met a CAPS score of 50 and did not meet DSM-IV criteria for psychotic disorder or substance abuse (according to the SCID-I). TCs were included when they met the A1 criteria for PTSD (the person experienced, witnessed or was confronted with an event or events that involved actual or threatened death or serious injury, or a threat to physical integrity of self or others), with a CAPS score below 18. Furthermore, TCs did not meet DSM-IV criteria for