Psychoneuroendocrinology 66 (2016) 1–10

Contents lists available at ScienceDirect

Psychoneuroendocrinology

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

Acute stress alters autonomic modulation during sleep in women approaching menopause

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ARTICLE INFO

Article history:
Received 29 October 2015
Received in revised form
14 December 2015
Accepted 15 December 2015

Keywords:
Insomnia
Menopause
Trier social stress task
Cortisol
Hyperarousal
Heart rate variability

ABSTRACT

Hot flashes, hormones, and psychosocial factors contribute to insomnia risk in the context of the menopausal transition. Stress is a well-recognized factor implicated in the pathophysiology of insomnia; however the impact of stress on sleep and sleep-related processes in perimenopausal women remains largely unknown. We investigated the effect of an acute experimental stress (impending Trier Social Stress Task in the morning) on pre-sleep measures of cortisol and autonomic arousal in perimenopausal women with and without insomnia that developed in the context of the menopausal transition. In addition, we assessed the macro- and micro-structure of sleep and autonomic functioning during sleep. Following adaptation to the laboratory, twenty two women with (age: 50.4 ± 3.2 years) and eighteen women without (age: 48.5 ± 2.3 years) insomnia had two randomized in-lab overnight recordings: baseline and stress nights. Anticipation of the task resulted in higher pre-sleep salivary cortisol levels and perceived tension, faster heart rate and lower vagal activity, based on heart rate variability measures, in both groups of women. The effect of the stress manipulation on the autonomic nervous system extended into the first 4 h of the night in both groups. However, vagal tone recovered 4–6 h into the stress night in controls but not in the insomnia group. Sleep macrostructure was largely unaltered by the stress, apart from a delayed latency to REM sleep in both groups. Quantitative analysis of non-rapid eye movement sleep microstructure revealed greater electroencephalographic (EEG) power in the beta1 range (15–≤23 Hz), reflecting greater EEG arousal during sleep, on the stress night compared to baseline, in the insomnia group. Hot flash frequency remained similar on both nights for both groups. These results show that pre-sleep stress impacts autonomic nervous system functioning before and during sleep in perimenopausal women with and without insomnia. Findings also indicate that women with insomnia had increased EEG arousal and lacked recovery in vagal activity across the stress night suggesting a greater sensitivity to stress in this group.

1. Introduction

Sleep difficulties are more common in midlife women transitioning to menopause compared with pre-menopause, with prevalence rates of insomnia symptoms ranging between 40 and 56% in the menopausal transition (Joffe et al., 2010; Kravitz et al., 2003, 2008; Nowakowski et al., 2009; Ohayon, 2006; Polo-Kantola, 2011) and with 26% qualifying for a DSM-IV diagnosis of insomnia (Ohayon, 2006). We have shown that women who developed severe first-onset insomnia in the menopausal transition have a significant sleep deficit, with almost 50% of them having polysomnographic (PSG)-defined short sleep duration (<6 h). They also had more wakefulness after sleep onset (WASO) and poorer sleep efficiency compared with controls (Baker et al., 2015). Sleep

Abbreviations: AASM, academy of sleep medicine; ANS, autonomic nervous system; BMI, body mass index; EEG, electroencephalography; HFa, absolute high frequency integrated power in arbitrary units; HFnp, high frequency power as a proportion of total power; HFpf, peak frequency in the high frequency range; HR, heart rate; HRV, heart rate variability; NREM, non-rapid-eye-movement sleep; PSG, polysomnography; REM, rapid-eye-movement sleep; REML, rapid-eye-movement sleep latency; RMSSD, root mean square of differences between adjacent normal-to-normal R intervals; SDNN, standard deviation of normal-to-normal R intervals; SE, sleep efficiency; SOL, sleep onset latency; STRAW, stages of reproductive aging workshop; TIB, time in bed; TP, total power; TST, total sleep time; WASO, wake after sleep onset.

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http://dx.doi.org/10.1016/j.psyneuen.2015.12.017
0306-4530/

difficulties and insomnia disorder in the menopausal transition have been linked to several factors, including changing reproductive hormone levels (decrease in estradiol and increase in follicle stimulating hormone) (de Zambotti et al., 2015a; Kravitz et al., 2008), hot flashes (Baker et al., 2015; Kravitz et al., 2008; Ohayon, 2006), and psychosocial factors (Sassoon et al., 2014; Woods and Mitchell, 2010). Another important factor that could contribute to the development and/or exacerbation of insomnia in midlife women is susceptibility to stress.

It is hypothesized that there exists a trait-like vulnerability to insomnia driven by an augmented response to stress (Harvey et al., 2014). Stress exposure at baseline is a significant predictor of insomnia one year later, particularly in individuals with high sleep reactivity (more likely to have difficulty sleeping in stressful situations, such as before an important meeting the following day), an effect mediated by the extent of cognitive intrusion elicited by the stress exposure (Drake et al., 2014). Insomnia that develops in response to stress could be related to underlying levels of chronic hyperarousal (Bonnet and Arand, 2003), a core feature of the hyperarousal model of insomnia, indexed by increased heart rate, pre-sleep cognitive arousal, sympathetic activity, and brain activation (reviewed in (Levenson et al., 2015; Riemann et al., 2015)). While individuals with insomnia in the general population may not necessarily experience more frequent stressful life events, they perceive the impact of these events more negatively and consider their lives to be more stressful compared with good sleepers, with the pathway between daily stress and poor sleep being mediated by high levels of pre-sleep arousal (Morin et al., 2003).

There are limited studies that have investigated associations between stress and insomnia in the context of the menopausal transition. The Study of Women Across the Nation (SWAN) reported that midlife women (51.2 ± 2.1 years) who showed a chronic stress profile characterized by more annual events that were "very and still upsetting" over a period of up to 9 years before a PSG study, had a poorer subjective sleep quality and more PSG-defined wakefulness, and were more likely to report insomnia than women with low or moderate stress profiles (Hall et al., 2015). These findings suggest that high levels of chronic stress may precipitate sleep continuity disturbances in midlife women (Hall et al., 2015). While Shaver et al. (2002) did not find a difference in perceptions of stress exposure in midlife women with and without insomnia, they found that the insomnia group had more psychological distress and a greater morning-evening difference in urine cortisol levels compared with controls.

Hot flashes (transient periods of flushing, sweating, and a sensation of heat (Kronenberg, 1990) are a major contributor to sleep disturbance in midlife women. They emerge as estrogen levels decline but their mechanism is more complex than just estrogen withdrawal, with several lines of evidence implicating involvement of the autonomic nervous system (de Zambotti et al., 2013; Freedman, 2014; Thurston et al., 2012). Stress or emotional situations are cited as the most frequent trigger for hot flashes (Kronenberg, 1990) raising the possibility that stress in symptomatic perimenopausal women could induce more frequent hot flashes during the night, which could further disturb sleep.

Given the evidence of a relationship between stress exposure/reactivity and insomnia, studies have used acute experimental stress protocols to investigate physiological pathways linking stress and sleep disturbance. Findings are mixed regarding the impact of an acute stress on sleep architecture and sleep continuity, with some finding a longer sleep onset latency and/or more frequent awakenings in response to stress and others finding no effect (see Kim and Dimsdale, 2007; for review). Quantitative electroencephalographic and electrocardiogram measures of physiological arousal during sleep may be sensitive to the effects of stress, as shown by Hall et al. (2007, 2004). A group of young healthy adults exposed to an acute experimental anticipatory stress task before bedtime had similar sleep architecture but lower vagal activity during sleep, as indexed by high frequency power derived from spectral density analysis of heart rate variability, with the effect persisting across the night, compared to a control group (Hall et al., 2007). Brosschot et al. (2007) showed that daily stress, mediated by worry duration, is associated with a prolonged physiological response (higher heart rate and lower heart rate variability) that persists during sleep even when the stressor is no longer present. In patients with primary insomnia, high levels of perceived stress and more frequent avoidance behaviors are associated with electroencephalographic (lower EEG delta power and higher EEG beta power) and/or electrocardiographic (lower high frequency power) indicators of physiological arousal during NREM sleep (Hall et al., 2007). No relationships between psychological stress and sleep architecture were found.

Here, we aimed to investigate the effect of stress on sleep, autonomic nervous system (ANS) functioning during sleep, as well as the frequency of hot flashes, in perimenopausal women without a history of insomnia but with a current diagnosis of insomnia that developed in the approach to menopause. We used an acute experimental psychosocial stress anticipation protocol (impending Trier Social Stress Test, Kirschbaum et al., 1993) implemented before bed. We hypothesized that women with menopausal-onset insomnia would be more sensitive to the stress paradigm (greater sleep disturbance, higher heart rate and lower vagal functioning during the stress night compared to a baseline night) compared to a control group of women who were transitioning to menopause without the onset of insomnia.

2. Material and methods

2.1. Participants and screening

The study was reviewed and approved by SRI International's Institutional Review Board. Participants were recruited from the San Francisco Bay Area community and gave written informed consent. Sample characteristics and screening procedures are fully described in Sassoon et al. (2014).

Briefly, all women had to be in the menopausal transition (menstrual cycle lengths that differed by more than 7 days from normal or skipping cycles, but not with amenorrhea longer than 11 months), according to Stages of Reproductive Aging Workshop (STRAW) criteria (Soules et al., 2001), have an intact uterus and at least one ovary, and a body mass index (BMI) of 32 $kg.m^{-2}$ or lower. Exclusion criteria were use of hormone therapy, severe medical conditions (e.g., hypertension or diabetes), or current sleep medication and/or antidepressant use.

All women underwent a structured clinical interview (SCID, First et al., 1998) including a customized module querying DSM-IV criteria for insomnia (Morin and Espie, 2003). Sleep disturbance needed to be coincident with the onset of the menopausal transition; none of the participants had a lifetime history of DSM-IV insomnia. None of the participants met criteria for current other Axis-I disorders (except nicotine dependence, 2 in the control group and 5 in the insomnia group). All women had a clinical/adaptation in-lab PSG assessment, to confirm absence of sleep-disordered breathing (apnea–hypopnea index >5) and/or periodic limb movement disorder (periodic limb movement index >10).

Comparisons of sleep composition between women with insomnia and controls (Baker et al., 2015) and between different menstrual cycle phases in both groups of women (de Zambotti et al., 2015b) as well as hormone-sleep relationships (de Zambotti et al., 2015a) have been previously published. The current data were