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Sleep and 24-h activity rhythms in relation to cortisol change after a very low-dose of dexamethasone

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Summary The hypothalamic-pituitary-adrenal (HPA) axis plays an important role in sleep. Nevertheless, the association of sleep and its 24-h organization with negative feedback control of the HPA axis has received limited attention in population-based studies. We explored this association in 493 middle-aged persons of the Rotterdam Study, a large population-based study (mean age 56 years, standard deviation: 5.3 years; 57% female). The negative feedback of the HPA axis was measured as the change in morning saliva cortisol after the intake of 0.25 mg dexamethasone the night before. Actigraphy allowed us to measure the stability and fragmentation of the activity rhythm and to estimate total sleep time, sleep onset latency and wake after sleep onset. A sleep diary kept during the week of actigraphy was used to assess self-reported total sleep time, sleep onset latency, number of awakenings and perceived sleep quality. In our study, enhanced negative feedback of the HPA axis was found in association with unstable activity rhythms ($B = 0.106$, 95% confidence interval (CI): 0.002; 0.210), total sleep time ($B = 0.108$, 95%CI: 0.001; 0.215) and poor subjective sleep quality ($B = 0.107$, 95%CI: 0.009;

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0.206) after multivariate adjustment. These results indicated that the 24-h organization, duration and experience of sleep are all associated with the negative feedback control of the HPA axis.

1. Introduction

The hypothalamic-pituitary-adrenal (HPA) axis determines the stress response of humans as it regulates the release of cortisol by a negative feedback control (Dedovic et al., 2009). Cortisol shows a typical diurnal pattern with peaks when stress is increased. The diurnal pattern is regulated by the suprachiasmatic nucleus (SCN), the body's central pacemaker, which is responsible for the overall co-ordination of the HPA axis and synchronizing the time of day and neuroendocrine output (Buijs et al., 2003).

The HPA axis plays an important role in the regulation of sleep (Buckley and Schatzberg, 2005). However, research on the association of sleep parameters with cortisol secretion is not consistent (Elder et al., 2014). In population-based studies, it has been found that saliva awakening cortisol was not associated with sleep quantity and quality in healthy middle-aged adults (Zhang et al., 2011), and that cortisol levels in urine were not associated with objective sleep duration (Rao et al., 2013). In contrast, others have observed that self-reported sleep duration and disturbances were associated with the diurnal slope in cortisol secretion in the population (Kumari et al., 2009b). None of these studies, however, assessed experimentally induced activation of the HPA-axis. Cortisol levels can be manipulated experimentally by performing a behavioral stress test. A recent publication found that sleep deprivation was associated with both elevated resting cortisol and an exaggerated cortisol response after the Trier Social Stress Test (Minkel et al., 2014). Cortisol levels can also be manipulated pharmacologically to assess the functioning of the HPA axis. Results of studies which assessed the HPA axis after pharmacological manipulation in relation to sleep are also mixed; poor sleep can lead to increased activity of the HPA axis, for example in chronic insomniacs (Vgontzas et al., 2001). However, self-rated sleep was not related to cortisol levels after dexamethasone intake in a combined dexamethasone/corticotrophin-releasing-hormone (CRH) test (Hori et al., 2011), nor were sleep disorders (Lattova et al., 2011). Research has been complicated by the use of objective versus subjective measures of sleep in different studies (Rao et al., 2013). In addition, both the HPA axis and sleep behaviors are affected by stress. However, most studies on sleep and the function of the HPA axis have been done in the laboratory, and rarely in the home situation. This itself might affect hormone regulation, which could further complicate the interpretation and generalizability of the results. In addition, sleep and cortisol secretion both have strong circadian rhythms, which could affect the association between sleep and the HPA axis (Buckley and Schatzberg, 2005). However, not much is known about the 24-h organization of rest activity rhythms in reference to the negative feedback of the HPA axis in population-based samples.

In the current study we assessed the negative feedback of the HPA axis with a very low-dose dexamethasone suppression test (DST). The DST is specifically designed to measure the negative feedback of the HPA axis and has mostly been used in clinical populations. Initially, assessment of the negative feedback of the HPA axis was developed to diagnose Cushing's disease (Lindholm, 2014), but it has also been proposed as a biomarker for psychiatric diseases (Arana et al., 1985). Diminished negative feedback of the HPA axis has been found in melancholic depression, eating disorders and alcoholism, while in contrast an enhanced negative feedback has been associated with posttraumatic stress disorder, stress-related bodily disorders and chronic fatigue syndrome (Ehlert et al., 2001). Within the general population a dose of 1 mg dexamethasone, which is comparable to that applied in clinical populations, would suppress saliva cortisol almost completely in all persons (Huizenga et al., 1998b). Therefore we implemented a very low-dose DST to assess the effect of 0.25 mg of dexamethasone on cortisol in saliva. A dose of 0.25 mg dexamethasone has been suggested for a more informative assessment of the sensitivity of the HPA axis feedback in healthy adults (Huizenga et al., 1998b). We specifically tested the level of cortisol after a very low-dose of dexamethasone controlled for baseline cortisol.

We explored whether the 24-h organization of the activity rhythm, objective and subjective sleep parameters, and perceived sleep quality were related with the negative feedback control of the HPA axis in the general population by conducting an experiment with a very low-dose DST. Enhanced negative feedback of the HPA was measured as the reduction in morning cortisol after a low dose of dexamethasone the prior evening. Both sleep and cortisol have a strong circadian organization, therefore we hypothesized that disturbed 24-h activity rhythms were related with the negative feedback control of the HPA axis. Results for the association of sleep with the negative feedback control have been mixed; to our knowledge, objectively measured habitual sleep has only been studied in relation to the negative feedback control of the HPA axis in adolescents (Pesonen et al., 2014). Lastly, we expected subjective sleep quality to be associated with the feedback of the HPA axis.

2. Methods

2.1. Study population

The current study was embedded in the Rotterdam Study, a population-based cohort of middle-aged and elderly inhabitants of Rotterdam, the Netherlands (Hofman et al., 2013). In 2006, a new cohort with inhabitants aged 45 and over was added (RSIII-1). The study was conducted in accordance with the guideline proposed in the World Medical Association