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Influence of exogenous atrial natriuretic peptide on the nocturnal hypothalamic-pituitary-adrenal axis and sleep in healthy men

Cüneyt Demiralay [a,1,*], **Holger Jahn** [a,1], **Michael Kellner** [a], **Alexander Yassouridis** [b], **Klaus Wiedemann** [a,b]

[a] *University Hospital Hamburg-Eppendorf, Department of Psychiatry and Psychotherapy, Hamburg, Germany*
[b] *Max Planck Institute of Psychiatry, Munich, Germany*

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Summary Atrial natriuretic peptide (ANP), originally found in the cardiac atria, is also widely distributed in the central nervous system (CNS) and has been predominantly found in the hypothalamus and the pituitary gland. Previous in vitro and in vivo studies have provided evidence for an inhibitory control of ANP at all regulatory levels of the hypothalamo-pituitary-adrenocortical (HPA) system. In vivo studies in man demonstrated that ANP inhibits stimulated pituitary-adrenal secretion during wakefulness. On the other hand, it has been reported that various neuropeptides not only influence the neuroendocrine compound of sleep, but also exert specific effects on the sleep electroencephalogram (EEG). To further characterize the role of ANP in the regulation of the nocturnal HPA axis activity and consecutive sleep regulation, we investigated sleep-endocrine effects of intravenously administered ANP in healthy men during nocturnal sleep. Eight volunteers underwent three trial conditions in random order and in a single-blind design receiving ANP infusion at the beginning of the 1st or the 2nd half of the night, or placebo. Sleep was assessed by polysomnography and blood samples were drawn in 30-min intervals for determination of adrenocorticotrophic hormone (ACTH) and cortisol during the entire night. While the ACTH and cortisol secretion during ANP infusions remained unchanged, an immediate increase of ACTH and cortisol secretion occurred after each infusion period for approximately 2 h without changing basal levels and the circadian course of both hormones. Sleep EEG parameters were neither directly affected by ANP infusions nor by the following ANP-induced ACTH and cortisol secretion. The presence of such clear-cut enhancement of the pituitary-adrenal release indicates a rebound effect of ANP on HPA secretory activity and supports the idea that ANP acts as corticotropin-releasing hormone (CRH)-inhibiting factor.

* Corresponding author at: University Hospital Hamburg-Eppendorf, Department of Psychiatry and Psychotherapy, Martinistrasse 52, D-20246 Hamburg, Germany. Tel.: +49 40 7410 53223; fax: +49 40 7410 53461.
E-mail address: c.demiralay@uke.de (C. Demiralay).
[1] Shared first authorship.

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1. Introduction

Atrial natriuretic peptide (ANP), originally located in the cardiac atria, is also widely distributed in the central nervous system (CNS), including the hypothalamus, the pituitary gland and in the amygdala, suggesting an involvement in the regulation of central nervous autonomic and neuroendocrine function as well as emotional behaviour (Engler et al., 1999). Besides its natriuretic, diuretic and vasorelaxatory properties (Levin et al., 1998), previous in vitro and in vivo studies have provided evidence for an inhibitory control of ANP at all regulatory levels of the hypothalamo-pituitary-adrenocortical (HPA) system (Wiedemann et al., 2000). Alterations of HPA axis activity are considered to have important implications for various stress-related mental diseases such as depression and anxiety disorders (Holsboer and Ising, 2008). Therefore, the endogenous mechanisms mediating the inhibition of the main humoral stress response are of utmost interest to psychiatric research (Wiedemann et al., 2000).

In vitro and in vivo studies in rats have shown that ANP acts as a hypothalamic corticotropin-release inhibiting factor (Dayanithi and Antoni, 1990; Ibanez-Santos et al., 1990; Kovács and Antoni, 1990). Moreover, intravenous infusion of ANP antiserum in rats results in a marked increase in stimulated and basal HPA system activity (Fink et al., 1991; Antoni et al., 1992). Several studies in humans have shown that ANP has an inhibitory effect on the CRH-stimulated ACTH and cortisol secretory response (Kellner et al., 1992, 1995; Bierwolf et al., 1998; Wiedemann et al., 2001).

Evening administration of ANP inhibits the pituitary's response to CRH more profoundly than morning administration, pointing to a circadian change in the sensitivity of the HPA axis to the inhibitory action of the peptide (Kellner et al., 1995). Under normal physiological conditions the HPA axis activity is governed by a circadian rhythm. Both the nadir and the major surge of ACTH and cortisol release occur during night sleep (Steiger, 2002). On the other hand, a mutual interaction between endocrine activity and sleep electroencephalogram (EEG) is well documented. In addition, various neuropeptides not only influence the neuroendocrine compound of sleep but also exert specific effects on sleep EEG (Steiger, 2007). However, ANP effects on pituitary-adrenal secretory activity during nocturnal sleep have yet to be investigated in human studies.

Hence, to further characterize the role of ANP in the regulation of HPA axis activity and consecutive sleep regulation, we investigated sleep-endocrine effects of intravenously administered ANP in healthy men during nocturnal sleep.

Since the trough and the circadian peak of HPA axis secretory activity occur during the 1st and the 2nd half of the night respectively, the nocturnal sleep period allows observations in a state of low as well as rising activity. To investigate a possibly different sensitivity of the HPA axis and sleep regulation to an inhibiting modulator during the night, we administered ANP infusions at the beginning of the 1st and the 2nd half of the night and simultaneously recorded sleep EEG measures. Any possible procedural effects were controlled in a single-blinded manner by placebo conditions. The main hypotheses to be tested were (a) that ANP differently inhibits HPA axis activity in the 1st and the 2nd half of the night, and (b) that ANP mediated inhibition of the HPA axis has an impact on stress hormone sensitive sleep parameters such as rapid-eye-movement (REM) sleep, non-REM sleep and slow-wave sleep (SWS).

2. Materials and methods

2.1. Substances

Human α-ANP was obtained from Clinalfa (Läufelfingen, Switzerland).

2.2. Experimental subjects

Eight male volunteers aged 21–30 years (25.25 ± 1.1; mean $\pm$ SEM) with normal body mass index (20.73 ± 0.55 kg/m^2; mean $\pm$ SEM) and in good health were studied in a sleep research unit. Each subject received a thorough medical examination and was evaluated with a semistructured interview. Participants had no history of drug abuse, psychiatric illness, recent major stressful live events, or sleep disturbances such as sleep deprivation or shift working during the 3 months prior to our experiment. Furthermore, all subjects had refrained from the use of alcohol during the 2 days preceding the polysomnography, excessive coffee intake (restricted to 1 cup in the morning), or nicotine intake (restricted to 3 cigarettes the day before the investigation). In addition, all subjects had been free of prescription and nonprescription drugs such as salicylates or antihistamines for at least 3 months. Urinary drug screens (barbiturates, benzodiazepines, opiates, cannabinoids, phencyclidine, cocaine, amphetamines, and related compounds) were negative for each volunteer and at each occasion. The study was approved by the Ethics Committee on human experiments at the Max Planck Institute of Psychiatry (Munich), and all subjects signed written informed consent.

2.3. Investigation procedure

Each volunteer spent a total of 4 nights — each night separated from the following by about 1 week — in the laboratory. The 1st night served for adaptation to the sleep laboratory setting. Following the adaptation night the volunteers underwent in three different nights 3 trial conditions in random order and in a single-blind design and received in each night an infusion at the beginning at the 1st half of the night as well as at the beginning of the 2nd half of the night:

ANP infusion at the beginning at the 1st half of the night (*ANP1st*). According to previous investigations (Kellner et al., 1995; Wiedemann et al., 1995, 2001; Arlt et al., 2003) 60 ml of saline (0.9% NaCl) containing 200 μg ANP was given as continuous infusion at a rate of 30 ml/h from 2300 h to 0100 h. To control for application effects in the verum condition, a normal saline infusion was given from 0300 h to 0500 h.

ANP infusion at the beginning at the 2nd half of the night (*ANP2nd*). Accordingly, the saline infusion was given from 2300 h to 0100 h and the ANP infusion was given from 0300 h to 0500 h.