Sleep and Endocrinology

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A bidirectional interaction between sleep electroencephalogram and endocrine activity is well established in humans. The studies suggest that various hormones (peptides and steroids) participate in sleep regulation. Growth hormone (GH)-releasing hormone (GHRH) stimulates GH and slow wave sleep (SWS), and inhibits cortisol, whereas corticotropin-releasing hormone (CRH) exerts opposite effects. Changes in the GHRH:CRH ratio contribute to sleep endocrine aberrations during normal aging. In addition, galanin and neuropeptide Y promote sleep, whereas, in the elderly, somatostatin impairs sleep. In human vasoactive intestinal polypeptide appears to play a role in modulating rapid eye movement (REM) nonREM cycle. Cortisol stimulates SWS and GH, probably by feedback inhibition of CRH. Neuroactive steroids exert specific effects on the sleep EEG.

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Introduction

Human sleep is characterized by the cyclic occurrence of periods of non-REM sleep (NREMS) and rapid eye movement sleep (REMS) that can be seen on a sleep electroencephalogram (EEG), and by distinct pattern of hormone secretion that can be analyzed by nocturnal blood sampling. Several hormones have the capacity to affect sleep but the physiological significance of hormonal modulation of sleep is unclear. There are bidirectional interactions between sleep and the endocrine system. Manipulation of the sleep wake behavior by sleep deprivation results in changes of hormone secretion and inversely, the sleep EEG is specially affected by changes of hormone levels. During the past decade much knowledge has been accumulated about the roles of hormones in the physiology of sleep regulation and the pathophysiology of disturbed sleep from simultaneous investigation of sleep EEG and nocturnal hormone secretion and from experiments with manipulation of hormones in humans and animals.

Hypothalamo-Pituitary-Somatotrophic (HPS) system

Growth hormone (GH) is the best documented hormone with a strong sleep related secretory pattern. GH is produced by anterior pituitary somatotroph cells. Synthesis and secretion of pituitary GH are controlled by two hypothalamic neurohormones: growth hormone releasing hormone (GHRH) which stimulates, and somatostatin which inhibits GH. GH secretion is also stimulated by ghrelin which is a hormone released by the endocrine cells of the stomach. The somatotrophic axis is a fundamental anabolic system for the body. It stimulates tissue growth via cell division and via stimulation of protein synthesis. The analysis of the interaction between sleep and the somatotrophic axis may promote understanding the mechanism of coupling body
metabolism to sleep, and may provide clues to sleep regulation. In the mouse, the GHRH gene is found within the genomic region linked to EEG slow wave activity during sleep.\(^2\)

**Growth hormone-releasing hormone**

After repetitive i.v. boluses of GIIRII during the first few hours of the night in young normal men, SWS and GII secretion increased and cortisol decreased.\(^3\)\(^-\)\(^5\) No major changes of sleep EEG were found after repetitive i.v. GIIRII during the early morning hours.\(^5\) The sleep-promoting activity of GIIRII varies with gender and age in humans. Strong responses are observed in young male subjects. Instead of enhancing slow wave sleep, GHRH increases stage 2 NREMS and sleep continuity in the elderly. Only a weak sleep promoting effect of GII RH was found in the elderly.\(^7\) In male GHRH inhibited ACTH during the first half of the night and cortisol during the second half of the night. In contrast, these hormones increased in women. Similarly, NREMS, particularly stage 2 sleep increased and wakefulness decreased in males whereas opposite sleep impairing effects occurred in females. These data suggest a reciprocal antagonism between GIIRII and CRH in men, but a synergism between GHRH and CRH in women.\(^8\)\(^,\)\(^9\)

**Somatostatin**

Ooctreotide is more potent than exogenous somatostatin. After repetitive i.v. administration of the somatostatin analogue octreotide, NREMS and SWS decreased in healthy elderly subjects.\(^10\)\(^,\)\(^11\) whereas it had no effect on young normal men.\(^3\) These data suggest a reciprocal interaction of GIIRII and somatostatin in sleep regulation similar to their action on GII release. The same dose of somatostatin which was not effective in young men impaired sleep in the elderly probably due to a decline of endogenous GHRH.

**Ghrelin and GH secretagogues**

Ghrelin is the recently isolated endogenous ligand of the GH secretagogue (GHS) receptor.\(^12\) Besides GIIRII, ghrelin stimulates GII release and induces appetite in humans.\(^13\) Similar to the effects of GHRH, repetitive i.v. ghrelin enhanced SWS, slow wave activity (SWA) and GH in young normal males.\(^14\) The GII releasing effect of GIIRII is mimicked by synthetic GHSs such as growth hormone releasing peptide 6 (GHRP 6) and MK 677 that do not act via the GIIRII receptor. After administration of GHRP 6, stage 2 sleep, GH, ACTH and cortisol secretion were elevated.\(^15\) One week of oral mediation with MK-677 in young healthy men resulted in an increase of SWS.\(^16\)

**Galpin**

Galpin is a peptide that is widely located in the mammalian brain and coexists in neurones with various peptides and classical neurotransmitters participating in sleep regulation. It also stimulated GH via GHRH in humans.\(^17\) REMS deprivation induced galpin gene expression.\(^18\) Under repetitive i.v. administration of galpin to young normal men, SWS and the duration of REMS periods increased, whereas the secretion of GH and cortisol remained unchanged.\(^15\) The increase in REM sleep and in delta power after galpin may be explained by a reduction of the activity of the locus diflaveus, as it is known that galpin decreases the activity of neurons in the locus coeruleus.\(^20\)

**Hypothalamo-Pituitary-Adrenocortical (HPA) system**

The hypothalamo pituitary adrenocortical (HPA) system mediates the reaction to acute physical and psychological stress. The stress reaction is a prerequisite for the individual survival. It starts with the release
of corticotropin-releasing hormone (CRH) from the parvocellular cells of the hypothalamus. This results in the secretion of corticotropin (ACTH) from the anterior pituitary and finally in the secretion of cortisol from the adrenal cortex. HPA hormones have been shown to exert specific effects on sleep EEG. On the other hand, changes of the sleep pattern affect the release of these hormones. There are a bidirectional interaction between the sleep EEG and the HPA system.

**Corticotropin-releasing hormone**

After pulsatile i.v. boluses of human CRH in young normal male subjects, SW3 and REMS decreased and the GII surge was blunted whereas cortisol increased during the first half of the night.21 The responsiveness of sleep EEG to CRH appears to increase during aging. After a administration of ovine CRH shortly after sleep onset in young- and middle-aged normal subjects, sleep EEG remained unchanged in young men but in middle-aged subjects wakefulness increased and SWS decreased.22

**ACTH**

Pulsatile i.v. administration of the synthetic ACTH analogue ebiratide prompted a set of sleep EEG changes corresponding to a general CNS activation, whereas REMS, GII and cortisol remained unchanged.23 This study suggests that i.v. administered peptides may induce central effects independently of changes in peripheral hormone secretion and the blood brain interface may not be an obstacle for these effects.

**Cortisol**

After pulsatile i.v. cortisol administration, SW3, SWA and GII increased whereas REMS decreased in male subjects.24,25 As CRH and cortisol induced opposite effects on SWS and GII, these effects may be mediated by negative feedback of endogenous CRH, not by the elevation of peripheral cortisol levels.24,25

**Neuropeptide Y**

The prolongation of sleep latency by CRH was antagonized dose dependently by neuropeptide Y (NPY) in rats.26 In young normal male subjects, repetitive i.v. administration of NPY induced decreases in sleep latency, and first REMS period, and increases in stage 2 sleep and sleep period time. Furthermore, cortisol and ACTH secretion were blunted.27 These data show that NPY participates in sleep regulation, particularly in the timing of sleep onset as an antagonist of CRH.

**Vasoactive intestinal polypeptide**

No significant effects on sleep were found after the lower dosage, but the higher dosage of vasoactive intestinal polypeptide (VIP) induced a deceleration of the nonREM REM cycle with REM and nonREM sleep periods increasing during the first three sleep cycles. In addition, a tendency to increased REM to nonREM ratios was found. Furthermore, the cortisol nadir occurred earlier and the GII peak was blunted.28 These data show that VIP has a specific effect on the temporal organization of sleep structure and of sleep associated hormone secretion. It appears likely that the suprachiasmatic nucleus is involved.

**Estrogen**

In postmenopausal women estrogen replacement therapy enhanced REMS and reduced intermittent wakefulness during the first two sleep cycles in comparison with baseline values. The normal decrease in SWS and SWA from the first to the second cycle reoccurred.29 These data suggest that estrogen treatment after menopause can help to restore the normal sleep–EEG pattern in women.
Summary

Sleep is a time of considerable activity in various endocrine systems. A bidirectional interaction exists between the sleep EEG and nocturnal hormone secretion. Hyposecretion and hypersecretion of various hormones are regularly linked to disturbed sleep. During the first half of the night, SWG and GH preponderate, whereas ACTH and cortisol levels are low. In contrast, during the second half of the night the amounts of REM, ACTH and cortisol are high whereas SWG and GH secretion are low. In humans a sexual dimorphism in the effects of GIIRI on sleep is found. Opposite to the effects in males, GHRH impairs sleep and stimulates HPA hormones in females. During aging, parallel changes in SWG and GH secretion occur. In the elderly, the amplitude of most hormones, except prolactin, is reduced. A reciprocal interaction between GHRH and CRH plays a key role in sleep-endocrine regulation. In males, CRH impairs sleep, enhances vigilance, stimulates ACTH and cortisol and reduces GH release. In contrast, GHRH promotes sleep, stimulates GH and inhibits ACTH and cortisol. NPY and ghrelin are also sleep promoting peptides, whereas somatostatin impairs sleep as an antagonist to GIIRI. The REM nonREM cycle is modulated by VIP. Finally, the sleep EEG changes after menopause and the beneficial effect of estrogen replacement therapy suggest a role of estrogens in sleep regulation.

REFERENCE


