SLEEP AND ENDOCRINE REGULATION

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1. ABSTRACT

A bidirectional interaction exists between sleep electroencephalogram (EEG) and endocrine activity in various species including humans. Various hormones (peptides, steroids) were shown to participate in sleep regulation. A key role was shown for the reciprocal interaction between sleep-promoting growth hormone-releasing hormone (GHRH) and sleep-impairing corticotropin-releasing hormone (CRH). Changes in the GHRH:CRH ratio result in changes of sleep-endocrine activity. There is good evidence that the change of this ratio in favor of CRH contributes to aberrances of sleep during aging and depression. Besides of GHRH ghrelin and galanin promote SWS, whereas somatostatin is another sleep-impairing factor. NPY acts as a CRH antagonist and induces sleep onset. Prolactin enhances rapid eye movement sleep (REMS) in rats. SWS is enhanced in patients with prolactinoma. Other studies on the influence of prolactin of human sleep are lacking. There is a controversy whether CRH promotes REMS.

In humans vasocative intestinal polypeptide (VIP) appears to play a role in the temporal organization of sleep, since after VIP administration the NREMS-REMS cycle decelerated. Several neuroactive steroids (pregnenolone, progesterone, allopregnanolone, dehydroepiandrosterone) exert specific effects on sleep EEG via GABA_A receptors. Cortisol appears to enhance REMS. Finally gonadal hormones participate in sleep regulation. Estrogen replacement therapy and CRH-1 receptor antagonism in depression are beneficial clinical applications of the basic research presented here.

2. INTRODUCTION

The two major methods for the investigation of sleep in various species including humans are the sleep electroencephalogram (EEG) and the assessment of endocrine activity (e.g. by collection of hormone profiles). The combination of these electrophysiological and neuroendocrinological methods in normal human subjects, in patients with various disorders, under baseline conditions and after administration of synthetic and endogenous CNS active compounds and in related animals models showed that (i) during sleep a considerable activity of various endocrine systems occurs and (ii) a bidirectional interaction exists between the electrophysiological and neuroendocrine components of sleep. Particularly it was shown that certain hormones play a specific role in sleep regulation.

Human sleep shows the cyclic occurrence of periods of nonREM sleep (NREMS) and rapid eye movement sleep (REMS). During the first NREMS period the major portion of slow wave sleep (SWS) occurs. Correspondingly in EEG spectral analysis (1), (2) the major portion of slow wave activity (SWA) is found in the first sleep cycle. The secretion of various hormones shows distinct patterns as described in detail in the corresponding chapters below. In short, during the first half of the night the growth hormone (GH) surge preponderates whereas corticotropin (ACTH) and cortisol levels are low, during the second half of the night ACTH and cortisol are high whereas GH is low (see Figure 1). This pattern suggests (i) a reciprocal interaction of the
hypothalamo-pituitary-somatotrophic (HPS) and the hypothalamo-pituitary-adrenocortical (HPA) systems (the corresponding peripheral endpoints are GH and cortisol respectively) and (ii) the existence of common regulators of sleep EEG and sleep-associated hormone secretion. Indeed there is good evidence, that a reciprocal interaction of the key hormones of the HPS and HPA systems, GH-releasing hormone (GHRH) and corticotropin-releasing hormone (CRH) plays a major role in sleep regulation.

A sexual dimorphism of sleep-endocrine activities was reported in young normal humans. Cortisol secretion is higher in females than in males. Most men show a single GH peak during the first half of the night, whereas in women frequently a pre-sleep GH surge and at least one additional GH peak during the second half of the night is found (3).

Sleep EEG and nocturnal hormone secretion change throughout the life span (4). In females the menopause is a major turning point towards impaired sleep (5), whereas in men the sleep quality declines continuously during aging.

The one hormone which is most clearly linked to the NREMS-REMS cycle is renin. Plasma renin activity (PRA) shows oscillations of about 90 min period strongly linked to the NREMS-REMS cycles. PRA reaches its peak during NREMS and its acrophase during REMS periods (6). Also in rats PRA is low in REMS and high in NREMS (7).

Leptin, the protein product of the obese (ob) gene is released from adipocytes in the periphery. It acts within in the hypothalamus and reduces food intake (8). The maximum of serum leptin is found between 0000 and 0400 h. An inverse relationship exists between leptin and cortisol particularly in women (9, 10). Leptin levels are higher in women than in men (11, 12).

3. HYPOTHALAMO-PITUITARY-SOMATOTROPHIC (HPS) SYSTEM

3.1. Basic activity

GH stimulates tissue growth and protein anabolism. These effects are mediated in part by insulin-like growth factor-1 (IGF-1). The synthesis and secretion of GH is promoted by GHRH and inhibited by somatostatin. Recently ghrelin was identified as an additional stimulus for GH release. Ghrelin is an endogenous ligand of the GH secretagogue (GHS) receptor and is also involved in the regulation of the energy balance (13). Synthetic GHSs were known already before the cloning of the GHS receptor. All these components of the HPS system appear to be involved in sleep regulation.

In humans the major peak of GH secretion during 24 h is found near to sleep onset. This GH surge is associated to the first period of SWS (14, 15, 16). In one study GH concentrations were determined every 30 sec in normal young males. Maximal GH secretion was found within minutes after the onset of SWS (17). A close temporal relationship was reported between GH secretion and SWS (18). However, GH may be released prior to sleep onset (16).

The GH surge appears to be widely sleep dependent and is suppressed during sleep deprivation (19, 20). Furthermore in sleep deprived, but relaxed young men in supine position an unchanged nocturnal GH peak was observed (21). During the second half of the night GH levels are low. Similarly it was shown that about one third of SWS periods are not associated with GH secretion (22). Already during the third decade of the life span distinct parallel decreases of SWS, SWA and GH secretion start. Near to the onset of the fifth decade the GH pause occurs.

In several animal species (rhesus monkeys, adult rats, goats, cows and dogs) an episodic release of GH, but no link between sleep and GH secretion was found (reviewed in: 23, 24). Also in calves (25) and growing pigs (26) a relationship between sleep-wake cycle and GH release was reported. In lambs the highest GH production rate was found during SWS and REMS (24). In contrast in immature rats a correlation between GH concentration and the duration of sleep during preceeding 10 minutes was reported (27).

Hypothalamic GHRH mRNA is dependent on a circadian rhythm. In the rat the highest concentration is found when sleep propensity reaches its maximum in these night active animals at the beginning of the light period (28). Furthermore hypothalamic GHRH contents display sleep-related variations with low levels in the morning, increases in the afternoon (peak at the transition from the light of the dark period) and decline at night (29). A major role of GHRH in the sleep promotion by sleep deprivation appears likely since GHRH antibodies antagonized this effect in the rat (30). Furthermore hypothalamic GHRH mRNA increased after sleep deprivation in rats (31, 32). The sleep rebound following sleep deprivation was inhibited in rats by microinjections of a GHRH antagonist into the area preoptica (32).

3.2. Sleep in disorders of the HPS system

In patients with isolated GH deficiency in comparison to normal controls SWS was reduced whereas total sleep time and time spent in stages 1 and 2 increased (33). Furthermore a decrease in SWA in these patients was reported (34). In children with psychosocial dwarfism the amount of SWS was low. After several weeks in a new environment, during recovery of growth, sleep quality improved, and particularly SWS increased (35).

Excessive GH levels are found in patients with acromegaly. In these patients obstructive sleep apnea syndrome is frequent due to hyperplasia of their upper airway soft tissue (36). But also patients with acromegaly without sleep apnea have daytime sleepiness and an abnormal sleep structure. One year after adenectomy REMS and SWS time increased in a sample of these patients (37). In this study EEG power spectrum analysis was used to calculate sleep energy. At baseline REMS and SWS energy were higher than after adenectomy.
3.3. Effects of HPS hormone administration on the sleep EEG

3.3.1. Growth hormone-releasing hormone (GHRH)

GHRH is an important endogenous sleep-promoting substance. Icv GHRH increases SWS in rats and rabbits. The same effect is found when GHRH is injected into the medial preoptic area in rats. Similarly, repetitive iv GHRH during the first few hours of the night increased cortisol decrease in young normal men. Mimicking the pulsatile endogenous release appears to be a crucial methodological issue since sleep remained unchanged after GHRH infusion. Sleep promotion in young men by GHRH was confirmed after iv and intranasal administration. The effects of GHRH on sleep were investigated in three states with a change of the GHRH/CRH ratio in favor of CRH — (i) the second half of the night in young normal men, (ii) in elderly normal men and women and (iii) in patients with depression. Repetitive iv GHRH during the early morning hours prompted no major effects on sleep EEG. GH increased whereas HPA hormones remained unchanged. At daytime the response of GH to GHRH is blunted in older men. Similarly only a weak sleep-promoting effect of GHRH was found in the elderly. The first NREMS period was prolonged and the number of awakenings decreased. Intranasal GHRH in elderly subjects had only a relatively weak sleep-promoting effect. In a pilot study the hypothesis was tested that after priming (e.g. iv GHRH every 2 days for 12 days) the sleep-promoting effect of GHRH would be restored in the elderly. The study results in two subjects do not support this hypothesis. The influence of pulsatile iv GHRH during the first few hours of the night was tested in drugfree patients of both sexes with depression (age range 19-76 years) and matched controls. A sexual dimorphism in the response to GHRH was found. In male patients and controls GHRH inhibited ACTH during the first half of the night and cortisol during the second half of the night. In contrast these hormones were enhanced in females, regardless whether they were healthy or depressed. Similarly NREMS and particularly stage 2 sleep increased and wakefulness decreased in male patients and controls whereas opposite sleep-imparing effects were found in women. These data confirm a reciprocal antagonism of GHRH and CRH in males. Calcium levels in GABAergic neurons cultured from rat fetal hypothalamus increased when perfused with GHRH. It is thought that many hypothalamic GHRH responsive neurons are GABAergic.

3.3.2. Growth hormone, insulin-like growth factor-1 (IGF-1)

Negative feedback inhibition of GHRH after administration of GH in humans, cats and rats or higher dosages of icv IGF-1 decreases NREMS. On the other hand GH antagonism impaired sleep. Low dose icv IGF-1 stimulated NREMS in rats. GH administration of GH in humans, cats and rats (54) increased and cortisol decreased in young normal men. In all these data point to a reciprocal interaction of GHRH and somatostatin in sleep regulation similarly to their relationship in GH regulation. 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. This theory is supported by the observation that infusion of the somatostatin antagonist arginine enhanced SWS in elderly men, probably since the action of endogenous GHRH was facilitated.

3.3.3. Somatostatin

After iv somatostatin selective increases of REMS were reported in rats. In rats systemic administration of the somatostatin analogue octreotide decreased NREMS. Similarly SWS was reduced in young normal men after subcutaneous octreotide. Octreotide is known to be more potent than exogenous somatostatin. This explains that repetitive iv somatostatin impaired sleep in normal elderly controls, whereas it had no effect in young normal men. In all these data point to a reciprocal interaction of GHRH and somatostatin in sleep regulation similarly to their relationship in GH regulation. 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. This theory is supported by the observation that infusion of the somatostatin antagonist arginine enhanced SWS in elderly men, probably since the action of endogenous GHRH was facilitated.

3.3.4. Ghrelin and GH secretagogues

Similar to the effects of GHRH repetitive iv ghrelin enhanced SWS and GH in young normal men. In contrast to the effects of GHRH, which blunted cortisol in young men, ACTH and cortisol increased, particularly during the first half of the night after ghrelin. The pattern of hormone changes after ghrelin resembles the effects of repetitive iv administration of the synthetic GHSs GH-releasing peptide-6 and hexarelin. The sleep EEG-effects of these compounds however differed from the influence of ghrelin. After GHRP-6 sleep stage 2 increased, whereas after hexarelin SWS and SWA decreased, probably due to a change of the GHRH/CRH ratio in favor of CRH. In mice ghrelin promoted NREMS. Oral administration of the GHSs, MK-677, for one week had a distinct sleep-promoting effect in young men and only a weak effect in elderly controls.

3.4. Animal models of HPS system changes

Very big supermice slept more than normal mice. In giant transgenic mice in which the metallothionine-1 promoter stimulates expression of rat GH (MT-rGH) plasma GH is permanently elevated; there are no secretion pulses. During the light period NREMS was modestly higher and REMS was almost doubled in these mice compared to normal mice, whereas sleep did not differ between groups at night. After sleep deprivation the MT-rGH mice continued to sleep more than normal mice. In dwarf homozygous (lit/lit) mice with non-functional GHRH receptor the amounts of NREMS and REMS were lower than in normal control mice. In the dwarf mice infusion of GH by Alzet minipumps prompted normalization of REMS, but not of NREMS within 9 days. In dwarf homozygous (lit/lit) mice with non-functional GHRH receptor the amounts of NREMS and REMS were lower than in normal control mice. In the dwarf mice infusion of GH by Alzet minipumps prompted normalization of REMS, but not of NREMS within 9 days. GH, ghrelin and octreotide had no effect on sleep EEG in dwarf mice. These results suggest that (i) GHRH deficiency is associated with decreases in REMS, (ii) decreases in GH lead to decreases in REMS, (iii) the actions of GHRH,
ghrelin and octreotide on sleep EEG require intact GHRH receptor signaling (73).

4. HYPOTHALAMO-PITUITARY ADRENOCORTICAL (HPA) SYSTEM

4.1. Basic activity
The hypothalamic-pituitary-adrenocortical (HPA) system mediates the reaction to acute physical and psychological stress. The stress reaction starts with the release of CRH from the parvocellular portion of the paraventricular nucleus of the hypothalamus. This results in the secretion of ACTH from the anterior pituitary and finally in the secretion of cortisol (in humans) or corticosterone (in rats) from the adrenocortex. Various co-factors contribute to this cascade (reviewed in: 74).

In humans the pattern of cortisol secretion is inverse to that of GH. After sleep onset cortisol reaches its quiescent period. Between 0200 and 0300 h the first peak of cortisol release occurs which is followed by further rises until awakening (75). ACTH is the prime stimulus of nocturnal cortisol secretion in man. Nevertheless the secretion of ACTH and cortisol may dissociate (76, 77). Most but not all studies reported an increase of HPA hormones during sleep deprivation (review: 78).

Controversial reports exist on the effects of age on HPA hormones. Elevated and unchanged cortisol levels have been reported in the elderly. Most studies agree that the amplitude of the cortisol rhythm is blunted. The analysis of the largest sample of normal male subjects investigated so far revealed a modest effect of aging on the 24 h mean cortisol level (79). Aging was associated with an elevation of the evening cortisol nadir, whereas morning maximum cortisol values did not differ across the age ranges. Evening cortisol levels increased after the age of 50 years, when sleep became more fragmented and REMS declined.

The genetic factors that contribute to the pattern of cortisol release were investigated in monozygotic and dizygotic pairs of male, normal twins. Genetic control was reported for the timing of the cortisol nadir and for the proportion of overall temporal variability associated with pulsatility. For the 24-h mean and the timing of the morning acrophase environmental effects were found (80). Similarly to humans plasma concentration of ACTH and cortisol/corticosterone reach their nadir during early sleep and display their acrophase near to the onset of the active period in rhesus monkeys (81, 82) and rats (83). No temporal relationship between cortisol levels and sleep or the secretion of various hormones including GH was found in rhesus monkeys (82).

4.2. Sleep in disorders with pathological changes of HPA activity
4.2.1. Addison’s and Cushing’s disease
In Addison’s disease the capacity of the adrenal glands to produce corticosteroids is severely reduced. No major aberrances of the sleep of these patients were reported (84, 85). Addison’s patients were compared intrindividually under two conditions, either continuous hydrocortisone replacement or short term hydrocortisone withdrawal. After hydrocortisone replacement REMS increased in comparison to withdrawal. Hence cortisol may be needed to facilitate the initiation and maintenance of REMS (86). Excessive cortisol levels are produced in Cushing’s disease, either of central, or peripheral origin. This results in the disappearance of the circadian rhythm of cortisol (75). In these patients, SWS is decreased (85, 87). Furthermore aberrances of sleep continuity, shortened REMS latency and elevated REMS density (a measure for the amount of REMs) were observed (87).

4.2.2. Depression, insomnia, brain injury
CRH overactivity plays a key role in the pathophysiology of affective disorders. Characteristic sleep-EEG findings in depressed patients are disturbed sleep continuity, a decrease of NREMS and REMS desinhibition (reviewed in: 88, 89). Well documented endocrine changes include signs of (i) HPA overactivity (reviewed in: 74 and (ii) HPS dysfunction (reviewed in: (90). In patients with depression cortisol and ACTH levels are elevated throughout the night or 24 h, respectively, in comparison to normal controls (91, 51), whereas the circadian pattern of cortisol is preserved (see Figure 1). A positive correlation between age and cortisol levels was reported particularly in female patients (51). Elevated cortisol plasma and norepinephrine CSF levels throughout 30 h, but normal ACTH plasma and CRH CSF levels have recently been found (92). GH was blunted in most (90, 93, 94) but not in all (91) studies. Obviously there are similarities in the sleep-endocrine changes during depression and during normal aging.

Longitudinal comparison of sleep-endocrine activity between acute depression and recovery showed decreases of ACTH (91) and cortisol (91, 90) in adult patients after recovery. The pathological sleep EEG and low GH levels, however, remained unchanged after recovery in patients, who were drug-free during the examinations (90). These data corroborate that hypercortisolism as a state marker of depression in adult patients. In contrast abnormalities of sleep EEG and of cortisol are infrequent in prepubertal children with depression (95). The decrease of cortisol in adult patients after recovery is similar to the normalization of pathological results of HPA system challenge tests and of CRH CSF levels in remitted patients (reviewed in: 74). The persistence of most sleep-EEG (96) and GH changes (93) after recovery has been confirmed over a period of three years. Obviously cortisol normalizes independently from the sleep architecture. Hence hypercortisolism in depression is not secondary to shallow sleep. Interestingly, patients with primary insomnia had increased nocturnal cortisol and a shorter quiescent period than controls (97). Similar increases of ACTH and cortisol are found throughout 24 h in these patients in comparison to controls (98). These observations suggest similarities in the pathophysiology of primary insomnia and of depression. This is of particular interest since epidemiological studies reported an elevated risk for depression in patients with persisting insomnia (99).
The metabolic aberrances during depression appear to result in a biological scar as reflected by long persisting changes of sleep EEG and GH in remitted patients. Similarly in patients who survived severe brain injury, several months later cortisol did not differ from controls, whereas GH and sleep stage 2 time were lower (100). Probably either HPA overactivity due to stress under the intensive care situation after brain injury or treatment with glucocorticoids in some patients contribute to these changes.

4.3. Effects of HPA hormone administration on the sleep EEG

4.3.1. Corticotropin-releasing hormone (CRH)

Various studies show that the administration of HPA hormones or their antagonists modulates sleep. After icv CRH SWS decreases in rats (38) and rabbits (101). In rats after 72 h of sleep deprivation CRH reduced SWS, prolonged sleep latency and increased REMS (102). Pulsatile iv human CRH (4 x 50µg) in young normal men had a similar effect on NREMS as SWS decreased, whereas REMS decreased. Furthermore the GH surge was blunted and cortisol increased during the first half of the night (103). Hourly iv injections of 10 µg CRH (0800 – 1800) did not induce sleep-EEG changes during the following night, whereas melatonin decreased (104) pointing to a reciprocal interaction between HPA activity and melatonin secretion. In young healthy men EEG activity in the sigma frequency range increased throughout the first 3 sleep cycles both after a single iv bolus of CRH during the first SWS period and during wakefulness (105). The responsiveness of sleep to CRH appears to increase during aging. This theory is suggested by a study comparing the influence of a single dose of ovine CRH given 10 min after sleep onset in young and middle-aged normal subjects (106). In young men sleep EEG remained unchanged, whereas wakefulness increased and SWS decreased in the middle-aged subjects.

Studies on the effects of CRH antagonists in rats reported conflicting results. The CRH antagonists, α-helical CRH and astressin reduced wakefulness in a dose-related manner when given before the dark period (107). It is thought that CRH contributes to the regulation of physiological waking periods. In another study (108) α-helical CRH was effective only in stressed rats. In these animals REMS was enhanced and decreased to values of the non-stressed condition after the substance. On the other hand REMS remained unchanged in stressed rats after astressin, whereas increased wakefulness decreased (109). After sleep deprivation α-helical CRH diminished selectively the REMS rebound in rats. Stress acting via CRH appears to be the major factor inducing the REMS rebound after sleep deprivation (110). Some of this preclinical work (102); (108, 110) supports the hypothesis that CRH promotes REMS. According to their work Chang and Opp (109) suggested, that CRH is not directly involved in the regulation of REMS. They hypothesized that the increase of REMS in stressed rats mentioned before (108) is mediated by prolactin. Similarly from the human study the influence of endogenous CRH on REMS is uncertain, however, since CRH has suppressed REMS (103). Studies on the sleep-EEG effects of ACTH and cortisol help to differentiate the central and peripherally mediated sleep-EEG changes after CRH in humans (see below). Furthermore treatment of patients with depression with the CRH-1 receptor antagonist NBI-30775 induced a normalization of sleep EEG-changes, as SWS increased and REM density and the number of awakenings decreased during a four week trial (111). This study suggests that (i) CRH overdrive contributes to shallow sleep and REMS desinhibition in depression as well, and (ii) CRH-1 receptor antagonism is a way to counteract these changes. It is unlikely that prolactin is involved in the REMS desinhibition in depression, since prolactin levels are unchanged in these patients (see 5.1).

4.3.2. ACTH

After nocturnal infusions of ACTH REMS decreased in normal controls (112, 84), whereas cortisol and GH increased (113). Repetitive iv administration of the synthetic ACTH (4-9) analogue ebiratide induced a set of sleep-EEG changes corresponding to a general CNS activation, whereas REMS, GH and cortisol remained unchanged (114).

4.3.3. Glucocorticoids and mineralocorticoids

Since the pioneering work of Gillin (115) it is known that certain synthetic and endogenous steroids affect sleep (116). Also continuous infusion (2300 – 0700) of cortisol (117) and pulsatile iv (1700 – 0700) cortisol (118) increased SWS and reduced REMS in young normal men. GH increased after cortisol (118). Similarly SWS, SWA and GH increased and REMS decreased after pulsatile iv cortisol in normal elderly subjects (119) and in patients with depression (120). Since CRH (103) and cortisol exerted opposite effects on SWS (117, 118) and GH (119, 118) it appears unlikely that these effects are mediated by the peripheral cortisol levels. It is more likely that negative feedback inhibition of endogenous CRH prompts these changes. Because CRH (103), ACTH (113) and cortisol (117, 118) suppress REMS in contrast to ebiratide. REMS suppression may be mediated by cortisol after each of these hormones. In a similar vein the inhibition of cortisol synthesis by metyrapone reduced SWS and cortisol in controls whereas REMS was not affected (121). In this study endogenous CRH was probably enhanced since ACTH was distinctly elevated. In the rat sc corticosterone increased wakefulness (122).

Sleep-EEG changes after subchronic treatment in patients with multiple sclerosis with the GR agonist methylprednisolone differed from acute effects of cortisol. REMS latency was shortened, REMS density increased and a major portion of SWS shifted from the 1st to the 2nd sleep cycle. These changes are similar to the sleep EEG in patients with depression (123). As an alternative to CRH feedback inhibition, action on the central cortical steroid receptors was suggested as a way in which acute cortisol administration modulates sleep (117). Two types of these receptors occur in the CNS, the mineralocorticoid receptor (MR) and the glucocorticoid receptor (GR). Since the MR antagonist canrenoate reduced SWS, whereas the mixed MR and GR agonist cortisol...
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enhanced SWS and inhibited REMS, it was postulated that the MR regulates SWS whereas the GR regulates REMS. This theory is challenged however, since (i) in another study MR agonists and antagonists did not affect sleep EEG (124), (ii) SWS was increased in elderly subjects under cortisol although the number of MRs is known to decrease distinctly during aging (119), (iii) MRs and GRs coexist frequently in cells as heterodimers (see 125).

In a single case after the mixed GR and progesterone receptor antagonist mifepristone, ACTH and cortisol increased and sleep quality was disrupted distinctly. In a complementary set of experiments on the effects of GR and MR antagonists normal controls participated in 4 protocols (126): (A) placebo only; in the other protocols prior to the examination nights dexamethasone was given orally, the following day at 1400 h either (B) placebo or (C) the MR antagonist spironolactone or (D) mifepristone were given orally. Pretreatment with dexamethasone did not modulate the sleep EEG. After the combination of dexamethasone with spironolactone REMS decreased. Dexamethasone followed by mifepristone decreased SWS and REMS and increased the number of awakenings. Pretreatment with dexamethasone suppressed ACTH and cortisol. Mifepristone, but not spironolactone counteracted this effect.

In another study the effects of mifepristone, the progesterone receptor agonist megestrol acetate and placebo were compared in normal subjects (127). Mifepristone and megestrol exerted opposite effects on hormones, but compounded their impairing effects on sleep quality. After mifepristone HPA hormones were enhanced in the morning and GH was blunted, whereas megestrol had opposite effects. Again mifepristone disturbed sleep and megestrol selectively reduced REMS. The combination of these substances induced shallow sleep and suppressed REMS.

4.4.1. Adrenocortical rats

The secretion of thyroid stimulating hormone (TSH) and of the thyroid hormone thyroxin is related to circadian rhythm (134, 135). The minimum of TSH levels is found during daytime. TSH rises during the night and reaches its maximum by midnight. Then the levels decline during early morning hours. The course of thyroxin release is inverse to that of TSH. Thyroxin levels are low during the night and increase during daytime. One study reported declining TSH levels during REMS periods (136).

4.4.2. Rat strains with reduced HPA activity

The synthesis and release of CRH is reduced in the Lewis rat due to a hypothalamic gene defect in comparison to the related Fisher 344 and Sprague-Dawley rat strains. Lewis rats spent less time awake and more time in SWS than the intact strains. REMS did not differ between strains. After icv CRH waking was enhanced similarly in Lewis and Sprague-Dawley rats. This indicates that the mechanisms mediating the response to exogenous CRH are intact in the Lewis rats (133).

5. HYPOTHALAMO-PITUITARY-THYREOID (HPT) SYSTEM

5.1. Basic activity

The secretion of thyroid stimulating hormone (TSH) and of the thyroid hormone thyroxin is related to circadian rhythm (134, 135). The minimum of TSH levels is found during daytime. TSH rises during the night and reaches its maximum by midnight. Then the levels decline during early morning hours. The course of thyroxin release is inverse to that of TSH. Thyroxin levels are low during the night and increase during daytime. One study reported declining TSH levels during REMS periods (136).

5.2. Sleep in hypo-, hyperthyroidism

Changes of sleep-wake behavior are characteristic symptoms of diseases of the thyroid gland. It is well known that hyperthyroidism is linked with insomnia, whereas fatigue occurs frequently in patients with hypothyroidism. Astonishingly there are only a few data on sleep EEG in these diseases. One study reported that SWS was reduced in patients with hypothyroidism in comparison to normal controls. These changes normalized after therapy (137).

5.3. Effects of thyreotropin-releasing hormone (TRH) administration

After pulsatile iv thyreotropin releasing hormone (TRH) sleep efficiency decreased and the cortisol morning rise occurred earlier in young normal men. All other sleep-EEG, cortisol and GH variables remained unchanged (138).

6. PROLACTIN

6.1. Basic activity

Prolactin is both a circulating hormone and a neuroprotein. It was localized particularly in the hypotalamus (review: (139). In humans prolactin rises after sleep onset and reaches its peak during the second or
the last third of the night (75). In contrast to various other hormones prolactin is neither affected by aging (4) nor by depression (140). During the recovery night after sleep deprivation prolactin increased both in young and elderly normal subjects (141).

A relationship between prolactin secretion and the NREMS-REMS cycle in humans was reported with prolactin nadirs during REAMS periods and rising prolactin levels during NREMS periods (142). By using EEG spectral analysis a temporal relationship between SWA and prolactin secretion was found in young human subjects (142). Decreased dopaminergic inhibition of pituitary prolactin release has been suggested as a cause of increased prolactin secretion during NREMS. On the other hand a positive correlation between sleep cycles and plasma prolactin concentrations was not confirmed by another study (143). Instead, a study on circadian influences of sleep-wake and light-dark cycles on prolactin release led to the conclusion that the nocturnal rise in prolactin is not sleep-associated but rather is rest dependent (144). The prolactin secretory rate was enhanced during the total sleep period independent of sleep quality, and experimentally impaired sleep did not influence prolactin release in normal humans (145).

In Sprague-Dawley and Wistar rats maximum plasma prolactin concentrations occur at the dark period, whereas in another strain prolactin pulses were observed at the end of the light period (review: 139).

In the twin study mentioned before (see 3.1) the genetic and environmental influences on prolactin secretion during waking and sleep were investigated (146). It was found that baseline daytime prolactin concentrations are partially under genetic influence, and that the amplitude and overall waves shape of the secretory profile at daytime are genetically determined. When the environmental effect of sleep was controlled by normalizing for sleep maintenance, it was shown that the secretory response to a standardized sleep/circadian stimulus is also partly genetically controlled.

6.2. Sleep in prolactinoma

Comparison of patients with hyperprolactinoma and normal controls showed a separate increase of SWS in the patients (147).

6.3. Effects of hormone administration

6.3.1. Prolactin

Promotion of REMS by prolactin has been demonstrated in cats, rabbits and rats. Subcutaneous injection of prolactin selectively stimulated REMS in rabbits. The same effect occurred after intrahypothalamic injection of prolactin in the rat (148). Also systemic administration of prolactin during the light period stimulated REMS, whereas prolactin injected during the dark period inhibited REMS (149). The REMS-promoting effect of prolactin was also found in pontine cats after hypophysectomy (150). Antiserum to prolactin decreased REMS in rats (151). Longterm hyperprolactinemia in rats that were grafted with a prolactin secreting tumor under the kidney capsule resulted in an increase in nocturnal REMS whereas REMS during the day decreased progressively (152). In another experiment in adult rats, bearing juvenile rat anterior grafts under the capsule of the kidney distinct increase in REMS and enhanced duration of NREMS with a trend to increased SWA was found (153). Intrahypothalamic injection of prolactin antiserum to rats decreased REMS (148).

6.3.2. Vasoactive intestinal polypeptide (VIP)

Vasoactive intestinal polypeptide (VIP) stimulates REMS after icv administration in laboratory animals (154). When VIP was given to rats in the dark period NREMS and REMS increased (7, 155). It is thought that stimulation of prolactin is involved in the promotion of REMS after VIP, since the REMS promoting activity of systemic VIP was inhibited by immunoneutralisation of the circulating prolactin in the rat (151). VIP antibodies neutralized a REMS-promoting substance that accumulated in CSF of sleep-deprived cats (156). Subsequently an increase of VIP was found in CSF of REMS-deprived cats (157). Central administration of VIP antibodies in rats (155) or a VIP antagonist given to rats (158) decreased REMS. VIP microinjections into the pontine reticular tegmentum enhanced REMS in rats. This effect could last up to 8 days (159). It is thought that interaction with the cholinergic system mediates the enhancement of REMS.

Two doses of VIP exerted different effects in young normal human males (160). Pulsatile administration of 4 x 10 µg VIP decreased prolactin levels, whereas sleep EEG remained unchanged. After 4 x 50 µg VIP however prolactin increased. Furthermore the NREMS-REMS cycles were decelerated (see Figure 2). Each cycle was prolonged, the cortisol nadir appeared advanced and the GH surge was blunted (160). These findings suggest that VIP exerts a specific effect on the temporal organization of sleep-endocrine activity including the timing of the cortisol nadir. It appears likely that VIP affects the circadian clock, resulting in prolonged sleep cycles and earlier occurrence of the cortisol nadir. Blunted GH surge may be explained as a result of the advanced elevated HPA activity. It is unclear whether the effect of systemic VIP are the same as the actions of intracerebral VIP. The mechanisms of promotion of REMS by intracerebral VIP might be different from the sleep response to systemic VIP. For example, systemic VIP did not reach the brain stem whereas it may leak into the hypothalamus and modulate SCN activity as suggested by the findings in humans.
6.4. Animal models of changed prolactin activity
In genetically hypoprolactinemic rats a decrease of REMS was reported (161). However the recordings were done at room temperature. For these hairless rats this temperature is a cold environment and cold exposure decreased REMS. In a warm environment sleep durations of these rats did not differ from normal rats. The circadian sleep-wake rhythm however was changed. A decent difference between SWS and REMS rhythms occurred. The circadian SWS rhythm remained unchanged, whereas the circadian REMS rhythm was reverse (3/4 during night, 1/4 during day) (139).

7. GONADAL HORMONES

7.1. Basic activity
In young females during puberty highest values of estradiol were found between 1400 and 1600 h and lowest values during the night (162). In a small group of adult women no clear interaction between estradiol levels and sleep was found (163). In males testosterone rises constantly throughout the night (75).

7.2. Sleep in women
In women the menstrual cycle, pregnancy and the menopause reflect distinct changes in endocrine activity and have some impact on sleep regulation. Only few studies addressed these issues so far.

7.2.1. Menstrual cycle effects on sleep
In normal women sleep EEG was recorded every second night throughout one entire menstrual cycle. The percentage of REMS tended to be higher in the early follicular than in the late luteal phase and the percentage of NREMS showed a significant menstrual cycle rhythm with higher values in the luteal compared to the follicular phase. In NREMS EEG power density in the upper frequency range of the sleep spindles (14.25 – 15.0 Hz) exhibit a large variety across the menstrual cycle, with maximum in the luteal phase (164). Normal cycling female rats did not show changes in daytime sleep patterns across the estruscycle, but had significantly less REMS during proestrus nights than during metestrus and diestrus nights (165).

7.2.2. Sleep in pregnancy
Sleep EEG was recorded in nine healthy women during each trimester of pregnancy. Waking increased from the second to the third trimester, whereas REMS decreased from the first to the second trimester. In NREMS a progressive reduction of power density was observed (166). Comparison between the third trimester of pregnancy and one month postpartum showed a decrease of REMS latency (167). In the rat pregnancy increased nocturnal NREMS across the entire period, whereas REMS was enhanced only during the early period. After pregnancy enhanced sleep returned to baseline (168).

7.2.3. Sleep changes in the menopause
A sharp decline in the sigma frequency range in women during menopause was reported, whereas in men these changes occurred more gradually (5). After menopause sleep-endocrine alterations associated with depression are accentuated. This hypothesis is supported by a study on sleep-endocrine activity in pre- and postmenopausal women with depression and matched controls. Cortisol was enhanced in postmenopausal patients, while a decrease was found in postmenopausal controls. Sleep-EEG changes are characteristically associated with depression, namely it disturbed sleep continuity. Decrease of SWS and an increase of REMS density are prominent in post- but not in premenopausal patients. An inverse correlation was found between the decline in SWS and sleep continuity and FSH secretion in patients with depression. These observations suggest a role of menopause for these sleep-EEG changes. In contrast in premenopausal patients a shift in SWS and SWA from the first to the second NREMS period was found, which was not related to age or hormone secretion (169).

7.3. Effects of gonadal hormone administration
7.3.1. Gonadal hormone administration in adults
Administration of gonadotropic hormones to adult animals exerts minimal effects on sleep or on sex differences in sleep (170). Similarly only weak effects of high chronic dosages (80-100 mg) of estrogen in transsexual men who underwent cross-gender therapy to women were found. Stage 1 sleep increased in these patients (171).

7.3.2. Estrogen replacement therapy
In postmenopausal women estrogen replacement therapy by skin patch (50 µg of estradiol per day) enhanced REMS and reduced intermittent wakefulness during the first two sleep cycles. The normal decrease in SWS and SWA from the first to the second cycle (172). These data suggest that estrogen treatment after menopause can help to restore the normal sleep-EEG pattern in women.

7.4. Animal models – ovarectomy, castration
REMS was enhanced in adult female rats with ovarectomy and suppressed by subsequent estradiol replacement (173). After castration REMS increased in neonatal mice. This effect was reversible by administration of testosterone (174).

8. NEUROACTIVE STEROIDS

8.1. Introduction
Certain steroids exert direct effects only on neuronal membranes and thereby rapidly affect CNS excitability. These substances are called neuroactive steroids (175). It is thought that their effect on neuronal excitability is mediated by the gamma-aminobutyric acid (GABA)_A-receptor complex. Neuroactive steroids appear to be involved in the regulation of anxiety, memory and sleep. Glial cells are capable of synthesizing certain neuroactive steroids independently of peripheral steroid sources (176). Various neuroactive steroids exerted specific effects on sleep EEG in humans and rats.

8.2. Effects of neuroactive steroids administration on the sleep EEG
8.2.1. Pregnenolone, pregnenolone sulfate
When pregnenolone was given to young men it exerted sleep-EEG changes resembling the effects of a
partial inverse agonist at the GABA_A receptor as SWS increased and EEG power in the spindle frequency range decreased (1). Similarly in rats after subcutaneous pregnenolone at the beginning of the light period SWA increased (177). Intraperitoneal administration of pregnenolone sulfate in rats increased REMS (178).

8.2.2. Progesterone, allopregnanolone

The dose-dependent hypnotic effect of iv progesterone was reported as early as in 1954 (179). After oral progesterone NREMS, especially stage 2 sleep increased and SWA decreased in young men (180). Furthermore EEG power in the higher frequency range (> 15 Hz) tended to be elevated. In this study great interindividual variability in the bioavailability of progesterone and consequently in the time course of the concentrations of its metabolite allopregnanolone was observed. Therefore two subgroups were formed, one with an early peak and one with a late peak. The time course of the allopregnanolone peak was associated with the changes in the EEG power spectra. The initial increase in the EEG activity in the spindle and alpha range in the first few hours of sleep appeared to be restricted to the subjects with an early allopregnanolone peak, whereas the decrease of SWA occurred mainly in those showing a later peak of this metabolite. The sleep-EEG changes after progesterone in humans are similar to those induced by agonists at the GABA_A receptor, e.g. benzodiazepines and appear to be mediated in part via the conversion of progesterone into allopregnanolone. Similar observations were reported in rats (181). Intraperitoneal administration of three doses of progesterone at night onset in rats prompted dose-dependently decreases of NREMS latency, wakefulness and REMS and increases of REMS latency and of pre-REMS, an intermediate state between NREMS and REMS. Furthermore EEG activity decreased in the lower frequencies and was enhanced in the higher frequencies. Sleep-EEG effects of two doses of ip allopregnanolone itself were studied in rats (182). Both doses reduced NREMS latency and the higher dose increased preREMS. Furthermore in NREMS EEG activity decreased in the lower frequencies (< 7 Hz) and increased in the higher frequencies (≥ 13 Hz). These data confirm benzodiazepine-like effects of allopregnanolone on sleep.

8.2.3. THDOC

3-alpha, 21-dihydroxy-5-alpha-pregnan-20-one (THDOC) was found to exert electrophysiological effects similar to barbiturates and shortened sleep latency in rats (183).

8.2.4. Dehydroepiandrosterone (DHEA), DHEA sulfate (DHEAS)

A single oral dose of dehydroepiandrosterone (DHEA) increased selectively REMS in young normal men (184). This finding is compatible to a mixed GABA_A agonistic/antagonistic effect. After ip DHEA sulfate (DHEAS) a dose-dependent effect on EEG power was observed. 50 mg/kg DHEAS augmented EEG power in the spindle-frequency range, whereas 100 mg/kg DHEAS had the opposite effect. Sleep architecture remained unchanged after either dosage of DHEAS (185).

9. MELATONIN

9.1. Basic activity

Melatonin secretion is related to the light-dark cycle and is maximal rest and sleep periods (186).

9.2. Effects of melatonin administration

Study results on a beneficial effect of melatonin in young and elderly subjects are ambiguous (187). A possible side effect of long-term treatment with melatonin is a blunting of sexual steroids in men and women. So far there is a lack of sufficient data from clinical studies in order to recommend melatonin as a different effective sleeping pill. Some studies suggest that due to phase-shifting properties, melatonin may be helpful in the treatment of rhythm disturbances, like jet lag and disturbed rhythms in blind patients (186, 188).

10. OTHER PEPTIDES

10.1. Galanin

Galanin is a peptide that is widely located in the mammalian brain and coexists in neurons with various peptides and classical neurotransmitters participating in sleep regulation. It is also known to stimulate GH via GHRH in man (189). Sleep in the rat remained unchanged after icv galanin, whereas a role for galanin in sleep regulation is suggested by the finding that REMS deprivation induced galanin gene expression (190). Under repetitive iv administration of galanin to young normal men SWS and the duration of REMS periods increased, whereas the secretion of GH and cortisol remained unchanged (191). A cluster of GABAergic and galaninergic neurons was identified in the ventrolateral preoptic area, which is thought to stimulate NREMS (192). NPY exerts a dual action on the HPY system. After icv administration low doses of NPY suppressed corticosterone in the rat, whereas higher doses enhanced corticosterone and ACTH (193). Similarly increases of hypothalamic CRH levels after NPY (194) and a CRH antagonistic action of NPY as well were described. NPY is found in several neuronal pools in the CNS and NPY actions may greatly vary with these action sites.

10.2. Neuropeptide Y (NPY)

In sleep regulation NPY, besides GHRH appears to be a physiological antagonist of CRH. Similarly opposite effects of CRH and NPY were found in animal models of anxiety (reviewed in 195). (i) After icv administration of NPY to rats EEG spectral activity changed similarly to the effects of benzodiazepines (196). (ii) The prolongation of sleep latency by CRH was antagonized dose-dependently by NPY stage in rats (197). (iii) In young normal men repetitive iv administration of NPY prompted decreases of sleep latency, the first REMS period, and increases of 2 sleep and sleep period time and blunted cortisol and ACTH secretion (198). (iv) In patients with depression of both sexes with a wide age range and age-matched controls the sleep latency was shortened after NPY whereas cortisol and ACTH as levels and the first REMS period remained unchanged (199). These data suggest that NPY participates in sleep regulation, particularly in the timing of sleep onset as an antagonist of CRH acting via the GABAA receptor.
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Figure 3. Model of peptidergic sleep regulation. Abbreviations: NPY – Neuropeptide Y, GHRH – growth hormone (GH)-releasing hormone, CRH - corticotropin-releasing hormone, SRIF – somatostatin, REM – rapid eye movement sleep, I to IV – indicate stages of NREMS.

10.3. Pituitary adenylate cyclase activating polypeptide (PACAP)

Pituitary adenylate cyclase activating polypeptide (PACAP) is a member of the VIP family. Icv injection of PACAP at dark onset enhanced REMS (200).

11. PERSPECTIVE

A bidirectional interaction between sleep EEG and endocrine activity is well established. Various hormones (peptides, steroids) exert specific effects on the sleep EEG in several species including humans. In Figure 3 a model of peptidergic sleep regulation in humans is proposed. The effects of CRH-1 receptor antagonism in depression, of arginine vasopressin in the elderly and of estrogen replacement therapy in the menopause are promising hints for a clinical application of research in this exciting area. It is well documented that a reciprocal interaction of the neuropeptides GHRH and CRH plays a keyrole in sleep regulation. GHRH promotes sleep, at least in males, whereas CRH enhances vigilance and impairs sleep. Changes in the CRH:GHRH ratio in favor of CRH contribute to shallow sleep, elevated cortisol secretion and blunted GH during depression and aging. Interestingly recent data suggest CRH-like effects of GHRH in women. Several studies, particularly the administration of the CRH-1 receptor agonist (NBI-30775) in patients with depression and some studies on the effects of CRH antagonists in the rat model suggest that CRH promotes REMS. However, other studies failed to support this view. NPY is another antagonist of CRH, particularly in the timing of sleep onset in humans and rats. Besides of CRH somatostatin appears to be another sleep-impairing peptide. Cortisol was shown to promote SWS in normal human controls, probably due to feedback inhibition of CRH. Furthermore REMS was suppressed in humans after cortisol, whereas REMS decreased after short term withdrawal of hydrocortisone substitution in Addison's patients. In contrast subchronic administration of the GR agonist methylprednisolone in patients with multiple sclerosis prompted some sleep-EEG changes resembling those in patients with depression. These data suggest that physiological cortisol levels are a prerequisite of REMS maintenance and that synergism of elevated CRH and glucocorticoid levels contributes to REMS desinhibition during depression. Besides of GHRH galanin and ghrelin were shown to promote SWS. Studies in dwarf mice suggest that intact GHRH receptors are the prerequisite for sleep promotion by ghrelin. Galanin is colocalized with GABA in the ventrolateral preoptic nucleus. Many hypothalamic GHRH responsive neurons are GABAergic. Galanin, ghrelin and CRH may either act in a synergistic fashion or these peptides may be part of a cascade resulting in the promotion of NREMS. Probably GABAergic neurons mediate the effects of these peptides. Furthermore GABAA receptors are targets of various neuroactive steroids, which modulate sleep in a specific fashion. Pregnenolone promotes SWS in humans and rats. Progesterone, most likely via allopregnanolone, acts in a benzodiazepine-like fashion in humans and rats, whereas DHEA promotes REMS in humans. Promotion of REMS was also observed in various animals after prolactin, which is thought to mediate REMS promotion by VIP. In humans only the effects of excessive prolactin levels in prolactinoma patients were investigated. These patients show an increase of SWS. In young normal men after VIP the NREMS/REMS cycle was decelerated, probably by action on the SCN. Finally the changes of sleep EEG after the menopause and the beneficial effect of estrogen replacement therapy point to a role of estrogen in sleep regulation.

Whereas much knowledge has accumulated about the endocrine regulation of sleep, the exact interaction of all these factors is not yet finally known.

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