Pathology of Sleep, Hormones and Depression

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Key words

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Abstract

In patients with depression, characteristic changes of sleep electroencephalogram and nocturnal hormone secretion occur including rapid eye movement (REM) sleep disinhibition, reduced non-REM sleep and impaired sleep continuity. Neuropeptides are common regulators of the sleep electroencephalogram (EEG) and nocturnal hormone secretion and changes in their activity appear to contribute to the aberrances of sleep in affective disorders. A reciprocal interaction of the sleep-promoting growth hormone-releasing hormone (GHRH) and corti-

cotrophin-releasing hormone (CRH), which promotes wakefulness and REM sleep, plays a key role in sleep regulation, at least in male subjects. Also galanin and ghrelin promote sleep in men. Neuropeptide Y is involved in the timing of sleep onset. The effects of peptides of sleep are influenced by the time of administration, age, gender and depression. In healthy subjects and in remitted depressed patients motoric memory learning is consolidated during sleep. This effect is absent in depressed patients who are at least 30 years old, and is probably related to elevated glucocorticoid levels.

Introduction

Disturbed sleep and impaired cognition are frequent symptoms in patients with depression. Objective assessment of their sleep by polysomnography (sleep electroencephalogram [EEG]) reveals characteristic changes. Furthermore nocturnal hormone secretion shows aberrances in affective disorders. Here we review studies on the interaction between depression, sleep, memory and endocrine activity focusing particularly on work of our laboratory.

Simultaneous investigation of sleep EEG and nocturnal hormone secretion shows that in young healthy subjects during the first half of the night slow-wave sleep (SWS) and the major peak of growth hormone (GH) secretion during 24 h preponderate, whereas the second half of the night is dominated by rapid eye movement (REM) sleep and the secretion of the hormones of the hypothalamic-pituitary-adrenocortical (HPA) system corticotrophin (ACTH) and cortisol [1]. During normal ageing and during an episode of depression changes of sleep-endocrine activity occur. Well documented sleep-EEG changes in depression include disinhibition of rapid eye

movement (REM) sleep (shortened REM latency, prolonged first REM period, elevated REM density, a measure of the amount of rapid eye movements during REM sleep), impaired non-REM sleep (reduced time spent in sleep stage 2 and SWS) and changes of sleep continuity (prolonged sleep latency, frequent nocturnal awakenings and early morning awakening) [2]. Similarly during aging more shallow sleep develops [3]. ACTH and cortisol secretion are elevated in depressed patients. The amplitude of the nocturnal course of these hormones is dampened in the elderly resulting in an elevated nadir. GH secretion is blunted during ageing and in a depressive episode as well [1]. The sleep-endocrine pattern in young healthy subjects and its changes related to depression and ageing suggest that there exist endogenous factors which are common regulators of sleep EEG and hormones, linking, for example, SWS and GH or HPA activity and REM sleep, respectively.

Bibliography

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Table 1 Effects of neuropeptides on human sleep.

Peptide	Sex	Sample	Time	Effects on					
				wake	NonREM	REM	other	GH	Cortisol
GHRH	m	h vol	so	↓	↑	÷		↑	↓
GHRH	m	y h vol	morn.	÷	÷	÷		(↑)	÷
GHRH	f/m	elder	so	(↓)	(↑)	÷		(↑)	÷
GHRH	f	h vol	so	↑	↓	÷		↑	÷/↑
GHRH	m	dep pat	so	↓	↑	÷		↑	↓
GHRH	f	dep pat	so	↑	↓	÷		↑	↑
ghrelin	m	y h vol	so	÷	↑	(↓)		↑	↑
ghrelin	m	y h vol	morn.	÷	÷	÷		↑	↑
ghrelin	m	elder	so	÷	↑	↓		↑	↑
ghrelin	f	elder	so	÷	÷	÷		↑	↑
ghrelin	m	dep pat	so	↓	↑	÷		↑	↑
ghrelin	f	dep pat	so	↑	÷	↓		↑	↑
somatostatin	m	y h vol	so	÷	÷	÷			
somatostatin	f/m	elder	so	↑	↓	↓			
octreotide	m	y h vol	so	↑	↓	↓			
CRH	m	y h vol	so	÷	↓	↓		↓	↑
CRH	f	y h vol	so	↑	↓	↑		÷	↑
ACTH(4-9)	m	y h vol	so	(↑)	(↓)			÷	÷
NPY	m	y h vol	so	÷	↑	÷	slat ↓, SPT ↑	÷	↓
NPY	f/m	h vol	so	÷	÷	÷	slat ↓	÷	÷
NPY	f/m	dep pat	so	÷	÷	÷	slat ↓		
galanin	m	y h vol	so	÷	↑	÷		÷	÷
galanin	f/m	dep pat	day	÷	÷	÷	REMLat ↓		

GHRH = growth hormone-releasing hormone, CRH = corticotrophin-releasing hormone, ACTH(4-9) = adrenocorticotrophin (4-9) analogue ebitatide, NPY = neuropeptide Y; f = female, m = male; h vol = healthy volunteers, y = young, dep pat = patients with depression; time = time of administration, so = around sleep onset (mostly 22:00–01:00), morn. = early morning (04:00–07:00), day = at daytime (09:00–12:00); ÷/↑ means controversial findings on effects, (↑) means weak effects; non-REM = non-rapid-eye-movement sleep, REM = rapid-eye-movement sleep, slat = sleep latency, SPT = sleep period time, REMLat = REM latency; GH = growth hormone

Effects of Neuropeptides on Sleep

Indeed preclinical studies have shown that the releasing hormones GH-releasing hormone (GHRH) and corticotrophin-releasing hormone (CRH), besides their endocrine actions, regulate sleep. After central administration of GHRH to rats SWS increases, whereas CRH impairs sleep [4]. In mice overexpressing CRH in the central nervous system (CNS) REM sleep is elevated in comparison to the wild type [5]. We tested whether similar effects are found after pulsatile intravenous (i.v.) administration of these peptides to humans. Indeed in young male healthy volunteers after GHRH, SWS and GH increased and cortisol was blunted [6]. In contrast after CRH, SWS decreased during the second half of the night, the GH peak was blunted and cortisol increased during the first half of the night [7]. These findings (see also **Table 1**) confirm the view that a reciprocal interaction of GHRH and CRH plays a key role in sleep-endocrine regulation [8]. It is unlikely that the changes of sleep EEG after GHRH and CRH are mediated by the elevated secretion of GH or cortisol, respectively. Other studies showed that SWS decreases after acute administration of GH to humans [9] and laboratory animals [10], whereas SWS and GH are elevated after cortisol administration to healthy volunteers [11]. These changes can be explained by feed-back inhibition of the related releasing hormones GHRH and CRH. Therefore we suggest that peptides act directly in the brain and affect there sleep EEG. This view is supported by the observation that sleep EEG is influenced by the ACTH (4–9) analogue ebitatide. In young male volunteers after ebitatide a set of sleep-EEG changes occurred mirroring cerebral activation. In detail SWS decreased and sleep latency and wakefulness increased during the first third of the night. The plasma

concentrations of cortisol and GH remained unchanged, however [12]. Similarly SWS increased in healthy male subjects after the neuropeptide galanin in absence of changes of GH and cortisol secretion [13]. The latter observation is in line with Saper's hypothesis that a cluster of neurons containing galanin and GABA in the ventrolateral preoptic area participates in the promotion of non-REM sleep [14]. The findings after ebitatide and after galanin administration demonstrate that peptides are able to modulate sleep EEG independently from peripheral hormones. Obviously the blood-brain interface is not an obstacle for these effects. Repetitive pulsatile administration of peptides appears to be a crucial methodological issue since after nocturnal infusions and single i.v. injections of GHRH sleep remained unchanged [15].

The effects of peptides on sleep EEG and hormone secretion are influenced by time of administration, age, sex and depression. The same dosage of GHRH which enhanced SWS after administration around sleep onset did not prompt major sleep-EEG changes when given during the morning hours, an interval with high endogenous HPA activity [16]. The response of GH after GHRH given at daytime is reduced in elderly men compared to young men [17]. Similarly GHRH administration to healthy women and men who were 60 years of age and older prompted only weak sleep promoting effects. In this sample the number of nocturnal awakenings decreased and the time spent in non-REM sleep during the first sleep cycle was prolonged [18]. A sexual dimorphism in the effects of GHRH on sleep-endocrine activity was found in a large sample of drug-free female and male patients with depression of a wide age range and in matched healthy controls. In male patients and control subjects a sleep promoting effect was confirmed as the amount of

non-REM sleep increased and the time spent awake during the sleeping period decreased. Similar to our previous study HPA hormones were blunted as ACTH declined during the first half of the night and cortisol decreased during the second half of the night after this peptide [19,20]. In depressed and healthy women, however, opposite effects were found. Sleep was impaired as intermittent wakefulness increased and non-REM sleep decreased. ACTH and cortisol were elevated in female patients and control subjects [19,20]. This sexual dimorphism was confirmed in a study in young healthy female volunteers with injection of 2 dosages of GHRH or placebo during the same interval of the menstrual cycle. Again sleep impairing effects of GHRH were found in women, whereas cortisol levels did not differ between GHRH and placebo conditions [21].

Somatostatin is the counterpart of GHRH in the regulation of GH release. We tested whether similarly its action on sleep is opposite to that of GHRH. In young healthy men sleep remained unchanged after pulsatile i.v. somatostatin administration [6]. The same dosage of somatostatin which did not affect sleep in young healthy men impaired sleep in healthy seniors [22]. Obviously the sleep promoting effect of GHRH declines during ageing whereas the sleep impairing action of somatostatin increases. After subcutaneous administration of the highly potent somatostatin analogue octreotide, sleep was impaired in young healthy men [23]. These data suggest that somatostatin participates not only in the regulation of GH secretion but also in sleep regulation in an opposite fashion to GHRH.

The effects of CRH were more distinct in young healthy women than in young healthy men. In women CRH prompted a decrease of stage 3, one component of SWS, an increase of intermittent wakefulness and an increase of the time spent in REM sleep during the first third of the night, all changes resembling sleep-EEG alterations in depressed patients [24]. Vice versa during a clinical trial with the CRH-1-receptor antagonist R 121919 after 4 weeks the amount of SWS increased, the number of awakenings and REM density decreased [25]. These findings suggest that CRH-1-receptor antagonism helps to normalize impaired sleep in depressed patients. Furthermore, the view is corroborated that CRH overactivity contributes to the sleep-EEG changes in depression.

Neuropeptide Y (NPY) is thought to be an endogenous CRH antagonist. In a preclinical study CRH prolonged sleep onset latency and decreased sleeping time in rats. These changes were counteracted dose-dependently by NPY [26]. In another study benzodiazepine-like EEG changes after NPY were described in rats [27]. Similarly after repetitive i.v. administration of NPY to young healthy men benzodiazepine-like changes of sleep EEG were found, including shortened sleep latency and increases of sleep period time and the time spent in sleep stage 2. Nocturnal ACTH and cortisol levels decreased after NPY in this sample. These findings are compatible with a CRH antagonistic and a benzodiazepine-like action as well. In another study we investigated the sleep-endocrine effects of NPY in drug-free patients of both sexes and in matched healthy controls. These samples were older than the young volunteers in our previous study. Again sleep latency was prolonged after NPY, but other sleep-EEG variables and ACTH and cortisol secretion remained unchanged. Probably timing of sleep onset is a major effect of NPY [28].

Beside GHRH and somatostatin, ghrelin is the third peptide involved in GH secretion. Ghrelin binds to the GH-secretagogue receptor and stimulates in addition to GHRH the secretion of GH. Furthermore, it is involved in the energy balance as the most

potent endogenous stimulus for food intake and body weight [29]. After repetitive i.v. injections of ghrelin to healthy young volunteers SWS and correspondingly EEG delta waves increased [30]. These effects resemble those of GHRH in young men. The pattern of endocrine changes after ghrelin differs, however, from the effects of GHRH in young male subjects. After ghrelin, GH and cortisol increased [31], whereas after GHRH GH increased, too, but cortisol decreased [6]. In a series of studies the influence of time of administration, age, sex and depression on the effects of ghrelin on sleep-endocrine activity were investigated. Similar to GHRH ghrelin did not affect sleep EEG after administration to healthy young men during the early morning hours [31]. A sleep-promoting effect of ghrelin was preserved in elderly healthy men as non-REM sleep increased [32]. In young [33] and in postmenopausal [32] healthy women, however, sleep EEG remained unchanged after ghrelin. Endocrine effects were similar in both sexes with increases of GH and cortisol. In male drug-free patients with depression again a sleep-promoting effect of ghrelin occurred. In contrast in female patients REM sleep decreased, whereas non-REM sleep remained unchanged [34]. The interactions between ghrelin, GHRH and CRH in sleep regulation and the secretion of cortisol and GH were studied in male healthy volunteers who underwent 4 protocols receiving placebo (A), ghrelin (B), ghrelin and GHRH (C), or ghrelin and CRH (D) in pulsatile fashion in a randomized cross-over study [35]. Non-REM sleep increased in all verum conditions compared to placebo. REM sleep was decreased in conditions B, C and D compared to placebo. After the combination of CRH and ghrelin the time spent awake decreased and sleep efficiency increased; furthermore, REM latency decreased compared to the other conditions. CRH enhanced the ghrelin-induced cortisol concentration but had no relevant effect on GH. In turn, after GHRH the ghrelin-induced GH concentration was elevated whereas cortisol secretion remained unchanged. In all, ghrelin exhibited distinct sleep effects, which tended to be enhanced by both GHRH and CRH. CRH exerted sleep-improving and REM permissive effects when co-administered with ghrelin.

As mentioned before galanin stimulates sleep in healthy male volunteers [13]. The effect of a morning injection of galanin was tested versus placebo in a sample of patients with depression who were on a stable treatment with trimipramine. In contrast to most other antidepressants trimipramine does not suppress REM sleep. After galanin REM latency increased and the score of the Hamilton depression rating scale decreased between morning and noon [36]. These findings point to an acute antidepressive effect of galanin.

Taken together these data can be integrated in the following model (see • Fig. 1). At least in men a reciprocal interaction of GHRH and CRH appears to play a key role in sleep endocrine regulation. In young healthy subjects GHRH is thought to be active during the first half of the night, resulting in the preponderance of SWS and GH and the nadirs of ACTH and cortisol. Ghrelin and galanin may act as cofactors to GHRH. Alternatively there may be a cascade of actions of these 3 peptides. Timing of sleep onset appears to be the major effect of NPY. The second half of the night is dominated by CRH possibly with somatostatin as its cofactor. During this interval REM sleep, ACTH and cortisol dominate, SWS is rare and GH secretion is low. The GHRH/CRH ratio is changed in favour of CRH during an acute episode of depression related to CRH overdrive and during ageing due to reduced activity of GHRH. This may explain the similar changes of sleep endocrine activity during ageing and during depression.

Fig. 1 Model of normal and peptidergic sleep regulation. Model of normal and impaired peptidergic sleep regulation. It is thought that during the first half of the night the influence of GHRH preponderates resulting in the high amounts of SWS and GH. Galanin and ghrelin may be co-factors to GHRH. NPY influences timing of sleep onset. During the second half of the night CRH and its co-factor somatostatin dominate. Changes in the GHRH/CRH balance during depression and ageing result in similar alternations of sleep-endocrine activity. GHRH = growth hormone-releasing hormone, CRH = corticotrophin-releasing hormone, SRIF = somatostatin, NPY = neuropeptide Y (from Der Nervenarzt, Schlafendokrinologie, 66, 1995, 15-27, Steiger A, Fig. 2).

After exogenous GHRH sleep was impaired. Further studies are needed to clarify possible gender differences in sleep regulation.

Sleep-Related Memory Consolidation in Depression

A rapidly growing body of evidence supports a major role of sleep in the consolidation of both declarative memory and procedural skills. Furthermore, memory processes are influenced by stress hormones in a distinctive pattern. Since disturbed sleep is a major symptom and endocrine changes are a major biomarker of affective disorders, it was suggested that sleep-related neuroplasticity might be impaired in depression [37]. While cognitive

impairments are indeed a well-known phenomenon in psychiatric patients, most studies of memory processes have concentrated on short-term retention periods only, demonstrating impairments specifically for the declarative memory system. When assessed before and after a night of sleep, however, the consolidation also of procedural motor skills was observed to be impaired in depressed patients: While patients treated with antidepressants and healthy control subjects showed a comparable training effect during daytime, only controls experienced further improvements after a night of sleep, while patients experienced a decrease in motor memory performance [37,38]. These impairments were strongly modulated by age, being most pronounced in patients above the age of 30 years and thereby coinciding with the age threshold above which depression-related sleep disturbances are most pronounced. Since sleep-related memory consolidation also negatively correlated with age in healthy control subjects, this pattern of memory impairment mirrors synergistic effects of age and depression on nocturnal activity of the HPA system. Remitted patients receiving maintenance therapy with antidepressants sleep-related memory consolidation was found similar to healthy volunteers [37]. Of note, pathological alterations of HPA hormone activity diminish in remitted patients, while sleep disturbances can be observed even after remission [39].

Surprisingly, while acutely depressed patients showed worse declarative learning during the day, the sleep-related aspects of declarative memory turned out to be preserved, rendering this a double dissociation of declarative and procedural wake- and sleep-related memory impairments in depression [40]. It has been proposed that procedural memory consolidation specifically depends on REM sleep, while declarative memory consolidation depends on SWS [41]. While many antidepressants suppress REM sleep, it is unlikely that pharmacological REM sleep suppression explains overnight impairments of procedural memory in depressed patients. On the one hand, remitted patients receiving these drugs improve overnight in their procedural memory performance [37]. Furthermore, patients receiving drugs which do not suppress REM sleep like trimipramine, mirtazapine and bupropion experience sleep-related memory impairments to the same or even greater degree [37,40]. Likewise, healthy subjects deprived of REM sleep either pharmacologically [42] or manually [43] do not experience procedural memory impairment overnight, and a daytime nap without REM sleep may lead to procedural memory enhancement compared to a wake control condition [44]. Hence, depression- or pharmacotherapy-related alterations of sleep architecture do not seem to underlie overnight impairments of procedural memory consolidation in depressed patients. To test the hypothesis that alternatively endocrine changes play an important role in memory consolidation impairments, in a further study 4 groups we compared: i) patients with multiple sclerosis receiving glucocorticoid therapy, ii) patients with multiple sclerosis receiving mitoxantrone, iii) patients with depression and iv) healthy control subjects. Patients with multiple sclerosis after mitoxantrone and healthy subjects showed an unimpaired sleep-related memory consolidation. In contrast after glucocorticoid therapy in multiple sclerosis and in depressed patients whose cortisol levels are expected to be elevated decreases of procedural memory performance were observed after a night of sleep. These findings suggest that the lack of sleep-related memory consolidation in patients receiving exogenous gluco-

corticoids and in depressed patients is due to elevated nocturnal HPA hormones rather than sleep-EEG changes [45].

Conclusions

Ehlers and Kupfer submitted previously [8] the “extended” 2-process model of sleep in depression. Originally Borbély [46] suggested that a sleep-dependent process S and a sleep-independent circadian process C participate in sleep regulation. Furthermore, it was hypothesized that a deficiency in process S accumulation plays a major role in sleep-EEG changes in depression [47]. According to Ehlers and Kupfer’s model [8] GHRH and CRH are suggested to represent process S and process C, respectively. The findings reported here support this view at least in male subjects. A change of the GHRH/CRH ratio in favour of CRH appears to contribute to the characteristic changes of sleep endocrine activity in patients with depression. The resulting elevation of cortisol levels appears to contribute to the impaired memory consolidation during sleep in depression. In addition to GHRH and CRH the sleep promoting peptides galanin and ghrelin, the sleep impairing somatostatin and NPY, which influences the time of sleep onset appear to be involved in sleep regulation. Their interaction with GHRH and CRH needs further elucidation. Furthermore clarification is necessary about the role of GHRH and ghrelin in the sleep regulation of women.

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Conflict of Interest

The authors declare no conflict of interest.

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