*Sleep*, 20(11):1038–1052


*State of the Art Review*

# Neuropeptides and Human Sleep

Axel Steiger and Florian Holsboer

*Max Planck Institute of Psychiatry, Department of Psychiatry, Munich, Germany*

**Summary:** Results from preclinical studies have validated the participation of neuropeptides in sleep regulation. In recent human and clinical studies it has been shown that peripheral administration of various peptides results in specific changes in the sleep electroencephalogram in humans. Furthermore, it has been demonstrated that certain peptides are common regulators of the electrophysiological and neuroendocrine components of sleep. It is now well established that the balance between the neuropeptides growth hormone-releasing hormone (GHRH) and corticotropin-releasing hormone (CRH) plays a key role in normal and pathological sleep regulation. In young normal subjects, GHRH stimulates slow-wave sleep and growth hormone secretion but inhibits cortisol release, whereas CRH has the opposite effect. During normal aging and during acute depression, the GHRH:CRH ratio is changed in favor of CRH, resulting in disturbances in sleep endocrine activity. In addition to GHRH, galanin, growth hormone-releasing peptide, and neuropeptide Y also promote sleep, unlike ACTH(4–9), which disturbs sleep. In elderly subjects, sleep deteriorates after acute administration of somatostatin but improves after chronic treatment with vasopressin. Vasoactive intestinal polypeptide decelerates the non-rapid eye movement–rapid eye movement cycle and advances the occurrence of the cortisol nadir. The impact of delta sleep-inducing peptide, cholecystokinin, and thyrotropin-releasing hormone on human sleep regulation is not yet clear. This paper reviews recent work investigating the influence of these various neuropeptides on sleep. **Key Words:** Sleep—Peptides—HPA system—Somatotropic system—Depression—Aging.

Neuropeptides act as neuromodulators and neurotransmitters in the central nervous system (CNS), participating in the regulation of various behaviors, including sleep. Many preclinical studies have shown that various peptides exert specific effects on the sleep electroencephalogram (EEG) in several species [for review, see Obál et al. (1)]. Furthermore, various peptides produced in and secreted from hypothalamic neurons also act as the releasing or inhibiting factors of pituitary hormones, thus regulating peripheral hormonal homeostasis. As the result of pioneering work conducted about 25 years ago (2–5), it is now well established that hormones show distinct patterns of nocturnal secretion and that there are temporal and functional associations between these patterns and the non-rapid eye movement–rapid eye movement (non-REM–REM) cycle, particularly in humans. More than 10 years ago, researchers in several laboratories (6–9) demonstrated that certain peptides such as growth hormone-releasing hormone (GHRH) and corticotropin-releasing hormone (CRH) influence nocturnal hormone release and the sleep EEG. By performing intriguing experiments they were able to show that these substances are common regulators of the neuroendocrine and neurophysiological components of sleep [for review, see Krueger and Obál (10)]. Over the last 10 or more years, human and clinical research has investigated the role of these and other peptides in the regulation of normal and pathological sleep in humans. This paper reviews the current level of knowledge in this area of research.

## THE HYPOTHALAMIC-PITUITARY-ADRENOCORTICAL SYSTEM

CRH produced and released from parvocellular neurons of the paraventricular nucleus is the key regulator of the hypothalamic-pituitary-adrenocortical (HPA) system. Release of CRH (e.g. during exposure to stress) is followed by the enhanced secretion of adrenocorticotropin hormone (ACTH) from the anterior pituitary and cortisol from the adrenal cortex. In addition to these effects on peripheral hormone secretion, CRH exerts various influences on behavior (11), including

Accepted for publication August 1997.
Address correspondence and reprint requests to Axel Steiger M.D., Max Planck Institute of Psychiatry, Department of Psychiatry, Kraepelinstrasse 10, D-80804 Munich, Germany.

sleep. After intracerebroventricular (icv) administration of CRH to rats, more shallow sleep was found than after the administration of vehicle (6). In normal young male controls, when the physiological pulsatile release of the peptide was mimicked by repetitive hourly intravenous (iv) boluses of 4 × 50 μg CRH between 2200 and 0100 hours, slow-wave sleep (SWS) decreased during the second half of the night and REM sleep diminished throughout the night. Furthermore, the nocturnal growth hormone (GH) surge was blunted and cortisol levels were elevated during the first half of the night (12). These data suggest that CRH has sleep-disturbing effects. Apparently, administration of CRH during the first few hours of the night is followed by fast endocrine responses of cortisol and GH, whereas the effects on the sleep EEG are longer lasting and the decrease of SWS occurs, albeit delayed, in the morning hours. Furthermore, it has been shown that some symptoms of depression (shallow sleep, hypercortisolism, and blunted GH levels) can be provoked experimentally in normal subjects by CRH, which is believed to be hypersecreted in major depression (13). Similarly, after iv CRH administration to normal controls, SWS and sleep efficiency decreased but sleep stages 1 and 2 increased significantly (14); these symptoms have also been found in depression. Repetitive administration of CRH appears to be the crucial methodological issue because, after continuous nocturnal infusion of CRH, the sleep EEG remained unchanged (15).

Furthermore, potency of the effect that CRH can have on the sleep EEG appears to depend on the selected interval for administration as well as on the dosage. For example, hourly injections of 10 μg CRH from 0800 to 1800 hours failed to modulate the sleep EEG of the coming night in young normal men (16). In this study, plasma melatonin concentrations were measured from 0800 to 0300 hours and were found to be blunted after CRH in comparison to placebo, which is consistent with the reciprocal interaction between HPA activity and melatonin secretion. From these findings it may be concluded that CRH affects sleep only when it is given in a sufficiently high dosage during the first half of the night (12) but not when a low dosage is given in the daytime (16). On the other hand, the latter strategy was sufficient to significantly inhibit melatonin secretion in healthy volunteers. Interestingly, reduced total and nocturnal melatonin secretion is frequently found in patients with depression (17,18). It appears likely that this so-called low-melatonin syndrome in depression is due to a direct effect of CRH secretion at the pineal gland, although there is no direct correlation between the sleep EEG and melatonin changes during depression. A role for ACTH and for the consecutively increased cortisol levels in the altered levels of melatonin secretion can be excluded because in the same study repetitive injections of 1 μg ACTH from 0800 to 1800 hours did not affect melatonin levels. Except for a nonsignificant decrease in time spent in REM sleep, there was no change in the sleep EEG, although cortisol was elevated in response to ACTH administration (16).

Two studies have been conducted to examine the effects of continuous infusions of ACTH. In one study, a higher dose of ACTH (40 IU, corresponding to about 350 μg) was given to healthy volunteers over a period of 8 hours starting at 0800, 1500, or 2330 hours. In addition, three patients with Addison's disease received the same dose of ACTH starting at 0800 hours (19). In the normal controls, ACTH produced a marked reduction in REM sleep after all three protocols. Furthermore, it reduced total sleep time in these subjects after the infusions beginning at 0800 and 1500 hours, with SWS also decreased after the 0800-hours infusion. In the patients with Addison's disease, only a slight reduction in REM sleep was reported. The authors suggested that ACTH affects sleep through its effects on corticosteroid secretion. Similarly, in another study, nocturnal infusion of ACTH (0.55 IU/hour, corresponding to about 5 μg/hour) starting at 2200 hours suppressed REM sleep in normal controls. In this second study, increases of cortisol and GH were observed throughout the night under ACTH (15).

The ACTH(4–9) analog ebiratide, which induces several behavioral effects but is devoid of endocrine effects (20), was used to differentiate between the central (sleep EEG) and peripheral (adrenocortical activation) effects of ACTH (21). As expected, pulsatile administration of this compound had no effect on peripheral GH and cortisol levels. However, several sleep EEG changes were found after ebiratide that are compatible with a general CNS activation: sleep period time and sleep efficiency index decreased, and sleep onset latency was prolonged. During the first third of the night, intermittent wakefulness increased and SWS was reduced. REM sleep was reduced only during the second third of the night, although the total amount remained unchanged over the entire night (21). This study indicates that CRH (12) and ACTH exert different specific effects on the sleep EEG. Furthermore, it demonstrates that the blood-brain barrier does not prevent central effects of intravenously administered peptides because the ACTH(4–9) analog affected the sleep EEG without any measurable peripheral effect. Another method of differentiating between the central and peripheral mechanisms in the sleep EEG effects of CRH is through the administration of cortisol. After continuous nocturnal (2300–0700 hours) infusion of cortisol (22), and after pulsatile iv administration from 1700 to 0700 hours (23), SWS increased and REM

sleep decreased in young normal controls. In the second study, increased GH secretion was reported. The opposing effects of CRH (12) and cortisol on SWS (22,23) and GH (23) contradict the assumption that the effects of CRH are mediated by stimulation of cortisol. Clearly, cortisol that is elicited physiologically by CRH via ACTH exerts effects opposite to those of exogenous CRH (12). These data suggest that cortisol acts by negative feedback inhibition of CRH. Because CRH (12), ACTH (15), and cortisol (22,23) suppress REM sleep—in contrast to ebiratide, which has only a slight effect on stage REM—it appears possible that REM suppression was mediated by cortisol in all these experiments. This is not contradicted by the lack of significant REM suppression after pulsatile daytime administration of ACTH, because in this study the nocturnal cortisol levels were not elevated (16). Our view is further supported by the fact that the inhibitor of cortisol synthesis, metyrapone, diminished SWS and, marginally, also cortisol levels in young normal men but did not change REM sleep (24). In this study, endogenous CRH was probably elevated as ACTH concentrations were remarkably enhanced. Further clarification is needed on the role of hypothalamic CRH in REM sleep regulation: In the rat, CRH enhanced REM sleep after sleep deprivation (25), which fits with the frequently observed disinhibition of REM sleep in patients with depression (26,27).

## ARGININE VASOPRESSIN

Arginine vasopressin (AVP) is another peptide participating in the regulation of CNS functions and peripheral hormone secretion as well as playing a role in the regulation of salt and water homeostasis. The peptide acts as a cofactor of CRH in the activation of the HPA system (28). Preclinical and clinical data suggest that in addition to overactive CRH neurons, coexpressed AVP is also increased at the corticotropic level in depression (29). After intranasal administration of AVP to controls, a slight but significant increase in stage 2 sleep was found, whereas SWS and REM sleep tended to decrease (30). Under continuous nocturnal infusions of AVP, REM sleep was suppressed in young normal men (31). Because cortisol was determined only four times during the night in this study, the conclusion that cortisol did not induce the observed sleep EEG changes seems premature. A further clarification of this issue appears necessary, particularly because icv infusions of AVP in rats prompted increases of intermittent wakefulness, an effect also mimicked by an AVP agonist. Infusion of an AVP antagonist decreased duration of waking, with REM sleep not being affected by any of these protocols (32). These experiments suggest that acute administration of this peptide causes sleep disturbances. A recent study, however, suggests improvement of sleep in elderly subjects can be achieved by subchronic intranasal administration of AVP. In a double-blind and randomized study, the effects of a 3-month period of daily intranasal AVP treatment to normal elderly women and men before and after bedtime were studied (33). This treatment increased sleep period time, time spent in SWS, and, during the second half of the night, the amount of REM sleep. The authors suggest a compensation of the age-related AVP deficiency of the nucleus suprachiasmaticus. This result suggests that AVP could be helpful for the treatment of age-related sleep disorders.

## THE SOMATOTROPIC SYSTEM

In humans there is a rather strict temporal association between the major portion of SWS after sleep onset and the GH surge (2,3,5,34), although the nocturnal GH increase can occur prior to sleep onset in normal controls (34,35). Normal aging (36,37) and acute episodes of depression (38–41) are accompanied by a decrease in SWS as well as a diminshed GH surge. It has frequently been reported that sleep deprivation is accompanied by blunted GH release, which is evidence for a mutual functional relationship (4,42,43). Although the GH surge in young men does not differ between nights with undisturbed sleep and those with total sleep deprivation (44), these observations suggest a common factor promoting both sleep and GH release, the latter being stimulated at the pituitary level by GHRH. Studies in rats and rabbits in several laboratories have demonstrated that sleep, in particular SWS, is promoted by central GHRH administration, with sleep becoming shallower after experimental inhibition of GHRH [for review, see Krueger and Obál (10)].

Three independent laboratories have shown that peripherally administered GHRH also promotes sleep in humans. In young normal controls, repetitive hourly administration of 4 × 50 μg GHRH from 2200 to 0100 hours prompted increases of SWS and GH secretion and a blunting of cortisol secretion (45). Comparable to the findings after CRH (12) was the observation that the effect of GHRH given in the first 4 hours of the night was long lasting. SWS remained elevated up to the last third of the night, when it seldom occurs spontaneously. In addition, the inhibition of cortisol release was most marked during the second half of the night, when the HPA system is usually activated. This study also demonstrates that a pulsatile administration of GHRH is necessary to closely mimic the physiological secretion pattern and evoke these observed effects. A study comparing repetitive versus continuous administration of GHRH underlined that this is crucial when

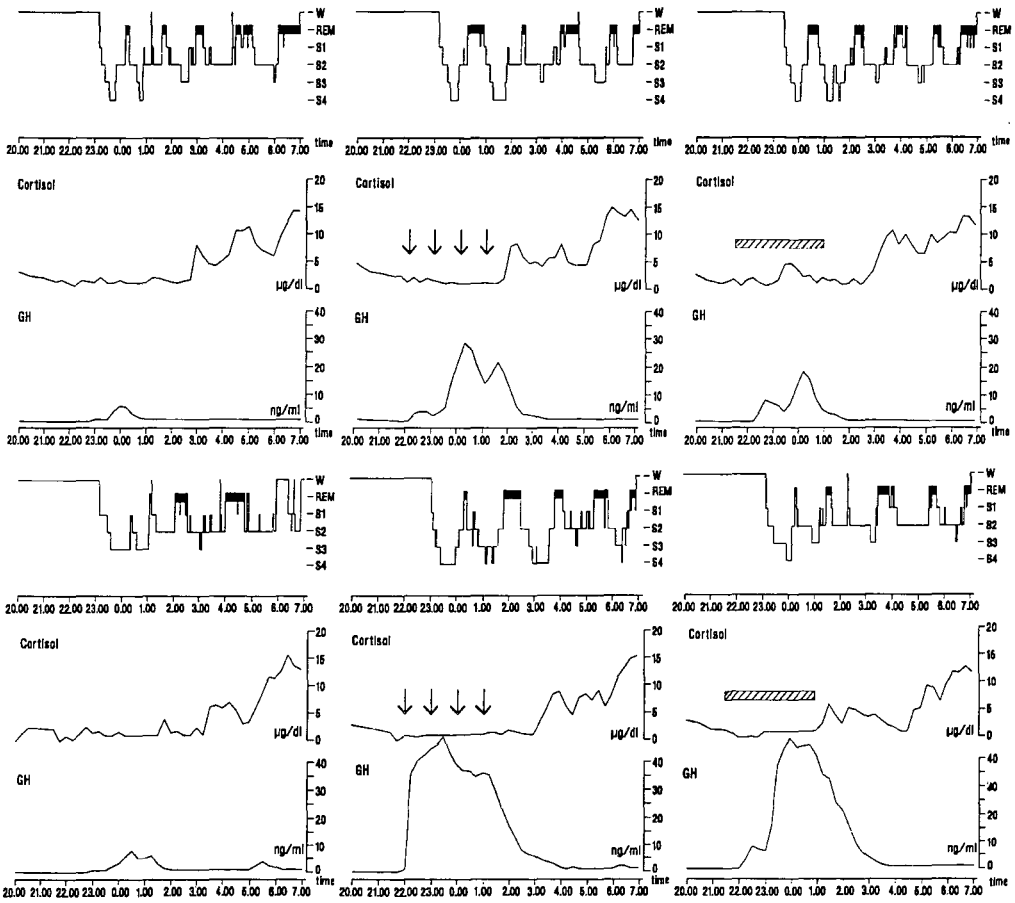


**FIG. 1.** Profiles of sleep (top), cortisol (middle), and growth hormone (GH; bottom) plasma levels from two representative subjects (upper part, lower part). Left panel, placebo condition. Middle panel, episodic GH-releasing hormone (GHRH) condition (arrows). Right panel, continuous GHRH condition (hatched bar). Lights were turned off at 2300 hours, subjects were awakened at 0700 hours. Abbreviations: W, wakefulness; S1, S2, S3, S4, sleep stages 1–4; REM, rapid eye movement sleep. Reprinted by permission of The Endocrine Society from "Greater efficacy of episodic than continuous growth hormone releasing hormone (GHRH) administration in promoting slow wave sleep (SWS)", by Marshall L, et al. in *Journal of Clinical Endocrinology and Metabolism,* vol. 81, no. 3, 1009–13. Copyright 1996 by The Endocrine Society.

central effects are being studied (46). In this same investigation, increases of SWS and GH (and, furthermore, of REM sleep) were found only after a protocol identical to our initial study (45). In contrast, sleep EEG remained unchanged when GHRH was continuously infused (Fig. 1), which had also been observed in an earlier study (47).

Conflicting results exist on the effects of single doses of GHRH. Young normal men were allowed to sleep from 2000 until 0800 hours in one study and received GHRH iv (50 µg) in two protocols, at either 0900 or 2000 hours (48). In both protocols, the sleep EEG was not influenced by GHRH, and GH secretion was elevated only after the evening administration of GHRH. In another study, 0.5 µg/kg GHRH was given to healthy men (22–38 years old) either prior to sleep onset or coinciding with sleep onset. EEG spectral analysis showed a significant increase in the lower frequency range (4–10 Hz) during the first 100 minutes of sleep, whereas all other sleep–EEG variables, including SWS time, remained unchanged. GH increased significantly after GHRH, but cortisol and ACTH were not affected (49). Kerkhofs et al. (50) applied 0.3 µg/kg GHRH in three different protocols: 1) after the onset of the first SWS period, 2) after 60 seconds of the third REM period, and 3) after sleep deprivation lasting until 0400 hours. The results of the three protocols, respectively, were as follows: 1) unchanged SWS but increased REM sleep; 2) a decrease in intermittent wakefulness and increases in SWS and, by trend, of sleep period time; and 3) a decrease in intermittent wakefulness. Finally, one single GHRH bolus (100 µg) at 2300 hours followed by 50 µg CRH at 2330 hours was given to male subjects who were awake, and lights were then turned off at 0100 hours. In comparison with baseline conditions (lights off at 2300 hours, saline treatment only), a significant increase in SWS during the second half of the night was found (51). In this study, GHRH appears to even override the sleep-disturbing influence of CRH. A recent

study (52) suggests that during repetitive administration an adequate dosage of GHRH per bolus is required. In this trial, normal controls participated in three protocols with the administration of 1) placebo or 2) GHRH by a single dosage of 50 μg at 2200 hours or 3) 5 bolus injections of 10 μg each every 15 minutes starting at 2145 hours. In this study, stage 4 sleep increased and wakefulness decreased slightly but significantly after the single bolus, although the repetitive injections did not influence sleep.

Together, these data confirm that GHRH is a sleep-promoting substance in humans. Clearly, exogenous administration is most effective when the pulsatile mode of administration is used during the first few hours of the night, with appropriate dosage and intervals between injections. Nevertheless, single boluses of GHRH are capable of modulating sleep, although the efficacy appears to depend on the time of administration. Kerkhofs et al. (50) concluded from their data, mentioned above, that GHRH is most effective when given during intervals of shallow sleep. This hypothesis is not, however, supported by a set of studies involving the administration of GHRH in three situations in which shallow sleep is a frequent finding: 1) in the early morning hours, 2) in subjects with depression, and 3) in elderly subjects.

In study 1, the efficacy of GHRH was tested in young normal men in the early morning hours when the physiological amount of SWS is low (53). To perform this investigation, the aforementioned protocol with pulsatile administration of 4 × 50 μg GHRH from 2200 to 0100 hours (45) was modified, with the administration shifted to between 0400 and 0700 hours. Examination of hormone secretion and the sleep EEG started, as in the original study, at 2200 or 2300 hours, respectively (45), but was extended until 1000 hours to clarify whether subjects slept longer after GHRH or after placebo. The effects of GHRH on the sleep EEG were weak, and the only significant change was a decrease in REM density. There was neither an increase in SWS nor a prolongation of the sleep period time. GH was significantly enhanced during the administration of GHRH, whereas cortisol and ACTH levels remained unchanged. This study suggests that GHRH is less influential in young normal controls if it is given during the second half of the night, when the amounts of time spent in SWS and the spontaneous secretion of GH are low but the activity of the HPA system is increasing. On the other hand, GHRH given repetitively during the first few hours of the night (45), or by single boluses after sleep onset until the third REM period (50), or during partial sleep deprivation (51) exerts enduring effects that last until the second half of the night. These observations support the notion (6) that there is a time window near sleep onset when the physiological action of GHRH takes place, coinciding with relatively low activity of CRH neurons.

In study 2, the aforementioned protocol with the administration of GHRH near to sleep onset (45) was repeated to test the efficacy of GHRH in patients of both sexes with an acute episode of depression (54), because it is well established that shallow sleep, disinhibition of REM sleep, blunted GH release, and hyperactivity of the HPA system are frequent symptoms of depression (27,40,55). Again, the effects of GHRH differed, being weaker in depressed patients than in young normal subjects. There were several nonsignificant trends toward improved sleep quality, with SWS time and REM time tending to increase and intermittent wakefulness tending to decrease. However, similar to study 1, the only significant sleep EEG change after GHRH was a decrease in REM density during the second half of the night. The GH surge was distinctly augmented, and cortisol and ACTH levels remained unchanged. These endocrine effects were also found in a subgroup of five younger patients who were compared to age-matched normal controls. In these patients and controls, GH increased, whereas cortisol levels were blunted after GHRH only in normal controls (54).

An analogous protocol was applied in study 3 to healthy elderly men and women (56). Normal aging is accompanied by changes in the sleep EEG and in sleep-associated hormone secretion, similar to those occurring during acute depression. Shallower sleep, including a decrease in SWS, shortened REM latency, blunted GH secretion and an advanced occurrence of the rise in cortisol with a corresponding increase in cortisol concentration during the first half of the night are well-documented findings associated with increasing age (37,57). In the elderly subjects studied, iv GHRH demonstrated some sleep-promoting effects, but these were much weaker than in young subjects (45,46). Under GHRH the number of intermittent awakenings decreased significantly, and the first nonREM period was prolonged. The GH surge was enhanced significantly, although less so than in young subjects, with cortisol and ACTH levels not affected (56). This study demonstrated a reduced efficacy of GHRH on the sleep EEG and nocturnal hormone secretion in the elderly compared to young subjects. Similarly, the GH response to the daytime administration of GHRH is markedly reduced in the elderly compared to young controls (58,59).

Iovino et al. (58) had previously reported that in daytime this loss of efficacy of GHRH on GH release in the elderly can be revised after "GHRH priming" (100 μg GHRH iv every second day for 12 days). After priming, the effect of GHRH on GH release in

old men did not differ from that in young men. Recently, Murck et al. (60) tested whether the efficacy of GHRH on sleep-endocrine activity is also enhanced after GHRH priming. To do this, the sleep EEG and nocturnal hormone secretion of two elderly men were investigated on four occasions. Either placebo or 4 × 50 μg GHRH was given between 2200 and 0100 hours at baseline on two consecutive nights according to a randomized schedule. Then, following 12 days with GHRH priming in accordance with Iovino et al. (58), the effect of GHRH was retested and, finally, a second retest was performed after a placebo period of 12 days. In both subjects, the efficacy of GHRH was not improved by priming. Sleep quality even deteriorated in comparison with baseline after priming, and this effect was still present at the end of the study. These data contradict the hypothesis that GHRH priming may be useful in prompting a "rejuvenation" of sleep-endocrine activity in the elderly.

Somatostatin inhibits GH release, thus opposing the effects of GHRH. Research on the effect of somatostatin on sleep in animals has produced conflicting data. In the rat, somatostatin either stimulated REM sleep (61) or reduced non-REM sleep (62). In young normal men, neither continuous (63), nor single (64), nor repetitive iv (45) administration had any effect on the sleep EEG. In elderly normal controls of both sexes, however, repetitive administration of somatostatin caused sleep to deteriorate: Total sleep time and REM time decreased, and intermittent wakefulness increased (65) (Fig. 2). The data from the studies in elderly controls (56,60,65) support the opposing effects of GHRH and somatostatin, not only on GH release but also on the sleep EEG: While GHRH improves sleep, somatostatin disturbs it. This observation fits with preclinical findings showing that the activity of the GHRH system declines during aging, whereas the somatostatin system remains largely unchanged (66). These data suggest that the capacity of GHRH to counteract the sleep-disturbing effects of somatostatin and (as discussed in detail below) of CRH declines with increasing age. This may contribute to the age-related changes of the sleep EEG and of sleep-associated hormone secretion. Pulsatile administration of cortisol is capable of counteracting some of these age-related changes. Bohlhalter et al. (67) investigated the effects of pulsatile iv administration of cortisol from 1700 to 0700 hours in elderly controls, analogous to the protocol in young subjects mentioned above (23). As in the young subjects, SWS, delta, and theta power and GH release were enhanced, although these effects were weaker in the elderly subjects. Furthermore, REM sleep decreased. It is possible that cortisol reinforced the effects of GHRH by the inhibition of CRH, somatostatin, or both in this study. The studies on cortisol effects in young and old subjects (66,67) showed that cortisol and CRH have opposing effects on SWS and GH. Correspondingly, administration of GH to normal controls led to a decrease in SWS (68), which may be explained by feedback inhibition of GHRH. Furthermore, REM sleep was enhanced in this study, as it was in two other studies after GHRH in young normal subjects (46,50). These data support the view that the increase in SWS after GHRH represents a direct central effect following peripheral administration. This points toward the passage of this peptide through the blood-brain barrier or effects that are mediated through GHRH receptors outside the blood-brain barrier. On the other hand, the increase in REM sleep may be mediated by enhanced GH levels, a hypothesis that is supported by preclinical data. SWS increased after iv GHRH administration to hypophysectomized rats, but REM sleep was not affected. In contrast, both SWS and REM sleep were enhanced in intact animals in this experiment (69).

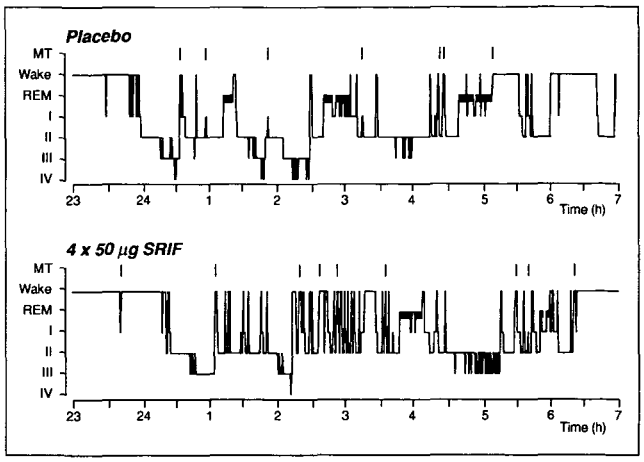


**FIG. 2.** Sleep pattern in one subject after placebo and somatostatin (SRIF). Abbreviations: MT, movement time; REM, rapid eye movement sleep; I–IV, non-REM sleep stages 1–4. Reprinted by permission of Elsevier Science, Inc. from "Somatostatin impairs sleep in elderly human subjects", by Frieboes RM, et al. in *Neuropsychopharmacology*, vol. 16, 339–45. Copyright 1997 by The American College of Neuropsychopharmacology.

In patients with acromegaly due to autonomous GH-secreting tumors, central GHRH is probably suppressed, which may explain the observation that the amount of SWS was low but increased after adenectomy in these patients (70). On the other hand, less SWS was found in subjects with dwarfism than in aged-matched normal controls (71), which is probably due to central GHRH deficiency. These clinical findings also support a causal relationship between GHRH and SWS.

## INTERACTION OF SOMATOTROPIC AND HPA SYSTEMS

Ehlers and Kupfer (72) were the first to submit the hypothesis of a reciprocal interaction between GHRH and CRH in sleep regulation. The data summarized above demonstrate that GHRH triggers SWS and GH release and inhibits cortisol secretion through suppression of CRH. The latter neuropeptide, CRH, exerts the opposite effects, as it stimulates cortisol via ACTH enhancement and inhibits SWS and GH release. Thus, CRH has activating as well as sleep-suppressing effects, which is in accordance with its role as the key regulator of behavioral adaptation to exposure to stress. In contrast, GHRH is a sleep promoter, as high GHRH release is associated with enhanced SWS. When GHRH levels are reduced, sleep consequently becomes shallow. Similarly in rats, hypothalamic GHRH mRNA levels peak around light onset when the animals tend to sleep, then decline during the light phase and remain low during the dark phase when they are active (73). We suggest that, correspondingly, in young normal subjects endogenous GHRH levels are highest during the first half of the night, resulting in the maximum occurrence of SWS and GH and in the nadir of cortisol. During the second half of the night, CRH predominates and, correspondingly, cortisol is released and the amounts of SWS and GH are low. Changes in the GHRH:CRH ratio may account for alterations in sleep endocrine activity. For example, there is strong evidence that CRH is excessively released during depression, whereas during aging the activity, efficiency, or both of GHRH decrease. As a result, CRH predominates in both conditions, producing similar changes in sleep endocrine activity. With increasing age, the progressively increasing influence of somatostatin may act as an additional sleep-disturbing factor (Fig. 3). During the recovery night after a period of sleep deprivation, changes in sleep endocrine activity occur, contrary to those found during depression and aging—namely, increases in SWS and GH (74). Furthermore, after prolonged sleep deprivation, blunted cortisol levels have been reported (75). It is possible that GHRH is excessively produced during sleep deprivation and overrides the effects of CRH. Everything points to GHRH (76) being an endogenous antagonist of CRH, calling for the search for peptidomimetics derived from GHRH that are suitable for use as sleep inducers and possibly also as antidepressants.

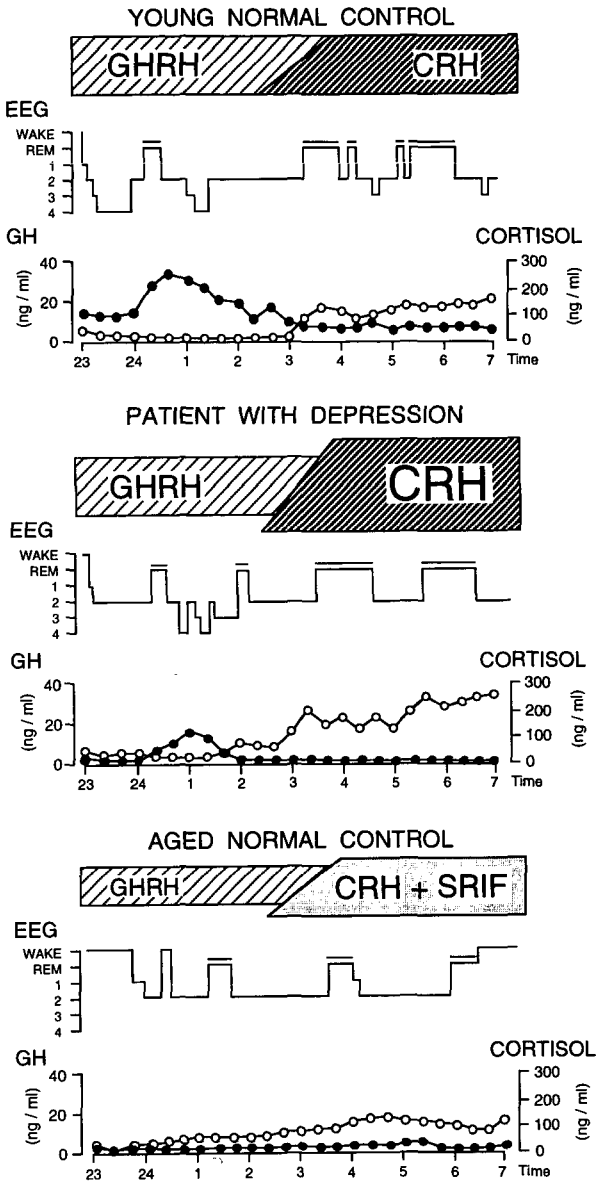


**FIG. 3.** Hypothesized reciprocal interaction of growth hormone-releasing hormone (GHRH) and corticotropin-releasing hormone (CRH) in normal sleep regulation (young healthy control subjects), during hypothalamic-pituitary-adrenocortical (HPA) system hyperactivity (patients with depression) and during decreased HPA efficacy (elderly control subjects). In the elderly, somatostatin (SRIF) is believed to contribute, besides CRH, to the impairment of sleep.

## GROWTH HORMONE SECRETAGOGUES

Growth hormone-releasing peptide-6 (GHRP) is a synthetic hexapeptide acting as a secretagogue for GH (77), but it does not act via the somatotrophic GHRH receptor (78). A specific GHRP receptor was recently identified, cloned, and found in hypothalamic and pituitary tissues (79). Repetitive administration of 4 × 50 μg GHRP to young normal men increased stage 2 sleep, GH, cortisol, and ACTH release (80). Hence, GHRP shares the promoting effects of GHRH (45) on nocturnal GH release and non-REM sleep in that instead of SWS after GHRH, stage 2 sleep is prolonged after GHRP. Surprisingly, GHRH and GHRP influence HPA activity in opposite ways. The effect of GHRP upon sleep appears to depend on the dosage, route, and time

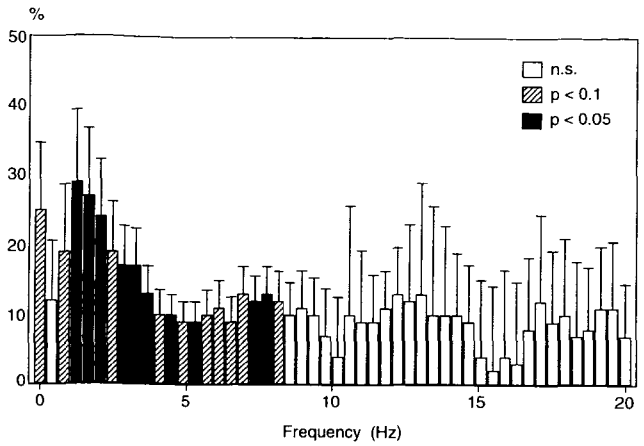


**FIG. 4.** Spectral power changes after 4 × 50 μg galanin in non-rapid eye movement sleep. Galanin enhances the electroencephalographic activity in the delta and theta frequency ranges (ns, not significant). From Murck et al. (in preparation).

of administration. Stage 2 sleep during the second half of the night was reduced after oral GHRP but increased after intranasal GHRP (81). A lower dose of GHRP iv (1 μg/kg body weight) at the beginning of the third REM period (82) did not induce sleep EEG changes. After 1 week of oral treatment with another GH secretagogue, MK677 (a novel analog of GHRP), SWS increased in young healthy volunteers, whereas the levels of GH and cortisol remained unchanged (78). These data are the first to suggest hypnotic properties of a peptidomimetic after oral administration. Future research will be directed toward the identification of an as yet unknown endogenous ligand of the GHRP receptor that may be involved in sleep regulation.

## GALANIN

Galanin 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 (83). The sleep EEG in the rat remained unchanged after icv galanin, but a role for galanin in sleep regulation is supported by the finding that REM sleep deprivation induced galanin gene expression (84). In young normal male controls, the effects of two doses of galanin (4 × 50 μg and 4 × 150 μg) were studied (85). After the lower dose, REM sleep was prolonged for the first three sleep cycles, with stage 2 sleep being reduced for the whole night. EEG spectral analysis revealed a significant increase in delta power, also for the whole night (Fig. 4). The effects of the higher dose were less distinct, with a significant increase in REM sleep during the third sleep cycle and a trend to an increase in REM sleep for the first three cycles. These data suggest that, like GHRH, galanin is a sleep-promoting peptide with more pronounced effects at lower dosages. As in the study with ebiratide mentioned above (21), the sleep EEG was modulated, but the secretory patterns of GH, cortisol, and prolactin remained unchanged. It is possible that the effects of galanin may have been mediated by a subtle release of hypothalamic GHRH into sleep-promoting areas of the brain. The amount of GHRH secreted into the portal vein was perhaps not sufficient to augment the nocturnal GH release. An alternative and perhaps more plausible explanation derives from the observation that galanin decreases the activity of neurons in the locus coeruleus (86), a structure that is involved in the regulation of reciprocal changes of REM and non-REM sleep (87). High activity of the locus coeruleus, composed mainly of noradrenergic neurons in coexistence with large amounts of galanin (88,89), inhibits REM sleep. Galanin may induce a disinhibition of REM sleep by suppressing the activity of the locus coeruleus. Experiments in rats demonstrated that the spontaneous discharge rate of noradrenergic locus coeruleus neurons is low in REM sleep and SWS but high in the waking state (90). Furthermore, cooling of the locus coeruleus in the cat induced SWS followed by REM sleep (91). During normal sleep, the inhibition of the locus coeruleus discharge after galanin may lead to a reduction of thalamocortical activity followed by EEG synchronization (92), e.g. occurrence of delta activity. Hence, the increases in REM sleep and in delta power after galanin may be explained by a reduction of the activity of the locus coeruleus. Interestingly, the effects of CRH on the locus coeruleus and the sleep EEG are the opposite of those produced by the lower dosage of galanin: CRH neurons innervate the locus coeruleus and increase the discharge rate of its neurons (93). As mentioned above, suppression of SWS was found after CRH in rats (6) and humans (12). Furthermore, REM sleep was reduced after CRH in humans (12). Although the latter effect may be mediated by enhanced cortisol secretion as mentioned before, an antagonism of galanin and CRH in sleep regulation appears possible. Furthermore, it remains to be clarified how GHRH and galanin interact in sleep regulation. Either these peptides are two independent sleep-promoting factors, or there is a cascade leading from galanin to GHRH, which itself appears to be an antagonist of CRH.

## DELTA SLEEP-INDUCING PEPTIDE

Delta sleep-inducing peptide (DSIP) was first detected in the cerebral venous blood of rabbits that had been subjected to sleep by electrical stimulation of the intralaminar thalamic area (94). Promotion of SWS after DSIP has been confirmed in several animal species,

although not all preclinical studies reproduced these effects, and even an impairment of sleep after DSIP has been reported [for reviews, see Graf and Kastin (95) and Borbély and Tobler (96)]. To our knowledge, only one study has investigated the effects of DSIP on the sleep EEG in normal men, and it found only minor effects (97). Studies on the efficiency of DSIP in the treatment of insomnia have produced conflicting results. One laboratory reported improved sleep under DSIP in patients with insomnia (98), but others have failed to confirm this finding (99,100). On the basis of these reports, it remains unclear whether DSIP is a sleep-promoting substance [see also Borbély and Tobler (96)]. On the other hand, several studies investigating DSIP-like immunoreactivity (DSIP-LI) suggest a role for the peptide in sleep regulation. Neurons containing DSIP-LI are found widely distributed in the rat brain, with high concentration in areas associated with sleep regulation (e.g. reticular formation, raphe nuclei) (101). One study tested the hypothesis that DSIP-LI levels should be elevated in association with episodes of SWS in humans. Plasma DSIP-LI levels were collected every 30 minutes for 24 hours from a sample of healthy men and women, volunteers between 23 and 49 years old. In contrast to expectations, a diurnal rhythm for plasma DSIP-LI levels was found, with the maximum during wakefulness at 1500 hours and the minimum at 0100 hours. The DSIP-LI levels in SWS were significantly lower than during wakefulness, the lowest occurring in REM sleep. No increase in DSIP-LI levels before, during, or after a significant percentage of SWS periods was found. However, a close correlation between the diurnal rhythm of DSIP-LI and that of body temperature was detected. The authors concluded that endogenous elevations of DSIP may be associated with suppression of SWS and REM sleep, and that the circadian rhythm of DSIP is coupled directly or indirectly to that of body temperature (102). This study with normal controls is at variance with a report that investigated cerebrospinal fluid DSIP-LI and the sleep EEG in patients with schizophrenia (103). The authors reported significant correlations between DSIP-LI concentrations in the cerebrospinal fluid and stage 3 sleep throughout the night and between DSIP-LI and SWS during the first non-REM period. Finally, Seifritz et al. (104) measured DSIP-LI, cortisol, and GH in young normal male controls during nocturnal sleep (2300–0800 hours), nocturnal sleep deprivation (2300–0500 hours), and morning recovery sleep (0500–0800 hours) after sleep deprivation. Significant decreases of plasma DSIP-LI were found at the transition from wakefulness to sleep in both evening sleep and morning recovery sleep. No sleep stage specificity and no correlation with cortisol and GH secretion were found for DSIP-LI. The data suggest that DSIP is induced by mechanisms that are involved in the initiation of sleep.

## NEUROPEPTIDE Y

Neuropeptide Y (NPY) is known to participate in food intake, anxiolysis, and sedation and to play a dual role in HPA activity by elevating ACTH and corticosteroids in animals after higher doses but blunting after lower doses (88). In two separate studies, young normal male controls received two dosages of NPY (4 × 50 μg and 4 × 100 μg) (105). The major effect of the lower dose was a blunting of cortisol and ACTH secretion throughout the night, whereas the sleep EEG remained largely unaffected. After the higher dose, only marginal suppression of ACTH and cortisol secretion occurred, but sleep onset latency was markedly shortened, and during the second half of the night EEG delta power decreased. These findings suggest that NPY is capable of modulating sleep onset and HPA activity. Obviously, NPY shares some, but not all, properties of $GABA_A$ receptor agonists such as benzodiazepine hypnotics, particularly the shortening of sleep latency, reduction of delta power, and blunting of HPA hormones (106,107). These findings are similar to the recent report that icv administration of NPY in the rat produced dose-dependent effects on electrophysiological measures (108). Spectral analysis of the EEG revealed a slowing of delta activity in the frontal cortex and a speeding up of low-frequency theta activity in the cortex, hippocampus, and amygdala. In addition, at higher doses EEG power was reduced at all frequencies in the cortex and at high frequencies (8–32 Hz) in the amygdala. Furthermore, auditory processing as assessed by event-related potentials was affected most distinctly in the frontal cortex, where dose-dependent decreases of the so-called N1 component were found. All these effects resemble those caused by anxiolytics such as benzodiazepines (108). The human (105) and animal (108) data support, at least in part, the hypothesis that NPY is also a physiological antagonist to CRH (109). This theory derives from animal studies, suggesting a reciprocal regulation of behavioral responsiveness to stressful stimuli. "Anxiogenic-like" effects of CRH were found in several animal models of anxiety. For example, transgenic mice that overexpress CRH have exaggerated anxiety-related behavior (110), whereas suppression of CRH by antisense probes directed against CRH mRNA or the suppression of CRH-receptor synthesis is anxiolytic (111,112). In contrast, NPY exerted anxiolytic-like effects. In normal males, shortened sleep latency and reduced cortisol and ACTH release after NPY are in contrast to a decrease in SWS and hypercortisolism after CRH [see above, Holsboer et al. (12)]. Because

$GABA_A$ agonists are known to suppress CRH (113), it appears possible that NPY participates in the regulation of behavior, including sleep, as the antagonist of CRH acting via the $GABA_A$ receptor. On the other hand, the decrease in delta power under 4 × 100 μg NPY in normal controls resembles the effect of CRH in animals (6).

## THYROTROPIN-RELEASING HORMONE

Clinical experience teaches us that sleep disturbances are concomitant with diseases of the thyroid gland, although there have been few sleep EEG studies in this field. Only one study has investigated the effects of thyrotropin-releasing hormone (TRH) in normal controls. The subjects repetitively received 4 × 50 μg TRH (114). The only effects on the sleep EEG were a decrease in the sleep efficiency index and a tendency to an increase in intermittent wakefulness. The cortisol morning rise appeared advanced, but there were no other changes of cortisol and GH release. These results do not suggest a major role for TRH in human sleep regulation.

## CHOLECYSTOKININ

Cholecystokinin (CCK) is a peptide that is present in both the gastrointestinal tract and the CNS. It participates in meal terminations via the CCK-vagal reflex (115) and has also been characterized as a satiety factor. Satiety has been described as a continuum of behavior starting with feeding cessation and progressing to sleep (116). Chronic icv infusion of CCK to rats increased the number of REM periods per hour of non-REM sleep (117). Correspondingly, after nocturnal intramuscular administration of the CCK analog caerulein to healthy volunteers, a slight increase in REM sleep was observed (118). Infusion of the CCK analog cerulitide did not, however, affect the sleep EEG of normal controls (119). At present, the role of CCK on human sleep regulation remains unclear, and further research applying repetitive administration of CCK analog is necessary to clarify this issue. Another issue that needs clarification is the relationship between the induction of paniclike attacks, both in panic attack patients and in normal controls, after CCK (120) and its effect on sleep.

## VASOACTIVE INTESTINAL POLYPEPTIDE

Vasoactive intestinal polypeptide (VIP) stimulates REM sleep after icv administration in laboratory animals (121). Preclinical data suggest that stimulation of prolactin is involved in the promotion of REM sleep

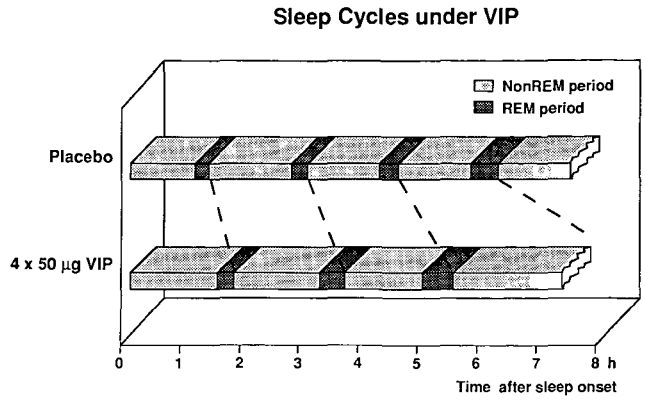


**FIG. 5.** Summarized sleep cycles on basis of conventional sleep-electroencephalographic analysis under placebo and 4 × 50 μg vasoactive intestinal polypeptid (VIP), n = 10. Reprinted by permission of The American Physiological Society from "VIP decelerates nonREM-REM cycles and modulates hormone secretion during sleep in men", by Murck H, et al. in *American Journal of Physiology*, vol. 271, R905-11. Copyright 1996 by The American Physiological Society.

after VIP (122). When VIP was given to rats in the dark period, both non-REM sleep and REM sleep increased (122,123). Two dosages of VIP (4 × 10 μg and 4 × 50 μg) were given repetitively to young normal men (124). Under the higher dosage of VIP the sleep cycles were decelerated during the first three cycles due to increased duration of both REM and non-REM sleep periods (see Fig. 5). Furthermore, there was a tendency to increased REM:non-REM ratios. After 4 × 50 μg, the cortisol nadir appeared advanced, and after midnight the plasma cortisol levels were enhanced and the GH peak was blunted. Prolactin levels were increased during the first half of the night after the higher dosage but were blunted throughout the night after the lower dosage. The latter effect was the only significant change after the lower dosage of the peptide. Spectral analysis did not reveal any influence of either dosage on the substructure of sleep stages. The data demonstrate that VIP has a specific effect on the temporal organization of the sleep pattern and of sleep-associated hormone secretion. Three effects of 4 × 50 μg VIP were postulated to be attributable to effects on the circadian clock: 1) The sleep cycles are prolonged; 2) circadian distribution of REM sleep is advanced, possibly indicating that a condition that controls the relative amount of REM sleep is also advanced; and 3) the cortisol nadir appears advanced after VIP. The blunted GH surge may be explained as a result of advanced elevated activity of the HPA system corresponding to the advanced cortisol nadir. Together, these findings suggest that VIP affects the circadian clock, which is in concordance with its neuroanatomical distribution. VIP-like immunoreactive neurons have been found in the rat forebrain, particularly in the ventrolateral part of the suprachiasmatic nucleus

(SCN) (125,126), a structure that is known to have circadian clock function. In the rat, the VIP content of this structure decreases during the light phase and continuously increases during the dark phase (127). It has been suggested that VIP in the SCN is not regulated by an endogenous rhythm but rather is driven by light–dark cycles. Thus, VIP-containing neurons in the CNS may mediate some of the entrainment effects of light. In animal experiments, the circadian rhythm of locomotor activity mediated by the SCN was affected by VIP; for example, a phase-delaying effect on diurnal activity in hamsters was found when VIP was injected into the SCN, especially when VIP was given in combination with peptide histidine, isoleucine, and gastrin-releasing peptide (128). A phase-delaying effect was found in the rat after central injection of these substances near the time of activity onset in the evening, when VIP concentration is low (127). Apparently, an artificial increase of central VIP after administration may shift the circadian clock to phase delay or advance. The direction of this action may depend on factors related to the activity–sleep pattern. In contrast to humans, the rat is active at night, so the shift may result in a delay in rats but in a phase advance in humans. Hence, these data suggest that the SCN is involved in the sleep endocrine effects of VIP in humans. It appears unlikely that in humans prolactin mediates the sleep EEG effects of VIP.

The circadian rhythmicity of the VIP-plasma level gradually disappears during aging (129) and the VIP content of the SCN also declines at this time (130). A post mortem study demonstrated that the SCN volume of patients with Alzheimer's dementia is distinctly decreased in comparison to controls (131). In these patients the sleep-wake cycle is severely disturbed (132,133), which could be caused by decreased VIP activity due to a decreased volume of the SCN.

## CONCLUSIONS

The reviewed data demonstrate that different neuropeptides exert distinct effects on human sleep. The hypothesis derived from animal research that certain peptides such as GHRH and CRH are factors in the regulation of the sleep EEG and sleep-associated hormone secretion (10,72) is strongly supported by the findings in humans. Repetitive iv injections of peptides have been demonstrated to be a successful method of inducing sleep EEG changes and elucidating the role of peptides in sleep regulation. However, recent data show that the intranasal and even oral administration of neuropeptides and their synthetic analogs also result in sleep EEG changes, demonstrating that the blood-brain barrier does not necessarily prevent the central effects of peripherally administered neuropeptides. Nonparenteral routes appear essential for the future clinical use of peptides. Besides ourselves (12,124), others (134) have also extensively discussed how peptides may enter the brain. In addition to the possibility that peptides may act via peripheral receptors on the CNS, entry via the circumventricular organs as well as active transport through the blood-brain barrier are possible mechanisms. Several peptides, including GHRH and CRH, cross the blood-brain barrier intact (135): Active transport through the blood-brain barrier has also been demonstrated for the ACTH(4–9) fragment analog ebiratide (136) and NPY (137). Finally, it has been suggested that endogenous serum peptides as large as immunoglobulin M (500 kDa) may enter the CNS via the circumventricular organs and leaky vessels in the subarachnoid space of the pial surface (138).

The reported data demonstrate specific effects of various peptides on sleep regulation. Some substances such as GHRH, galanin, and NPY have been shown to promote sleep, whereas CRH, ACTH(4–9), and, in the elderly, somatostatin impair sleep. VIP is suggested to influence the temporal organization of the REM–non-REM cycle. In contrast to their extremely short half-life, most of the investigated substances promote long-lasting changes in the sleep EEG, suggesting a genomic action.

It appears unlikely that the impact of neuropeptides on sleep regulation is restricted to the substances investigated so far, with the exact interaction with other substances participating in sleep regulation such as classical neurotransmitters, cytokines, and neuroactive steroids [for review, see Friess et al. (139)] being largely unclear. Results from animal studies have suggested a link between GHRH and interleukin-6 (10). Furthermore, concerning the interaction of various peptides, data from preclinical studies have suggested an effect of GHRP-6 on NPY (140) and AVP (141).

We expect that knowledge about the role of peptides in human sleep regulation will contribute to the development of peptidomimetics that will be used as hypnotics in the future. These substances would correspond better to human physiology than the sleeping pills available today.

**Acknowledgement:** Studies performed in the laboratory of the authors were supported by a grant from the Deutsche Forschungsgemeinschaft (Ste 486/1-2).

## REFERENCES

1. Obál F Jr, Opp M, Sary G, Krueger JM. Endocrine mechanisms in sleep regulation. In: Inoué S, Krueger JM, eds. *Endogenous sleep factors.* The Hague: SPB Academic Publishing, 1990: 109–20.
2. Quabbe HJ, Schilling E, Helge H. Pattern of growth hormone

secretion during a 24-hour fast in normal adults. *J Clin Endocrinol Metab* 1966;26:1173–77.
3. Takahashi Y, Kipnis DM, Daughaday WH. Growth hormone secretion during sleep. *J Clin Invest* 1968;47:2079–90.
4. Sassin JF, Parker DC, Mace JW, Gotlin RW, Johnson LC, Rossman LG. Human growth hormone release: relation to slow-wave sleep and sleep-waking cycles. *Science* 1969;165:513–5.
5. Weitzman ED. Circadian rhythms and episodic hormone secretion in man. *Annu Rev Med* 1976;27:225–43.
6. Ehlers CL, Reed TK, Henriksen SJ. Effects of corticotropin-releasing factor and growth hormone-releasing factor on sleep and activity in rats. *Neuroendocrinology* 1986;42:467–74.
7. Nistico G, De Sarro GB, Bagetta G, Muller EE. Behavioural and electrocortical spectrum power effects of growth hormone releasing factor in rats. *Neuropharmacology* 1987;26:75–8.
8. Obál F Jr, Alföldi P, Cady AB, Johannsen L, Sary G, Krueger JM. Growth hormone-releasing factor enhances sleep in rats and rabbits. *Am J Physiol* 1988;255:R310–6.
9. Opp M, Obál F Jr, Krueger JM. Corticotropin-releasing factor attenuates interleukin 1-induced sleep and fever in rabbits. *Am J Physiol* 1989;257:R528–35.
10. Krueger JM, Obál F Jr. Growth hormone-releasing hormone and interleukin-1 in sleep regulation. *FASEB J* 1993;7:645–52.
11. Dunn AJ, Berridge CW. Physiological and behavioral responses to corticotropin-releasing factor administration: is CRF a mediator of anxiety or stress responses? *Brain Res Brain Res Rev* 1990;15:71–100.
12. Holsboer F, von Bardeleben U, Steiger A. Effects of intravenous corticotropin-releasing hormone upon sleep-related growth hormone surge and sleep EEG in man. *Neuroendocrinology* 1988;48:32–8.
13. Holsboer F. Neuroendocrinology of affective disorders. In: Bloom FE, Kupfer DJ, eds. *Neuropsychopharmacology. 4th generation of progress.* New York: Raven Press, 1995:957–70.
14. Tsuchiyama Y, Uchimura N, Sakamoto T, Maeda H, Kotorii T. Effects of hCRH on sleep and body temperature rhythms. *Psychiatry Clin Neurosci* 1995;49:299–304.
15. Born J, Späth-Schwalbe E, Schwakenhofer H, Kern W, Fehm HL. Influences of corticotropin-releasing hormone, adrenocorticotropin, and cortisol on sleep in normal man. *J Clin Endocrinol Metab* 1989;68:904–11.
16. Kellner M, Yassouridis A, Manz B, Steiger A, Holsboer F, Wiedemann K. Corticotropin-releasing hormone inhibits melatonin secretion in healthy volunteers—a potental link to low-melatonin syndrome in depression? *Neuroendocrinology* 1997; 16:339–45.
17. Beck-Friis J, Ljunggren JG, Thoren M, Von Rosen D, Kjellman BF, Wetterberg L. Melatonin, cortisol and ACTH in patients with major depressive disorder and healthy humans with special reference to the outcome of the dexamethasone suppression test. *Psychoneuroendocrinology* 1985;10:173–86.
18. Miles A, Philbrick DR. Melatonin and psychiatry. *Biol Psychiatry* 1988;23:405–25.
19. Gillin JC, Jacobs LS, Snyder F, Henkin RI. Effects of ACTH on the sleep of normal subjects and patients with Addison's disease. *Neuroendocrinology* 1974;15:21–31.
20. Greven HM, De Wied D. The influence of peptides derived from corticotropin (ACTH) on performance. Structure activity studies. *Prog Brain Res* 1967;37:429–42.
21. Steiger A, Guldner J, Knisatschek H, Rothe B, Lauer C, Holsboer F. Effects of an ACTH/MSH(4–9) analog (HOE 427) on the sleep EEG and nocturnal hormonal secretion in humans. *Peptides* 1991;12:1007–10.
22. Born J, De Kloet ER, Wenz H, Kern W, Fehm HL. Gluco- and antimineralocorticoid effects on human sleep: a role of central corticosteroid receptors. *Am J Physiol* 1991;260:E183–8.
23. Friess E, von Bardeleben U, Wiedemann K, Lauer C, Holsboer F. Effects of pulsatile cortisol infusion on sleep-EEG and nocturnal growth hormone release in healthy men. *J Sleep Res* 1994;3:73–9.
24. Jahn H, Wiedermann K, Steiger A. Effects of metyrapone treatment upon hormonal secretion and sleep. *Eur Neuropsychopharmacol* 1996; Suppl 3:175.
25. Marrosu F, Gessa GL, Giagheddu M, Fratta W. Corticotropin-releasing factor (CRF) increases paradoxical sleep (PS) rebound in PS-deprived rats. *Brain Res* 1990;515:315–8.
26. Lauer C, Riemann D, Wiegand M, Berger M. From early to late adulthood. Changes in EEG sleep of depressed patients and healthy volunteers. *Biol Psychiatry* 1991;29:979–93.
27. Reynolds CF III, Kupfer DJ. Sleep research in affective illness: state of the art circa 1987. *Sleep* 1987;10:199–215.
28. Rinaman L, Sherman TG, Stricker EM. Vasopressin and oxytocin in the central nervous system. In: Bloom FE, Kupfer DJ, eds. *Neuropsychopharmacology. 4th generation of progress.* New York: Raven Press, 1995:531–42.
29. Barden N, Reul JM, Holsboer F. Do antidepressants stabilize mood through actions on the hypothalamic-pituitary-adrenocortical system? *Trends Neurosci* 1995;18:6–11.
30. Timsit-Berthier M, Mantanus H, Devos JE, Spiegel R. Action of lysine-vasopressin on human electroencephalographic activity. Night sleep pattern, auditory evoked potential, contingent negative variation. *Neuropsychobiology* 1982;8:248–58.
31. Born J, Kellner C, Uthgenannt D, Kern W, Fehm HL. Vasopressin regulates human sleep by reducing rapid-eye-movement sleep. *Am J Physiol* 1992;262:E295–300.
32. Arnauld E, Bibene V, Meynard J, Rodriguez F, Vincent JD. Effects of chronic icv infusion of vasopressin on sleep-waking cycle of rats. *Am J Physiol* 1989;256:R674–84.
33. Perras B, Pannenborg H, Marshall L, Pietrowsky R, Born J, Fehm HL. Three months of intranasal vasopressin increased sleep time, slow wave sleep and REM sleep in healthy old humans. *Exp Clin Endocrinol Diabetes* 1997; Suppl 1:23.
34. Steiger A, Herth T, Holsboer F. Sleep-electroencephalography and the secretion of cortisol and growth hormone in normal controls. *Acta Endocrinol (Copenh)* 1987;116:36–42.
35. Jarrett DB, Greenhouse JB, Miewald JM, Fedorka IB, Kupfer DJ. A reexamination of the relationship between growth hormone secretion and slow wave sleep using delta wave analysis. *Biol Psychiatry* 1990;27:497–509.
36. Prinz PN, Weitzman ED, Cunningham GR, Karacan I. Plasma growth hormone during sleep in young and aged men. *J Gerontol* 1983;38:519–24.
37. Van Coevorden A, Mockel J, Laurent E, et al. Neuroendocrine rhythms and sleep in aging men. *Am J Physiol* 1991;260: E651–61.
38. Jarrett DB, Kupfer DJ, Miewald JM, Grochocinski VJ, Franz B. Sleep-related growth hormone secretion is persistently suppressed in women with recurrent depression: a preliminary longitudinal analysis. *J Psychiatr Res* 1994;28:211–23.
39. Jarrett DB, Miewald JM, Kupfer DJ. Recurrent depression is associated with a persistent reduction in sleep-related growth hormone secretion. *Arch Gen Psychiatry* 1990;47:113–8.
40. Steiger A, von Bardeleben U, Herth T, Holsboer F. Sleep EEG and nocturnal secretion of cortisol and growth hormone in male patients with endogenous depression before treatment and after recovery. *J Affect Disord* 1989;16:189–95.
41. Voderholzer U, Laakmann G, Wittmann R, et al. Profiles of spontaneous 24-hour and stimulated growth hormone secretion in male patients with endogenous depression. *Psychiatry Res* 1993;47:215–27.
42. Beck U, Brezinova V, Hunter WM, Oswald I. Plasma growth hormone and slow wave sleep increase after interruption of sleep. *J Clin Endocrinol Metab* 1975;40:812–5.
43. Van Cauter E, Kerkhofs M, Caufriez A, Van Onderbergen A, Thorner MO, Copinschi G. A quantitative estimation of growth hormone secretion in normal man: reproducibility and relation to sleep and time of day. *J Clin Endocrinol Metab* 1992;74: 1441–50.
44. Mullington J, Hermann D, Holsboer F, Pollmächer T. Age-dependent suppression of nocturnal growth hormone levels during sleep deprivation. *Neuroendocrinology* 1996;64:233–41.
45. Steiger A, Guldner J, Hemmeter U, Rothe B, Wiedemann K, Holsboer F. Effects of growth hormone-releasing hormone and somatostatin on sleep EEG and nocturnal hormone secretion in male controls. *Neuroendocrinology* 1992;56:566–73.
46. Marshall L, Moelle M, Boeschen G, Steiger A, Fehm HL, Born

J. Greater efficacy of episodic than continuous growth hormone releasing hormone (GHRH) administration in promoting slow wave sleep (SWS). *J Clin Endocrinol Metab* 1996;81: 1009–13.
47. Kern W, Halder R, al-Reda S, Späth-Schwalbe E, Fehm HL, Born J. Systemic growth hormone does not affect human sleep. *J Clin Endocrinol Metab* 1993;76:1428–32.
48. Garry P, Roussel B, Cohen R, et al. Diurnal administration of human growth hormone-releasing factor does not modify sleep and sleep-related growth hormone secretion in normal young men. *Acta Endocrinol (Copenh)* 1985;110:158–63.
49. Kupfer DJ, Jarrett DB, Ehlers CL. The effect of GRF on the EEG sleep of normal males. *Sleep* 1991;14:87–8.
50. Kerkhofs M, Van Cauter E, Van Onderbergen A, Caufriez A, Thorner MO, Copinschi G. Sleep-promoting effects of growth hormone-releasing hormone in normal men. *Am J Physiol* 1993;264:E594–8.
51. Antonijevic IA, Murck H, Frieboes R-M, Steiger A. Slow wave sleep, but not exogenous GHRH, blunts cortisol and ACTH stimulation by CRH in men. *Exp Clin Endocrinol Diabetes* 1997; Suppl 1:111.
52. Marshall L, Boes N, Strasburger C, Born J, Fehm HL. Differential influences on sleep of growth-hormone releasing hormone at different concentrations. *Exp Clin Endocrinol Diabetes* 1997; Suppl 1:113.
53. Schier T, Guldner J, Colla M, Holsboer F, Steiger A. Changes in sleep-endocrine activity after growth hormone-releasing hormone depend on time of administration. *J Neuroendocrinol* 1997;9:201–5.
54. Steiger A, Guldner J, Colla-Müller M, Friess E, Sonntag A, Schier T. Growth hormone-releasing hormone (GHRH)-induced effects on sleep EEG and nocturnal secretion of growth hormone, cortisol and ACTH in patients with major depression. *J Psychiatr Res* 1994;28:225–38.
55. Linkowski P, Mendlewicz J, Kerkhofs M, et al. 24-hour profiles of adrenocorticotropin, cortisol, and growth hormone in major depressive illness: effect of antidepressant treatment. *J Clin Endocrinol Metab* 1987;65:141–52.
56. Guldner J, Schier T, Friess E, Colla M, Holsboer F, Steiger A. Reduced efficacy of growth hormone-releasing hormone in modulating sleep endocrine activity in the elderly. *Neurobiol Aging* (in press).
57. Bliwise DL. Sleep in normal aging and dementia. *Sleep* 1993; 16:40–81.
58. Iovino M, Monteleone P, Steardo L. Repetitive growth hormone-releasing hormone administration restores the attenuated growth hormone (GH) response to GH-releasing hormone testing in normal aging. *J Clin Endocrinol Metab* 1989;69:910–3.
59. Shibasaki T, Shizume K, Nakahara M, et al. Age-related changes in plasma growth hormone response to growth hormone-releasing factor in man. *J Clin Endocrinol Metab* 1984; 58:212–4.
60. Murck H, Frieboes R-M, Schier T, Steiger A. Longtime administration of growth hormone-releasing hormone (GHRH) does not restore the reduced efficiency of GHRH on sleep endocrine activity in 2 old-aged subjects—a preliminary study. *Pharmacopsychiatry* 1997;30:122–4.
61. Danguir J. Intracerebroventricular infusion of somatostatin selectively increases paradoxical sleep in rats. *Brain Res* 1986; 367:26–30.
62. Beranek L, Obál F Jr, Bodosi B, Taishi P, Laczi F, Krueger JM. Inhibition of non-REM sleep in response to a long-acting somatostatin analogue, sandostatin, in the rat. *J Sleep Res* 1996; Suppl 1:14.
63. Parker DC, Rossman LG, Siler TM, Rivier J, Yen SS, Guillemin R. Inhibition of the sleep-related peak in physiologic human growth hormone release by somatostatin. *J Clin Endocrinol Metab* 1974;38:496–9.
64. Kupfer DJ, Jarrett DB, Ehlers CL. The effect of SRIF on the EEG sleep of normal men. *Psychoneuroendocrinology* 1992; 17:37–43.
65. Frieboes R-M, Murck H, Schier T, Holsboer F, Steiger A. Somatostatin impairs sleep in elderly human subjects. *Neuropsychopharmacology* 1997;16:339–45.
66. Sonntag WE, Boyd RL, Booze RM. Somatostatinergic gene expression in hypothalamus and cortex of aging male rats. *Neurobiol Aging* 1990;11:409–16.
67. Bohlhalter S, Murck H, Holsboer F, Steiger A. Cortisol enhances nonREM sleep and growth hormone secretion in elderly subjects. *Neurobiol Aging* 1997;18:423–9.
68. Mendelson WB, Slater S, Gold P, Gillin JC. The effect of growth hormone administration on human sleep: a dose-response study. *Biol Psychiatry* 1980;15:613–8.
69. Obál F Jr, Floyd R, Kapás L, Bodos B, Krueger JM. Effects of systemic GHRH on sleep in intact and in hypophysectomized rats. *Am J Physiol* 1996;270:E230–7.
70. Åström C, Christensen L, Gjerris F, Trojaborg W. Sleep in acromegaly before and after treatment with adenomectomy. *Neuroendocrinology* 1991;53:328–31.
71. Åström C, Lindholm J. Growth hormone-deficient young adults have decreased deep sleep. *Neuroendocrinology* 1990; 51:82–4.
72. Ehlers CL, Kupfer DJ. Hypothalamic peptide modulation of EEG sleep in depression: a further application of the S-process hypothesis. *Biol Psychiatry* 1987;22:513–7.
73. Bredow S, Taishi P, Obál F Jr, Guha-Thakurta N, Krueger JM. Hypothalamic growth hormone-releasing hormone mRNA varies across the day in rat. *Neuroreport* 1996;7:2501–5.
74. Davidson JR, Moldofsky H, Lue FA. Growth hormone and cortisol secretion in relation to sleep and wakefulness. *J Psychiatry Neurosci* 1991;16:96–102.
75. Follenius M, Brandenberger G, Bandesapt JJ, Libert JP, Ehrhart J. Nocturnal cortisol release in relation to sleep structure. *Sleep* 1992;15:21–7.
76. Barbarino A, Corsello SM, Della Casa S, et al. Corticotropin-releasing hormone inhibition of growth hormone-releasing hormone-induced growth hormone release in man. *J Clin Endocrinol Metab* 1990;71:1368–74.
77. Bowers CY, Sartor AO, Reynolds GA, Badger TM. On the actions of the growth hormone-releasing hexapeptide, GHRP. *Endocrinology* 1991;128:2027–35.
78. Copinschi G, Van Onderbergen A, L'Hermite-Baleriaux M, et al. Effects of a 7-day treatment with a novel orally active nonpeptide growth hormone secretagogue, MK-677, on 24-hour growth hormone profiles, insulin-like growth factor-I and adrenocortical function in normal young men. *J Clin Endocrinol Metab* 1996;81:2776–82.
79. Howard AD, Feighner SD, Cully DF, et al. A receptor in pituitary and hypothalamus that functions in growth hormone release. *Science* 1996;273:974–7.
80. Frieboes R-M, Murck H, Maier P, Schier T, Holsboer F, Steiger A. Growth hormone-releasing peptide-6 stimulates sleep, growth hormone, ACTH and cortisol release in normal man. *Neuroendocrinology* 1995;61:584–9.
81. Frieboes R-M, Murck H, Antonijevic IA, Holsboer F, Steiger A. Sleep-endocrinological effects of GH-releasing peptide-6 in man after different routes of application. *Exp Clin Endocrinol Diabetes* 1997; Suppl 1:1.
82. Kerkhofs M, Van Cauter E, Thorner MO, Copinschi G. Growth hormone (GH), GH-releasing hormone (GHRH). GH-releasing peptide (GHRP) and sleep in man. *J Sleep Res* 1996; Suppl 1: 107.
83. Davis TM, Burrin JM, Bloom SR. Growth hormone (GH) release in response to GH-releasing hormone in man is 3-fold enhanced by galanin. *J Clin Endocrinol Metab* 1987;65:1248–52.
84. Toppila J, Stenberg D, Alanko L, et al. REM sleep deprivation induces galanin gene expression in the rat brain. *Neurosci Lett* 1995;183:171–4.
85. Murck H, Maier P, Frieboes R-M, Schier T, Holsboer F, Steiger A. Galanin promotes REM sleep in man. *Pharmacopsychiatry* 1995;28:201.
86. Seutin V, Verbanck P, Massotte L, Dresse A. Galanin decreases the activity of locus coeruleus neurons in vitro. *Eur J Pharmacol* 1989;164:373–6.

87. McCarley RW, Massaquoi SG. Neurobiological structure of the revised limit cycle reciprocal interaction model of REM cycle control. *J Sleep Res* 1992;1:132–7.
88. Bartfai J. Galanin. A neuropeptide with important central nervous system actions. In: Bloom FE, Kupfer DJ, eds. *Neuropsychopharmacology. 4th generation of progress.* New York: Raven Press, 1995:563–71.
89. Köhler C, Hallman H, Melander T, Hökfelt T, Norheim E. Autoradiographic mapping of galanin receptors in the monkey brain. *J Chem Neuroanat* 1989;2:269–84.
90. Aston-Jones G, Bloom FE. Activity of norepinephrine-containing locus coeruleus neurons in behaving rats anticipates fluctuations in the sleep-waking cycle. *J Neurosci* 1981;1:876–86.
91. Cespuglio R, Gomez ME, Faradji H, Jouvet M. Alterations in the sleep-waking cycle induced by cooling of the locus coeruleus area. *Electroencephalogr Clin Neurophysiol* 1982;54: 570–8.
92. McCormick DA, Pape HC, Williamson A. Actions of norepinephrine in the cerebral cortex and thalamus: implications for function of the central noradrenergic system. *Prog Brain Res* 1991;88:293–305.
93. Valentino RJ, Foote SL, Aston-Jones G. Corticotropin-releasing factor activates noradrenergic neurons of the locus coeruleus. *Brain Res* 1983;270:363–7.
94. Monnier M, Hoesli L. Humoral transmission of sleep and wakefulness. II. Hemodialysis of sleep-inducing humor during stimulation of the thalamic hypnogenic area. *Pflügers Arch* 1965;282:60–75.
95. Graf MV, Kastin AJ. Delta-sleep-inducing peptide (DSIP): a review. *Neurosci Biobehav Rev* 1984;8:83–93.
96. Borbély AA, Tobler I. Endogenous sleep-promoting substances and sleep regulation. *Physiol Rev* 1989;69:605–70.
97. Schneider-Helmert D, Schönenberger GA. Effects of DSIP in man. Multifunctional psychophysiological properties besides induction of natural sleep. *Neuropsychobiology* 1983;9:197–206.
98. Schneider-Helmert D, Graf M, Schönenberger GA. Synthetic delta-sleep-inducing peptide improves sleep in insomniacs. *Lancet* 1981;1:1256–7.
99. Monti JM, Debellis J, Alterwain P, Pellejero T, Monti D. Study of delta sleep-inducing peptide efficacy in improving sleep on short-term administration to chronic insomniacs. *Int J Clin Pharmacol Res* 1987;7:105–10.
100. Bes F, Hofman W, Schuur J, Van Boxtel C. Effects of delta sleep-inducing peptide on sleep of chronic insomniac patients. A double-blind study. *Neuropsychobiology* 1992;26:193–7.
101. Feldman SC, Kastin AJ. Localization of neurons containing immunoreactive delta sleep-inducing peptide in the rat brain: an immunocytochemical study. *Neuroscience* 1984;11:303–17.
102. Friedman TC, Garcia-Borreguero D, Hardwick D, et al. Decreased delta-sleep and plasma delta-sleep-inducing peptide in patients with Cushing syndrome. *Neuroendocrinology* 1994; 60:626–34.
103. Van Kammen DP, Widerlöv E, Neylan TC, et al. Delta sleep-inducing-peptide-like immunoreactivity (DSIP-LI) and delta sleep in schizophrenic volunteers. *Sleep* 1992;15:519–25.
104. Seifritz E, Müller MJ, Schönenberger GA, et al. Human plasma DSIP decreases at the initiation of sleep at different circadian times. *Peptides* 1995;16:1475–81.
105. Bohlhalter S, Antonijevic IA, Brabant G, Holsboer F, Steiger A. Short term pulsatile administration of neuropeptide Y suppresses ACTH and cortisol secretion, promotes sleep, but does not affect leptin secretion in man. *Exp Clin Endocrinol Diabetes* 1997; Suppl 1:111.
106. Copinschi G, Van Onderbergen A, L'Hermite-Baleriaux M, et al. Effects of the short-acting benzodiazepine triazolam, taken at bedtime, on circadian and sleep-related hormonal profiles in normal men. *Sleep* 1990;13:232–44.
107. Steiger A, Guldner J, Lauer C, Meschenmoser C, Pollmächer T, Holsboer F. Flumazenil exerts intrinsic activity on sleep EEG and nocturnal hormone secretion in normal controls. *Psychopharmacology* 1994;113:334–8.
108. Ehlers CL, Somes C, Lopez A, Kirby D, Rivier JE. Electrophysiological actions of neuropeptide Y and its analogs: new measures for anxiolytic therapy? *Neuropsychopharmacology* 1997;17:34–43.
109. Heilig M, Koob GF, Ekman R, Britton KT. Corticotropin-releasing factor and neuropeptide Y: role in emotional integration. *Trends Neurosci* 1994;17:80–5.
110. Stenzel-Poore MP, Heinrichs SC, Rivest S, Koob GF, Vale WW. Overproduction of corticotropin-releasing factor in transgenic mice: a genetic model of anxiogenic behavior. *J Neurosci* 1994;14:2579–84.
111. Skutella T, Criswell H, Moy S, et al. Corticotropin-releasing hormone (CRH) antisense oligodeoxynucleotide induces anxiolytic effects in rat. *Neuroreport* 1994;5:2181–5.
112. Liebsch G, Landgraf R, Gerstberger R, et al. Chronic infusion of a CRH1 receptor antisense oligodeoxynucleotide into the central nucleus of the amygdala reduced anxiety-related behavior in socially defeated rats. *Regul Pept* 1995;59:229–39.
113. Owens MJ, Bissette G, Nemeroff CB. Acute effects of alprazolam and adinazolam on the concentrations of corticotropin-releasing factor in the rat brain. *Synapse* 1989;4:196–202.
114. Hemmeter U, Steiger A, Guldner J, Rothe B, Holsboer F. Effects of TRH on sleep EEG and nocturnal release of growth hormone and cortisol. *Pharmacopsychiatry* 1992;25:104.
115. Smith GP, Jerome C, Cushin BJ, Eterno R, Simansky KJ. Abdominal vagotomy blocks the satiety effect of cholecystokinin in the rat. *Science* 1981;213:1036–7.
116. Antin J, Gibbs J, Holt J, Young RC, Smith GP. Cholecystokinin elicits the complete behavioral sequence of satiety in rats. *J Comp Physiol Psychol* 1975;89:784–90.
117. DeMesquita S, Haney WH. Effect of chronic intracerebroventricular infusion of cholecystokinin on respiration and sleep. *Brain Res* 1986;378:127–32.
118. Watanabe N, Sakai T, Tada K, Masuno J, Moroji T. The effects of caerulein on nocturnal sleep. *Prog Neuropsychopharmacol Biol Psychiatry* 1986;10:749–54.
119. Pietrowsky R, Fehm HL, Er A, Bathelt B, Born J. Influences of the cholecystokinin analog ceruletide on human sleep and evoked potentials. *Neuropsychobiology* 1990;23:41–7.
120. de Montigny C. Cholecystokinin tetrapeptide induces panic-like attacks in healthy volunteers. *Arch Gen Psychiatry* 1989; 46:511–7.
121. Drucker-Colin R, Bernal-Pedraza J, Fernandez-Cancino F, Oksenberg A. Is vasoactive intestinal polypeptide (VIP) a sleep factor? *Peptides* 1984;5:837–40.
122. Obál F Jr, Payne L, Kacsoh B, et al. Involvement of prolactin in the REM sleep-promoting activity of systemic vasoactive intestinal peptide (VIP). *Brain Res* 1994;645:143–9.
123. Riou F, Cespuglio R, Jouvet M. Endogenous peptides and sleep in the rat. III. The hypnogenic properties of vasoactive intestinal polypeptide. *Neuropeptides* 1982;2:265–77.
124. Murck H, Guldner J, Frieboes R-M, et al. VIP decelerates non-REM-REM cycles and modulates hormone secretion during sleep in men. *Am J Physiol* 1996;271:R905–11.
125. Van den Pol AN, Tsujimoto KL. Neurotransmitters of the hypothalamic suprachiasmatic nucleus: immunocytochemical analysis of 25 neuronal antigens. *Neuroscience* 1985;15:1049–86.
126. Besson J, Sarrieau A, Vial M, Marie JC, Rosselin G, Rostene W. Characterization and autoradiographic distribution of vasoactive intestinal peptide binding sites in the rat central nervous system. *Brain Res* 1986;398:329–36.
127. Morin AJ, Denoroy L, Jouvet M. Daily variations in concentration of vasoactive intestinal peptide immunoreactivity in hypothalamic nuclei of rats rendered diurnal by restricted-schedule feeding. *Neurosci Lett* 1993;152:121–4.
128. Albers HE, Liou SY, Stopa EG, Zoeller RT. Neurotransmitter colocalization and circadian rhythms. *Prog Brain Res* 1992;92: 289–307.
129. Rolandi E, Franceshini R, Cataldi A, Barreca T. Twenty-four-hour secretory pattern of vasoactive intestinal polypeptide in the elderly. *Gerontology* 1990;36:356–60.
130. Chee CA, Roozendaal B, Swaab DF, Goudsmit E, Mirmiran M. Vasoactive intestinal polypeptide neuron changes in the se-

nile rat suprachiasmatic nucleus. *Neurobiol Aging* 1988;9:307–12.
131. Swaab DF. Brain aging and Alzheimer's disease, "wear and tear" versus "use it or lose it". *Neurobiol Aging* 1991;12:317–24.
132. Witting W, Mirmiran M, Bos NP, Swaab DF. Effect of light intensity on diurnal sleep-wake distribution in young and old rats. *Brain Res Bull* 1993;30:157–62.
133. Van Someren EJ, Mirmiran M, Swaab DF. Non-pharmacological treatment of sleep and wake disturbances in aging and Alzheimer's disease: chronobiological perspectives. *Behav Brain Res* 1993;57:235–53.
134. Kastin AJ, Coy DH, Schally AV, Miller LH. Peripheral administration of hypothalamic peptides results in CNS changes. *Pharmacol Res Commun* 1978;10:293–312.
135. Begley DJ. Peptides and the blood-brain barrier: the status of our understanding. *Ann NY Acad Sci* 1994;739:89–100.
136. Terasaki T, Takakuwa S, Saheki A, et al. Absorptive-mediated endocytosis of an adrenocorticotropic hormone (ACTH) analogue, ebiratide, into the blood-brain barrier: studies with monolayers of primary cultured bovine brain capillary endothelial cells. *Pharm Res* 1992;9:529–34.
137. Drewe J, Fricker G, Behrens U, Gutmann H, Beglinger C, Huwyler J. Are peripheral gut hormones able to cross the blood-brain barrier? *Naunyn Schmiedebergs Arch Pharmacol* 1997;355:R106.
138. Broadwell RD, Sofroniew MV. Serum proteins bypass the blood-brain fluid barriers for extracellular entry to the central nervous system. *Exp Neurol* 1993;120:245–63.
139. Friess E, Wiedemann K, Steiger A, Holsboer F. The hypothalamic-pituitary-adrenocortical system and sleep in man. *Adv Neuroimmunol* 1995;5:111–25.
140. Dickson SL, Luckman SM. Indication of c-fos messenger ribonucleic acid in neuropeptide Y and growth hormone (GH)-releasing factor neurons in the rat arcuate nucleus following systemic injection of the GH secretagogue, GH-releasing peptide-6. *Endocrinology* 1997;138:771–7.
141. Korbonits M, Forsling ML, Trainer PJ, Besser GM, Grossman AB. Growth hormone secretagogues (GHRP-6, hexarelin and the non-peptide analogue L-692,419) stimulate the release of arginine-vasopressin from the rat hypothalamus *in vitro*. 22nd International Symposium Growth Hormone and Growth Factors in Endcrinology and Metabolism, Vienna, 1996;111.