

**Review****Hormones, hormonal agents, and neuropeptides involved in the neuroendocrine regulation of sleep in humans**Grigorios Kotronoulas<sup>1</sup>, Antonios Stamatakis<sup>2</sup>, Fotini Stylianopoulou<sup>2</sup><sup>1</sup>*Cancer Care Research Centre (CCRC), University of Stirling, Stirling, Scotland, UK; HESMO Scholar (2009-2010),*<sup>2</sup>*Laboratory of Biology-Biochemistry, Faculty of Nursing, University of Athens, Athens, Greece***ABSTRACT**

Sleep is an essential ubiquitous biological process, a periodical state of quiescence in which there is minimal processing of sensory information and no interaction with conspecifics or the environment. Despite relevant research on sleep structure and testing of numerous endogenous sleep-affecting chemicals, questions as to the precise mechanisms and functions of sleep remain without satisfactory responses. The purpose of this review is to report on current evidence as regards the effect of several endogenous and exogenous hormones, hormonal agents, and neuropeptides on sleep onset or wake process, when administered in humans in specific doses and via different routes. The actions of several peptides are presented in detail. Some of them (growth hormone releasing hormone, ghrelin, galanin, neuropeptide Y) seem to promote sleep, whereas others (corticotropin, somatostatin) impair its continuity.

**Key words:** Ghrelin, GHRH, Hormones, Melatonin, NPY, Neuroendocrine regulation, Neuropeptides, Sleep, Sleep disorders, Wakefulness

**INTRODUCTION**

Sleep is an essential ubiquitous biological process, a periodical state of quiescence in which there is minimal processing of sensory information and no interaction with conspecifics or the environment.<sup>1,2</sup> However, sleep is more than the absence of being awake; it is a homeostatically regulated process, without the revitalising force of which survival might not be feasible.<sup>3,4</sup>

One difficulty in understanding sleep is that it is not a unitary state but a combination of two substates of distinct brain activity actively generated in specific brain regions.<sup>1,2</sup> Therefore, sleep definition requires the combined input from an electroencephalogram (EEG), an electrooculogram (EOG), and an electromyogram (EMG). The resulting polysomnogram identifies the sleep state and stages.<sup>5</sup> One state is characterised in most mammals by Rapid Eye Movements (REM) and is usually termed REM Sleep (REMS); the other, in which no rapid eye movements occur, is known as non-REM Sleep (NREMS). In humans, NREMS is usually subdivided into stages 1-4, which correspond roughly to increasing depth of sleep and decreasing muscle tone.<sup>2</sup> Stages 3 and

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4 are often grouped together under the label "Slow Wave Sleep" (SWS).<sup>5</sup> In NREMS a large increase of growth hormone (GH) secretion, together with suppression of cortisol secretion is observed.<sup>5,6</sup> REMS is a completely different sleep stage, characterized by a virtual absence of muscle tone in antigravity muscles, a largely awake brain, and dreaming. It is of interest also that the metabolic rate in NREMS is increased above resting waking levels.<sup>5,6</sup> In the normal sequence (called "sleep architecture"), waking is followed by NREMS's lighter stages (1 and 2) and then within 10 to 20 minutes by SWS. These stages of deeper sleep are maintained for nearly one hour in normal young subjects but are much shorter (5-10 min), if present at all, in older individuals. Lighter stages of NREMS then re-appear and the first REM period is initiated.<sup>1</sup> This cycle is repeated three to four times during the night but with decreasing amounts of SWS and increasing amounts of REMS.<sup>5</sup> Each stage of sleep has a characteristic EEG frequency and waveform.<sup>5,7</sup>

The timing, duration, and depth, or intensity, of sleep is regulated by two interacting processes: a homeostatic that maintains the duration and intensity of sleep within certain boundaries and a circadian which determines the timing of sleep and governs several physiological variables, including core body temperature and the production of hormones such as cortisol and melatonin.<sup>2</sup> The interaction of the homeostatic and circadian facets of sleep regulation has been formalised in the two-process model of sleep regulation.<sup>8,9</sup>

The simultaneous application of electrophysiological and neuroendocrinological methods in normal men and women under baseline conditions and after administration of synthetic and active endogenous central nervous system (CNS) compounds has shown (a) a considerable activity of various endocrine systems during sleep, and (b) a bidirectional interaction between the electrophysiological and neuroendocrine components of sleep.<sup>10,11</sup>

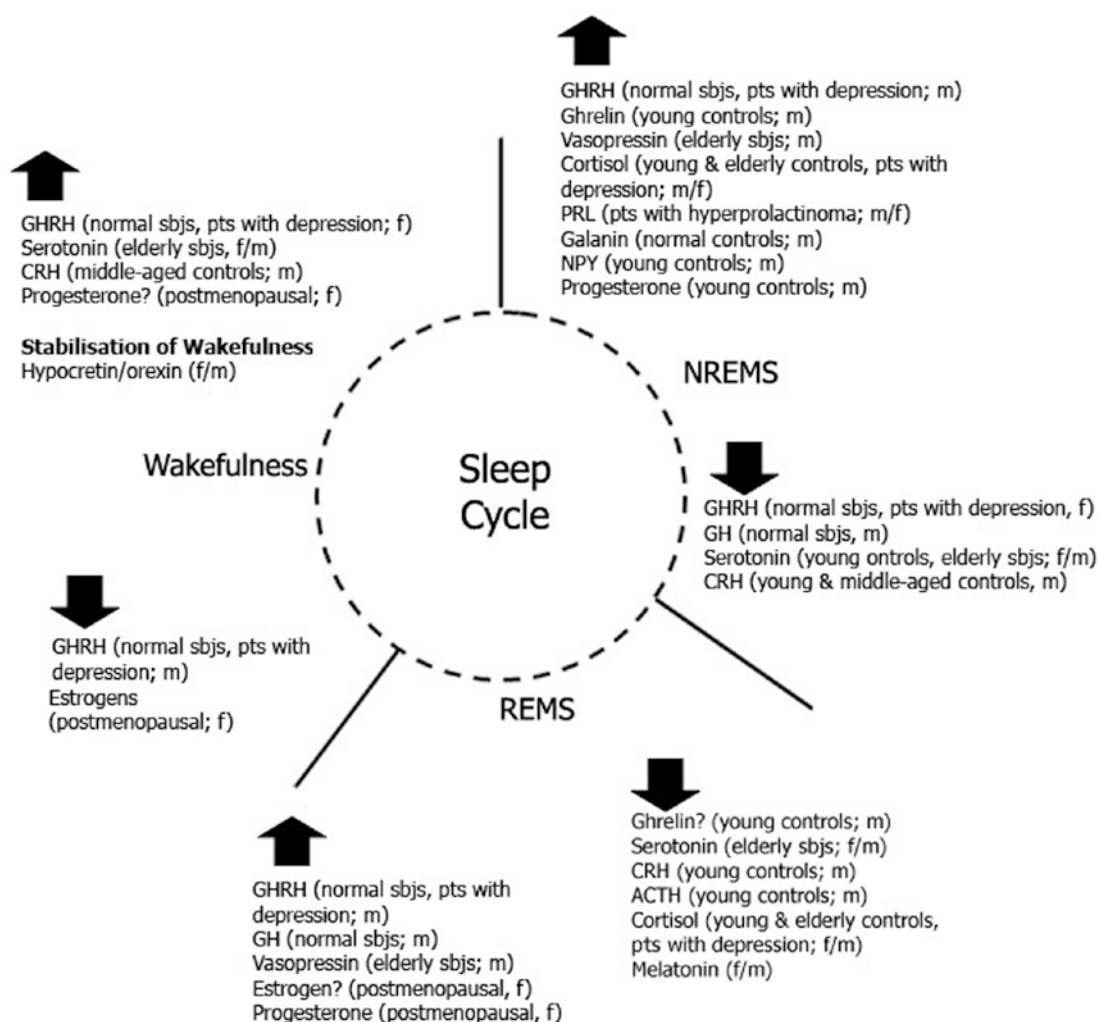
The nocturnal secretion of various hormones shows distinct patterns. During the first half of the night a surge of growth hormone (GH) predominates, whereas adrenocorticotropin (ACTH) and cortisol levels are low; during the second half, ACTH and cortisol rise,

whereas GH declines. This pattern suggests (a) a reciprocal interaction of the hypothalamo-pituitary somatotrophic (HPS) and the hypothalamopituitary-adrenocortical (HPA) axes, their peripheral endpoints being GH and cortisol, respectively, and (b) the existence of common regulators of sleep EEG and sleep-related hormone secretion. A sexual dimorphism of sleep-endocrine activity has been found in young normal subjects: cortisol levels are higher in females than in males and most male subjects show a single GH peak around sleep onset, whereas females show a pre-sleep GH surge and additional GH peaks during the second half of the night.<sup>12</sup>

Obviously, bidirectional interactions exist between sleep and the endocrine system.<sup>13</sup> Several hormones have the capacity to affect sleep but the physiological significance of hormonal modulation of sleep is generally unclear. Plasma concentrations of many hormones display sleep-related variations, suggesting that sleep influences hormone secretion. However, sleep and hormone levels may run in parallel without a cause-effect relationship. For instance, circadian regulation may synchronise these events. Interestingly, even though in the past fifty years much has been learned about sleep structure,<sup>11</sup> new functional pathways of sleep are continuously being uncovered and a whole range of novel agents appear linked to them. The purpose of the present review is to provide an updated overview of literature data regarding the effect of several endogenous and exogenous hormones, hormonal agents, and neuropeptides on the sleep onset or wake process (Figure 1) in humans, as well as their relevance to pathological conditions resulting in altered sleep patterns.

## 1. GROWTH HORMONE-RELEASING HORMONE (GHRH)

The endogenous substance with a well documented sleep-promoting activity is GHRH.<sup>10</sup> Besides its well-known function in stimulating pituitary GH release, GHRH may have a direct role in promoting NREMS.<sup>14,15</sup> The GHRH-induced NREMS is characterised by supranormal EEG slow waves. After central and systemic administration of GHRH, duration and intensity of SWS increase in humans.<sup>16</sup> However, negative outcomes have been reported as well.<sup>17</sup> In



**Figure 1.** The effect of hormones and hormonal agents on the sleep-wake cycle in humans [pts: patients; sbjs: subjects; m: male; f: female; ↑: increase; ↓: decrease; ?: inconsistent effect].

addition, no change<sup>14</sup> or decrease in REMS during the first half of the night<sup>18</sup> has been observed.

In humans, the frequency of delta waves during the first 100 min of sleep was significantly enhanced following bedtime injection of GHRH.<sup>15</sup> When the injections were given during sleep, stimulatory effects on SWS were observed.<sup>19</sup> However, no major changes of sleep EEG were found after repetitive i.v. GHRH during the early morning hours.<sup>20</sup>

The sleep-promoting activity of GHRH varies with age and gender in humans.<sup>21</sup> Strong responses have been observed in young subjects, with sleep promotion after i.v.<sup>15</sup> and intranasal<sup>22</sup> administration of GHRH. In the elderly, instead of enhancing SWS, GHRH

increases stage 2 NREMS and sleep continuity. Steiger et al<sup>14</sup> tested the effect of repetitive i.v. boluses of GHRH during the first few hours of the night in young normal men. After GHRH infusion, SWS and GH secretion increased and cortisol decreased. An increase in NREMS and a decrease in wakefulness were observed during the recovery night in normal, sleep-deprived men and women after repetitive administration of GHRH.<sup>23</sup> On examining the effect of intranasal administration of GHRH in young and aged humans, Perras et al<sup>22</sup> found that intranasal GHRH reduced cortisol nadir concentrations at the beginning of sleep and reduced the sleep-induced elevation in GH concentrations during early sleep. SWS increased, with this influence primarily exerted

during the second half of sleep time.

In a study by Guldner et al,<sup>24</sup> the effects of GHRH on sleep were examined in three states with a change of the GHRH/CRH ratio in favour of CRH. It was concluded that only a weak sleep-promoting effect of GHRH was found in the elderly.<sup>24</sup> GHRH does not seem to promote sleep in females. A sexual dimorphism in response to GHRH was also found in drug-free patients with depression and in controls.<sup>25</sup>

If endogenous GHRH is a physiological NREMS-regulatory substance, then its suppression should be associated with decreases in NREMS.<sup>13</sup> This point of view has been widely studied. A competitive GHRH antagonist<sup>26</sup> elicited dose-dependent decreases in the duration and intensity of NREMS and increases in sleep latency. Moreover, injection of a GHRH peptide antagonist into the same area where GHRH is injected inhibits NREMS and attenuates sleep rebound after sleep deprivation.<sup>27</sup> Furthermore, intracerebroventricular (i.c.v.) administration of antibodies to GHRH decreases NREMS in patients with depression.<sup>23</sup> Affinity-purified antibodies to GHRH significantly suppress both NREMS and REMS for at least 12 hours during the light (rest) period and prevent the sleep rebound that normally occurs after 3 h of sleep deprivation.<sup>28</sup> While GH deficiency (GHD) often reflects hypothalamic GHRH deficiency in aged subjects, so far GHRH replacement therapy has not yielded consistent improvements in sleep, possibly due to lack of sustained activity throughout the night.<sup>29</sup> On the other hand, various types of benign tumours may lead to ectopic, peripheral GHRH hypersecretion, causing GHRH-associated acromegaly.<sup>30</sup> In these patients, feedback inhibition of GHRH may contribute to the decrease of SWS.

## 2. GHRELIN & ANALOGUES

Ghrelin is the recently isolated endogenous ligand of the orphan GH secretagogue (GHS) receptor type 1a (GHS-R1a).<sup>31,32</sup> Like synthetic GHS, ghrelin possesses a strong GH-releasing effect in humans.<sup>33,34</sup> Furthermore, ghrelin enhances HPA hormones and prolactin when given during the daytime.<sup>35</sup>

Ghrelin itself has recently been reported to be a sleep-promoting factor in humans. Similarly to GHRH, repetitive i.v. ghrelin administration en-

hanced SWS, Slow Wave Activity (SWA), and GH in young normal males.<sup>36</sup> In a recent study,<sup>37</sup> sleep EEG and the nocturnal levels of ghrelin were examined simultaneously. A trend was found suggesting a lower time spent in stage I sleep in subjects with high nocturnal ghrelin levels. However, the authors suggested that under normal conditions plasma ghrelin levels show no distinct interaction with sleep.<sup>37</sup> Other studies have demonstrated that when ghrelin was administered in early morning, it did not affect sleep in 12 healthy males.<sup>38</sup>

On the other hand, in two studies acute administration of the synthetic peptidyl GHS, MK-0677, modified the sleep pattern in normal subjects.<sup>39,40</sup> In fact, prolonged treatment with oral MK-0677 (25 mg once daily) in elderly subjects increases the length of REM sleep phases, meanwhile decreasing rapid eye movement latency.<sup>41</sup> Hexarelin, another synthetic GHS, exerts similar actions by decreasing stage 4 sleep during the first half of the night and EEG delta power during the entire night.<sup>42</sup>

## 3. SOMATOSTATIN (SRIH) & ANALOGUES

SRIH inhibits hypothalamic GHRHergic neurons (thus, GHRH release) and, after being released into the pituitary circulation, leads to inhibition of GH secretion directly in the pituitary.<sup>13</sup> SRIH has five receptors named sst1 to SST5. Inhibition of the somatotrophic axis is mediated by the SST2 receptors. An unbalanced gain on chromosome 17q and promoter polymorphisms have been shown to play a role in the regulation of SST2 receptor expression, increasing overall and event-free survival in pediatric patients with neuroblastoma.<sup>43</sup>

SRIH inhibits NREMS, presumably via its effects on GHRH secretion and stimulates REMS.<sup>4</sup> Interestingly, SRIH's action shows an age-dependence. Repetitive i.v. administration impaired sleep in healthy elderly subjects,<sup>44</sup> whereas the same substance had no effect on young normal men.<sup>14</sup> These data suggest a reciprocal interaction of GHRH and SRIH in sleep regulation similar to their action on GH release. This theory is further supported by the fact that arginine, a SRIH antagonist, given as an infusion, increased SWS in elderly men, probably through enhancement of endogenous GHRH secretion.<sup>45</sup>

The half-life of SRIH within tissues is only a few minutes. Therefore, instead of SRIH, hydrolysis-resistant analogues, such as octreotide, are often used experimentally. Octreotide stimulates SST2 and SST5 receptors and is more potent than exogenous SRIH.<sup>13</sup> Octreotide-induced impairment of NREMS has been verified in humans after subcutaneous infusion.<sup>46</sup> After 1-3 h postinjection, when intensity of NREMS increases, the accumulated GHRH is gradually released from the hypothalamus. Therefore, a possible explanation for the biphasic sleep response to octreotide is that octreotide suppresses sleep via inhibiting GHRH release, and this period is followed by excessive GHRH release and deep NREMS.<sup>13</sup>

Recently, two novel neuropeptides have been discovered (Urotensin II, Cortistatin). Interestingly, despite structural similarity of these peptides to SRIH, their sleep-related actions differ widely. Urotensin II is considered to be involved in REMS regulation,<sup>47</sup> while cortistatin has been shown to induce SWS.<sup>48</sup> SRIH analogue treatment is usually prescribed in acromegaly patients, in whom increased daytime sleepiness as well as delayed sleep onset have been reported.<sup>49</sup>

#### 4. CORTICOTROPIN-RELEASING HORMONE (CRH)

Various human studies have shown that administration of HPA hormones or their antagonists affect sleep. The common denominator of the effect of the HPA axis on sleep EEG is CRH, which decreases SWS and increases wakefulness.<sup>5</sup>

Pulsatile i.v. boluses of human CRH (4X50 µg) in young normal male subjects led to a decrease in SWS with an increase in light sleep and awakenings.<sup>50</sup> The time interval, the dosage, and the protocol of the administration appear to be crucial methodological issues. As a matter of fact, whereas after continuous nocturnal infusion of CRH the sleep EEG remained unchanged,<sup>51</sup> EEG spectral variables were altered after a single i.v. bolus of CRH in young healthy men.<sup>52</sup> Conversely, in sleep-deprived healthy humans, CRH induces higher increases in NREMS if given during the recovery night compared to placebo.<sup>23</sup> The responsiveness of sleep EEG to CRH appears to increase during ageing, since sleep disruption

with CRH is more pronounced in middle-aged men compared to young men.<sup>53</sup> In young men, sleep EEG remained unchanged; in middle-aged subjects, however, wakefulness increased and SWS decreased. CRH antagonists have also been used to study the impact of CRH on sleep-EEG, but the results are conflicting.<sup>10</sup> CRH can contribute to both stressed and non-stressed waking. This waking effect is consistent with an increase in light sleep in humans given exogenous CRH.<sup>50</sup> More importantly, CRH has an arousing and waking effect even in the absence of stress.<sup>54</sup> The hypothesis that CRH promotes REMS is also supported.<sup>50</sup> However, it is claimed that the influence of endogenous CRH on REMS is uncertain as the amount of REMS decreases after CRH. Similarly, in a study of depressed patients, a CRH antagonist decreased REM latency after short-term but not long-term administration.<sup>55</sup>

Furthermore, it has been proposed<sup>7</sup> that MR and GR receptors (see §6) can modify CRH levels by being either activated or suppressed via their feedback relationships with CRH. CRH suppression is enhanced by MR mediated inhibition at the paraventricular nucleus (PVN). This would augment CRH suppression in the early sleep period and at the time of the nocturnal nadir, when SWS is expected to occur. On the other hand, excessive GR activation at the level of the amygdala (as opposed to inhibition at the PVN) may activate CRH and decrease SWS. A HPA axis overdrive, due to enhanced secretion of CRH combined with an impaired negative feedback via GR, seems to be most consistently observed in patients with depressive features<sup>56</sup> and has been suggested as a potential biomarker for depression. Depressed patients show clear sleep-EEG alterations, including disrupted sleep, low amounts of SWS, a short REM latency, and a high REM frequency.

It has been proposed that the downregulation of CRH activity is a final and common step of antidepressant treatment. In a recent study, three polymorphisms in the CRH receptor 1 (CRHR1) gene were tested in conjunction with six weeks of antidepressant treatment in patients suffering from major depressive disorder (MDD). The polymorphisms were associated with differential therapeutic response to antidepressants in patients with high-anxiety, supporting the idea that the CRHR1 gene is likely to be related to the antidepressant response in MDD.<sup>57</sup>

## 5. ADRENOCORTICOTROPIN (ACTH)

In clinical studies, nocturnal infusions of ACTH suppress REMS in normal subjects,<sup>58</sup> while cortisol and GH stimulates REMS.<sup>51</sup> An experiment in healthy volunteers showed that the expectation of waking up at a certain time induces a marked increase in ACTH before the end of sleep.<sup>59</sup> The researchers studied the levels of ACTH in association with sleep termination under three experimental conditions: an early planned awakening, a late planned awakening, and a surprise condition in which sleep was terminated earlier than expected by the subjects. Arousal from sleep in each of the three conditions prompted an increase in ACTH and cortisol. The most interesting finding was that the early planned awakening was preceded by a distinct increase of ACTH within the last hour before waking, while ACTH secretion surge occurred only after sleep termination in the surprise condition, in which the subjects did not expect to be awakened at this particular time.<sup>5</sup> This change was interpreted as an adaptive response to the stress of waking. The anticipatory increase in ACTH may facilitate spontaneous waking.<sup>5</sup> It remains unclear whether or not ACTH participates in sleep regulation<sup>60</sup> or the observed changes represent an associated phenomenon.

## 6. CORTISOL, GLUCOCORTICOID, AND MINERALOCORTICOID RECEPTOR LIGANDS

The human endogenous cortisol rhythm is characterised by a nadir that takes place at about midnight,<sup>7</sup> followed by a rise at about 2-3 hours after sleep onset that continues into the early waking hours. A cortisol peak occurs at about 09:00. As the day continues, a gradual decline in cortisol levels occurs leading to the nadir at about midnight.

In brain, cortisol preferentially binds to high affinity mineralocorticoid receptors (MR, type I) in the hippocampus and to low affinity glucocorticoid receptors (GR, type II) in the hypothalamus, pituitary, cortex, and elsewhere<sup>61</sup> and modulates the underlying circadian rhythm. The effect of MR predominates in the early nocturnal period and is most prominent at the time of the nocturnal nadir. In contrast, the effect of GR dominates in the morning when cortisol levels are highest.<sup>7</sup>

Studies exploring the effects of the HPA axis on sleep initially focused on the direct effects of glucocorticoids on sleep rather than the effects of CRH, but these results can now be reconciled given the known effects of CRH on sleep EEG and the indirect effects of glucocorticoids through CRH regulation. It is proposed that the effect of both exogenous and endogenous cortisol on SWS depends on cortisol levels capable of achieving maximal nocturnal CRH suppression.<sup>7</sup> In addition, both the type of receptor activated by cortisol (MR or GR) and the location of the activated receptor influences CRH (see §4) and, consequently, EEG pattern. Since the MR antagonist canrenoate reduces SWS, whereas the mixed MR and GR agonist cortisol enhances SWS and inhibits REMS, it was postulated that the MR regulates SWS, whereas the GR regulates REMS. However, in another study it was shown that MR agonists and antagonists did not alter sleep EEG.<sup>62</sup> Interestingly, in elderly controls, SWS increased after cortisol, although the number of MRs is known to decrease dramatically during ageing,<sup>63</sup> suggesting that the effects of MRs on sleep are indirect.

It has been shown that continuous nocturnal infusion of cortisol<sup>64</sup> and pulsatile i.v.<sup>65</sup> administration increase SWS and reduce REMS in young normal subjects and in healthy elderly subjects.<sup>63</sup> Recently, several studies suggested that the effect of cortisol on sleep EEG depends on GR mediated feedback on CRH, with elevated cortisol leading to suppression of CRH, resulting in an increase in SWS.<sup>66</sup> The effect of exogenous cortisol in decreasing SWS at high doses has not yet been explained. Since CRH and cortisol exert opposite effects on SWS and on GH, it is more likely that these changes are mediated by negative feedback inhibition of endogenous CRH rather than by stimulation by cortisol.<sup>10</sup> In patients with major depression, hourly injected cortisol (1mg/kg BW) increased duration and intensity of NREMS, particularly in male patients, and stimulated GH release, while REMS parameters were not affected by the infusion.<sup>67</sup> Nevertheless, another study reported that glucocorticoids acutely decreased REM sleep and increased time spent awake.<sup>68</sup>

In Addison's disease, where production of corticosteroids is severely reduced, no major EEG disturbances of sleep have been reported.<sup>69</sup> In contrast,

hypercortisolism and disturbed sleep are frequent symptoms in Cushing's disease and in depression. In Cushing's disease, SWS is decreased<sup>70,71</sup> with increased sleep latency, enhanced waketime, and REMS disturbances. In depressed patients in whom both cortisol and ACTH were elevated throughout the night an increased number of awakenings, early morning awakenings, decrease of NREMS, and REMS disinhibition<sup>72</sup> were observed.

Dexamethasone which activates GR has been shown to increase awakening.<sup>64</sup> Administration of dexamethasone is thought to be equivalent to the administration of a high dose of cortisol. The mechanism for the effect of GC on sleep EEG is attributed to direct GR activation.

Consistent with the dose-related effect of glucocorticoids on MR versus GR activation, the administration of hydrocortisone to healthy males can at times increase SWS and at other times increase wakefulness and stage 1 sleep, the latter occurring at higher doses.<sup>64</sup> Regarding GR activation in humans, in a study where methylprednisolone was administered to multiple sclerosis patients for ten days, a major portion of SWS was shifted from the first to the second sleep cycle, REMS latency was shortened, and REM frequency increased.<sup>73</sup> Lately, the GR antagonist, mifepristone, was found to improve sleep and reduce HPA axis activity during acute administration and post-discontinuation in non depressed patients with chronic insomnia.<sup>74</sup>

## 7. GALANIN

Galanin is a peptide with widespread distribution in the mammalian brain and coexists in neurones with various neurotransmitters participating in sleep regulation.<sup>10</sup> It is also known to stimulate GH via GHRH in man. Existing data support galanin's role in sleep regulation. Murck et al<sup>75</sup> found that during pulsatile i.v. administration of galanin to young normal men, SWS and the duration of REMS periods increased, whereas the secretion of GH and cortisol remained unchanged.<sup>76</sup> As this effect could imply an antidepressive action, i.v. administration of galanin in patients with depression was studied, revealing significant changes in sleep-EEG parameters, mainly due to an increase in REM latency. This might imply an acute

antidepressive effect of galanin, probably via a mechanism related to therapeutic sleep deprivation.

Recent studies on the possible role of galanin in the pathogenesis of panic disorder in females have focused on six single nucleotide polymorphisms (SNPs) within the gene coding for galanin, which are associated with either increased vulnerability or resistance. Since panic attacks can occur at any time, even during sleep, galanin and its receptors appear to be a promising target for the pharmacological therapy of these affective disorders.<sup>77</sup>

## 8. ADENOSINE (ADE)

ADE is an endogenous sleep-promoting substance which exerts its somnogenic action via activation of brain A(2A) receptors in the ventrolateral preoptic nucleus.<sup>78</sup> The hypnogenic properties of ADE were first recognised in cats and rodents. In supporting the aforementioned, the most widely used psychoactive stimulant, caffeine, well known for its wake-promoting activity, is an ADE receptor antagonist.

A functional polymorphism of the ADE deaminase gene has been associated with interindividual variability in sleep architecture and the sleep EEG in humans.<sup>79</sup> SWS is longer and sleep is deeper in the heterozygous carriers than in the homozygous. Heterozygous carriers of the polymorphism exhibit 20%-30% lower enzymatic activity in erythrocytes and leucocytes than homozygous individuals and may be at increased risk for developing autism. In contrast, the presence of a distinct polymorphism in the adenosine A2A receptor gene was shown to affect the EEG during sleep and wakefulness in a non-state-specific manner after caffeine intake by healthy volunteers.

## 9. ARGININE VASOPRESSIN (AVP)

The neuropeptide AVP is a major cofactor of CRH in the activation of the stress reaction. Chronic intranasal AVP improved sleep in normal elderly subjects as total sleep time, SWS, and REMS increased.<sup>80</sup> Genetic variations in the AVP receptor 1b gene (AVPR1b), via which AVP exerts its regulating effects on RMES, have been associated with a protective effect for recurrent major depression.<sup>81</sup>

Nocturia is a prevalent symptom that can adversely affect the quality of sleep. Low nocturnal AVP and urine osmolality may play a role in the pathophysiology of enuresis and nocturnal polyuria (NP).<sup>82</sup> The AVP analogue desmopressin has consistently shown nocturia and sleep quality improvement in patients with proven NP.<sup>83,84</sup>

### 10. NEUROPEPTIDE Y (NPY)

Besides GHRH, NPY is thought to act as a physiological antagonist of CRH.<sup>10</sup> A variety of sleep-EEG effects of NPY have been reported. In humans, when NPY was repetitively administered i.v. in 20 young normal male subjects, it led to decreases in sleep latency and in the first REMS period as well as in increases in stage 2 sleep and sleep period.<sup>85</sup> Cortisol and ACTH secretion were blunted. In patients with depression of both sexes and in age-matched controls sleep latency was shortened after NPY while cortisol and ACTH levels and the first REMS period remained unchanged.<sup>86</sup>

### 11. VASOACTIVE INTESTINAL POLYPEPTIDE (VIP)

As a member of the secretin-glucagon peptide family, VIP displays structural homology to GHRH, binding to the same receptors.<sup>13</sup> This close relationship is particularly interesting since, in the mid 80s, VIP emerged as a peptide for which consistent sleep promoting activity (enhancement of both NREMS and REMS) was observed initially in rats.<sup>87</sup> After pulsatile i.v. administration of 4X50 µg VIP, NREMS-REMS cycles were decelerated in young normal males. Each cycle was prolonged, the cortisol nadir appeared earlier, and the GH acrophase was blunted.<sup>88</sup> These data suggest that VIP affects the circadian clock, resulting in prolonged sleep cycles and an earlier occurrence of the cortisol nadir.

### 12. PROLACTIN (PRL)

Prolactin modulates REMS possibly through a central action. Thus, intracerebral injection of PRL or anti-PRL antibodies stimulates or inhibits REMS, respectively.<sup>89</sup> It is likely that intracerebral PRL modulates REMS under physiological conditions,

whereas pituitary PRL provides additional stimulating influence when PRL secretion is high, e.g., in stress.<sup>4,16</sup> Human studies examining the effects of PRL on sleep are scarce; however, in patients with prolactinoma, SWS is increased selectively when compared to normal controls.<sup>90</sup>

### 13. ESTROGENS – PROGESTERONE

An abrupt decline in the sigma frequency range has been reported in women after the onset of menopause, whereas in men these changes develop more gradually.<sup>10</sup> In postmenopausal women sleep-endocrine alterations associated with depression are accentuated. In a study of pre- and postmenopausal women with depression and matched controls,<sup>91</sup> a decrease in SWS and an increase in REMS frequency was observed in post- but not in premenopausal women. An inverse correlation was found between the decrease in SWS as well as sleep continuity, and follicle stimulating hormone (FSH) secretion in patients with depression. These observations suggest a role of menopause in these sleep-EEG changes.

Much of the research on hormone replacement therapy (HRT) focuses on the role of estrogens and its positive effects on sleep in women after menopause. Compared to placebo, estrogen replacement therapy (ERT) has been shown to reduce insomnia.<sup>92</sup> Other reported benefits of ERT include improvement in falling asleep, diminished nocturnal restlessness, and fewer awakenings.<sup>93</sup> One possible explanation for these actions is that ERT relieves climacteric symptoms (e.g. hot flashes), leading to remarkable improvements in sleep.<sup>94</sup> Another hypothesis is that ERT directly affects the circadian rhythm, or acts on sleep architecture, thus “normalising” the distribution of SWS in menopausal women, leading to a pattern resembling that of younger subjects.<sup>95</sup> An additional effect of estrogens on sleep architecture is their effect on REMS, the increase in REMS being a consistent finding.<sup>94</sup> In postmenopausal women ERT given for four weeks by skin patch enhanced REMS and reduced intermittent wakefulness during the first two sleep cycles compared to baseline values. A normal decrease in SWS and SWA from the first to the second cycle was observed.

Despite the above data showing effects of estrogens



on sleep in postmenopausal women, the estrogen receptor-alpha (ER-alpha) genotypes (PvuII and XbaI polymorphisms) have been associated with vaginal dryness and hot flashes but not with sleep alterations.<sup>96</sup> On the other hand, both case-control and prospective cohort studies have consistently linked night shift work with breast cancer risk and, more recently, endometrial cancer, both of which are highly sensitive to estrogens.<sup>97</sup>

Despite the proven effects of estrogens on sleep regulation, women starting HRT often also take progesterone to protect themselves against the harmful endometrial effects of estrogens. Studies of progesterone's effects on sleep have yielded variable results.<sup>94</sup> There is some evidence that when progesterone is added to the HRT regimen, there is no improvement in sleep.<sup>98</sup> However, there is a possibility that various types of progesterone can affect sleep differently. Montplaisir et al<sup>99</sup> tested the sedating effects of progesterone by comparing HRT with two different progestogens: medroxyprogesterone acetate and micronized progesterone. They found that women treated with micronized progesterone had improvement in sleep efficiency. On the other hand, a Finnish study investigating the effects of estrogen-progestin treatment (EPT) on sleep in pre- and postmenopausal women, found that both groups receiving EPT had a significantly greater number of awakenings than the corresponding placebo group. Although, researchers could not conclude if EPT actually deteriorates sleep, available evidence indicates that no benefit from EPT in terms of sleep quality<sup>100</sup> is achieved.

#### 14. DEHYDROEPIANDROSTERONE (DHEA)

After a single oral dose of DHEA, REMS increased selectively in young normal men.<sup>101</sup> After intraperitoneal (i.p.) infusion of DHEA sulphate (DHEAS) a dose-dependent effect on EEG potency was found. Interestingly, a DHEAS dosage of 50 mg/kg augmented EEG potency in the spindle-frequency range, whereas a dosage of 100 mg/kg had the opposite effect. Sleep architecture remained unchanged after either dosage of DHEAS.<sup>102</sup> However, Dayal et al<sup>103</sup> concluded that, compared with no hormone therapy, none of the supplemental hormone regimens (receiving DHEA daily over a period of 12 weeks)

was associated with significant changes in sleep in 50 postmenopausal women.

#### 15. MELATONIN

After almost 50 years of research the physiological role of melatonin still remains unclear.<sup>104</sup> Nevertheless, the endogenous melatonin rhythm exhibits a close association with the endogenous circadian component of the sleep propensity rhythm. This may imply that melatonin is an internal sleep 'facilitator' in humans and therefore possibly useful in the treatment of insomnia and readjustment of circadian rhythms. There is evidence that administration of melatonin: (i) induces sleep when the homeostatic drive to sleep is insufficient and (ii) inhibits the drive for wakefulness emanating from the circadian pacemaker. Therefore, exogenous melatonin can act as a soporific agent, a chronohypnotic, and/or a chronobiotic.<sup>105</sup>

However, whether melatonin is causally involved in sleep mechanisms is shrouded in ambiguity. The ability to sleep is retained in the absence of detectable endogenous melatonin during the day and in tetraplegic patients.<sup>106</sup> Melatonin production varies enormously between individuals and does not correlate with sleep quality or sleep-maintenance in elderly subjects without<sup>107</sup> or with insomnia.<sup>108</sup> By contrast, numerous laboratory studies have clearly demonstrated that administration of melatonin acutely affects sleep in humans. Exogenous melatonin elicits all the physiological effects which occur in the evening during endogenous melatonin secretion. Indeed, exogenous melatonin is most effective when endogenous levels are low during the biological day. It elicits time-dependent soporific effects, which have been corroborated with electrophysiological measures of sleepiness such as EEG theta activity during wakefulness.<sup>105</sup> The most consistent effect found in those studies was that sleep latency was shorter after melatonin, even at rather low doses.<sup>109</sup> On the other hand, sleep consolidation or sleep efficiency was not affected by night-time melatonin administration, whereas during daytime an improvement in sleep efficiency could be found.

Zhdanova<sup>110</sup> mentions that, in general, melatonin can promote sleep in healthy humans if administered during habitual hours of wakefulness; it can be helpful in patients with insomnia and it can facilitate the

effects of common hypnotics, thus reducing their effective dose and facilitating their withdrawal. Melatonin can acutely increase the homeostatic drive for sleep and ease the transition between wakefulness and sleep as well. On the other hand, Van den Heuvel et al<sup>111</sup> claim that melatonin acts as a hypnotic only in those individuals for whom endogenous melatonin increases sleep propensity and its action is an appropriate consequence of environmental darkness. Under this perspective, melatonin can exert hypnotic-like effects but only under limited circumstances, depending on dose, time of administration, age, and other factors.<sup>112</sup>

Altered melatonin secretion has been found in Alzheimer's disease and in Parkinson's disease. Attempts to compensate for melatonin deficiency have shown that administration of this compound can improve sleep efficiency in both diseases.<sup>113</sup> Despite these findings there are still discrepancies regarding its use in patients with Parkinson's disease.<sup>114</sup> Melatonin also decreases sleep latency and number of awakenings per night and increases total sleep time in individuals with intellectual disabilities.<sup>115</sup> Various lines of evidence show that depressed patients exhibit disturbances in both the amplitude and shape of the melatonin secretion rhythm and that exogenous melatonin can improve their quality of sleep. Moreover, a growing number of epidemiologic studies have evaluated the relationship between night shift work, as well as the effect of varying duration of sleep on peak melatonin secretion at night. Specifically, lower nightly melatonin levels have been shown in night workers. Although the evidence for an association between sleep duration and breast cancer risk is unclear, overall there is increasing support for a potentially important link between melatonin and breast cancer risk.<sup>97</sup> A possible link between diminished secretion of melatonin and increased exposure to light during night-time has been suggested.<sup>116</sup> Ultimately, genome-wide association studies<sup>117-119</sup> have shown that variation in the melatonin receptor 1B (MTNR1B)—a receptor known to be linked to the circadian rhythm of sleep—is associated with insulin and glucose concentrations as well as with the risk of type 2 diabetes (T2D). Blocking the melatonin ligand-receptor system has been suggested as a therapeutic avenue in T2D.<sup>117</sup>

A new treatment option in primary insomnia has

been introduced with PR (prolonged-release) melatonin, which significantly improves morning alertness and quality of sleep compared with placebo in patients over the age of 55.<sup>120</sup> Several clinical data are available for the melatonin agonists ramelteon, agomelatine, beta-methyl-6-chloromelatonin (TIK-301), and tasimelteon (VEC-162) in humans with regard to their contribution in the treatment of sleep-wake disorders.<sup>121</sup> Ramelteon, the first to be approved for the treatment of chronic insomnia, has been shown to enhance subjective sleep quality in some, but not all, studies,<sup>122</sup> especially in adults with generalized anxiety disorder,<sup>123</sup> and in menopausal women.<sup>124</sup> Agomelatine, which combines the properties of a 5-HT(2C) antagonist and a melatonergic MT(1)/MT(2) receptor agonist, has been found to be very effective in re-setting the disturbed sleep/wake cycle and in improving the clinical status of major depressive disorder (MDD).<sup>125</sup>

## 16. THYROTROPIN-RELEASING HORMONE (TRH)

Clinical data suggest that sleep can be modulated by TRH,<sup>126</sup> but the role of TRH in the regulation of sleep in humans has not yet been clarified. Hemmeter et al<sup>127</sup> examined the effects of pulsatile administration of TRH on the sleep EEG pattern and the nocturnal secretions of cortisol and GH in healthy male subjects. In contrast to the well-known effects of CRH on the sleep pattern, TRH seems to exert only a weak effect on the sleep EEG, which is reflected in a slight decrease in sleep efficiency associated with a trend to wakefulness during the night. The activating, albeit weak, effect of TRH on the sleep EEG and nocturnal cortisol secretion in healthy volunteers confirms and adds to the results previously observed in animals. On the basis of these findings, it is likely that TRH may contribute to the disturbed sleep continuity seen in depressed patients, probably acting in a synergistic manner with CRH. In patients with hyperthyroidism, SWS is reduced,<sup>72</sup> whereas in MDD, TRH administration may lead to slight sleep EEG alteration<sup>128</sup> or no alteration at all.<sup>129</sup>

## 17. HYPOCRETIN/OREXIN

The hypothalamic neuropeptides hypocretin-1 and 2 (also known as orexin A and B) have attracted

tremendous interest since their discovery. In 2000, Nishino et al<sup>130</sup> published the first report on hypocretin deficiency in human narcoleptics. Since then, several studies on the association between hypocretin and sleep-regulation have been published.<sup>131-135</sup> Hypocretin signaling is crucial for maintaining wakefulness and regulating REMS. However, it is not required to generate (REM) sleep or wakefulness, as narcoleptic patients still show these vigilance states. The hypocretin/orexin system stabilises rather than generates vigilance states. As narcolepsy is characterised by sudden, inappropriate vigilance state transitions, hypocretin is needed to suppress such switches: it is necessary to keep the inherently unstable “sleep-wake switch” in the wake position.<sup>136</sup>

In humans, narcolepsy is associated with a specific variant of the human leukocyte antigen (HLA) complex.<sup>137</sup> Genome-wide analysis shows that narcoleptic humans also exhibit a specific genetic mutation in the T-cell receptor alpha locus.<sup>138</sup> These genetic anomalies may underlie the attack of the autoimmune system and the killing of the critical hypocretin neurons. Hence, the absence of hypocretin-producing neurons in narcoleptic humans may be the result of an autoimmune disorder.<sup>139</sup> Cerebrospinal fluid (CSF) histamine levels are also reduced in human narcolepsy. As histamine is a wake-promoting amine known to decrease during sleep, decreased histamine could either reflect or mediate daytime sleepiness in these pathologies.<sup>140</sup> Hypocretin deficiency is also found in symptomatic cases of narcolepsy and excessive daytime sleepiness with various neurological conditions such as Guillain-Barre syndrome, MA2-positive paraneoplastic syndrome, and neuromyelitis optica related disorder.<sup>141</sup> These findings in humans have led to the establishment of a new diagnostic test of narcolepsy based on CSF hypocretin-1 levels.

Dysfunction of the hypocretin system has been reported in multiple sclerosis with hypothalamic lesions and hypersomnia.<sup>142</sup> In patients with obstructive sleep apnea (OSA), lower levels of plasma orexin A have been found, especially in those who are ex- or current smokers. These results indicate that smoking may affect orexin levels in OSA patients with potential effect on their altered sleep patterns.<sup>143</sup> In Parkinson's disease, orexin is most likely involved in clinically significant sleep attacks (SAs)<sup>144</sup> and restless

legs syndrome.<sup>145</sup> Abrogation of D3 receptor stimulation may increase orexin and thereby inhibit SAs.<sup>144</sup> A -909T/C gene polymorphism may explain in part the sudden onset of sleep in Parkinson's disease.<sup>146</sup> A role for the orexin/hypocretin system in alertness and abnormal feeding behaviours in patients with attention-deficit/hyperactivity disorder (ADHD) has also been suggested; however, this hypothesis of over-activation of orexin neurons remains to be confirmed.<sup>147</sup> Furthermore, in anorexia nervosa, abnormal activity of orexin (along with leptin) or their receptors may constitute one of the mechanisms of hyperactivity in these patients.<sup>148</sup> Regarding obesity, multiple epidemiologic studies have shown an association between short sleep and higher body mass.<sup>149</sup> Sleep disturbances are linked to a dysregulation of the neuroendocrine control of appetite.<sup>148</sup>

## SYNOPSIS

The reported data have shown that various hormones (peptides and steroids) exert specific effects on the sleep EEG. Some peptides promote sleep while others increase wakefulness (Figure 1). Hormones that induce sleep (at least in males) include: GHRH, galanin, vasopressin, prolactin, estrogens and melatonin.

GHRH may have a direct role in promoting NREMS (especially duration and intensity of SWS) and REMS in humans with, however, diverse effects depending on gender and age. Interestingly, a synergism of GHRH and CRH is suggested in women, which may contribute to the increased prevalence of depression among females. Similarly, ghrelin lowers the time spent in stage 1 sleep, especially in young normal males.

Regarding cortisol, its effect on SWS depends on optimal cortisol levels to achieve maximal nocturnal CRH suppression. It is believed that the mineralocorticoid receptors regulate SWS, whereas the glucocorticoid receptors regulate REMS, although inconsistencies still exist. Several sleep alterations have been observed in diseases where cortisol production is altered (such as Addison's and Cushing's).

Galanin's enhancement of SWS and REMS both in young normal men and in patients with depression has indicated a possible acute antidepressive effect in

the latter. In patients of both sexes with depression sleep latency is shortened after NPY. Data on the effect of VIP on sleep pattern in humans are inconsistent; VIP affects the circadian clock, resulting in prolonged sleep cycles and an earlier occurrence of the cortisol nadir. Although prolactin modulates REMS, human studies examining the effects of PRL on sleep are scarce; however, in patients with prolactinoma increases in SWS have been observed.

A role for menopause has been suggested for several sleep disruptions. In postmenopausal women with depression decreases in SWS and an increase in REMS frequency is observed. Compared to placebo, estrogen replacement therapy has been shown to reduce insomnia, relieve climacteric symptoms, and possibly act directly on the circadian rhythm or sleep architecture (via REMS modulation).

Melatonin secretion has been found to be altered in Alzheimer's and Parkinson's diseases and in MDD. Melatonin induces sleep when the homeostatic drive to sleep is insufficient, while it inhibits the drive for wakefulness emanating from the circadian pacemaker. However, the question as to whether melatonin is involved in sleep mechanisms has not been answered. Despite ambiguity, there is increasing support for a potentially important link between night shift work, melatonin secretion, and risk for breast cancer. In addition, genome-wide association studies show that variation in the melatonin receptor 1B, apart from its links with the circadian rhythm of sleep, is associated with a higher risk for type 2 diabetes.

Several hormones lead to sleep disruptions or produce only weak effects on sleep architecture, some of the effect showing gender and/or age dependence. SRIH impairs sleep in healthy elderly subjects, whereas it has no effect on young normal men, probably due to a decline of endogenous GHRH in the elderly. In contrast, the SRIH analogue, octreotide, immediately elicits suppression of NREMS and may be the culprit for sleep disruptions (increased daytime sleepiness, delayed sleep onset) in acromegalic patients. Similarly, CRH decreases SWS and increases wakefulness in young normal male subjects, with an increase in light sleep and awakenings, while it promotes REMS. However, findings are still inconsistent. DHEA increases REMS selectively in young normal men. Conversely,

ACTH suppresses REMS in normal controls, while an anticipatory increase in ACTH in the morning may facilitate spontaneous waking. The role of TRH in the regulation of sleep has not yet been clarified. Studies of progesterone's effects on sleep have yielded variable results. In contrast to progesterone, which when in the hormone replacement therapy regimen does not alter sleep, micronized progesterone itself leads to enhancement in sleep efficiency.

Hypocretin/orexin signalling is crucial for maintaining wakefulness and regulating REMS, as deduced from studies in narcoleptics.

All in all, the aforementioned evidence suggests that several hormones and hormonal agents may be involved in the regulation of sleep mechanisms in a manner proportional to the changes in their metabolic rhythm imposed by sleep. Given their interactions with the body's circadian clock, these molecules could be used in the future to treat sleep disorders. The present review has demonstrated that current evidence points to highly promising utilization of these molecules for treating sleep disorders, though more research is required before they are fully introduced into clinical practice.

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