SLEEP REGULATION: A BIDIRECTIONAL INTERACTION BETWEEN BRAIN AND THE ENDOCRINE SYSTEM

Giuseppe Marano, Gianandrea Traversi, Valeria Catalano, Serena Dittoni, Giacomo Della Marca, Salvatore Mazza, Marianna Mazza

Abstract

The purpose of this review is to summarize the current neuroendocrine knowledge base with particular emphasis on the bidirectional interaction on sleep regulation between the endocrine and the nervous system. These complex systems interact at multiple levels, both neuroendocrine and neuronal pathways are involved in the control of the humoral and cellular responses. Various hormones (peptides and steroids) participate in sleep regulation. A keyrole was shown for the reciprocal interaction between sleep-promoting growth hormone-releasing hormone (GHRH) and sleep-impairing corticotropin-releasing hormone (CRH). Besides of GHRH and CRH various other peptides and steroids participate in sleep regulation, many of them act via GABAergic mechanisms. In the light of neurobiological theories, primary insomnia may be conceptualised as the final common pathway of the interaction of a genetic vulnerability to an imbalance between arousing and sleep-inducing brain centres with perpetuating mechanisms such as maladaptive behaviours, learned sleep-preventing associations and cognitive factors.

Key Words: sleep, EEG, hormones, neuroendocrinology, nervous system, hypothalamic-pituitary-adrenal axis

Abbreviations: 5-HT = serotonin; **ACTH** = adrenocorticotropic hormone; **ADE** = adenosine**; ANS** = autonomic nervous system; **AVP** = arginine vasopressin; **CNS =** Central Nervous System; **CRH** = corticotrophin-releasing hormone; **CSF** = cerebrospinal fluid; **DHEA** = dehydroepiandrosterone**; EEG =** electroencephalogram; **EMG** = electromyography; **EOG =** electrooculography; **FASPS** = familial advanced sleep phase syndrome; **$GABA_A$** = gamma-aminobutyric acid; **GH** = growth hormone; **GHRH** = growth-hormone releasing hormone; **GR** = glucocorticoid receptor; **HPA** = hypothalamic-pituitary-adrenal; **HPS** = hypothalamo-pituitarysomatotrophic; **i.c.v. =** intracerebroventricular; **i.v.** = intravenous administration; **IL-6** = interleukin-6; **LH** = luteinizing hormone; **MR** = mineralocorticoid receptor; **NE** = norepinephrine; **NPY** = neuropeptide Y; **NREM =** non rapid eye movement; **NREMS** = non rapid eye movement sleep; **PGO** = Ponto-geniculo-occipital; **PRL** = prolactin; **PVN** = paraventricular nucleus; **REM =** rapid eye movement; **REMS** = rapid eye movement sleep; **SCN =** suprachiasmatic nucleus; **SRIH** = somatostatin**; SWA =** slow wave activity; **SWS =** slow wave sleep; **TRH** = thyrotropin-releasing hormone**; VIP =** vasoactive intestinal polypeptide; **VLPO** = ventrolateral preoptic area

Declaration of interest: none

Giuseppe Marano, *MD*, Gianandrea Traversi, *MD,* Valeria Catalano, *PsyD*, Serena Dittoni, *MD*, Giacomo Della Marca, *MD,* Salvatore Mazza, *MD*, Marianna Mazza*, *MD, PhD*.
Department of Neurosciences, Catholic University of Sacred Heart of Rome, Italy.

***Corresponding author:**
Marianna Mazza, MD, PhD
Department of Neurosciences, Institute of Psychiatry and Clinical Psychology, Università Cattolica del Sacro Cuore di Roma, Via Ugo De Carolis, 48 00136 Roma (Italy)
Tel: +39 06 35348285, Fax: +39 06 35501909, E-mail: mariannamazza@hotmail.com marianna.mazza@rm.unicatt.it

Introduction

The hypothesis that sleep is regulated, in part, by humoral mechanisms is an ancient one, being first proposed by Aristotle, who suggested that vapors emanating from the stomach during food digestion were transported throughout the body causing sleepiness (Krueger et al. 1998). Later, some researchers postulated the fundamental idea of the existence of a sleep regulatory substance chemically specificated (Krueger et al. 1998). Afterwards, many investigators showed the accumulation of sleep-promoting substances in cerebrospinal fluid (Krueger and Obál 1993, Krueger and Majde 1994).

A necessary step in deciphering sleep function is to determine the mechanism by which the brain produces sleep. The brain and the endocrine system are the two major adaptive systems of the body. Advances in the field of neuroimmunology and neuroendocrinology have shown that the central nervous system (CNS) and endocrine system are intimately linked and do not function as independent systems (Felten et al. 1987, Blalock 1994, Jiang et al. 1998, Dantzer 2004, Wrona 2006). There is a strong evidence that the CNS

Submitted November 2011, Accepted May 2011

© 2011 Giovanni Fioriti Editore s.r.l.

receives messages from the endocrine system and vice versa messages from the brain modulate endocrine functions (Elenkov et al. 2000), thus, the brain and the endocrine system are involved in a functional cross-talk, whose main function is to maintain homeostasis. Two fundamental processes have been implicated in sleep regulation (Borbély and Tobler 1989, Krueger et al. 1998). One of them is determined by the circadian pacemakers and is proposed to act as a sleep threshold. This process describes the common experience that the easiness of falling asleep varies with the circadian rhythm. The other process, called homeostatic sleep regulation, encompasses the fact that the daily duration of sleep is fairly constant in a given individual. The concept of homeostatic sleep regulation implies that sleep is wake dependent; unusually long wake periods are followed by enhanced sleep. These circadian and homeostatic processes result from the interaction of humoral and neural mechanisms (Steriade and McCarley 1990, Krueger et al. 1998).

The circadian rhythm of sleep is regulated by complex interactions between the neural and endocrine systems. Neuroendocrine peptides signal the CNS to regulate normal sleep patterns, alter sleep during disease and induce the altered behavior and symptoms associated with illness. Patients often link their insomnia to a wide variety of mental states, from anxiety or depression to difficulties in interpersonal relationships, family discord, problems at work and financial troubles. In individual cases, it is not easy to establish which of these factors is responsible for sleep impairment (Culebras 2000). However, insomnia is not entirely the result of psychological events such as a disordered lifestyle, alcohol and drug abuse, bone and muscle pain, bronchitis, gastritis, colitis, prostate hypertrophy can all lead to insomnia. This is especially true in the elderly, whose sleep is lighter and more fragmented and who frequently suffer from pains and resort to chronic sleep medication. Insomnia tends to run in families, and patients often have other relatives who suffer from anxiety, depression, irritability and insomnia (Culebras 2000). Hence, both a genetic predisposition and living with emotionally disturbed people can lead to chronic insomnia in the same family. Neurological disorders entail sensory-motor deficits and behavioral problems and may thus favor the onset of insomnia as they are a source of serious worries for the patient and his family. CNS diseases may, however, involve the nervous system structures responsible for the physiological control of wake and sleep and therefore lead to sleep impairment (Culebras 2000).

In a notable way a profound and generalized impact of sleep on the endocrine system should therefore be expected. Sleep regulation is configured as the reciprocal action and influence of brain and endocrine system. The metabolism and hormone secretion might control sleep but the physiological processes driving this bidirectional relationship have not been fully elucidated. Sleep has an effect on the production and hormones' action influencing the secretion of peptides and varying blood levels of many hormones. Sleeping and neuropeptides are intricately related. This paper argues for a conceptualization of a bidirectional relationship between brain and endocrine system. The purpose of this review is to evaluate existing evidence provided by literature data and to consider how findings from the available studies indicated the possible existence of a bidirectional relationship between brain and endocrine system. The review discusses characteristics of sleep regulation and synthesis of hormones involved in sleep leading to a greater recognition of their impact on multiple aspects of individuals' lives. Sleep disorders can occur as a result of habitual behavior or due to the presence of a pathological condition. Specific references to insomnia are among the purposes of the present paper to facilitate a more comprehensive knowledge and to enhance the early recognition and treatment of sleep disorders as well as to generate further research on the role and the impact of humoral mechanisms on sleep regulation.

Neurobiology and Neuroanatomy of sleep

Sleep is a function of the brain. Like wakefulness, sleep originates in centers located in the brainstem, hypothalamus, thalamus and basal forebrain. The hemispheric cortex also intervenes in the development of sleep as a resonating organ, but appears to have no primary functions. Lesions of any nature affecting these segments of the nervous system will be reflected in an alteration of sleep and vigilance. Not all sleep disorders can be explained on a neuroanatomical basis suggesting neurochemical alteration of functions that remain to be uncovered (Culebras 2000).

To understand sleep generation, one must comprehend the origin of wakefulness. Neurons involved in promoting wakefulness are located in the reticular formation of the brainstem (ventral medullary, central pontine, and midbrain reticular formation), posterior hypothalamus, and basal forebrain (nucleus basalis of Meynert or substantia innominata, nucleus of diagonal band, and septal nucleus), subthalamus, and reticular nuclei of the thalamus (ventromedial, intralaminar, and midline thalamic nuclei). Wakefulness is maintained by tonic activity in the reticular activating system reinforced via collaterals by sensory input (Culebras 2000). The most powerful influences are acoustic and painful stimuli. Reticular system activation ascends via the brainstem reticular formation into the nonspecific thalamic system, from where it is transmitted to the cortex of the forebrain. An alternative extrathalamic route originates in the subthalamus, posterior hypothalamus, and basal forebrain projecting to the entire cortical mantle (Culebras 2000).

Basic mechanisms and physiological characteristics of sleep regulation

A combination of electroencephalography, electromyography (EMG), and electrooculography (EOG) are used in the laboratory setting to objectively identify different stages of sleep (Datta and Hobson 1995, Datta et al. 1997). These measurements are collectively known as polysomnography (Datta and Maclean 2007). A widely held, albeit simplified, operational definition of sleep is that of a natural state characterized by a reduction in voluntary motor activity, a decreased response to stimulation (i.e., increased

arousal threshold), and stereotypic posture. Sleep is readily distinguishable from other states of altered "consciousness," such as coma and anesthesia, in that it is easily reversible and self-regulating. During wakefulness, the cortical EEG typically contains desynchronized high-frequency, low-amplitude waves in the 14- to 30-Hz range (i.e., beta waves), presumably reflecting differences in the timing of processing of cognitive, motor, and perceptual functions. During "quiet rest," when the eyes are closed, EEG oscillations predominate in the 8- to 12-Hz range and are referred to as alpha waves (Fuller et al. 2006).

Recent studies show that the oscillations during REMS are driven by neurons in the precoeruleus area in the pons and that the REMS atonia is caused by neurons in the adjacent sublaterodorsal area (Lu et al. 2006). These "REM-on" zones are inhibited by a nearby "REM-off" region, including the ventrolateral periaqueductal gray matter and lateral pontine tegmentum. The REM-on area also can inhibit the REM-off area, and the mutual inhibition between these regions produces a "flip-flop" switch, which ensures sharp and complete transitions between REM and NREM sleep. This REM switch is in turn modulated by cholinergic neurons (which promote REMS) and noradrenergic and serotoninergic neurons (which inhibit REMS) (McCarley 2004, Fuller et al. 2006). By virtue of the self-reinforcing nature of these switches (i.e., when each side is firing, it reduces its own inhibitory feedback), the flip-flop switch is inherently stable in either end state but avoids intermediate states. The flip-flop design thus ensures stability of the behavioral state and facilitates rapid switching between behavioral states. Flip-flop switches also possess, at times, the undesirable property of abruptly undergoing unwanted state transitions. The frequency of unwanted state transitions may increase if one side of the switch is "weakened," as the weakened side becomes less able to inhibit the other side, thereby biasing the switch more toward a midpoint where smaller perturbations may trigger a state transition (Fuller et al. 2006).

Association between circadian rhythm and sleep regulation

It is well known fact that the central pacemaker for the mammalian circadian clock is located within the suprachiasmatic nucleus (SCN) (Moore and Eichler 1972, Stephan and Zucker 1972, Drucker-Colín et al. 1984, Prosser and Gillette 1989, Ralph et al. 1990). Several genes expressed both in the SCN nucleus and in non-neural tissues are involved in circadian rhythm regulation (Lowrey and Takahashi 2004), and the use of gene microarrays reveals that expression of several hundred genes in the mouse liver vary in a cyclical pattern over the course of a 24-hour day (Lowrey and Takahashi 2004). Currently, it is believed that the timing of sleep and wakefulness is mediated by two interconnected processes: a homeostatic regulatory process that increases during waking and decreases during sleep, together with a circadian clock-dependent mechanism (Lowrey and Takahashi 2004). Clock-dependent mechanisms clearly influence sleep-wake cycles during jet lag and appear responsible for chronic sleep disorders associated with inappropriate sleep-wake cycles, such as those that occur in shift workers (Lowrey and Takahashi 2004, Majde and Krueger 2005).

Although relatively little is known regarding the genetic basis of sleep, there is a wealth of information on the genetics of circadian clock function across species. Sleep and circadian function are distinct processes that interact in living organisms. Even though these two systems can operate independently, recent studies indicate a more intimate relationship (Kilduff et al. 2008). Over the last decade, genetic material has been collected from individuals and families with circadian rhythm disturbances including familial advanced sleep phase syndrome (FASPS) and familial delayed sleep phase syndrome. To date, two genetic causes of FASPS have been reported. The first described cause is a mutation in h*PER2*, a homolog of the fly gene that was the first gene determined to be necessary for proper circadian rhythmicity (Toh et al. 2001). This mutation occurs in a region that is important for the suppressor function of the PER2 protein in the core molecular clock (Xu et al. 2007). The second known cause is a mutation in a gene encoding a protein kinase called *casein kinase I δ* (*CKI δ*) (Xu et al. 2005). *CKI δ* is also a human homolog of fly and hamster genes known to be critical for proper circadian function. Transgenic mice harboring the human mutation also have a circadian phenotype. This mutation leads to a lowered enzymatic activity which then causes the circadian phenotype. Recently, Kilduff and colleagues have identified a mutation in another transcriptional suppressor of the molecular clock that leads to a natural short sleep phenotype in humans. This discovery represents a new opportunity for us to begin to probe the mechanisms of sleep homeostasis in humans (Kilduff et al. 2008).

Sleep and the endocrine system in infancy

Despite the fact that infants spend more time asleep than awake, an understanding of the importance and effects of sleep on the pathophysiology of illness in infancy is a relatively recent development. In newborn infants, the signature EEG features that characterize different sleep stages in adults are not discernible and a combination of EEG and behavioral criteria is often used to assign sleep state during this period of development (Anders et al. 1971, Heraghty et al. 2008). In preterm and term newborns, the predominant sleep state is active sleep, whose proportion diminishes rapidly over the first few months after birth to reach 25% of total sleep time (approaching adult values) at the age of 6 months (Ficca et al. 2000). There are complex interactions between the development of diurnal rhythms and hormonal secretion during sleep in infancy (Rivkees 2003). Growth hormone is secreted exclusively during sleep, melatonin passes through the placenta, so that maternally derived melatonin can drive fetal diurnal rhythms (Breen et al. 1996). Melatonin has radical scavenging properties (Reiter et al. 1995), and it has been proposed that it can function as a tissue protector as well as having a role in brain development (Reiter et al. 1995, Breen et al. 1996, Ardura et al. 2003,

Jan et al. 2007). Maturation of the diurnal rhythm of melatonin production takes place from about 2 months, although maturation is delayed in premature infants (Welin et al. 2007). This has led to the suggestion that melatonin might help establish circadian rhythms in preterm infants (Ardura et al. 2003, Jan et al. 2007). The development of a diurnal pattern of cortisol production varies between infants but is commonly present from 2 months of age (Kennaway et al. 1992). It is not clear when this occurs in preterm infants, but one small study found onset at a similar postnatal age to the development of a diurnal sleep–wake cycle (Santiago et al. 1996). However, a delay in the overnight reduction of cortisol production was found in infants with intra-uterine growth retardation, with the possibility that this reflects fetal programming that continues into adulthood (Jackson et al. 2004).

Gender differences in sleep regulation

Most studies on sleep have been performed selectively in men or male. This is because females are more heavily influenced by cyclic sex hormones that may affect sleep-wake structures. Indeed, women often develop sleep disturbances in association with reproductive events. During the menstrual cycle, some women feel sleepier during the luteal phase than the follicular phase (Kimura 2005). During pregnancy, sleep dynamics change in women (Driver and Shapiro 1992, Hertz et al. 1992) and its significance associated with human pregnancy is detected by a quantitative analysis of sleep EEG. A progressive reduction of power density during NREMS occurs in the third trimester (Brunner et al. 1994), likely resulting in sleep maintenance insomnia. On the contrary at postpartum, the power in lower frequency bands during NREMS recover or rather increase (Nishihara et al. 2004). Changes in power density of sleep EEG dependent on reproductive potentials could be produced in part by an interference with progesterone that is capable of modulating the gamma-aminobutyric acid ($GABA_A$) receptor complex responsible for the regulation of sleep (Wilson 1992, Lancel et al. 1999, Kimura 2005).

Recently argued are gender differences in sleep regulation by particular sleep-promoting substances. For instance, growth-hormone releasing hormone (GHRH) is known to act on the somatotropic axis, stimulate growth hormone (GH) secretion, and promote NREMS (Obál and Krueger 2001). However, the action in females is a bit different from those confirmed in male subjects. Nevertheless in both genders exogenously administered GHRH is capable of increasing plasma levels of GH, sleep not being affected in females or even inhibited during the night (Antonijevic et al. 2000a). This can be explained on the basis of gender differences in hormonal regulation. It was originally published in 1968 by Takahashi *et al*. that the dominant release of GH in humans corresponds with an occurrence of deep sleep that appears during the first cycle of overnight sleep (Takahashi et al. 1968). However, this does not to apply to the case of young women: the peak levels of plasma GH are lower than male peaks, but the dominant release can happen more often during the night corresponding with deep sleep at both the first and second cycles (Antonijevic et al. 1999). It has been discovered that females possess a more activated HPA axis, in which baseline levels of stress hormones (e.i. glucocorticoids) are higher than in males (Spinedi et al. 2002). In the case of females, GHRH may not counteract the HPA system, but rather stimulate stress reaction, then result in suppression of SWS (Antonijevic et al. 1999, Kimura 2005).

Both men and women often suffer from disturbed sleep. Recent studies report that a deterioration in sleep EEG starts earlier in men than women (Ehlers and Kupfer 1997). However, women suffer more than men when a component of their reproductive function declines (Antonijevic et al. 2000b). Sleep problems are a major complaint in postmenopausal women. Lower levels of ovarian hormones but higher secretion of gonadotropins from the pituitary gland are a key complex in creating uncomfortable sleep hygiene. Hormonal replacement therapy (HRT) has been attempted mostly in Western countries to cure postmenopausal symptoms including insomnia. Estrogen replacement is reported to help restore the normal sleep EEG in postmenopausal women and further improving cognitive function during the day (Antonijevic et al. 2003). However, HRT is now under criticism because of the increased risks of mammary cancer and cardiovascular diseases (Rossouw et al. 2002).

After menopause when elderly women cope with a decline of ovarian function, vulnerability to sleep disorders as well as depression is still higher in women compared with men. In this case, it is difficult to predict what may explain the difference in the genders. It is necessary to investigate the sexual dimorphisms of sleep-wake activities to understand gender-specific regulation (Kimura 2005).

Neuroendocrine system during ageing

Ageing affects the endocrine system by altering cells, the hormones produced by these cells and hormone receptors or post-receptor processes in the target cells (Rehman and Masson 2001). Correspondingly in the elderly the amounts of SWS and SWA are low and sleep continuity is disturbed. REMS time and REMS latency decrease in higher age. During ageing GH secretion decrease (Van Cauter et al. 1998), in men about 70% of the daily GH output occurs during early sleep. In women, the contribution of sleep-dependent GH release to the daily output is lower (Rehman and Masson 2001). A decline in pulsatile release of GH may be directly or indirectly responsible for the age-related decline in protein synthesis. There is a negative correlation between the density of GH-binding sites in the human brain and increasing age (Lai et al. 1993). This reduction in the density of GH binding is found in several areas of the brain, including the choroid plexus, the hippocampus, the hypothalamus, the pituitary and the putamen (Rehman and Masson 2001). The reduced GH secretion in old age may be responsible of the increased risk of falls and fractures and GH deficiency may contribute to the development of cardiac failure (Rehman and Masson 2001).

The circadian rhythm of adrenocorticotrophic hormone and cortisol secretion is flattened in old people. The cortisol circadian profile is higher in the evening and night time in elderly subjects (Ferrari et al. 1996). Alterations in cortisol control may have a number of adverse clinical consequences such as depression (Rehman and Masson 2001). There is evidence of long-term damage to the hippocampal neurones from a chronically elevated cortisol stress response that may result in memory impairment (Lupien et al. 1994).

The serotonin (5-HT) secretion changes throughout the lifespan. Serotonin is one of the main regulators of circadian sleep/wake cycles, total brain 5-HT levels decrease with age (Bertler 1961) and deficiency of serotonin is associated with many psychiatric and neurological disorders, including sleep disorders and some forms of dementia (Rehman and Masson 2001).

Deterioration of the reproductive function with ageing is complex and conducted to a decrease in hormones concentrations (Zumoff et al. 1982, Tenover et al. 1987). Testosterone production shows loss of its circadian rhythm with ageing (Bremner et al. 1983). The production rate and plasma clearance of testosterone decrease in older men, testosterone is associated with an increase in grip and leg strength, as well as increased muscle mass and protein synthesis (Tenovr 1992, Sih et al. 1997). Women show reduced concentrations of luteinizing hormone (LH)-releasing hormone with advancing age. The sensitivity of the HPA axis to negative feedback is also attenuated in post-menopausal women, perhaps due to hypothalamic decline rather than to a pituitary hypofunction (Rossmanith et al. 1994, Rehman and Masson 2001). Elevated HPA activity impairs the capacity to cope with stress and elevates the risk for depression and cardiovascular diseases in higher age (Steiger 2003).

This complex pattern of age-related changes of sleep-endocrine activity mirrors a central process of ageing with major consequences to mental and physical health. The changes of sleep EEG correspond to a greater incidence of insomnia and other diseases (Steiger 2003).

Link between nervous system and the neuroendocrine axis

It is established a communications between the nervous system and the endocrine system as well as the implications of these linkages for physical and mental health, thereby focusing on the measurable interaction between psychological and physiological processes (Ziemssen and Kern 2007). Both endocrine and nervous (primarly sympathetic) system routes allow biologically active molecules such as multiple chemical messengers, growth factors and their respective receptors. Thus, these two elaborate systems relevant for sensing danger and mounting a counterattack to these threats are inextricably linked (Ziemssen and Kern 2007).

The two major pathways that link the brain and the endocrine systems are the autonomic nervous system (ANS) via direct neural influences and the neuroendocrine humoral outflow via the pituitary gland. The ANS regulates the function of all innervated tissues and organs throughout the vertebrate body with the exception of skeletal muscle fibres. Thus, it forms the major efferent component of the peripheral nervous system, containing integrative neuronal connections and even complete reflex arcs. The ANS is largely autonomous in that its activities are not under direct conscious control. The ANS consists of three components: the sympathetic (noradrenergic) and parasympathetic (cholinergic) systems, which originate in the CNS (with cell bodies in the brainstem and spinal cord), and the enteric system, which lies within the wall of the gastrointestinal tract (Ziemssen and Kern 2007).

The HPA axis comprises the neuroendocrine system that controls reactions to stress and has important functions in regulating various body processes such as digestion, the immune system and energy mobilisation (Chrousos 1995, Sapolsky et al. 2000, Ziemssen and Kern 2007). The key element of the HPA axis is the hypothalamus, which contains parvocellular and magnocellular neurones that synthesise and secrete vasopressin and corticotrophin-releasing hormone (CRH). These two peptides regulate the anterior lobe of the pituitary gland. In particular, CRH and vasopressin stimulate the secretion of adrenocorticotropic hormone (ACTH). ACTH, when released from the pituitary gland, in turn acts on the adrenal cortices, which produce glucocorticoid hormones. Glucocorticoids in turn act back at the hypothalamus and pituitary in an inhibitory fashion (negative feedback) (Keller-Wood and Dallman 1984, Ziemssen and Kern 2007).

Some studies in insomniac patients seem necessary to determine the extent of neuroendocrine abnormalities during early stages of the insomnia, during the chronic course and during successful treatment of the sleep deficit (Riemann et al. 2009). Irwin et al. (Irwin et al. 2003) demonstrated an association between insomnia, nocturnal sympathetic arousal and declines of nocturnal immunity. Vgontzas et al. (Vgontzas et al. 1999) found that the daytime secretion of interleukin-6 (IL-6) is negatively influenced by the quantity and quality of the previous night's sleep. Vgontzas and coworkers (Vgontzas and Chrousos 2002) demonstrated increased IL-6 levels in insomnia, though mainly during daytime, hypothesizing that this might explain the experience of increased daytime fatigue in insomniac patients. In a study by Burgos et al. (Burgos et al. 2006) it has been showed increased levels of IL-6 during night-time sleep in primary insomniacs. Data indicate the presence of neuroendocrine and neuroimmunological alterations in primary insomnia compatible with the assumption of hyperarousal. The direction of cause-effect relationships between these alterations, the insomnia disorder and the hyperarousal have yet to be determined. It has also been speculated that the sleep loss due to the insomnia may drive the neuroendocrine and neuroimmunological alterations, as it has been shown that short-term experimental sleep loss or sleep restriction may have sequelae similar to those described in chronic insomnia (Spiegel et al. 1999, Riemann et al. 2009).

The common denominator for the effect of the HPA axis on sleep EEG depends on CRH, with CRH decreasing SWS and increasing wakefulness. Furthermore, Buckley and Schatzberg proposed that

mineralocorticoid receptors (MRs) and glucocorticoid receptors (GRs) can be activated or suppressed to modify CRH levels via their feedback relationships on CRH. CRH suppression is enhanced by MR-mediated paraventricular nucleus (PVN) inhibition, particularly via the hippocampus. This would augment CRH suppression in the early sleep period and at the time of the nocturnal nadir, when SWS is expected to occur. In contrast, excess GR activation at the level of the amygdala (as opposed to at the PVN) may activate CRH (Reul and Holsboer 2002) and decrease SWS (Buckley and Schatzberg 2005). MR and GR can be activated by cortisol as well as by other agents. At low endogenous or exogenous cortisol levels at which only MRs are activated, SWS is enhanced. At medium cortisol levels at which MRs and PVN GRs are activated, SWS is enhanced. At very high cortisol levels or in times of stress, where possibly amygdala GRs are significantly occupied relative to PVN GRs, SWS is decreased (Buckley and Schatzberg 2005).

HPA axis hyperactivity can have many negative effects on sleep. It can lead to sleep fragmentation, decreased SWS, and shortened sleep time. Likewise, sleep disturbances can exacerbate HPA axis dysfunction, worsening the cycle (Buckley and Schatzberg 2005). In insomnia, HPA axis hyperactivity inhibits sleep and increases awakenings. Buckley and Schatzberg believed that this effect is mediated by increased nocturnal CRH and norepinephrine (NE), and that the increased nocturnal cortisol reported in insomnia (Rodenbeck and Hajak 2001, Vgontzas et al. 2001a, Rodenbeck et al. 2002) is a marker for elevated nocturnal CRH (and possibly elevated central NE). Likewise, fragmented sleep increases HPA axis activity, creating a vicious cycle. Furthermore, alterations in fatigue-producing cytokines may explain the daytime complaints of tiredness and fatigue. Correction of HPA axis abnormalities with GR and CRH antagonists, and possibly MR agonists, may offer a potential means to decrease nocturnal CRH and help restore normal sleep (Buckley and Schatzberg 2005). Additional studies to explore the role of the HPA axis in the etiology or clinical manifestations in sleep disorders as well as others are warranted. These may lead to new forms of prevention as well as treatment (Buckley and Schatzberg 2005).

Role of peptides in humoral mechanism of sleep regulation

Until recently, insomnia, especially primary insomnia, was mainly conceptualised as a psychological disorder caused by psychosocial stress and maintained by maladaptive behaviours and conditioned arousal leading to the subjective experience of disturbed sleep which could not, however, be corroborated by objective measures of sleep such as polysomnography (American Psychiatric Association 1994). It may turn out that insomnia can be conceptualised as a psychobiological disorder which is not only linked with alterations on a psychological level, but which is accompanied by measurable deviations in neuroendocrine variables, neurophysiological, structural and functional alterations of the brain (Riemann et al. 2009).

The concept of humoral, rather than neural, regulation of sleep dates as far back as to almost 100 years ago. Kuniomi Ishimori and Henri Piéron (Kubota 1989, Hayaishi and Matsumura 1995) independently and concurrently took samples of the cerebrospinal fluid (CSF) of sleep-deprived dogs and infused them into the brain of normal dogs. The recipient dogs soon fell asleep, thus these two authors became the first to demonstrate the presence of endogenous sleep-promoting substances, but the chemical nature of their sleep substances was not identified. During the next 90 years or so, nearly 50 endogenous sleep substances were reported by numerous investigators to be present in the brain, CSF, and other organs and tissues of mammals, although their physiological relevance has remained uncertain in most instances (Inoué 1989, Hayaishi 2005).

Data reported in literature (Steiger 2003) show that variuos peptides and steroids exert specific effect on sleep (**Table 1**). It appears likely, that a reciprocal interaction of the key hormones of the hypothalamo-pituitarysomatotrophic (HPS) and HPA systems, GHRH and CRH plays a major role in sleep regulation. Besides of GHRH and CRH various other peptides and steroids participate in sleep regulation, many of them act via GABAergic mechanisms (Steiger 2007).

At the molecular level, neuro- and endocrine signal molecules such as hormones, neurotransmitters and neuropeptides, or their receptors are member of the same superfamily which enable the mutual neuroendocrine communication interacting by subcellular and molecular mechanisms. At the neuroanatomical level, advances in neuroendocrine communication have been made in the role of discrete brain areas related to emotionality (Wrona 2006). It has been obseved a significant progress in sleep research on the humoral mechanisms of sleep regulation and opened up a new frontier by elucidating the interplay between the humoral regulation and the neural network. Many more important questions remain to be answered, hopefully the fruits of current studies will provide a basis for further studies to solve the remaining formidable problems pertaining to sleep.

Concluding remarks and future directions.

A series of findings over the past decade has begun to identify the interactions of human sleep structure and the endocrine system under physiological and pathophysiological conditions, including studies that probe the sleep effects of systemically administered HPA hormones (Friess et al. 1995b). Human sleep is regulated by a concerted action of various signal compounds acting at sleep-generating neurons whose central organization is not yet fully understood. During nocturnal sleep the endocrine system is remarkably active, the longest established finding being that GH release is associated with the initiation of sleep and that there is a steep morning rise of cortisol (Weitzman et al. 1966, Takahashi et al. 1968). Moreover, the effects of exogenously administered corticosteroids and of their excessive endogenous release (e.i. Cushing's disease) were recognized more than 20 years ago (Friess et al. 1995b).

A growing body of literature demonstrates that the hormones involved in the regulation of the HPA system

Table 1. *Sleep-associated hormone secrection of various neuropeptides and neuroactive steroids synthesized in the brain*

Hormone	Function
Growth hormone-releasing hormone (GHRH)	GHRH appears to play a key role in promoting NREMS, particularly improving the frequency of delta waves after GHRH administration (Marshall et al.1996). The sleep-promoting effects of GHRH varies with age: in young subjects enhances SWS and diminishes in wakefulness time, whereas in aged individuals induces NREMS and sleep continuity, showing a declined sleep-promoting in the elderly (Guldner et al. 1997, Kotronoulas et al. 2009).
Somatostatin (SRIH) and analogues	SRIH exerts an inhibitory action on NREMS. Marked age-dependent differences have been reported in the action of SRIH. SRIH impairs sleep in the elderly (Friboes et al. 1997), while it shows no effect in young subjects (Steiger et al. 1992; Kotronoulas et al. 2009). Recent studies have shown that two sleep-modulating peptides with structural similarity to the somatostatin family are implicated in a variety of sleep processes. Urotensin II modulates REM sleep (de Lecea and Bourgin 2008), whereas cortistatin promotes SWS (de Lecea 2005, Kotronoulas et al. 2009).
Ghrelin	Ghrelin has recently been identified as a sleep-promoting substance that increases SWS, SWA and GH in young men (Arvat et al. 2001, Weikel et al. 2003, Kotronoulas et al. 2009).
Cortisol, glucocorticoid and mineralcorticoid receptor ligands	Cortisol interacts strongly with mineralcorticoid receptors (MR, type I) and could be easily associated with the ligand-binding domain of glucocorticoid receptor (GR, type II). There are some reason to postulate that MR might modulate SWS and GR might modulate REMS (Kotronoulas et al. 2009). Cortisol enhances SWS and SWA (Friess 1994, Bohlhalter et al. 1997, Friess 2004) and decreases REM (Bohlhalter et al. 1997).
Corticotropin-releasing hormone (CRH)	CRH is the key hormone of HPA system. CRH plays an important role in wake and NREMS regulation (Romanowski et al. 2010). CRH has been reported to increase wakefulness (Vgontzas et al. 2001b) and to decrease SWS in young subjects and REM sleep (Holsboer et al. 1988, Vgontzas et al. 2001b, Kotronoulas et al. 2009).
Adrenocorticotropin (ACTH)	ACTH evokes a suppression of REM sleep (Fehm et al. 1993). Furthermore the precise function remains unclear, ACTH may act changes in sleep architecture (Steiger et al. 2002) or it may be a related phenomenon (Kotronoulas et al. 2009).
Arginine vasopressin (AVP)	AVP has been shown to exert a strong ameliorating effect on SWS and REMS (Steiger 2007, Perras et al. 1999, van West et al. 2004, Kotronoulas et al. 2009).
Prolactin (PRL)	Data accumulated have suggested the involvement of PRL in REMS regulation (Roky et al. 1995), but in humans studies PRL's effects are weak (Kotronoulas et al. 2009). Furthermore, patients affected by prolactinoma show increased SWS in comparison with control subjects (Frieboes et al. 1998).
Vasoactive intestinal polypeptide (VIP)	VIP promotes REMS and NREMS in animal models (Drucker-Colín et al. 1984). In young individuals VIP decelerates NREMS-REMS cycles (Murck et al. 1996). The results suggest that VIP may affect the circadian clock (Kotronoulas et al. 2009).

Table 1. *(continued)*

Hormone	Function
Galanin	The role of galanin as a possible sleep regulating neuropeptide can lead to increased SWS and duration of REMS periods in normal controls (Murck et al. 1999, Murck et al. 2004). Interestingly, galanin might play a role in susceptibility to female panic disorder because of six polymorphisms located within the gene coding for galanin (Unschuld et al. 2008, Kotronoulas et al. 2009).
Adenosine (ADE)	ADE is a homeostatic sleep factor (Huang et al. 2011) and plays a significant role in sleep-wakefulness regulation (Thakkar et al. 2008). Retey et al. found a polymorphism of ADE involved in sleep architecture (Rétey et al. 2005, Kotronoulas et al. 2009).
Hypocretin/Orexin	Hypocretin/Orexin play a key role in maintaining alertness and managing REMS (Nishino 2003 Taylor and Samson 2003; Nishino 2007, Watson et al. 2008, Kotronoulas et al. 2009).
Neuropeptide (NPY)	NPY induces decreases in sleep latency and in the first REMS period (Antonijevic et al. 2000c). In depressed subjects administration of NPY shortens sleep latency (Held et al. 2006, Kotronoulas et al. 2009).
Estrogens	Estrogens promotes an increase of REMS density in postmenopausal women (Shin and Shapiro 2003). Data have reported an improvement of sleep disorder after estrogen replacement therapy (Wiklund et al. 1993, Polo-Kantola et al. 1998, Kotronoulas et al. 2009).
Dehydroepiandrosterone (DHEA)	DHEA appears to enhance REMS in young controls (Friess et al. 1995a), whereas there are no appreciable changes in the REM sleep parameters of postmenopausal women (Dayal et al. 2005, Kotronoulas et al. 2009).
Melatonin	Melatonin has sleep-promoting properties and shortens sleep latency (Zhdanova et al. 1996). Zhdanova et al. found that supplemental melatonin can induce sleep in normal controls (Zhdanova 2005). Van den Heuvel et al. substained that melatonin might be effective as a sleep aid only under certain conditions (Van den Heuvel et al. 2005, Gehrman et al. 2009). Recent studies have demonstrated the efficacy of melatonin in insomniac patients (Wade and Downie 2008, Kotronoulas et al. 2009).
Thyrotropin-releasing hormone (TRH)	Data indicates that there may be an association between TRH production and sleep (Nishino et al. 1997), but the role of TRH remains unclear (Kotronoulas et al. 2009). TRH reveals a mild action in decrease of sleep efficiency (Hemmeter et al. 1998).

exert distinct and discernible effects upon the sleep EEG. These effects are part of the body's adaptation to specific demands such as coping with stress (Friess et al. 1995b).

The reviewed data show a bidirectional interaction between the brain and the endocrine system. Various HPA hormones exert specific effects on the sleep EEG. It is well documented that CRH enhances vigilance and impairs sleep. Changes in the CRH:GHRH ratio in favour of CRH appear to contribute to shallow sleep, elevated cortisol and blunted GH during depression and ageing. On the other hand, data suggest CRH-like effects of GHRH in women (Steiger et al. 2002).

There is compelling evidence to show that the endocrine system can communicate with the CNS (Wrona 2006). This mutual functional relationship include selective brain areas that may neutralize the effects of extreme stress and offers a new direction for therapy.

However, the exact mechanisms that underlie the

relationship that links anabolic processes in the body with behavioral rest and decreased cerebral metabolism remain to be elucidated. In the future studies it should be enlarged the knowledge of sleep in endocrine disorders and simultaneously investigate sleep EEG and HPA hormones in under-researched psychiatric disorders with HPA abnormalities. The continuance of research regarding the mechanisms of sleep regulation is imperative to elucidating the importance of functional sleep. Studies that seek to expand knowledge of sleep on the molecular and biochemical level have the potential to give new insight into diagnostic criteria and possible treatment strategies for many disorders of which disturbed sleep is symptomatic. Progressive research in intracellular signaling pathways holds perhaps the greatest potential to fully understanding the mechanisms by which men generate and maintain normal sleep.

References

American Psychiatric Association (1994). *Diagnostic and Statistical Manual of Mental Disorders DSM-IV-TR 4th*, Washington.

Anders T, Emde R, Parmelae A (1971). *Manual of standardized terminology, techniques, and criteria for scoring of states of sleep and wakefulness in newborn infants*. CA: UCLA Brain Information Service/NINDS Neurological Information Network, Los Angeles.

Antonijevic IA, Murck H, Frieboes R, Holsboer F, Steiger A (1999). On the gender differences in sleep-endocrine regulation in young normal humans. *Neuroendocrinology* 70, 4, 280-287.

Antonijevic IA, Murck H, Frieboes RM, Barthelmes J, Steiger A (2000a). Sexually dimorphic effects of GHRH on sleep-endocrine activity in patients with depression and normal controls - part I: the sleep eeg. *Sleep research online: SRO* 3, 1, 5-13.

Antonijevic IA, Stalla GK, Steiger A (2000b). Modulation of the sleep electroencephalogram by estrogen replacement in postmenopausal women. *American journal of obstetrics and gynecology* 182, 2, 277-282.

Antonijevic IA, Murck H, Bohlhalter S, Frieboes RM, Holsboer F, Steiger A (2000c). Neuropeptide Y promotes sleep and inhibits ACTH and cortisol release in young men. *Neuropharmacology* 39, 8, 1474-1481.

Antonijevic IA, Murck H, Frieboes RM, Uhr M, Steiger A (2003). On the role of menopause for sleep-endocrine alterations associated with major depression. *Psychoneuroendocrinology* 28, 3, 401-418.

Ardura J, Gutierrez R, Andres J, Agapito T (2003). Emergence and evolution of the circadian rhythm of melatonin in children. *Hormone research* 59, 2, 66-72.

Arvat E, Maccario M, Di Vito L, Broglio F, Benso A, Gottero C, Papotti M, Muccioli G, Dieguez C, Casanueva FF, Deghenghi R, Camanni F, Ghigo E (2001). Endocrine activities of ghrelin, a natural growth hormone secretagogue (GHS), in humans: comparison and interactions with hexarelin, a nonnatural peptidyl GHS, and GH-releasing hormone. *The Journal of clinical endocrinology and metabolism* 86, 3, 1169-1174.

Bertler A (1961). Occurrence and localization of catecholamines in the human brain. *Acta physiologica Scandinavica* 51, 97-107.

Blalock JE (1994). Shared ligands and receptors as a molecular mechanism for communication between the immune and neuroendocrine systems. *Annals of the New York Academy of Sciences* 25, 741, 292-298.

Bohlhalter S, Murck H, Holsboer F, Steiger A (1997). Cortisol enhances non-REM sleep and growth hormone secretion in elderly subjects. *Neurobiology of Aging* 18, 4, 423-429.

Borbély AA, Tobler I (1989). Endogenous sleep-promoting substances and sleep regulation. *Pharmacological reviews* 69, 2, 605-670.

Breen S, Rees S, Walker D (1996). The development of diurnal rhythmicity in fetal suprachiasmatic neurons as demonstrated by fos immunohistochemistry. *Neuroscience* 74, 3, 917-926.

Bremner WJ, Vitiello MV, Prinz PN (1983). Loss of circadian rhythmicity in blood testosterone levels with aging in normal men. *The Journal of clinical endocrinology and metabolism* 56, 6, 1278-1281.

Brunner DP, Münch M, Biedermann K, Huch R, Huch A, Borbély AA (1994). Changes in sleep and sleep electroencephalogram during pregnancy. *Sleep* 17, 7, 576-582.

Buckley TM, Schatzberg AF (2005). On the interactions of the hypothalamic-pituitary-adrenal (HPA) axis and sleep: normal HPA axis activity and circadian rhythm, exemplary sleep disorders. *The Journal of clinical endocrinology and metabolism* 90, 5, 3106-3114.

Burgos I, Richter L, Klein T, Fiebich B, Feige B, Lieb K, Voderholzer U, Riemann D (2006). Increased nocturnal interleukin-6 excretion in patients with primary insomnia: a pilot study. *Brain, behavior, and immunity* 20, 3, 246-253.

Chrousos GP (1995). The hypothalamic-pituitary-adrenal axis and immune-mediated inflammation. *The New England journal of medicine* 332, 20, 1351-1362.

Culebras A (2000). *Sleep disorders and neurological disease*. Marcel Dekker, Inc. New York.

Dantzer R (2004). Innate immunity at the forefront of psychoneuroimmunology. *Brain, behavior, and immunity* 18, 1, 1-6.

Datta S, Hobson JA (1995). Suppression of ponto-geniculo-occipital waves by neurotoxic lesions of pontine caudo-lateral peribrachial cells. *Neuroscience* 67, 3, 703-712.

Datta S, Maclean RR (2007). Neurobiological mechanisms for the regulation of mammalian sleep-wake behavior: reinterpretation of historical evidence and inclusion of contemporary cellular and molecular evidence. *Neuroscience and biobehavioral reviews* 31, 5, 775-824.

Datta S, Patterson EH, Siwek DF (1997). Endogenous and exogenous nitric oxide in the pedunculopontine tegmentum induces sleep. *Synapse* 27, 1, 69-78.

Dayal M, Sammel MD, Zhao J, Hummel AC, Vandenbourne K, Barnhart KT (2005). Supplementation with DHEA: effect on muscle size, strength, quality of life, and lipids. *Journal of women's health* 14, 5, 391-400.

de Lecea L (2005). Cortistatin: a natural somatostatin analog. *Journal of endocrinological investigation* 28, 11, 10-14.

de Lecea L, Bourgin P (2008). Neuropeptide interactions and REM sleep: a role for Urotensin II? *Peptides* 29, 5, 845-851.

Driver HS, Shapiro CM (1992). A longitudinal study of sleep stages in young women during pregnancy and postpartum. *Sleep* 15, 5, 449-453.

Drucker-Colín R, Aguilar-Roblero R, García-Hernández F, Fernández-Cancino F, Bermudez Rattoni F (1984). Fetal suprachiasmatic nucleus transplants: diurnal rhythm recovery of lesioned rats. *Brain research* 311, 2, 353-357.

Ehlers CL, Kupfer DJ (1997). Slow-wave sleep: do young adult men and women age differently? *Journal of sleep research* 6, 3, 211-215.

Elenkov IJ, Wilder RL, Chrousos GP, Vizi ES (2000). The sympathetic nerve—an integrative interface between two supersystems: the brain and the immune system. *Pharmacological reviews* 52, 4, 595-638.

Fehm HL, Späth-Schwalbe E, Pietrowsky R, Kern W, Born J (1993). Entrainment of nocturnal pituitary-adrenocortical activity to sleep processes in man—a hypothesis. *Experimental and Clinical Endocrinology* 101, 5, 267-276.

Felten DL, Felten SY, Bellinger DL, Carlson SL, Ackerman KD, Madden KS, Olschowki JA, Livnat S (1987). Noradrenergic sympathetic neural interactions with the immune system: structure and function. *Immunological reviews* 100, 225-260.

Ferrari E, Magri F, Locatelli M, Balza G, Nescis T, Battegazzore C, Cuzzoni G, Fioravanti M, Solerte SB (1996). Chrono-neuroendocrine markers of the aging brain. *Aging* (Milano) 8, 5, 320-327.

Ficca G, Fagioli I, Salzarulo P (2000). Sleep organization in the first year of life: developmental trends in the quiet sleep-paradoxical sleep cycle. *Journal of sleep research* 9, 1, 1-4.

Frieboes RM, Murck H, Schier T, Holsboer F, Steiger A (1997). Somatostatin impairs sleep in elderly human subjects. *Neuropsychopharmacology: official publication of the American College of Neuropsychopharmacology* 16, 5, 339-345.

Frieboes RM, Murck H, Stalla GK, Antonijevic IA, Steiger A (1998). Enhanced slow wave sleep in patients with prolactinoma. *The journal of clinical endocrinology and metabolism* 83, 8, 2706-10.

Friess E, Tagaya H, Grethe C, Trachsel L, Holsboer F (2004). Acute cortisol administration promotes sleep intensity in man. *Neuropsychopharmacology* 29, 3, 598-604.

Friess E, Trachsel L, Guldner J, Schier T, Steiger A, Holsboer F (1995)a. DHEA administration increases rapid eye movement sleep and EEG power in the sigma frequency range. *American Journal of Physiology* 268, 1, 107-113.

Friess E, V Bardeleben U, Wiedemann K, Lauer CJ, Holsboer F (1994). Effects of pulsatile cortisol infusion on sleep-EEG and nocturnal growth hormone release in healthy men. *Journal of Sleep Research* 3, 2, 73-79.

Friess E, Wiedemann K, Steiger A, Holsboer F (1995)b. The hypothalamic-pituitary-adrenocortical system and sleep in man. *Advances in neuroimmunology* 5, 2, 111-125.

Fuller PM, Gooley JJ, Saper CB (2006). Neurobiology of the sleep-wake cycle: sleep architecture, circadian regulation, and regulatory feedback. *Journal of biological rhythms* 21, 6, 482-493.

Gehrman PR, Connor DJ, Martin JL, Shochat T, Corey-Bloom J, Ancoli-Israel S (2009). Melatonin fails to improve sleep or agitation in double-blind randomized placebo-controlled trial of institutionalized patients with Alzheimer disease. *The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry* 17, 2, 166-169.

Guldner J, Schier T, Friess E, Colla M, Holsboer F, Steiger A (1997). Reduced efficacy of growth hormone-releasing hormone in modulating sleep endocrine activity in the elderly. *Neurobiology of Aging* 18, 5, 491-495.

Hayaishi O (2005). Molecular Mechanisms of Sleep-Wake Regulation: A Role of Prostaglandin D_2 and Adenosine. In Luppi PH (ed) *Sleep circuits and functions*. Boca Raton, pp. 65-79.

Hayaishi O, Matsumura H (1995). Prostaglandins and sleep. *Advances in neuroimmunology* 5, 2, 211-216.

Held K, Antonijevic I, Murck H, Kuenzel H, Steiger A (2006). Neuropeptide Y (NPY) shortens sleep latency but does not suppress ACTH and cortisol in depressed patients and normal controls. *Psychoneuroendocrinology* 31, 1, 100-107.

Hemmeter U, Rothe B, Guldner J, Holsboer F, Steiger A (1998). Effects of thyrotropin-releasing hormone on the sleep EEG and nocturnal hormone secretion in male volunteers. *Neuropsychobiology* 38, 1, 25-31.

Heraghty JL, Hilliard TN, Henderson AJ, Fleming PJ (2008). The physiology of sleep in infants. *Archives of disease in childhood* 93, 11, 982-5.

Hertz G, Fast A, Feinsilver SH, Albertario CL, Schulman H, Fein AM (1992). Sleep in normal late pregnancy. *Sleep* 15, 3, 246-251.

Holsboer F, von Bardeleben U, Steiger A (1988). Effects of intravenous corticotropin-releasing hormone upon sleep-related growth hormone surge and sleep EEG in man. Neuroendocrinology 48, 1, 32-38.

Huang ZL, Urade Y, Hayaishi O (2011). The role of adenosine in the regulation of sleep. *Current topics in medicinal chemistry* 11, 8, 1047-1057.

Inoué S (1989). *Biology of Sleep Substances*. CRC Press, Boca Raton.

Irwin M, Clark C, Kennedy B, Christian Gillin J, Ziegler M (2003). Nocturnal catecholamines and immune function in insomniacs, depressed patients, and control subjects. *Brain, behavior, and immunity* 17, 5, 365-372.

Jackson JA, Wailoo MP, Thompson JR, Petersen SA (2004). Early physiological development of infants with intrauterine growth retardation. *Archives of disease in childhood. Fetal and neonatal edition* 89, 1, 46-50.

Jan JE, Wasdell MB, Freeman RD, Bax M (2007). Evidence supporting the use of melatonin in short gestation infants. *Journal of pineal research* 42, 1, 22-27.

Jiang CL, Lu CL, Liu XY (1998). The molecular basis for bidirectional communication between the immune and neuroendocrine systems. *Domestic animal endocrinology* 15, 5, 363-369.

Keller-Wood ME, Dallman MF (1984). Corticosteroid inhibition of ACTH secretion. *Endocrine reviews* 5, 1, 1-24.

Kennaway DJ, Stamp GE, Goble FC (1992). Development of melatonin production in infants and the impact of prematurity. *The Journal of clinical endocrinology and metabolism* 75, 2, 367-369.

Kilduff TS, Lein ES, de la Iglesia H, Sakurai T, Fu YH, Shaw P (2008). New developments in sleep research: molecular genetics, gene expression, and systems neurobiology. *The Journal of Neuroscience* 28, 46, 11814-11818.

Kimura M (2005). Minireview: Gender-specific sleep regulation. *Sleep and Biological Rhythms* 3, 2, 75–79.

Kotronoulas G, Stamatakis A, Stylianopoulou F (2009). Hormones, hormonal agents, and neuropeptides involved in the neuroendocrine regulation of sleep in humans. *Hormones* 8, 4, 232-248.

Krueger JM, Fang J, Hansen MK, Zhang J, Obál F Jr (1998). Humoral Regulation of Sleep. *News in physiological sciences: an international journal of physiology produced jointly by the International Union of Physiological Sciences and the American Physiological Society* 13, 189-194.

Krueger JM, Majde JA (1994). Microbial products and cytokines in sleep and fever regulation. *Critical reviews in immunology* 14, 3-4, 355-379.

Krueger JM, Obál F Jr (1993). Growth hormone-releasing hormone and interleukin-1 in sleep regulation. *The FASEB journal: official publication of the Federation of American Societies for Experimental Biology* 7, 8, 645-652.

Kubota K (1989). Kuniomi Ishimori and the first discovery of sleep-inducing substances in the brain. *Neuroscience research* 6, 6, 497-518.

Lai Z, Roos P, Zhai O, Olsson Y, Fhölenhag K, Larsson C, Nyberg F (1993). Age-related reduction of human growth hormone-binding sites in the human brain. *Brain research* 621, 2, 260-266.

Lancel M, Faulhaber J, Holsboer F, Rupprecht R (1999). The GABA(A) receptor antagonist picrotoxin attenuates most sleep changes induced by progesterone. *Psychopharmacology* 141, 2, 213-9.

Lowrey PL, Takahashi JS (2004). Mammalian circadian biology: elucidating genome-wide levels of temporal organization. *Annual review of genomics and human genetics* 5, 407-41.

Lu J, Sherman D, Devor M, Saper CB (2006). A putative flip-flop switch for control of REM sleep. *Nature* 441, 7093, 589-594.

Lupien S, Lecours AR, Lussier I, Schwartz G, Nair NP, Meaney MJ (1994). Basal cortisol levels and cognitive deficits in human aging. *The Journal of neuroscience : the official journal of the Society for Neuroscience* 14, 5, 2893-2903.

Majde JA, Krueger JM (2005). Links between the innate immune system and sleep. *The Journal of allergy and clinical immunology* 116, 6, 1188-1198.

Marshall L, Mölle M, Böschen G, Steiger A, Fehm HL, Born J (1996). Greater efficacy of episodic than continuous growth hormone-releasing hormone (GHRH) administration in promoting slow-wave sleep (SWS). *The Journal of clinical endocrinology and metabolism* 81, 3, 1009-1013.

McCarley RW (2004). Mechanisms and models of REM sleep control. *Archives italiennes de biologie* 142, 4, 429-467.

Moore RY, Eichler VB (1972). Loss of a circadian adrenal corticosterone rhythm following suprachiasmatic lesions in the rat. *Brain research* 42, 1, 201-206.

Murck H, Antonijevic IA, Frieboes RM, Maier P, Schier T, Steiger A (1999). Galanin has REM-sleep deprivation-like effects on the sleep EEG in healthy young men. *Journal of psychiatric research* 33, 3, 225-232.

Murck H, Guldner J, Colla-Müller M, Frieboes RM, Schier T, Wiedemann K, Holsboer F, Steiger A (1996). VIP decelerates non-REM-REM cycles and modulates hormone secretion during sleep in men. *The American journal of physiology* 271, 4, 905-911.

Murck H, Held K, Ziegenbein M, Künzel H, Holsboer F, Steiger A (2004). Intravenous administration of the neuropeptide galanin has fast antidepressant efficacy and affects the sleep EEG. *Psychoneuroendocrinology* 29, 9, 1205-1211.

Nishihara K, Horiuchi S, Eto H, Uchida S, Honda M (2004). Delta and theta power spectra of night sleep EEG are higher in breast-feeding mothers than in non-pregnant women. *Neuroscience letters* 368, 2, 216-220.

Nishino S (2003). The hypocretin/orexin system in health and disease. *Biological psychiatry* 54, 2, 87-95.

Nishino S (2007). The hypocretin/orexin receptor: therapeutic prospective in sleep disorders. *Expert opinion on investigational drugs* 16, 11, 1785-1797.

Nishino S, Arrigoni J, Shelton J, Kanbayashi T, Dement WC, Mignot E (1997). Effects of thyrotropin-releasing hormone and its analogs on daytime sleepiness and cataplexy in canine narcolepsy. *The Journal of neuroscience : the official journal of the Society for Neuroscience* 17, 16, 6401-6408.

Obál F Jr., Krueger JM (2001). The somatotropic axis and sleep. *Revue neurologique* 157, 11, 12-15.

Perras B, Pannenborg H, Marshall L, Pietrowsky R, Born J, Lorenz Fehm H (1999). Beneficial treatment of age-related sleep disturbances with prolonged intranasal vasopressin. *Journal of Clinical Psychopharmacology* 19, 1, 28-36.

Polo-Kantola P, Erkkola R, Helenius H, Irjala K, Polo O (1998). When does estrogen replacement therapy improve sleep quality? *American journal of obstetrics and gynecology* 178, 5, 1002-1009.

Prosser RA, Gillette MU (1989). The mammalian circadian clock in the suprachiasmatic nuclei is reset in vitro by cAMP. *The Journal of neuroscience : the official journal of the Society for Neuroscience* 9, 3, 1073-1081.

Ralph MR, Foster RG, Davis FC, Menaker M (1990). Transplanted suprachiasmatic nucleus determines circadian period. *Science* 247, 4945, 975-978.

Rehman HU, Masson EA (2001). Neuroendocrinology of ageing. *Age and Ageing* 30, 4, 279-287.

Reiter RJ, Melchiorri D, Sewerynek E, Poeggeler B, Barlow-Walden L, Chuang J, Ortiz GG, Acuña-Castroviejo D (1995). A review of the evidence supporting melatonin's role as an antioxidant. *Journal of pineal research* 18, 1, 1-11.

Rétey JV, Adam M, Honegger E, Khatami R, Luhmann UF, Jung HH, Berger W, Landolt HP (2005). A functional genetic variation of adenosine deaminase affects the duration and intensity of deep sleep in humans. *Proceedings of the National Academy of Sciences of the United States of America* 102, 43, 15676-15681.

Reul JM, Holsboer F (2002). Corticotropin-releasing factor receptors 1 and 2 in anxiety and depression. *Current opinion in pharmacology* 2, 1, 23-33.

Riemann D, Kloepfer C, Berger M (2009). Functional and structural brain alterations in insomnia: implications for pathophysiology. *European Journal of Neuroscience* 29, 9, 1754-1760.

Rivkees SA (2003). Developing circadian rhythmicity in infants. *Pediatrics* 112, 2, 373-381.

Rodenbeck A, Hajak G (2001). Neuroendocrine dysregulation in primary insomnia. *Revue neurologique* 157, 11, 57-61.

Rodenbeck A, Huether G, Rüther E, Hajak G (2002). Interactions between evening and nocturnal cortisol secretion and sleep parameters in patients with severe chronic primary insomnia. *Neuroscience letters* 324, 2, 159-163.

Roky R, Obál F Jr, Valatx JL, Bredow S, Fang J, Pagano LP, Krueger JM (1995). Prolactin and rapid eye movement sleep regulation. *Sleep* 18, 7, 536-542.

Romanowski CP, Fenzl T, Flachskamm C, Wurst W, Holsboer F, Deussing JM, Kimura M (2010). Central deficiency of corticotropin-releasing hormone receptor type 1 (CRH-R1) abolishes effects of CRH on NREM but not on REM sleep in mice. *Sleep* 33, 4, 427-436.

Rossmanith WG, Reichelt C, Scherbaum WA (1994). Neuroendocrinology of aging in humans: attenuated sensitivity to sex steroid feedback in elderly postmenopausal women. *Neuroendocrinology* 59, 4, 355-362.

Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, Jackson RD, Beresford SA, Howard BV, Johnson KC, Kotchen JM, Ockene J; Writing Group for the Women's Health Initiative Investigators (2002). Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. *JAMA: the journal of the American Medical Association* 288, 3, 321-333.

Santiago LB, Jorge SM, Moreira AC (1996). Longitudinal evaluation of the development of salivary cortisol circadian rhythm in infancy. *Clinical Endocrinology* 44, 2, 157-161.

Sapolsky RM, Romero LM, Munck AU (2000). How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions. *Endocrine reviews* 21, 1, 55-89.

Shin K, Shapiro C (2003). Menopause, sex hormones, and sleep. *Bipolar disorders* 5, 2, 106-109.

Sih R, Morley JE, Kaiser FE, Perry HM 3rd, Patrick P, Ross C (1997). Testosterone replacement in older hypogonadal men: a 12-month randomized controlled trial. *The Journal of clinical endocrinology and metabolism* 82, 6, 1661-1667.

Spiegel K, Leproult R, Van Cauter E (1999). Impact of sleep debt on metabolic and endocrine function. *Lancet* 354, 9188, 1435-1439.

Spinedi E, Gaillard RC, Chisari A (2002). *Sexual dimorphism of neuroendocrine–immune interactions*. in: *Neuroendocrine–Immune Interactions*. Karger, Basel.

Steiger A (2002). Sleep and the hypothalamo-pituitary-adrenocortical system. *Sleep Medicine Reviews* 6, 2, 125-138

Steiger A (2003). Sleep and endocrinology. *Journal of Internal Medicine* 254, 1, 13-22.

Steiger A (2007). Neurochemical regulation of sleep. *Journal of psychiatric research* 41, 7, 537-52.

Steiger A, Guldner J, Hemmeter U, Rothe B, Wiedemann K, Holsboer F (1992). Effects of growth hormone-releasing hormone and somatostatin on sleep EEG and nocturnal hormone secretion in male controls. *Neuroendocrinology* 56, 4, 566-573.

Stephan FK, Zucker I (1972). Circadian rhythms in drinking behavior and locomotor activity of rats are eliminated by hypothalamic lesions. *Proceedings of the National Academy of Sciences of the United States of America* 69, 6, 1583-1586.

Steriade M, McCarley RW (1990). *Brainstem Control of Wakefulness and Sleep*. Plenum Press, New York.

Takahashi Y, Kipnis DM, Daughaday WH (1968). Growth hormone secretion during sleep. *The Journal of clinical investigation* 47, 9, 2079-2090.

Taylor MM, Samson WK (2003). The other side of the orexins: endocrine and metabolic actions. *American journal of physiology. Endocrinology and metabolism* 284, 1, 13-7.

Tenover JS, Matsumoto AM, Plymate SR, Bremner WJ (1987). The effects of aging in normal men on bioavailable testosterone and luteinizing hormone secretion: response to clomiphene citrate. *The Journal of clinical endocrinology and metabolism* 65, 6, 1118-1126.

Tenovr JS (1992). Effects of testosterone supplementation in the aging male. *The Journal of clinical endocrinology and metabolism* 75, 4, 1092-1098.

Thakkar MM, Engemann SC, Walsh KM, Sahota PK (2008). Adenosine and the homeostatic control of sleep: effects of A1 receptor blockade in the perifornical lateral hypothalamus on sleep-wakefulness. *Neuroscience* 153, 4, 875-880.

Toh KL, Jones CR, He Y, Eide EJ, Hinz WA, Virshup DM, Ptácek LJ, Fu YH (2001). An hPer2 phosphorylation site mutation in familial advanced sleep phase syndrome. *Science* 291, 5506, 1040-1043.

Unschuld PG, Ising M, Erhardt A, Lucae S, Kohli M, Kloiber S, Salyakina D, Thoeringer CK, Kern N, Lieb R, Uhr M, Binder EB, Müller-Myhsok B, Holsboer F, Keck ME (2008). Polymorphisms in the galanin gene are associated with symptom-severity in female patients suffering from panic disorder. *Journal of affective disorders* 105, 1-3, 177-184.

Van Cauter E, Plat L, Copinschi G (1998). Interrelations between sleep and the somatotropic axis. *Sleep* 21, 6, 553-566.

van den Heuvel CJ, Ferguson SA, Macchi MM, Dawson D (2005). Melatonin as a hypnotic: con. *Sleep medicine reviews* 9, 1, 71-80.

van West D, Del-Favero J, Aulchenko Y, Oswald P, Souery D, Forsgren T, Sluijs S, Bel-Kacem S, Adolfsson R, Mendlewicz J, Van Duijn C, Deboutte D, Van Broeckhoven C, Claes S (2004). A major SNP haplotype of the arginine vasopressin 1B receptor protects against recurrent major depression. *Molecular psychiatry* 9, 3, 287-292.

Vgontzas AN, Bixler EO, Lin HM, Prolo P, Mastorakos G, Vela-Bueno A, Kales A, Chrousos GP (2001a). Chronic insomnia is associated with nyctohemeral activation of the hypothalamic-pituitary-adrenal axis: clinical implications. *The Journal of clinical endocrinology and metabolism* 86, 8, 3787-3794.

Vgontzas AN, Bixler EO, Wittman AM, Zachman K, Lin HM, Vela-Bueno A, Kales A, Chrousos GP (2001b). Middle-aged men show higher sensitivity of sleep to the arousing effects of corticotropin-releasing hormone than young men: clinical implications. *The Journal of clinical endocrinology and metabolism* 86, 4, 1489-1495.

Vgontzas AN, Chrousos GP (2002). Sleep, the hypothalamic-pituitary-adrenal axis, and cytokines: multiple interactions and disturbances in sleep disorders. *Endocrinology and metabolism clinics of North America* 31, 1, 15-36.

Vgontzas AN, Papanicolaou DA, Bixler EO, Lotsikas A, Zachman K, Kales A, Prolo P, Wong ML, Licinio J, Gold PW, Hermida RC, Mastorakos G, Chrousos GP (1999). Circadian interleukin-6 secretion and quantity and depth of sleep. *The Journal of clinical endocrinology and metabolism* 84, 8, 2603-2607.

Wade A, Downie S (2008). Prolonged-release melatonin for the treatment of insomnia in patients over 55 years. *Expert opinion on investigational drugs* 17, 10, 1567-1572.

Watson CJ, Soto-Calderon H, Lydic R, Baghdoyan HA (2008). Pontine reticular formation (PnO) administration of hypocretin-1 increases PnO GABA levels and wakefulness. *Sleep* 31, 4, 453-464.

Weikel JC, Wichniak A, Ising M, Brunner H, Friess E, Held K, Mathias S, Schmid DA, Uhr M, Steiger A (2003). Ghrelin promotes slow-wave sleep in humans. *American journal of physiology. Endocrinology and metabolism* 284, 2, 407-415.

Weitzman ED, Schaumburg H, Fishbein W (1966). Plasma 17-hydroxycorticosteroid levels during sleep in man. *The Journal of clinical endocrinology and metabolism* 26, 2, 121-127.

Welin AK, Svedin P, Lapatto R, Sultan B, Hagberg H, Gressens P, Kjellmer I, Mallard C (2007). Melatonin reduces inflammation and cell death in white matter in the mid-gestation fetal sheep following umbilical cord occlusion. *Pediatric research* 61, 2, 153-158.

Wiklund I, Karlberg J, Mattsson LA (1993). Quality of life of postmenopausal women on a regimen of transdermal estradiol therapy: a double-blind placebo-controlled study. *American journal of obstetrics and gynecology* 168, 3, 824-830.

Wilson MA (1992). Influences of gender, gonadectomy, and estrous cycle on GABA/BZ receptors and benzodiazepine responses in rats. *Brain research bulletin* 29, 2, 165-172.

Wrona D (2006). Neural-immune interactions: an integrative view of the bidirectional relationship between the brain and immune systems. *Journal of neuroimmunology* 172, 1-2, 38-58.

Xu Y, Padiath QS, Shapiro RE, Jones CR, Wu SC, Saigoh N, Saigoh K, Ptácek LJ, Fu YH (2005). Functional consequences of a CKIdelta mutation causing familial advanced sleep phase syndrome. *Nature* 434, 7033, 640-644.

Xu Y, Toh KL, Jones CR, Shin JY, Fu YH, Ptácek LJ (2007). Modeling of a human circadian mutation yields insights into clock regulation by PER2. *Cell* 128, 1, 59-70.

Zhdanova IV (2005). Melatonin as a hypnotic: pro. *Sleep medicine reviews* 9, 1, 51-65.

Zhdanova IV, Wurtman RJ, Morabito C, Piotrovska VR, Lynch HJ (1996). Effects of low oral doses of melatonin, given 2-4 hours before habitual bedtime, on sleep in normal young humans. *Sleep* 19, 5, 423-431.

Ziemssen T, Kern S (2007). Psychoneuroimmunology—cross-talk between the immune and nervous systems. *Journal of neurology* 254, 2, I8-11.

Zumoff B, Strain GW, Kream J, O'Connor J, Rosenfeld RS, Levin J, Fukushima DK (1982). Age variation of the 24-hour mean plasma concentrations of androgens, estrogens, and gonadotropins in normal adult men. *The Journal of clinical endocrinology and metabolism* 54, 3, 534-538.