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HORMONAL ASPECTS OF SLEEP REGULATION

Petya Hristova[1], Anna Tolekova[2], Pavlina Teneva[2*], Magdalena Platikanova[3], Mario Milkov[4], Reni Kalfin[5]

[1]Medical Faculty, Trakia University, Armeyska 11, 6000 Stara Zagora, Bulgaria
[2]Medical College, Trakia University, Armeyska 9, 6000 Stara Zagora, Bulgaria
[3]Department of Hygiene, Epidemiology and Infectious Diseases, Medical Faculty, Trakia University, Armeyska 11, 6000 Stara Zagora, Bulgaria
[4]St. Petka Eye and Ear Clinic of Varna, Medical University, Ivan Drasov 12, 9002 Varna, Bulgaria
[5]Institute of Neurobiology, Bulgarian Academy of Sciences, Acad. G. Bonchev 23, 1113 Sofia, Bulgaria

[*]e-mail: pl.teneva@abv.bg

Abstract

The good quality of sleep is known to be strongly related with life quality and mental and physical health. Sleep regulation results from very complex interplay between many neural and humoral factors. The purpose of our study is to classify some main systems of hormones, that influence sleep.

A key player in sleep regulation is melatonin. At night there is a peak of melatonin secretion in both dark and light active species. It is referred to as a substance that keeps "dark appropriate" behavior. It is related with sleep promotion and it may help in sleep disorders. Other very important systems include two different hypothalamic-pituitary axes with reciprocal interactions - hypothalamic-pituitary-somatotropic (HPS) and hypothalamic-pituitary-adrenocortical (HPA) systems. The final effect on the sleep regulation depends on the ratio between growth hormone-releasing hormone (GHRH) and corticotropin-releasing hormone (CRH). The change in GHRH : CRH in favor of CRH has a role in the sleep-endocrine alterations during depression and aging. Enhanced activity of the hormones of HPA-system is thought to contribute to the downregulated melatonin levels and higher leptin levels in depression. Also, melatonin levels get lower after repetitive administration of CRH (the HPA -system inhibits melatonin effects). In literature there are very interesting data about separate regulation of the two type of sleep - slow wave sleep (SWS) and rapid eye movement sleep (REMS). GHRH promotes NREMS (in males) and CRH has the opposite effect - it promotes wakefulness. Some studies suggest that CRH promotes REMS. Also, it is suggested that GHRH has a role sleep promotion after sleep deprivation (SD). There are other neuropeptides (except those produced by the HSA and HSP systems) that have an effect on sleep regulation - galanin and neuropeptide Y that stimulate SWS. Steroid hormones also participate in sleep regulation. The main one is cortisol. It promotes SWS and supresses REMS in humans.

We can conclude that there are tree main systems in sleep regulation - melatonin and HPS and HPA system, acting reciprocally and some other accompanying hormones, making a link between them or acting in concert with them to enhance or decrease their effects.

***Key words**: Slow wave sleep, Rapid eye movement sleep, Hypothalamic-pituitary axes, Growth hormone-releasing hormone, Corticotrophin-releasing hormone, Melatonin.*

1. Introduction

The good quality of sleep is known to be strongly related with life quality and determines mental and physical health. Sleep regulation (SR) results from very complex interplay between many neural and humoral factors. Sleep and its regulation are a product of the interactions between two general regulatory systems - nervous and endocrine. The hypothalamus is the main integrative center of interactions between these two regulatory systems and the structure where the communications of the vegetative nervous and endocrine systems interface very closely. In the hypothalamic structure are localized neuronal centers of regulation of stress reactions, energy homeostasis

and feeding behavior. It also participates in sleep regulation. Any disturbance in these complex synergy leads to deviations in the individual parameters of sleep and wakefulness.

Based on these facts we suggest the hypothesis that all hormones or hormonal system which regulate sleep and wakefulness are responsible for regulation of stress reactions, energy homeostasis and feeding behavior.

2. Hormones and their impact on sleep regulation

2.1 Melatonin

Main role in sleep regulation has the famous powerful sleep regulator - melatonin [1]. The suprachiasmatic nucleus of the hypothalamus as a rhythm-generating system regulates secretion of melatonin. It has sleep-promoting function and a typical circadian rhythm - high level during the night and lower during the day [2 - 4]. Impairment of circadian rhythm leads to development of different disorders. Hernandez *et al.*, [5], studied the pattern of melatonin secretion in 20 patients with obstructive sleep apnoea syndrome (OSAS). Authors established that the circadian rhythm of these patients is disturbed - regular peak and decrease were lacking. The melatonin secretion of OSAS patients had a plateau in melatonin levels in the second part of the night and didn't have a decrease at the light part. So, this change of the circadian rhythm and pattern of secretion cause severe health problems. The lack of serum melatonin peak may be partially associated with the disturbances that these patients have in achieving a normal sleep-wake cycle. This leads to a "vicious circle" in the regulation of sleep - abnormal sleep causing lower secretion of melatonin and the lack of melatonin leading to sleep disorders. The importance of melatonin level for sleep is also confirmed by Wurtman. The study was among young people and showed 10-fold higher melatonin levels detected at night, as it causes faster sleep, better sleep quality, and faster sleep after premature waking. Typically, exogenous intake of melatonin in young people is able to regulate the sleep-wake cycle, whereas very high doses could desensitize melatonin receptors in the brain [6]. The process of aging causes decreasing of melatonin levels, and this makes sleep worse. Melatonin exhibits also antidepressant-like properties. The result from a study with patients with depression who were given exogenous melatonin showed that melatonin had strongly decreased the symptoms of depression [7]. Another study suggests that a melatonin has a hypnotic effect through influence on thermoregulatory mechanisms. Melatonin lowers body temperature and stimulates sleep [8]. It is a powerful final antioxidant [9]. Administration of melatonin produces animals weight lose through the activation of brown adipose tissue and increase of energy expenditure. It is well known that melatonin manage stress reaction. It restores stress-induced decline in the norepinephrine content of the hippocampus [10].

2.2 HPS and HPA systems

In sleep regulation an impact have two other hormonal systems, which originate from hypothalamic neurones. These systems are the hypothalamo-pituitary-somatotrophic (HPS) and hypothalamo-pituitary-adenocortical (HPA) system. The hypothalamo-pituitary-adenocortical (HPA) system has an effect on sleep regulation and physical and psychological stress. The stress reaction is managed by the release of cotricotropin-releasing hormone (CRH). This results in the secretion of cotricotropin (ACTH) and cortisol [11, 12]. HPA system hormones regulate the general parameters of sleep. But the relationship is bidirectional, because changes of sleep also affect the release of these hormones. Circadian rhythm of cortisol is stable and independent of sleep. During sleep we can observe the lowest and the highest concentration of ACTH and cortisol.

The different hormones included in HPA axis exert differentiated specific effects on the sleep. CRH impairs sleep and enhances wakefulness. Cortisol promotes slow-wave sleep (SWS) probably due to feedback inhibition of CRH. Changes in ratio between CRH and growth hormone-releasing hormone (GHRH) in favour of CRH leads to shallow sleep, elevated cortisol and low growth hormone (GH) secretion during depression and ageing [11 - 13]. Some experiments demonstrate specific sleep-EEG changes after the administration of ACTH. During sleep HPA hormones appear to be blunted. Sleep loss results frequently in increases of ACTH and cortisol. A better understanding of the effects of HPA system on sleep EEG can help for the treatment of psychiatric, endocrine and sleep disorders. The effect of Ginkgo biloba with trimipramine on the sleep of depressed patients may be explained as CRH-antagonistic effect [14].

HPA system regulates appetite, metabolism and stress reaction. CRH is anorexigenic factor, while cortisol exerts orixigenic effect. HPA-axis is a "stress management" system. The adequate response is very important for organism survival in condition of chronic stress. HPA axis enhances lipolysis, which makes it a key-player in metabolism too [12-13].

HPS system includes the main chain of hormone-GHRH/somatostatin - GH-IGF1 (somatomedins). GHRH promotes duration and intensity of SWS [15-16]. It is known that HPS axis stimulates REM sleep in normal subjects. HPS system is involved also in apetite and

stress regulation in addition to its regulatory impact of sleep. Some data shows that feeding motivation is elevated by HPS system. HPS-axis enhances lipolysis which makes it responsible to the metabolism regulation. The growth hormone secretion is elevated during -acute physical stress and is decreased in conditions of chronic stress [17, 18] (Table 1).

Table 1. Effects of some hormones on the regulation of REM- sleep and non-REM sleep

Substance	NREMS	REMS
GHRH	↑	–/↑
GHRH (females)	↓	–
GH	↓	↑
Ghrelin	↑	(↓)
CRH	↓	↓
Vasopressin	↑	↑
ACTH	(↓)	↓
Cortisol	↑	↓
Galanin	↑	–
NPY	↑	–
Estrogen (female, Postmenopausal)	–	(↑)

*Note: (↓) - weak effect; - no effect; –/↑ - controversial reports.

2.3 Ghrelin and leptin

Ghrelin plays key role in management of the sleep regulation, stress reactions and feeding behavior. It is an endogenous sleep - promoting factor which induces SWS. Ghrelin acts as an interface between HPA and HPS systems [13, 19]. It stimulates these two axes with reciprocal influence on sleep. As other sleep regulating systems ghrelin has also additional effects on human's organism - it has a dual role in stress reaction, anxiolytic and anxiogenic. Ghrelin is powerful orexigenic factor. It induces food intake and weight gain [20, 21]. Another key player from this regulatory system is leptin (Figure 1). Some experiments show that it stimulates sleep. Sleep curtailment in healthy young men is associated with its levels. Leptin inhibits food intake and decreases body weight. It is suggested that individuals with high level of adiposity and/ or increased plasma leptin concentration would be more stress-responsive [22, 23]. This means that leptin stimulates wakefulness, inhibits appetite as an anorexigenic hormone and increases intensity of stress reactions in human organism [22].

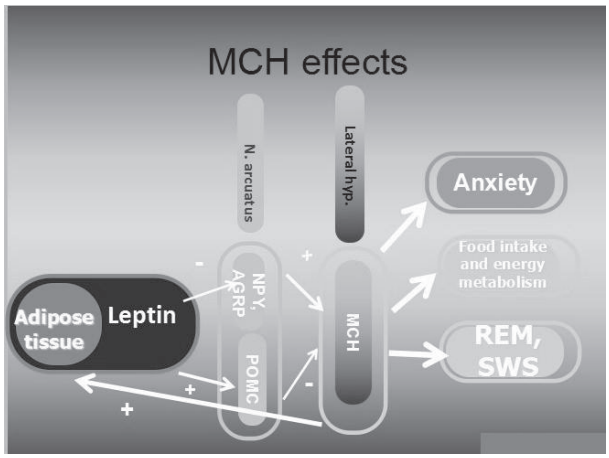

Figure 1. Scheme of regulatory relationships between adipose tissue, nucleus arcuatus and lateral hypothalamic region

2.4 Orexins (Hypocretins)/Melanin concentrating hormone system

Hypocretin/Melanin concentrating hormone system is very important component in the complex hormonal regulation of sleep. Hypocretin (orexin) neurons are localized in the dorsomedial, lateral and perifornical hypothalamic areas. Melanin-concentrating hormone (MCH) neurons are co-distributed with hypocretin neurons. Both types of neurons send strong projections to brainstem - neuronal center responsible for the onset and maintenance of REM. There are abundant contacts between both types of neurons at the level of hypothalamus.

MCH hormone directly regulates REM and SWS. It stimulates both phases of sleep. MCH has different effects apart of sleep regulation. Experiments show that acute and chronic icv injections of MCH stimulate food intake in rats and mice. Chronic icv application of MCH into the lateral ventricle leads to increase of body weight, white adipose tissue and liver mass in mice. It reduces brown adipose tissue functions and increases plasma glucose, insulin and leptin levels in mice [24 - 27].

Orexins(hypocretins) hormones are the other main factors in the complex process of regulating sleep. Orexin A (hypocretin 1) is a 33-amino acids peptide, while Orexin B (hypocretin 2) consists of 28 amino acids. Orexins normalize the sleep-wake pattern. A hypoactive orexins lead to narcolepsy [28] Hypocretin 1 increases metabolic rate and it is one of the mediators of energy metabolism. Recent studies show the possibility of orexins to mobilize a coordinated adaptive panic/defence response. Hyperactive orexins lead to pathological panic and anxiety states [29 - 31] (Table 2).

Table 2. Grouping of orexigenic and anorexigenic hormones based on their impact on sleep regulation

Anorexigenic hormones: wakefulness promotors	Orexigenic hormones: sleep promotors
1. Leptin	1. AgRP
	2. MCH
2. CRH	3. Orexin A and B
	4. Cortisol
3. Vasopressin	5. Ghrelin
	6. HPS system

3. Conclusions

- Reviewed data support our hypothesis that all hormones or hormonal system which regulate sleep and wakefulness are responsible for regulation of stress reactions, energy homeostasis and feeding behavior.
- The systematization of hormones clearly indicates that group of orexigenic hormones promote sleep and anorexigenic hormones promote wakefulness.

4. References

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