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Sleep and Endocrinology: *Hypothalamic-pituitary- adrenal axis and growth hormone*

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ABSTRACT

The supra-chiasmatic nucleus (SCN) is the primarily biological clock determining the circadian rhythm. The neurons of the nucleus making this clock have inherent rhythm and set in biological day and night. These periods usually corresponds to day/night, and indirectly to sleep-wakefulness cycle, in most individuals. Retino-hypothalamic tract carrying photic information from the retina provides the most important input to maintain the inherent rhythm of the SCN. The rhythmic discharges from the SCN to various neurons of the central nervous system, including pineal gland and hypothalamus, translate into circadian rhythm characteristic of several hormones and metabolites such as glucose. As a result there is a pattern of hormonal changes occurring during cycle of sleep wakefulness. Most characteristic of these changes are surge of melatonin with biological night, surge of growth hormone-releasing hormone (GHRH) at onset of sleep and surge of corticotropin- releasing hormone (CRH) during late part of the sleep. The cause and effect relationship of the hypothalamic releasing hormones and their target hormones on various phases of sleep including initial non rapid eye movement (NREM) phase at onset of sleep, and rapid eye movement (REM) phase near awakening, is an upcoming research area. Sleep electroencephalogram (EEG) determining the onset of NREM and REM sleep is an important tool complimenting the studies assessing relationship between various hormones and phases of sleep. The slow wave activity (SWA) corresponds to the intensity of sleep at its onset during the biological night of an individual. Besides, GHRH and CRH, several other peptide and steroid hormones such as growth hormone (GH), its secretagogues, ghrelin, neuropeptide Y, estrogen and dehydroepiandrosterone sulfate are associated or have the potential to change phases of sleep including initial slow wave-NREM sleep.

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The sleep disturbances with aging and depression are common and reflected as impaired SWA in the EEG and early morning awakening. Recognition of sleep associated endocrine changes has resulted into a number of studies assessing sleep promoting effect of compounds such as melatonin and CRH antagonists. These studies have potential implications for patients with sleep disturbances associated with depression, aging and those having frequent night shifts.

The misalignment of normal circadian rhythm and sleep wake cycle, as observed during night shift work, has been recognized to have important adverse consequences. These include difficulty in maintaining sleep during day time, and metabolic derangement such as obesity, impaired insulin secretion and associated glucose intolerance. Understanding of sleep-endocrine physiology is clinically important to deal with these adverse consequences.

OVERVIEW

On an average, humans spend one-third of their life in sleep. The adverse effects of misaligned sleep wake cycle, as in night shift worker, has given an impetus to the research related to the physiology of sleep and associated endocrine disturbances. The inherent aspects of this research are the factors determining normal sleep wake cycle and changes secondary to this. The hormone system coupled with nervous system control virtually all the major activities of the body. It is therefore natural to expect these two to have effect on sleep wake cycle. The purpose of this review is to present salient aspects of sleep physiology in relation to endocrine system. The information in this review was presented in the annual meeting of the National Academy of Medical Sciences held at Jodhpur, AIIMS, in 2013, and is based on two excellent reviews by Morris *et al.* (1) and Steiger (2) and other published data.

Sleep wake cycle and its integration with endocrine system :

The normal sleep wake cycle is influenced by circadian rhythm, hormonal changes and pressure for sleep after long working hours. Its architecture includes repeated phases of NREM and REM sleep. It begins with NREM sleep, which is reflected in the EEG as SWA.

The circadian system is primarily governed by the SCN located in the anterior hypothalamus with projections to the various parts of the brain. Inherent rhythmicity of the neurons in this nucleus with its downstream effect on hormones and autonomic nervous system determines the biological day and night. The biological day and night reflect phases of activity and inactivity respectively. The SCN entrained by solar day and night is responsible for biological day and night. Retino-hypothalamic tract helps in the integration of internal circadian system with external environment. This tract conveys the important information from external world through photic stimuli on the ganglion cell of retina to the SCN. Thus,

the pulsatility of SCN can be entrained by external environment. Other factors, which can entrain SCN, are body temperature and metabolites.

The circadian rhythm leads to a predictable form of change in hormone system. Some of these hormones themselves can have overriding effect on sleep wake cycle. The salient example of this is melatonin hormone, which is released during biological night but can be used to reset alteration in sleep wake cycle induced through jet lag or night shift. Another example related to use of information regarding endocrine changes during sleep is in the treatment of sleep disturbance observed in depressed and aged individuals. Attempts are on in various laboratories assessing the use of sleep associated hormones or their antagonists in modulating sleep disturbances.

Sleep and hormones

(A) Hypothalamic pituitary somatotroph axis

GHRH, somatostatin, GH, ghrelin and other GH secretagogues are important sleep modulating hormones (1,2). Normally, there is a surge of GH at the onset of sleep. In males there is only a single peak, but females have additional peaks of GH in the middle of the night. The sleep has a greater influence on GH than the circadian rhythm, which is indicated by the occurrence of GH surges irrespective of the onset of sleep during day or night. Its occurrence at multiple points during night, coinciding with SWA, further support the less important role of circadian system in explaining the association of GH surge with sleep (1,2). GHRH is the chief regulator of the GH surge and its slow wave sleep (SWS) promoting effect has been confirmed both by central and intravenous/intranasal administration of GHRH peptide in experimental animals as well as in human volunteers respectively (2-6). Though the hormone had no effect in the early morning in young subjects, it had a sleep promoting effect in normal elderly with prolongation of first NREM and decrease in the number of awakenings (2). Interestingly, a sexual dimorphism was observed in patients with depression. In males, GHRH inhibited cortisol during the second half of the night (7). However, in females where cortisol levels increased during second half, along with sleep impairing effect (2). This indicated antagonist action of GHRH on CRH-cortisol during sleep wake cycle in males but it has synergistic effect in females. In contrast to GHRH, no consistent pattern of change in sleep architecture has been reported on GH administration. This indicates the primary role of GHRH, rather than GH, in normal sleep architecture (8).

Ghrelin is hunger stimulating hormone produced from cells lining the fundus of the stomach. Besides, it is an endogenous GH secretagogue stimulating GH release. Weikel *et al* showed SWS promoting effect of intravenous administration of ghrelin in young males (9). However, in contrast to GHRH,

cortisol level increased after Ghrelin. The effect of synthetic GH secretagogues like GH-releasing peptide-6 and hexarelin are also under investigation. Similarly, galanin peptide, which is wildly distributed in brain, and which stimulated GH, can also have SWS promoting effect in normal males (10). Ghrelin, synthetic GH secretagogues and galanin deserve further investigation for their possible role in altering sleep.

Somatostatin and octreotide lead to impairment in NREM/SWS sleep (11). The effect of somatostatin is more marked in the elderly than the young subjects. Steiger *et al.,* suggested that somatostatin antagonist may be of help in the modulation of sleep disturbances in elderly males (2). The fact that somatostatin antagonist arginine increased SWS in elderly male indicated that the balance of GHRH/somatostatin in favour of GHRH would help sleep promotion in elderly.

(B) Hypothalamic pituitary adrenal axis

CRH, ACTH and cortisol are hormones, which are associated with sleep, especially at the termination of biological night or near awakening (1,2). It is well known that circadian system has strong influence on serum cortisol levels in human with level peaking in the biological morning and low in the early part of the biological night. These circadian rhythms are produced through hormonal and neuronal pathways. Projections from SCN and paraventricular nucleus are important for release of CRH. Neuronal signals to the intermediate lateral column of the spinal cord, and then to the adrenal cortex, result in increase in serum cortisol. CRH seems to be the prime regulator of sleep architecture, followed by corticosteroids (1,2). The effect of CRH seems to be reciprocal of GHRH, because in animal and experimental studies CRH administration reduced SWS, prolonged sleep latency and increased REM sleep (12,13). Besides, CRH administration in young volunteers also decreased GH surge along with increase cortisol after the sleep onset. The disturbing effect of CRH on sleep increases with aging (14). The importance of CRH in sleep disturbance is also indicated by the fact that patients with depression and elderly subjects have increased cortisol activity in the late half of the night, especially before wakening. It is interesting to recall the sexual dimorphism in the action of GHRH in females. Unlike males, GHRH in females had synergistic effect on CRH. The increased CRH/cortisol activity in the females, elderly and patients with Cushing's disease could explain the high prevalence of depression and sleep disturbances in these subjects. Interestingly, apart from decreasing SWS, CRH administration in human led to decrease in REM sleep also (2).

Theoretically, the effect of increased CRH described above could also be due to increases in the ACTH and cortisol activities. All the three hormones i.e., CRH, ACTH, GH lead to suppression of REM sleep. However, pulsatile

administration of synthetic ACTH analogue had no effect on cortisol and REM activity (2). Steiger *et al* suggested that CRH induced decrease in REM sleep in human could reflect a direct effect of cortisol (2). In fact, cortisol administration led to reduced REM sleep in young normal males (2). The effect of acute and chronic cortisol administration were found to be different (2). The acute administration of steroids resulted in increase SWS and GH release in elderly and young controls as well as in patients with depression (2,15,16). On the other hand, chronic glucocorticoid therapy resulted in decreased REM sleep latency, increase REM sleep density (17). As serum cortisol levels were maximum in the early morning hours, when the arousal from sleep also occurred, it is highly unlikely that cortisol determined the circadian rhythm of sleep.

Realizing the importance of CRH in sleep disturbances, research is ongoing on various CRH antagonist molecules in sleep disorders (2). CRH antagonist like alpha helical CRH and astressin could decrease the stress induced changes in sleep in experimental animals (2). Similarly, a four weeks trial with CRH receptor 1 antagonist (NBI-30775) led to increase in the SWS and decrease number of awakenings. Paradoxically REM was shown to be increased in these studies (2,18).

Misalignment of sleep with circadian rhythm and endocrine influences

One of the important functions of the circadian system is to maintain homeostasis of essential parameters such as body weight, appetite and balance of autonomic nervous system activity at various points of the day according to the requirement of activity. The system works in close association with biological day and night in most individuals. Long term deviation in the close harmony between circadian rhythm and sleep wake cycle has recently been recognized to result in several adverse consequences. A typical example of misalignment is seen in night shift workers like health professionals. Figueiro and White recently reviewed data on the effect of rotating night shift (19). Circadian disruption resulting from rotating shift work was associated with increased risk for metabolic syndrome, diabetes, cardiovascular disease and cancer (19). Marquezea *et al* investigated the relationship between night shift and body weight in 446 nursing staff (20). Logistic regression analysis showed that more time spent during night shift was associated with development of overweight/obesity (20). The increased risk of obesity associated with night shift work might translate into glycemic dysregulation. Monk *et al*., reported higher risk of diabetes among 1111 retired night shift workers aged > 65 years, with odd ratio of two which remained significant even after adjusting for BMI and gender (21). Pan *et al.,* followed 69269 women aged 42-67 years in Nurses' Health Study I (NHS I, 1988-2008), and 107915 women aged 25-42 in NHS II (1989-2007) without diabetes, cardiovascular disease, and cancer at baseline (22). The results showed that an

extended period of rotating night shift work was associated with increased risk of type 2 diabetes in women which was partly mediated through body weight (22). Caciari *et al.,* studied 163 health workers exposed to night work and compared with 252 similar controls who were not exposed for alteration of some cardiovascular risk parameters (23). Night workers had clinically significant changes in serum total cholesterol, HDL cholesterol and triglycerides. Puttonen *et al.,* studied associations between shift work with the metabolic syndrome in employees of an airline company (24). Findings of the cross-sectional study suggest that metabolic syndrome diagnosed by International Diabetes Federation (IDF) criteria and the National Institute of Health Adult Treatment Panel III (NCEP) guidelines was more prevalent among former male shift workers than current day workers who had never worked in shifts with Odds ratio of approximately 2.0. Currently, the pathophysiology of the disturbances in cardio metabolic system and glycemic dysregulation in misalignment of sleep with circadian rhythm is not very clear. However, alteration in GH, cortisol and their influence on insulin-glucose system would be a subject of further study.

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