Sleep Science

OVERVIEW

The "Forbidden Zone for Sleep" might be caused by the evening thyrotropin surge and its biological purpose is to enhance survival: a hypothesis

A "Zona Proibida para o Sono" pode ser causada pela elevação ao anoitecer dos níveis de tireoptropina e sua finalidade biológica é aumentar a sobrevivência: uma hipótese

José Carlos Pereira Jr.[1], **Rosana Cardoso Alves**[2]

ABSTRACT

It is possible for normal subjects to fall asleep during daytime wakefulness, and the propensity for daytime sleep varies being high in the mid-afternoon and lower in the early evening 2 or 3 hours before overnight sleep onset. This lowering of propensity for sleep in the few hours that precede overnight sleep is a paradoxical phenomenon termed the "Forbidden Zone for Sleep" or "Wake Maintenance Zone". During the day, thyrotropin levels, which reflect the activity of the hypothalamus-pituitary-thyroid axis, oscillate in a predictable rhythm: lower levels during afternoon and higher levels during the early evening Forbidden Zone for Sleep. The steep increase in thyrotropin levels in the early evening is called the "thyrotropin-evening-surge", with the higher levels just before overnight sleep onset. Thereafter thyrotropin levels decrease over the rest of the night reaching their low daytime levels. Considering the well-known role of the thyroid in vigilance and alertness, we propose that the negative correlation between thyrotropin levels and propensity to sleep is not a coincidence. Assuming that the circadian rhythms of any species are turned to facilitate survival, we propose that the Forbidden Zone for Sleep is an inherent part of the human circadian rhythm increases biological fitness. In this article, a medical hypothesis, we present evidence that in human's circadian rhythms the Forbidden Zone for Sleep is secondary to the thyrotropin evening surge.

Keywords: sleep disorders, circadian rhythm; sleep-wake transition disorders; receptors, thyrotropin; thyroid hormones.

RESUMO

Para indivíduos normais é possível adormecer em horários diurnos que correspondem à vigília, e a propensão para o sono diurno varia, sendo maior ao meio da tarde e menor ao anoitecer, nas 2 ou 3 horas que antecedem o início do sono. Essa propensão menor para o sono logo nas horas que antecedem o sono noturno é um fenômeno paradoxal que foi denominado "Zona Proibida do Sono" ou "Zona de Manutenção da Vigília". Durante o dia, os níveis de tireoptropina, que refletem a atividade do eixo hipotálamo-pitutária-tireoide, oscilam em um ritmo previsível: níveis menores à tarde, e maiores ao anoitecer, em horário que coincide com o fenômeno Zona Proibida do Sono. A elevação dos níveis de tireotropina ao anoitecer é marcante e foi denominada "impulso noturno da tireotropina". Esse impulso noturno tireotrópico, os mais elevados níveis de tireotropina durante as 24 horas, ocorre logo nas horas que antecedem o início do sono. Após, os níveis de tireotropina vão abaixando pelo resto da noite até alcançarem seus valores baixos durante o dia. Considerando a importância do hormônio da tireoide para a vigilância e o nível de alerta, propomos que essa correlação negativa entre níveis de tireotropina e a propensão ao sono não seja mera coincidência. Considerando que os ritmos circadianos de qualquer espécie animal desenvolveram-se para aumentar a sobrevivência da espécie, assumimos que a Zona Proibida para o Sono uma parte inerente ao ritmo circadiano humano, desenvolveu-se ao longo da evolução, com a finalidade de facilitar sua sobrevivência. Neste artigo, uma hipótese médica, apresentamos evidências de que a Zona Proibida para o Sono é causada pelo impulso noturno da tireotropina.

Palavras-chave: transtornos do sono do ritmo circadiano; transtornos da transição sono-vigília; receptores da tireotropina; hormônios tireóideos.

INTRODUCTION

All animals pass through daily rhythmic variations of their physiological functions. Through the course of evolution these daily variations have helped them to adapt and live in synchrony with the rhythms of the day[1]. The most notable daily rhythm is the alternation of light and darkness with day and night. Rhythms with a daily cycle are called "circadian rhythms". Among the most conspicuous of the human circadian rhythms is that of sleep and wakefulness. In normal entrained adults, wakefulness usually occupies the initial two thirds of the geophysical day, and sleep occupies the last third[1,2].

[1]Departamento de Pediatria da Faculdade de Medicina de Jundiaí, Jundiaí (SP), Brazil.
[2]Departamento de Neurologia da Faculdade de Medicina, Universidade de São Paulo (USP), São Paulo (SP), Brazil.
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Corresponding author: José Carlos Pereira Jr – Rua Francisco Telles, 250 – Vila Arens – CEP 13202-550 – Jundiai (SP), Brazil – E-mail: jcpereirajr@uol.com.br
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Circadian rhythms are endogenously generated, but maintain sensitivity to clues that beacon the phases of the day, so that can remain in synchrony with it[1]. Two opponent physiological processes interact to maintain the sleep-wakefulness rhythm well timed with the day. They are circadian rhythm process (PC), and sleep homeostasis process (PS). PS is not influenced by time cues, rather it only induces sleep, and its activity increases in parallel with the time spent awaken[3]. PC induces wakefulness during the first two thirds of the geophysical day, consolidates sleep in the last third, regulates sleep stages, and is susceptible to environmental stimuli, light being the most significant[3-6]. These stimuli may postpone (phase delay), or bring forward (phase advance) the sleep phase, resulting in the time of wakefulness, in the next cycle, beginning later or earlier in relation to the beginning of day, respectively[3-6]. A variety of experimental paradigms have demonstrated that the circadian pacemaker, located in the suprachiasmatic nucleus (SCN) of the hypothalamus, regulates propensity to sleep[2]. However, the mechanisms by which the SCN accomplishes this are not yet entirely elucidated. Several studies have demonstrated that the greatest drive to wakefulness during the circadian rhythm is present in the few hours prior to the major sleep phase. This narrow period of the wakefulness phase usually occurs in the early evening and has been termed the "Forbidden Zone for Sleep" (FSZ)[7], or "Wake Maintenance Zone"[8]. The timing, purpose, and mechanisms responsible for this intriguing elevated arousal immediately before the major sleep phase have not been elucidated. The levels of many hormones also cycle with a circadian rhythmicity[9], and among these the daily cycle of thyrotropin, or thyroid-stimulating hormone (TSH), levels are of the utmost importance to daily sleep-wakefulness oscillations. The circadian rhythm of TSH includes a steep increase in the evening[9] prior to sleep onset. The main goal of this article is to present evidence that the daily evening increase in TSH levels might be the (or one among others) causative factor, behind the FSZ. We also discuss the importance thyroid hormones (THs) have to biological circadian rhythms.

ACTIONS OF THYROID HORMONES SUGGESTING THEY ARE EFFECTORS OF THE CIRCADIAN PACEMAKER

THs virtually act on every organ system in the human organism: they increase basal metabolic rate; heat production; and oxygen consumption. They also alter the cardiovascular and respiratory function to increase blood flow and oxygen delivery to the tissues. A vast array of proteins are synthesized under the direction of THs, including the NA^+- K^+ ATPase, the Ca^{2+} ATPase transport proteins, β-1-adrenergic receptors, lysosomal enzymes, proteolytic proteins, and structural proteins[10]. However, these actions are mediated by genomic effects and thus occur slowly, although with a long duration[10]. Relative to the timescales of our circadian rhythms, the genomic actions of THs are quite slow, which would suggest that it is not by these mechanisms that THs can be considered one of the important effectors of the biological clock. However, the actions of THs on mitochondria[11] make them suitable to play an important role in circadian rhythms. Mitochondria are the organelles responsible for adenosine triphosphate (ATP) production, and THs increase their number and activity[10]. Neurons depend on neurotransmitter synthesis in axons terminals, which is dependent on ATP production for signaling activities. Mitochondria have receptors to THs on their surfaces, enabling a very quick response that increases ATP production. Thus, incrementing mitochondria activity is not dependent on slow genomic effects[10-12]. In the central nervous system, THs increase the velocity of thinking processes, and when levels of THs fall, thinking slows down. Hyperthyroidism induces insomnia, believed to be secondary to the excitatory effects of THs on the synapses[10]. Conversely, hypothyroidism induces hypersomnia; it is not unusual for hypothyroid patients to sleep for 12-14 hours a day[10]. It is interesting to note that lesions of the SCN in squirrel monkeys result in much more time spent sleeping compared to normal animals[3]. From the data above, it is reasonable to consider the hypothesis that the SCN, that governs the endocrine rhythms of the majority of the glands, reserves to THs an important role in the modulation of sleep propensity. THs have a remarkable range of actions in the nervous system, and they are essential to sensory system functioning[13]. Wakefulness is a condition with necessarily high vigilance and alertness. Knowing the importance of THs for sensory systems, it may be posited that without THs there is no wakefulness. Clinical observations have documented that hypothyroid patients are typified by low alertness levels, which lead to low levels of wakefulness. It is known that extreme deficiencies of THs can lead to myxedema coma[10]. During sleep, elevations of TSH levels are accompanied by an increase of the alpha waves, that is, an increase of the alpha wave index, which is considered and index of arousal from sleep[14], implying that THs are one, probably among many, of the factors responsible for arousability from sleep.

It is generally accepted that a decrease in sympathetic activation and an increase in parasympathetic discharge is required for sleep. The sympathetic mobilizes the organism to activity, and interacts closely with THs. Fibers from the sympathetic and parasympathetic nervous system penetrate the thyroid gland, providing additional mechanisms for regulation of THs output[15].

DAILY TSH PROFILE AND CIRCADIAN ASPECTS OF SLEEP-PROPENSITY

Analysis of the daily TSH profile and its correlation with sleep phase and propensity to sleep is of great relevance. Circulating TSH concentrations are low and relatively stable during the daytime. TSH then begins to climb in the early evening, with a steep increase before sleep onset, and peaks around the beginning of the sleep period. TSH levels progressively diminish throughout the sleep period until they reach their low daytime levels. The circadian trough of TSH levels normally occurs between midday and 6 p.m.[9]. Sleep-propensity usually varies significantly during the period between 7 a.m. and 11 p.m.; the greatest propensity occurs in the mid-afternoon[2] which coincides with the circadian trough of TSH levels, while the lowest sleep-propensity occurs in the evening during the steep circadian increase in TSH levels[2]. The pattern of increasing sleep-propensity with diminished TSH levels, and decreasing sleep propensity when TSH levels are increasing could be a mere coincidence. However, considering that THs affect reduction in the ability to sleep and can even result in insomnia, and that diminished THs cause somnolence[10], it is likely that there is a causal relationship between TSH levels and sleep-propensity. It is interesting that there is a lower sleep-propensity in late morning, when TSH levels are high, compared to mid-afternoon when TSH levels are low[2,9]. TSH levels are higher during sleep phase than during wakefulness[9]: This presents an apparent paradox in that TSH levels are higher during sleep phase than during wakefulness, but this is likely not without explanation. At the onset of sleep, the circadian rhythm imposes its sleep drive, or stops imposing wakefulness, and sleep onset occurs. During sleep there is a dramatic decline in the sleeping person's alertness, but some arousability remains during sleep state, as this is critical for survival purposes. The physiological and clinical profiles of THs suggest that THs comprise one of the putative systems that permit arousability from the sleep state. We assume that maintaining some alertness, so that sleep does not become a coma, requires greater TSH levels. Higher or lower levels of THs are not the "immediate" causing factor for wakefulness, or sleep, rather they are what allows arousability in both states. This arousability must necessarily be greater when the SCN is driving sleep states (or not driving wakefulness), and so, greater THs are needed during sleep. It has also been observed that episodes of slow wave sleep are selectively associated with decreases in TSH levels, that is, deep sleep occurred concomitantly with relatively diminished levels of TSH[16]. This provides further evidence that THs modulate sleep depth during the sleep phase. It has previously been held that the waveform of the daily profile of TSH levels is influenced by sleep[17,18]. This assumption is based on the fact that during sleep deprivation TSH levels increase. Inaccuracies in this interpretation may be inferred from physiological and therapeutics effects of thyroid hormones (activity inducers) that suggest that TSH modulates sleep and not vice versa. The greatest sleep-propensity is in mid-afternoon when TSH levels are at their lowest: could the increased sleep propensity be responsible for this low TSH levels?

This interpretation of the relationship between TSH levels and sleep-propensity seems incorrect. A more reasonable interpretation of the relationship between higher TSH levels and sleep deprivation is that TSH levels are the causal factor of sleep deprivation and not the reverse. As sleep deprivation is contrary to sleep-wake homeostasis, it is logical to infer that some function (or functions) must be executed to enable sleep curtailment. Considering the physiological profile of THs[10], they are well-fitted to this function. Taken together, the actions of THs, the daily TSH profile and its relation to sleep propensity, and the observations that TSH increases in sleep deprivation[17], allow one to logically assume that the FSZ is secondary to the TSH evening surge. Notwithstanding, other hormones might also be involved in the daily levels of sleep-propensity. For instance, cortisol may be one of the factors that influence sleep and propensity to sleep. However, the daily TSH profile levels, and their negative correlation with the daily variations in sleep-propensity, make THs the main candidate for causation of the FSZ.

THE HUMAN IS A DIURNAL ANIMAL WITH EVOLUTIONARY HISTORIES OF BOTH PREDATOR AND PRAY

Humans, as diurnal animals, rely mainly on vision to interact with environment. During the course of evolution they have been both predators and prey. When night came, men were more vulnerable than during day-light. To enhance survival, it was necessary for evolution to create in us a physiological condition that kept us alert and awake if we were caught by the daily coming of evening, before we had reached our primitive abodes and the safe environment for sleep they provided. FSZ is this physiological condition and evolution's solution that increased our survival in the early night. FSZ enhances the sharpness of all human's senses, which helps to counteract the weakening of the sight sense due to diminishing daylight. We posit that this increase in our general performance capacity synchronized with the early evening of the geophysical day is secondary to the TSH evening surge. THs stimulate all the somatosensory systems and increase the velocity of thinking[10,13]; these fully alert senses and high level of mental activity are why we are almost unable to sleep during the FSZ. Most probably, to the ancient man, this narrow phase of our circadian rhythm, the FSZ, began when darkness came, and ended when the an-

cient man's conscious mind perceived that the risks of the night had diminished because he was in the safety of his abode and among his peer group.

It has been theorized that the increased arousal just before the habitual sleep time, and the greatest sleep-propensity just before habitual waking up, help consolidate the sleep phase during the final part of the night and wakefulness during the day[19]. Considering man a diurnal animal, there is no doubt this organization of the rest-activity cycle facilitated his interactions with the environment, and enhanced survival. However, the FSZ is too high a drive for wakefulness that would not have to be so intense if its only finality were the correct positioning of the major components of our most important circadian rhythm along the geophysical day. More appropriately, this correct sleep-wake phases positioning should be considered a secondary gain of FSZ phenomenon that further enhances human survival. It is interesting to note that during sleep phase TSH levels reach their lowest values just before the habitual awakening time during the major sleep phase with the highest sleep-propensity[2,8].

THE FSZ AND THE MODERN HUMAN

When the sleeping brain systems are not active yet, the reticular activating system continuously stimulates the cortex and the peripheral nervous system. Both activated systems, in turn, send positive feedback signals to the reticular system stimulating it to maintain its excitatory outputs[10]. When sleeping, if a subject has a forced awakening caused by a random stimulus, his/her conscious mind determines if the stimulus is important enough to pay attention to, and if so, any action that must be taken. If the stimulus is considered to be relevant, although it is time to sleep, the conscious mind sends positive feedback to the reticular system, then receives from the reticular system and the peripheral nervous system (activated by the reticular system) the input required to create the awakened brain condition[10] necessary to react to what has caused the forced awakening. That is to say sleep deprivation. During sleep deprivation TSH levels increase sharply[17,18]. Logic, based on the actions of THs, allows one to posit that the increased hypothalamus-pituitary-thyroid axis is an integral part of the permissive mechanisms for sleep curtailment, as we previously suggested[20].

When the ancient humans gathered to spend the night, they most likely would not experience a stimulating evening; they would simply prepare themselves to sleep and wait for the lights of other day. Currently, there are many occupations that fill the evenings of the modern human. Whether for pleasure or work, these activities keep the conscious mind busy. As a result, the cortex continuously sends positive feedback to the reticular system, prolonging the FSZ period. A very similar scenario would have been experienced by an ancient human who could not get home in time. To brave the perils of the night, he would have to sharpen all his senses, to keep body and mind in a fully alert state. And as he was in a state of sleep deprivation, there is no doubt that he would increase his THs levels and prolong the FSZ.

FINAL COMMENTS

The FSZ phenomenon should be considered pertinent to "sleep hygiene" topics? In our experience, the answer to this question is "yes, it should". Parents frequently think and argue that because their children are not sleepy in the evening they have slept enough the previous night: "if they had not they would be sleepy". When it is difficult to wake them up the next morning, parents think the children are lazy, not they went to bed too late. People should be warned about the trick that the FSZ might play on their sleep hygiene. FSZ, that may have had the utmost importance in the evolution of mankind, can be a hindrance to the modern man trying to get all the sleep he needs.

Admittedly, indoor lights impair both sleep length and quality. Indoor lights allow the wakeful state of modern human to invade the nighttime that should belong to sleep phase. This is a bad habit, and the FSZ should be considered an accomplice. Light has the property of blocking, or diminishing, melatonin secretion from the pineal gland[2]; and it has been demonstrated previously that melatonin is a modulating factor of THs[21,22]. The extent to which this characteristic of melatonin is important for sleep hygiene has not yet been addressed.

There is robust evidence that the dopamine system is a modulating factor of the hypothalamus-pituitary-thyroid axis[23-26]. There is also evidence that some subjects exhibit weakened modulation of THs by the dopamine system[20]. When dopamine, and melatonin, cannot conveniently exert their modulating role on THs it is expected that the TSH evening surge be steeper and the FSZ be higher. It is known that iron scarcity diminishes the activity of dopamine system[27], thus it is reasonable to consider that lack of iron might cause a steeper evening TSH surge secondary to diminished modulation of THs by dopamine system.

The element iron is also an integral part of the CYP450 superfamily of enzymes, due to the fact that the component enzymes of CYP450 are all heme proteins[28-30]. CYP450 has an important role in the degradation of THs[31]. Iron scarcity may decrease CYP450 activity, and so, causing diminished degradation of THs. Many exogenous drugs that people use may influence the activity of the CYP450 superfamily enzymes. Those drugs that inhibit CYP450 enhance the actions of THs due to a decreased degradation of THs[30-32] also raising the possibility of a steeper evening TSH surge.

CONCLUSION

Scientists and clinicians should be aware of the importance that THs have for the basic science of sleep, as well as for clinical aspects of sleep-wake rhythm. It is important to recognize that THs are not affected by sleep. On the contrary, THs affect and modulate sleep. The systems that modulate THs like melatonin and dopamine systems, and likely others, should be a matter of interest to everyone who studies sleep medicine, and endocrinology.

Cognizance of the FSZ circadian phenomenon should be wide spread among physicians and the population in general. Awareness of FSZ phenomenon is of the utmost importance for sleep-hygiene principles.

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