Sleep deprivation and carcinogenesis: the role of melatonin

Privação de sono e carcinogênese: o papel da melatonina

Juliana Noguti¹, Daniel Araki Ribeiro¹²

ABSTRACT
Sleep is a biological manifestation which there is a periodic alternation between synchronized and desynchronized cerebral electrical activity. Although sleep occupies approximately a third of the human lifespan, the amount of time humans spend awake has increased over the years. Indeed, several of the functions of sleep have been associated with physiological alterations of organism subjected to acute or chronic sleep loss. Cancer is one of the most common causes of morbidity and mortality today in all over the countries. Studies have shown that there is evidence that melatonin, a pineal hormone involved in the circadian rhythm, may reduce the incidence and certainly the growth of tumors and it is associated with the biological process. In particular, this article reviews the association between sleep and carcinogenesis, focusing the role of melatonin involved to this mechanism.

Keywords: tumor markers, biological, sleep deprivation.

INTRODUCTION
Sleep is a global state, which controls mechanisms for several levels of biological organization, from genes and intracellular mechanisms to networks of cell populations and to all central neuronal systems at the organic level, including those that control movement arousal, autonomic functions, behavior and cognition. The term “sleep” is reserved for mammals and birds. Sleep is also part of the activity-rest cycle and share a number of common features with the poikilotherms rest state. Rapid eye movement (REM) is a unique physiological phenomenon present at least across mammalian species. REM sleep or total sleep (all stages of sleep cycle) has significant developmental and life sustaining functions to the extent that its loss is fatal. REM sleep is reduced in neurodegenerative diseases as for example Parkinson’s and Alzheimer disease.

Over the past several decades, there has been a trend towards a voluntary reduction in sleep time, there was a decrease of about 1.5 h when compared to the average sleep duration during the early 20th century. It is currently recognized the harmful effects of sleep deprivation. For example, some studies have shown myriad behavioral and physiologic effects caused by insufficient sleep. In humans, short periods of sleep deprivation can result in significant cognitive deficits while long-term disturbances in sleep have been associated with reduced longevity, yet the ways in which the body is compromised are not fully understood. In rats, prolonged sleep deprivation (2-3 weeks) leads to a syndrome characterized by increased food intake, weight loss, increased energy expenditure and progressive decline in body temperature which is invariable fatal. In addition, daytime sleepiness is the most commonly reported effect of sleep restriction, with a general population prevalence of 11% to 25%. Sleep loss affects neuronal responsiveness and brain excitability. Generally, the clinical features of sleep deprivation include longer reaction time, distraction, disturbances in attention and concentration, forgetfulness, irritability increases, work effectiveness decreases and motivation usually falls down.

Sleep deprivation also reduces brain maturation, spatial memory acquisition and memory consolidation. Furthermore, sleep loss results in inaccurate image...
formation on the retina and as consequence, the perceived images becomes dim and double vision and the disruption of visual perception may occur\(^{20}\). Visual disruption initially results in the tunnel vision\(^{21}\), but may affect the centre of the visual field as well, if the period of sleep deprivation is long\(^{21}\).

As reported in the literature, sleep deprivation contributed to a 20%-32% increase in the number of errors and a 14% increase to perform an electrocoagulation trial on a surgical laparoscope simulator\(^{22}\). It is plausible that during a real surgical operation, the surgeon's motivation partially compensates for the effects of weariness\(^{20}\). Thus, sleep has an immense and far reaching implications and consequences on public health, and damage caused by sleep deprivation must be recognized as a factor to several pathologies and behavioral changes at biological and molecular levels.

**Sleep deprivation and Carcinogenesis**

Cancer is one of the most common causes of morbidity and mortality today, with more than 10 million new cases and more than 6 million deaths each year worldwide. More than 20 million persons around the world live with a diagnosis of cancer and the most of all cancer cases occur in the developing countries. Cancer is responsible for about 20% of all deaths in high income countries and 10% in low-income countries\(^{24}\). Mammalian cells are frequently at risk of DNA damage from many sources and the permanent damage and proliferation of these cells is one of the causes of cancer. The replication of mammalian cells in a high-fidelity process assures an accurate passage of genomic information to the daughter cells.

However, their genome is constantly challenged by endogenous metabolic products and environmental factors that can alter its chemical structure, corrupt its encoded message, and, as a result, lead to the improper presence of single DNA breaks and/or double strand DNA breaks. Several cellular pathways have evolved to respond to these challenges to maintain genomic integrity in the host\(^{24}\). It has been documented that sleep deprivation causes harmful effects. In humans, short periods of sleep loss can result in significant cognitive deficits while long-term disturbances in sleep have been associated with reduced longevity\(^{17}\). It is well known that fatigue and disturbances in sleep are among the most common side-effects reported by patients suffering cancer. Sleep loss was able to induce genetic damage in blood and brain cells, especially following acute exposure. Since DNA damage is an important step in events leading genomic instability and carcinogenesis\(^{25}\), sleep loss could contribute to higher cancer risk in general population.

Emerging evidence suggests that disruption in the circadian rhythm may also increase risks of several types of cancer. In particular, night shift work has been associated with increased of cancer in the breast, endometrium, prostate and colorectum\(^{26-30}\). Thompson et al.\(^{31}\), found that shorter sleep duration is associated with an increased risk of colorectal adenomas in a population of patients undergoing routine screening colonoscopies. However, they found no evidence for an association of overall sleep quality with colorectal adenomas. Their data suggest that even a modest increase in sleep duration could have a substantial impact because of the high prevalence of colorectal adenomas, a well established precursor of colorectal cancer.

The pineal hormone melatonin is involved in the circadian regulation and facilitation of sleep and the enhancement of immune function. Derived from the essential amino acid tryptophan, melatonin is an indoleamine molecule that is found widely throughout nature\(^{32}\). Melatonin is synthesized and immediately secreted into blood vascular system and cerebrospinal fluid by the pineal gland during the night whereas the daytime production of melatonin is virtually nil\(^{33}\). The nocturnal melatonin signal provides time of day information to all the cells, tissues and organs of the body and is the most stable and reliable peripheral biomarker of the timing of the central biological clock. Since the duration of the melatonin defines the length of the biological night, the pineal gland not only acts as a clock but also as a calendar by providing an organism with information about seasonal changes in day length\(^{34}\). Indeed, during sleep deprivation, fatigue actually exhibits a circadian rhythm that closely tracks the melatonin rhythm.

The coincidence of pineal melatonin production and the occurrence of sleep during the night indicate an important relationship between these two processes\(^{35-36}\). Studies showed an increasing evidence suggesting that disruption of circadian rhythm by sleep deprivation and suppression of nocturnal production of melatonin may be the key mechanism underlying the shift work- cancer link\(^{36}\).

Once tumors are formed, melatonin also seems to control their growth by other means. Certainly, the classic work of Blask et al.\(^{37}\) has defined a mechanism which accounts for melatonin’s ability to limit the growth of cancer cells. One of the mechanisms may be the ability of melatonin to reduce severe DNA damage that is a consequence of unstable oxygen and nitrogen-based reactants\(^{38}\). These free radicals or related metabolites are notoriously destructive to macromolecules including DNA\(^{39}\). In experimental models of chemical carcinogenesis the physiological melatonin signal suppresses the initiation phase of tumorigenesis. One mechanism by which this may be accomplished is via melatonin’s ability to suppress the accumulation of DNA aducts (the resulting complex when chemicals bind to DNA) formed by carcinogens that cause damage and permanent alterations in DNA. Melatonin acts as a potent free radical scavenger and/or through its indirect actions to detoxify carcinogens via activation of the glutathione and related antioxidative pathways. In addition to protecting cells from DNA damage, melatonin might also promote the repair of DNA once damage has occurred\(^{34,37}\).

Killic et al.\(^{40}\) in studies unrelated to cancer proliferation, reported a marked inhibition of endothelin-1 (ET-1) synthesis by melatonin. ET-1 is known to be a potent vasoconstrictor peptide and it has been implicated in the regulation of cancer cells growth and also is elevated in the plasma of patients with various solid tumors. Furthermore, it is a powerful mitogen in a variety of cancer cells,
especially epithelial cell cancers. Interestingly, ET-1 seems to protect cells from undergoing apoptosis and promotes angio genesis in tumors by stimulating both endothelial and smooth muscle cell proliferation[9,10]. Once angiogenesis inhibitors could be used for treatment to enhance cancer cells death, perhaps suppressing the ET-1, it could provide an additional pathway to reduce the tumor growth.

There is no question that this is a field to explore, our cellular, tissue and metabolism are organized within the framework of circadian time structure that is synchronized by regular cycles of light during the day and darkness during the night. Future research must to prioritize the relationship between sleep disturbance and cancer development adding the role of melatonin in the process of carcinogenesis. Up to now the role of melatonin as a possibility for cancer treatment has been an enlightening and exciting one and this idea for future developments remains promising.

ACKNOWLEDGEMENTS

Funding for this study was provided by CAPES (scholarship to [N], and CNPq (fellowships to DAR).

REFERENCES