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REVIEW

Oxidative stress, cancer, and sleep deprivation: is there a logical link in this association?

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Abstract
Introduction Sleep disorders are associated with various human pathologies and interfere with biological processes essential for health and quality of life. On the other hand, cancer is one of the most common diseases worldwide with an average of 1,500 deaths per day in the USA. Is there a factor common to both sleep disorders and cancer that serves to link these conditions?
Discussion It is a normal process for cellular metabolism to produce reactive oxidant series (ROS). However, when the production of ROS overcomes the antioxidant capacity of the cell to eliminate these products, the resulting state is called oxidative stress. Oxidative DNA damage may participate in ROS-induced carcinogenesis. Moreover, ROS are also produced in the sleep deprivation process. The aim of this article is to review pathways and mechanisms that may point to oxidative stress as a link between sleep deprivation and cancer.

Keywords Sleep deprivation · Cancer · Oxidative stress

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Introduction

There is a major consensus that sleep is imperative for life maintenance [1–7]. On average, a third of our lives is spent in sleep [8]. Sleep controls mechanisms on several levels of biological organization, from genes and intracellular pathways to networks of cell populations and to all central neuronal systems, including those that control movement, arousal, autonomic functions, behavior, and cognition [9]. However, over the past several decades, there has been a trend towards a voluntary reduction in sleep time. Studies have shown several behavioral and physiological effects caused by insufficient sleep [10–13]. Reported consequences of insufficient sleep include neurocognitive alterations, psychomotor impairment, adverse mood effects, reduced quality of life, decreased work productivity, deficits in memory and decision making [14–16], cardiovascular diseases [17], increased risk for accidents [18–20], insulin resistance, and increased risk for obesity [21].

Additionally, there appears to be a link between sleep and immune defenses. Studies have indicated that reduced sleep may attenuate subsequent immune function [22, 23], impair the host defense mechanisms, and impact the susceptibility to viral and bacterial pathogens [24, 25]. Investigators have demonstrated that sleep deprivation decreases total cellularity of the bone marrow and peripheral blood concomitantly [26]. Furthermore, there is a decrease in natural killer cell mobilization and slowed recovery in healthy women after a poor night of sleep [27]. Thus, the effect of sleep on various endocrine and cytokine pathways suggests a relationship between sleep and the immune system [28].

Cancer is a major public health problem in the USA and other countries worldwide. Statistics show that one in four deaths in the USA is due to cancer. It is estimated that approximately 569,490 Americans will die from cancer in 2010, which is an average of 1,500 deaths per day [29]. According to the American Cancer Society, breast cancer is

the most common cancer diagnosed in US women and the second leading cause of death [30, 31] as is prostate cancer in men [32], following cancer of the lung and colorectum in both genders, accounting for half of total cancer deaths [29]. Oral cancer, globally, is the sixth most common cancer [33] and is a major problem in regions where tobacco habits in the form of chewing and/or smoking are prevalent. The occurrence of oral cancer varies by age, ethnic group, lifestyle, and a country's level of economic development [34]. There are numerous articles published in MEDLINE/-Pubmed databases that address questions focused on cancer and its epidemiology.

Oxidative stress occurs in a cell or tissue when the concentration of reactive oxygen species (ROS) generated exceeds the antioxidant capability of that cell [35]. ROS may interact with and modify the cellular protein, lipids, and DNA, resulting in altered target cell function [36–39). There is considerable evidence that ROS are involved in the pathogenesis of various human diseases [40]. Oxidative DNA damage may participate in ROS-induced carcinogenesis [41]. Moreover, there is evidence that ROS are also involved in the process of sleep deprivation [42–44]. Some investigators theorize that sleep decreases oxidative stress [42, 45] and that sleep is involved in the repair and detoxification process [46, 47]. This theory provides a link between sleep deprivation and carcinogenesis using oxidative stress as the common factor, specifically that sleep deprivation promotes oxidative stress and that oxidative stress may be causally linked to carcinogenesis. The pathways and signals for these associations between sleep deprivation and carcinogenesis remain unclear [3, 48–50].

Material and methods

The concept of this mini-review is to initiate a discussion about the topics of sleep deprivation and carcinogenesis by connecting them to oxidative stress and its signaling pathways. MEDLINE/Pubmed databases of the National Library of Medicine, Bethesda, Maryland, were searched for articles from 1992 to 2012, using the following terms: cancer, carcinogenesis process, sleep deprivation, and oxidative stress. Publications constituting case reports were excluded. Abstracts were reviewed, and relevant papers were identified. All relevant studies were included in this review.

Results

Oxidative stress network in cancer and sleep deprivation

Oxidative stress is defined as an imbalance between production of free radicals and reactive metabolites, the so-called ROS as well as reactive nitrogen species (RNS), both products of normal cellular metabolism. ROS and RNS are well recognized for playing a dual role as both deleterious and beneficial species, since they can be either harmful or beneficial to living systems [36]. Beneficial effects of ROS occur at low/moderate concentrations and involve physiological cellular responses to anoxia. Examples of this beneficial effect are defense against infectious agents and utility in a number of cellular signaling systems [51–53]. The harmful effects of free radicals are termed oxidative stress and nitrosative stress. For the purposes of this review, we will limit discussion to the oxidative stress process. Such oxidative stress occurs in biological systems when there is an overproduction of ROS with a relative deficiency of enzymatic and nonenzymatic antioxidants. This imbalance leads to damage of important biomolecules and whole cells with potential impact on the entire organism [54]. ROS evoke many intracellular events such as proliferation, gene activation, cell-cycle arrest, and apoptosis [55]. Excess ROS can damage cellular lipids, proteins, or DNA, inhibiting their normal function. Among the major biologically relevant free radical species in cells and biofluids are a one-electron product of oxygen reduction, the superoxide anion radical and its dismutation product. This product, hydrogen peroxide, activates nuclear factor-<kappa>B. Other oxidants induce protein tyrosine phosphorylation in immune cells [56, 57]. Because of this, oxidative stress has been implicated in a number of human diseases as well as in the aging process. Cells of the immune systems produce ROS during the oxidative burst triggered during inflammatory processes [58, 59]. Under these conditions, immune cells may react together to produce significant amounts of a much more oxidatively active molecule, the peroxynitrite anion (ONOO–). Peroxynitrite is a highly potent oxidizing agent that can cause DNA fragmentation and lipid oxidation [60].

Recent studies have shown an important role for ROS in tumor development [39, 61]. Under sustained environmental stress, ROS are produced over a long period, causing significant damage to cell structures and functions. Such damage may induce somatic mutations resulting in cancer [62]. Studies have shown interaction of ROS with all three stages of the mutation process: initiation, progression, and promotion [63–65]. ROS are known not only to attack DNA but additional cellular components including proteins and lipids leaving behind reactive species that can, in turn, couple to DNA bases. The most extensively studied DNA lesion is the formation of 8-hydroxyguanine [8-OH-G], the major premutagenic lesion generated from ROS [66]. This lesion is crucial because it is easily formed, becomes mutagenic, and is a potential biomarker of carcinogenesis. Such DNA mutation is a critical step in the carcinogenesis process. Elevated levels of oxidative DNA lesions have been noted in various tumors, though the exact role DNA lesions play in

carcinogenesis is not clear. DNA lesions have been linked with the initiation process of cancer [67]. ROS can also contribute to abnormal gene expression, blockage of cell-to-cell communication, and modification of second-messenger systems in the promotion stage, thus resulting in an increase in cell proliferation or a decrease in apoptosis of the initiated cell population [64]. Additionally, oxidative damage to protein-coding or noncoding RNA may potentially cause errors in protein synthesis or dysregulation of gene expression. Studies have shown that these mechanisms are present in various human diseases, especially chronic degeneration in neurons [68–71]. Accurate and reliable measurement of oxidative damage in the carcinogenesis process is relevant to understand the evolution of oxidative stress and distribution of ROS-induced damage in several pathologies.

Reimund [42] hypothesized that free radicals or ROS produced during waking are removed during sleep. Reimund postulated that sleep has an anti-oxidative function [42, 45]. Similarly, Ikeda et al. [45] showed that sleep decreases oxidative stress. Maintenance of steady state concentrations of ROS is essential for adequate functioning of aerobic organisms. However, in order to protect cells from the deleterious effects from ROS, a variety of systems has evolved [38]. Mammalian cells possess enzymatic antioxidant defenses to cope with ROS, such as superoxide dismutase (SOD) and glutathione peroxidase (GPx). SOD catalyzes the reaction of the superoxide anion to hydrogen peroxide and catalase. GPx catalyzes the breakdown of peroxides [38]. Reduced glutathione is a potent scavenger of free radicals and is also a substrate for glutathione-*S*-transferase, an enzyme responsible for a number of detoxification reactions within the cell [38]. Experimental studies have been performed to support the assertion that prolonged wakefulness may cause oxidative damage. Ramanathan and Siegel (2011) showed that sleep loss under sustained hypoxia leads to increased nitric oxide production in the rat hippocampus and increased total glutathione levels in the rat neocortex, brainstem, and cerebellum, protecting against oxidative stress. However, other investigators have described studies which measured oxidative stress in whole rat-brain homogenates under conditions of sleep deprivation, reporting the absence of oxidative stress in the brain [37, 72]. Apparently, the brain is capable of responding to stress by changing the activity of antioxidant enzymes, inducing heat shock proteins and upregulating uncoupling proteins, thus facilitating recovery from the oxidative damage [73, 74].

On the other hand, some investigators have demonstrated that sleep loss may induce oxidative stress in the brain and cause regional changes [43, 44, 47, 75]. It has been demonstrated that sleep loss produces effects similar to those that occur during aging [76–78]. Chang et al. (2008) reported that sleep deprivation significantly decreases hepatic phosphatidylcholine (the most prominent component of all plasma lipoprotein expressions) and sharply increases the oxidative stress in the hepatocytes. It has been demonstrated that phosphatidylcholine concentration may be reduced in many experimental-induced pathologies where oxidative stress is a contributing factor [79–81].

Obstructive sleep apnea (OSA) is a sleep-related respiratory disorder, which is characterized by repetitive episodes of complete (apnea) or partial (hypopnea) obstruction of airflow in the upper airway during sleep. It has been well documented that OSA plays an important role in several complications such as obesity, type 2 diabetes, metabolic syndrome, cardiovascular, and neurophysiological diseases [82–88]. Studies have also shown that hypoxia has been associated with various stages of tumor formation and progression [89–91]. Recently, studies have demonstrated the influence of sleep loss in cancer progression [50, 92]. The hypoxia caused by sleep disturbances may be key to increased levels of ROS. Hypoxia-inducible factor-1 (HIF-1) is a master regulator of O_2 homeostasis that controls multiple physiological processes by regulating the expression of hundreds of genes [93]. The over-expression of HIF-1 is correlated to proangiogenic mediators, such as vascular endothelial growth factor in tumor cells as well as apoptosis, glycolysis, and cell-cycle control mediators. These functions are central to the survival and expansion of malignant cell populations in an oxygen-deficient environment [94–97]. A recent study has demonstrated that the more severe the obstructive sleep apnea and sleep fragmentation is, the more severe the oxidative stress state becomes [98].

Oxidative stress appears to be an important factor in various human diseases. This review clearly implicates the role of ROS in various phases of the carcinogenesis process and the promotion of ROS in states of sleep loss. Our hypothesis suggests that oxidative stress may be a crucial factor in both processes. The causal effects between sleep deprivation and carcinogenesis remain to be elucidated.

Conflict of interest None.

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