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REVIEW ARTICLE

Potential Biological Consequences of Excessive Light Exposure: Melatonin Suppression, DNA Damage, Cancer and Neurodegenerative Diseases

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Abstract

This brief review summarizes some of the biological effects of light exposure at an inappropriate time (during the normal dark period) and the potential negative physiological consequences of this light exposure. Two major systems are significantly influenced by light at night. Thus, the circadian system and melatonin synthesis are altered when light is extended into the normal dark period or when the dark period is interrupted by light. This summary reviews the potential sequelae of chronic inappropriate light exposure and the suppression of endogenous melatonin levels. Given that melatonin is a free radical scavenger and antioxidant, conditions that involve free radical damage may be aggravated by light suppression of melatonin levels. The conditions of particular interest for this review are excessive DNA damage (which potentially leads to cancer), cellular destruction in neurodegenerative diseases and aging itself. Further research should be conducted to more accurately define the potential negative impact of light at abnormal times on animal and human pathophysiology.

Introduction

It has typically been assumed that the use of usual artificial light sources during the normal dark period is essentially inconsequential in terms of the physiology of mammals including man. With the discovery of an organ, the pineal gland, whose biochemical and secretory activity is inextricably linked to the prevailing light:dark environment, however, the implications of the possible "misuse" of light during the normal dark period have become of major interest. Throughout evolution, our predecessors were exposed to a photoperiodic environment where the duration of light (and darkness) was exclusively related to the interval that the sun was above the horizon. This allowed for highly regulated daily and seasonal changes in the light:dark cycle which control endogenous circadian [1] and circannual [2] rhythms. Not surprisingly, because of these predictable cycles of light and darkness, organisms evolved a complex of structures which translated this information into benefits for the species.

When Thomas Edison invented the light bulb, the human (and animal) environment changed dramatically [3,4]. With this advance, humans could readily manipulate the light:dark cycle allowing for light during the dark period. While benefits related to this discovery have been astronomical, not all of the resulting changes have served the human population well. Beyond the "abnormal" physio-

logical consequences associated with the application of light after sunset or before sunrise, issues related to the excessive use of artificial light have become a major concern. As a result, a number of international organizations have been formed to combat what now is conventionally referred to as "light pollution" and phrases such as "trespass light" have entered our lexicon.

The physiological consequences of excessive light exposure appear not to be trivial. The ability to maintain a lighted environment after sunset has encouraged humans to stay awake later into the night. In the United States an estimated 45 million people are sleep deprived nightly. Sleep deprivation is very costly in terms of reduced work efficiency as well as the development of disease and mortality, e.g., falling asleep while driving. Additionally, the inadvertent manipulation of intrinsic physiological processes, such as suppression of endogenous melatonin production, alters a variety of cellular functions which may lead to disease. This review summarizes some of the biological effects of the light:dark cycle both on a daily and on annual basis and points out some of the detriments that may be associated with excessive light exposure.

Light, Melatonin, DNA Damage and Cancer

The discovery of melatonin [5], its regulation by the light:dark cycle in the pineal gland [6] and the physiological impact of this organ [7] roughly 4 decades ago has spawned a vast amount of research and a plethora of reports illustrating the importance of light and melatonin in influencing physiological processes. While there are also numerous effects of light on organisms that are independent of a change in pineal physiology or melatonin secretion [4,8], this brief summary will consider some negative consequences of light that are related to the manipulation of melatonin production and secretion by the pineal gland.

In 1993, melatonin was discovered to be a free radical scavenger [9], being particularly effective in neutralizing the highly reactive hydroxyl radical (•OH) (like many organic molecules) when it was shown that each molecule of melatonin scavenges two •OH [10]. Given that this oxidant is a major contributor to cancer [11] and aging [12] and that ocularly-perceived light suppresses the production of the antioxidant melatonin [13], it became apparent that excessive light exposure may contribute to an increased cancer incidence given that DNA damage by free radicals is a common prelude to carcinogensis [11, 14–16]. The evidence is now compelling that melatonin effectively protects nuclear DNA from damage [17,18] and, in so doing, it may reduce the likelihood of cancer initiation [19]. While there are mechanisms to repair chromosomal damage [20], it is generally agreed that maintenance and repair processes are suboptimal because they require significant energy input which is normally diverted to reproduction at the expense of maintenance and repair. Thus, the mutilated products accumulate throughout a lifetime and increase the likelihood that the incidence of cancer increases in direct relation to age, i.e., it is an age-related disease [21].

While the •OH is certainly sufficiently reactive to damage the genome, other oxygen and nitrogen-based reactants are also capable of doing so. For example, the peroxynitrite anion ($ONOO^-$), which is formed when the superoxide anion ($O_2\bullet^-$) couples with nitric oxide (NO•), likewise damages DNA [22] and, as a consequence, would be expected to increase cancer risk. Likewise, a high energy form of oxygen, i.e., singlet oxygen ($^1O_2$), also is quite capable of attacking especially guanine bases and damaging DNA [23]. Additionally, the lipid peroxyl radical (ROO•) which is generated in lipid-rich cellular membranes during the oxidation of polyunsaturated fatty acids [24], may be capable of damaging DNA [14]. Likewise, the electrophilic carbonyl products [25] formed during the oxidative breakdown of lipids may be causative in DNA damage. Thus, the 4-hydroxyalkenals formed in membranes when free radicals and associated reactants oxidize lipids have mutagenic properties and produce detectable DNA damage [26]. Presumably it would be the lipid-related reactants formed in the nuclear membrane that would be most directly related to DNA damage, since they are in closest proximity to the genome. How these destructive agents are transported from the membrane to the DNA remains an unanswered question. Given, however, that melatonin is an effective inhibitor of lipid peroxidation [27], it would be expected also to reduce the associated DNA destruction and, hereby, protect against cancer. The latter possibly, however, has never been directly tested.

Since melatonin functions as a free radical scavenger and antioxidant [28], it would be expected that its concentration in body fluids and tissues would be proportional to their melatonin levels. While for most tissues such studies have not been performed, in the case of serum they have. In both rats [29] and humans [30], the nocturnal rise in serum melatonin concentrations is associated with a commensurate increase in the total antioxidant status of that fluid. The study in humans also revealed when light at night suppressed blood melatonin levels it likewise diminished the capacity of the serum to combat free radicals [30]. Thus, excessive light exposure at night not only deprives organisms of their augmented nocturnal melatonin increase, but this translates into reduced antioxidant protection. It has also been shown that exposure of rats to light at night accelerates DNA damage [20] and tumor growth [31]. While the former of these relates to reduction of the antioxidant melatonin, the latter may involve entirely different anticancer mechanisms of melatonin [32].

That melatonin protects DNA from free radical mutilation was shown shortly after the indole was documented to be a •OH scavenger [33]. In this study, rats were treated with massive quantities (300 mg/kg) of the chemical carcinogen, safrole, an agent that damages DNA via free radical mechanisms. The resulting products, DNA adducts, were measured in the liver 24 hours later. Safrole plus diluent-treated animals had abundant DNA damage 24 hours after administration of the carcinogen. When rats were treated with both safrole and either 0.2 mg/kg or 0.4 mg/kg of melatonin, the percent reduction in hepatic DNA adducts was 41% and 99%,

respectively. Such a marked inhibition was clearly much greater than anticipated considering the doses of melatonin used were 1,500 times (for the 0.2 mg/kg dose) and 750 times (for the 0.4 mg/kg dose) less than the quantity of safrole given (300 mg/kg).

Given the success of the initial experiment, Tan and colleagues [34] proceeded to test whether the physiological rise in melatonin at night impaired the ability of safrole to damage hepatic DNA. In this study, safrole (100 mg/kg) was given either during the day (when endogenous blood melatonin levels are low) or at night (when endogenous blood melatonin levels are 10–15 fold higher); the rats were killed 8 hours after safrole administration and hepatic adducts were measured. The results clearly showed that liver DNA damage was greater in the day-killed rats (low melatonin) than in the night-killed animals. Furthermore, preventing the nighttime rise in melatonin (by pinealectomy which reduces melatonin to the same level as does light exposure at night) increased DNA damage to the level of that seen in the liver of rats given the chemical carcinogen. Restoring the nighttime increase in melatonin by injecting the indole, again lowered the number of hepatic DNA adducts. This combination of experiments was the first to document the in vivo protection of DNA by melatonin and, additionally, they showed that the amount of melatonin endogenously produced by the pineal gland at night is sufficient to protect DNA from some free radical damage, even when the onslaught is massive.

Numerous other in vivo studies have confirmed the ability of melatonin to protect DNA from free radical thugs [16–18]. Likewise in may different organs melatonin has effectively stymied the destruction of the genome when free radicals are the marauding agents and a variety of methodologies have been employed to document the mutilation [35,36]. Ionizing radiation, due to the fact that it causes the hemolytic scission of the water molecule [37], is probably the best-known complete carcinogen. When water molecules, which are ubiquitously distributed in cells, are split, the •OH is generated and all cellular molecules come under attack. Melatonin, given prior to ionizing radiation, has proven highly protective against the resulting oxidation of DNA bases [38,39]. In one study in which human blood cells were irradiated, melatonin was compared with another well-known radioprotector, i.e., dimethylsulfoxide (DMSO), and found to be equally protective even when the concentration of melatonin was 500-fold less than that of DMSO [40]. Likewise, when purified calf thymus DNA was exposed to Fenton reagents, which generate the •OH, melatonin reduced the formation of 8-hydroxy-2-deoxyguanosine, a damaged DNA product, 60 and 70 times more effectively than did classic antioxidations (vitamins E and C, respectively) [41].

From the accumulated data it is obvious that melatonin is a powerful protector of nuclear DNA both in vitro and in vivo and factors which reduce its level in mammals, e.g., light exposure, would concomitantly increased free radical mutilation of the genome. This being the case, it follows that a rise in the incidence of cancer could be expected.

Light, Melatonin, Free Radical Damage and Aging

Free radical damage that persistently accumulates throughout the life of an organism is generally believed to contribute to the aging process and eventually to senescence. This is referred to as the free radical theory of aging and, since originally formulated by Harman [42], it has been endorsed by many scientists [43].

There are several features that make the free radical theory of aging viable. Firstly, in virtually all organs investigated, oxidatively damaged products in all cellular organelles do increase as age advances and, secondly, free radical generation itself accelerates as organisms become older. What has been perplexing, however, is that supplementing animals throughout life with various classical antioxidants has not substantially increased mean or maximal life span. In reference to the antioxidant melatonin, the outcomes of the studies have also not been totally uniform. The fact that endogenous melatonin levels diminish with age [44], however, has kept scientists focused on the possibility of an interaction between the drop in melatonin and the processes of aging. Also, in the human there are reports of a conserved melatonin rhythm in healthy elderly (as opposed to frail elderly); however, whether the preserved melatonin levels are a result or a cause of the good health or whether there is even a relationship between the two remains unknown.

An early report by Pierpaoli and Regelson [45] claimed mice lived longer than controls if they were given melatonin nightly in their drinking water throughout most of their life. The study, however, was poorly controlled and interpretation was complicated by the fact that no prolongation of life span was noted when melatonin was given during the day. Because of this apparent contradiction and other shortcomings of the report, the outcome of the investigation of Pierpaoli and Regelson [43] is not widely accepted.

Recently, Anisimov and co-workers [46] also claimed that mice treated with melatonin in their drinking water throughout much of their life (from 6 months of age) exhibited an increased life span but cautioned against its use because the longer-lived mice had a higher frequency of cancer. Given that cancer is an age-related disease, it is not surprising that longer-lived animals would develop more tumors. Thus, the claim that melatonin increased cancer risk is not tenable; had the control rats lived equally as long they may well have had a equivalent or even higher incidence of tumors. Furthermore, the findings of Anisimov et al [46] run contrary to numerous reports documenting an inhibitory effect of melatonin in the initiation [16] and growth [32] of tumors.

Perhaps the largest number of reports concerning the relationship of melatonin to the prolongation of life have utilized humans and have come from the laboratory of Lissoni [47]. In all of these studies melatonin was used as a supplemental drug in patients in which all conventional treatments for advanced cancer had failed. Thus, melatonin was given under the worst of conditions. Nevertheless, in the 1440 patients that were given melatonin under these extreme conditions, life span was extended and the quality of life was higher than in the control

patients not given supplemental melatonin. While the results are quite impressive, a shortcoming of this work is that the studies were not done in a double blind, placebo-controlled manner. Despite this, considering the positive nature of the results, the melatonin treatment procedures Lissoni [47] used should be considered as a possible supportive therapy for humans in the later stages of life.

Short-lived invertebrates are often used to test the efficacy of antioxidants and other molecules in prolonging life span. Recently, Bonilla et al [48] provided melatonin (100 μg/ml) in the nutrition medium to fruit flies throughout their life span. Relative to the controls not given melatonin, the melatonin-supplemented flies had a 33.2% increase in their maximal life span and a 13.5% increase in their median life span. In that other studies implicated free radical scavenging as the mechanism by which melatonin promoted longevity, the authors feel the antioxidant properties of the indole account for its ability to prolong life in this species.

What has been tested more widely than melatonin's effects on longevity has been the ability of the indole to defer the onset or to reduce the severity of age-related diseases [49,50]. For example, a variety of studies have shown that melatonin attenuates cell death induced by amyloid β-peptide [51], an agent believed to play a central role in Alzheimer's disease. The mechanisms of this protection are believed to relate to the antioxidant properties of melatonin [51]. In studies with Alzheimer's disease patients, melatonin supplementation was reported to defer the progression of the disease and to reduce the behavioral signs of this devastating condition [52–54].

Similar findings have been made with regard to experimental models of Parkinsonism [49,50]. This neurodegenerative condition is believed to be, in part, a consequence of free radical destruction of dopaminergic neurons in the pars compacta of the substantia nigra. The ability of neurotoxins to induce signs of Parkinson's disease in animals is reduced when they are given in conjunction with melatonin [55,56]. A recent study, however, claimed pharmacological levels of melatonin did not inhibit toxin-induced degeneration of the nigrostriatal pathway [57]. This investigation, however, was found to have many deficiencies which were pointed out by Yan [58].

Although the data showing melatonin's ability to reduce the biochemical and morphological toxicity of drugs that cause Parkinson-like signs in animals is not as uniform as the data for experimental Alzheimer's disease, nevertheless, when all the findings are evaluated they point to the possibility that melatonin may be protective against free radical-induced degeneration of dopaminergic neurons. While the antioxidant actions of melatonin in the central nervous system are usually cited as the reasons for the protective actions of the indole in these conditions, there are other means by which it may be protective. Of particular interest are the recent studies illustrating the ability of melatonin to influence mitochondrial physiology and energy metabolism [59,60]. These actions should be considered in any discussion of the potential mechanisms that may explain the beneficial neurobiological effects of melatonin.

Concluding Remarks

Especially the heavily industrialized countries use artificial light indiscriminately. Only in recent years have some of the biological consequences of this excessive light exposure been identified. Perhaps the major sequelae of light exposure during the night are the suppression of endogenous melatonin and the resetting of the biological clock.

While there have been few tests regarding the effects of excessive light exposure (and the consequential suppression of melatonin) on models of aging and age-related diseases, it is well documented that a reduction of melatonin due to pinealectomy accelerates the accumulation of free radical damage and seems to decrease life span in rats [61]. Presumably, the exposure of animals to long periods of light would cause similar changes. Since elderly individuals have reduced melatonin levels as a consequence of aging itself, it would seem judicious for them to preserve as much melatonin production as possible by avoiding light at night. This may not easy to achieve given that lights are often on at night in nursing homes to accommodate the health care professionals supervising the care of the elderly. Additionally, elderly and demented patients, because of their reduced sleep efficiency, often get up at night and, when they do, they probably turn on the light.

The chronic misuse of light during the normal dark phase may in fact impact health and general quality of life negatively. Certainly, it can no longer be assumed that the interruption of the dark period is innocuous or insignificant in terms of cellular physiology. Clearly, more research effort should be directed to investigating how reduced dark exposure influences animal and human performance and health, as emphasized by a recent publication showing an increased breast cancer risk in women who routinely perform night shift work [62].

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