



Review

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Artificial light at night: melatonin as a mediator between the environment and epigenome

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The adverse effects of excessive use of artificial light at night (ALAN) are becoming increasingly evident and associated with several health problems including cancer. Results of epidemiological studies revealed that the increase in breast cancer incidents co-distribute with ALAN worldwide. There is compelling evidence that suggests that melatonin suppression is linked to ALAN-induced cancer risks, but the specific genetic mechanism linking environmental exposure and the development of disease is not well known. Here we propose a possible genetic link between environmental exposure and tumorigenesis processes. We discuss evidence related to the relationship between epigenetic remodelling and oncogene expression. In breast cancer, enhanced global hypomethylation is expected in oncogenes, whereas in tumour suppressor genes local hypermethylation is recognized in the promoter CpG chains. A putative mechanism of action involving epigenetic modifications mediated by pineal melatonin is discussed in relation to cancer prevalence. Taking into account that ALAN-induced epigenetic modifications are reversible, early detection of cancer development is of great significance in the treatment of the disease. Therefore, new biomarkers for circadian disruption need to be developed to prevent ALAN damage.

1. Introduction

Light pollution has become a global concern, a fact substantiated by a recent resolution of the American Medical Association (AMA) 2 years ago asserting that light at night is a source of environmental pollution because it disrupts daily rhythms and suppresses nocturnal melatonin production by the pineal gland [1]. Artificial light at night (ALAN) exposures have been reported to be associated with serious ecological consequences and health risks including cancer [2–4]. Recently, the impact of light pollution as a new environmental risk factor and its relation to human breast and prostate cancers was discussed [5]. Breast cancer incidence has been increasing worldwide for the past few decades, being higher in developed countries than in undeveloped countries, suggesting that changes in lifestyle could account for the increase in breast cancer rates [6]. While much attention has been given to spatial variables in regard to lifestyle, less attention has been given to the impact of temporal variables on disruption of our biological clock, which is entrained by light/dark cycles. Unfortunately, in urbanized societies these reliable cycles are disappearing and losing their power of rhythmicity because of the extensive use of ALAN.

The cellular mechanisms underlying temporal organization of physiological processes and the consequence of their disruption are not fully understood; therefore, it is difficult to pinpoint the relations between health risks and disruption of temporal organization. Stevens *et al.* [7] raised a possible link between electrical power in breast cancer incidence and function of the pineal gland. Later, Stevens & Davis [8] raised the 'melatonin hypothesis' where the hormone indole is suggested to mediate the effect of ALAN exposure on breast cancer development. Melatonin production by the pineal gland occurs

mainly during the dark period and ALAN exposure abrogates the nocturnal enzymatic activity responsible for the production of the hormone [9]. The exact mechanism involved is not known, but it may be that the abolished nocturnal levels of melatonin increase circulating oestrogen levels and/or cause upregulation of oestrogen receptor- α positive breast cancer and eventually cause increased breast endothelial cell proliferation [10,11]. Other potential physiological and/or molecular dysfunctions mediated by disruption of the typical nocturnal melatonin rhythm such as metabolic, endocrine and epigenetic abnormalities have also been suggested [12,13].

Accumulated evidence has demonstrated that epigenetic modifications are involved in the pathogenesis of several malignant diseases, including prostate, gastric, lung and breast cancers [14–17]. In general, epigenetic mechanisms involve activation of oncogenes and deactivation of cancer suppressor genes, in which the gene expression in both cases is affected by chromatin remodelling of its binding sites of transcriptional factors [18]. Epigenetic regulation in breast cancer is increasingly being reported in both human and animal models. In the present review, we consider the evidence for association between ALAN and breast cancer incidences mediated by the suppression of melatonin production. We also review recent advances on the molecular regulation of epigenetic modifications in breast cancer, including aberrant DNA methylation and histone acetylation of related oncogenes and cancer suppressor genes. Finally, epigenetic modifications are also discussed here as a possible genetic basis for mediating the malignant effects of ALAN exposure.

2. Artificial light at night as a risk factor for breast cancer

In the past decade, several epidemiological studies have investigated the co-distribution between breast cancer incidence and light pollution [19–22]. These studies and others find compelling evidence supporting a potential role of electric light at night on breast cancer risk. In Israel, a significant positive correlation between night illumination levels (collected in the framework of the US Air Force Defense Meteorological Satellite Program) and breast cancer incidence (National Cancer Registry, Israel) was revealed, but not with lung cancer as a negative control [23]. In another study, Kloog *et al.* [24] revealed that breast cancer co-distributes with light pollution worldwide, whereas the correlation analysis failed to establish any significant relation between light at night and negative controls, colorectal, larynx and liver cancers.

Typically, bedroom spectral and irradiance compositions originating from indoor or outdoor illumination (light filtering through windows) are expected to be characterized by both low wavelength frequencies and low irradiance levels, particularly during the duration of nocturnal sleep. Indoor dim light signals during nocturnal sleep time can still penetrate throughout closed eyelids and be detected via sensitive retinal photoreceptors to regulate circadian functions. Supportively, the ‘blind’ mole rat *Spalax ehernbergi*, can detect light of both short and long wavelengths (479 nm and 697 nm, respectively) under increasing light intensities (73–498 $\mu\text{W cm}^{-2}$), though the eyes of the species are severely degenerate and the vestigial retina is completely concealed by a thick integument of skin and fur [25–27].

Exposure to blue wavelength light ($\lambda_{\text{max}} = 450 \text{ nm}$) from light-emitting diodes delivered through closed eyelids has also been shown to robustly suppress nocturnal melatonin levels and delay the melatonin onset phase [28,29]. Although the eyelids can filter optical signals and show an inverse relation between transmittance and wavelength frequency, light signals can still be detected on the retina and modulate circadian regulation [30].

In a longitudinal study, Verkasalo *et al.* [31] investigated the correlation between the degree of visual impairment (five categories ranging from moderate to total blindness) and breast cancer incidences in Finland. In their study, they cross-linked 17-year data from the Finnish Register of Visual Impairment and from the Finnish Cancer Registry to include 10 935 women with different visual impairment contributing to 56 000 person-years at risk. The analyses showed a significant inverse dose-dependent relation between the degree of visual impairment and cancer risk, whereby a 50% decrease in breast cancer incidence was estimated among totally blind women. Furthermore, the results of this study suggest a potential role for light in breast cancer prevalence mediated by suppression of melatonin production by the pineal gland.

In mammals, retinal photoreceptors serve a dual function of reacting to light stimulus for conscious sight and circadian entrainment. These functions are suggested to be supported by two distinct classes of retinal photoreceptors. Light detection for conscious sight is mediated by the conventional image-forming photoreceptors, rods and cones expressed in the outer retina. At the circadian level, the light signals are mediated by non-image-forming photoreceptors located in the inner retina and intrinsically photosensitive [32–34]. In gene-targeted studies, mice lacking the intrinsically photosensitive non-image-forming photoreceptors displayed intact visual perception and were incapable of detecting light for circadian responses, indicating that these photoreceptors may possibly be a central component in the circadian system, but not obligatory for visual perception [35]. Studies in totally blind humans demonstrated that light exposure can suppress melatonin production and phase shift its circadian rhythm [36,37]. These studies in human and non-human animals suggest a functional separation between image-forming and non-image-forming photoreceptors. Nevertheless, several studies in transgenic mice with dysfunction non-image-forming photoreceptors showed that these mice retain sufficient retinal photosensitivity to derive some responses [38–40]. Furthermore, blind individuals with low vision perception [41] and totally blind animals [42] display functional photo-entrained circadian responses such as circadian shifting, melatonin suppression and thermoregulation. Overall, these studies suggest that both the image-forming and non-image-forming photoreceptor pathways work simultaneously to provide complete circadian perception.

Generally, the literature suggests that women have longer habitual sleep time with 7–9 h in bed [43–46], higher melatonin amplitude and earlier melatonin peak levels compared with counterpart men [47]. Furthermore, tendencies for reduced sleep efficiencies and sleep difficulties of women have been also reported recently [48]. Taking into account the sleeping patterns described for women and the fact that light can certainly penetrate closed eyelids and efficiently alter circadian responses, bedroom ALAN should be of concern to women, particularly in modern societies.

In a comparative case–control study, the relations between night illumination conditions (emerging from outdoor and

indoor lighting) in the sleeping habitat and breast cancer risk were assessed for 1679 Israeli women (794 breast cancer patients and 885 controls) [49]. The results revealed a significant association between breast cancer incidence and ALAN coming from inside (light and/or TV on) and outside (impinging from street lamps, billboards, sports or shopping centres) the bedroom. To the best of authors' knowledge, this is the first study to show that not only are shift workers in a high risk group for breast cancer but also women sleeping in illuminated habitats. The effect of ALAN on breast cancer development is suggested to be mediated by the night-time suppression of the typical daily rhythm of melatonin, because the pineal hormone is produced in the dark phase of the 24 h cycle [50,51].

3. Melatonin suppression

The neuro-hormone melatonin (*N*-acetyl-methoxytryptamine) produced and secreted from the pineal gland under dark conditions (known as the 'hormone of darkness') is considered a 'Jack of all trades' as it is involved in many of our body functions [51,52]. Melatonin production in the pineal gland is sensitive to light and it was shown that even exposures of low intensity [53] and short duration [54] will suppress its production. Short wavelengths are very effective in suppressing melatonin production, which is wavelength dependent [55,56]. In human [57,58] and animals [59,60], pineal melatonin production is highly photosensitive to light of short wavelength (i.e. blue light). More recently, nocturnal production levels of melatonin have been shown to be inversely correlated with irradiances of narrowband blue LED light (peak $\lambda = 469$ nm; half peak bandwidth = 26 nm) and the suppression impact of this narrow spectrum was more severe than that of 4000k white fluorescent light at twice the energy of the former [56,61]. Interestingly, blue-shifted photosensitivity of the retinal non-visual photoreceptors is postulated to be a conserved adapted feature of all vertebrates, which initially was adapted to the local blue-rich spectral composition of oceanic environments and selected later to be a unique ocular feature of all terrestrial vertebrates [62]. ALAN pollution has become a major problem for both environment stability and human health. The association between high levels of ALAN and cancer incidence is one of the most discussed health issues in industrialized civilization [63]. The unfavourable impacts of ALAN exposure on tumorigenesis are expected to be associated with the suppression of nocturnal melatonin production [12]. One promising mechanism of action of melatonin-induced oncostatic effects is based on extensive research showing prominent epigenetic modifications in cancer cells [64]. Melatonin is suggested to be potentially effective in the treatment of breast cancer progression by modulating epigenetic markers [65].

4. Epigenetics

It was the British biologist Conrad H. Waddington [66] who defined epigenetics as the study of the way in which environment influences modification of traits (phenotypes) without a change in DNA sequence. He used this term for describing the interactions between genes and their products. In general, epigenetic modifications can be divided into two categories, DNA methylation and post-transcriptional histone modifications. In mammals, methylation of promoter CpG

sites by DNA methyltransferase plays a key role in the regulation of gene expression [67]. CpG methylation inhibits gene expression by preventing transcriptional factors binding to the gene promoter, whereas DNA hypomethylation increases the transcriptional activity of the gene [68,69]. Moreover, the N-terminal of histone proteins can undergo variant structure remodelling including methylation, acetylation, phosphorylation and other reactions. The most common histone remodelling is the acetylation of a lysine residue of the N-terminal ends. This modification increases gene expression by chromatin opening which makes it more accessible for transcriptional factors [70,71]. In contrast to DNA methylation, histone modifications can either lead to chromatin opening or closing, resulting in increasing or decreasing transcriptional activity of genes. The flexible regulation of gene expression by histone remodelling depends on the specific type of modification and the exact modified residue [71,72]. These epigenetic DNA modifications play a pivotal role in regulation of physiological, pathological, homeostatic and developmental mechanisms for survival [73,74].

As epigenetic modifications can occur in the adult mammal, they offer an alternative view in regard to the molecular mechanism involved. For example, DNA methylation of CpG sites will increase the rate of mutations of methylated cytosines by an order of magnitude [75]. It was also demonstrated that when DNA methylation patterns are altered owing to an environmental stimulus, these CpG sites will be more vulnerable to mutation than non-methylated sites [76].

Endocrine disruptors are environmental chemicals that affect the function of the endocrine system by mimicking or blocking the actions of hormones, altering hormone signalling or disrupting hormone production [76]. Endocrine disruption can have profound consequences owing to the crucial role of hormones in development and health [77]. The mechanism of action mediating genetic effects of environmental factors is not clear. However, several studies suggest that epigenetics plays a definite role in regulating environmentally induced genetic responses [78,79]. DNA methylation and histone proteins have been demonstrated to mediate a wide range of pathological conditions such as diabetes [80], reproductive disorders [81], autoimmune diseases [82], neurodegenerative diseases [83] and cancer [84] to environmental factors. A recent review, which has focused on the complex interplay between environmental factors and endocrine-related disorders, concluded that epigenetic modifications act as flexible mediators between environmental changes and endocrine disorders, and these flexible mediators show great potential for explaining endocrine flexibility in regulating developmental responses of individuals over their lifespan [85]. Therefore, the elucidation of the role of epigenetics in endocrine disruptor actions and in the aetiology of disease will definitely provide an insight into diagnosis and therapy of diseases resulting from environmental exposure [86]. Furthermore, it is likely that it will also be critical to consider epigenetic modifications in cases of normal endocrinology and metabolic events.

5. Artificial light at night, melatonin, epigenetics and breast cancer nexus

Disruption of the biological rhythms by ALAN has been increasingly associated with different types of malignant

tumours, particularly breast cancer. Temporal disruptions from ALAN have been suggested to increase breast cancer risk among women in response to shift work and sleep deprivation [87]. Furthermore, a dose–response meta-analysis of the malignant effect of night shift work provided clear evidence supporting a direct dose-dependent response for breast cancer with increasing years of night shift work [88]. According to several epidemiological screening studies, exposure to ALAN increases breast cancer risk by abolishing the distinctive night-time production of melatonin by the pineal gland [89]. Supportively, a high risk of breast cancer was reported in women with sleep deprivation during the sensitive night period when melatonin levels are expected to be at their highest [90]. In mice, ALAN exposure has been shown to stimulate breast and prostate cancer growth and development of metastases; these adverse effects of ALAN were lessened by exogenous melatonin treatment [91,92]. Furthermore, results of several studies demonstrate anti-oncogenic activity of melatonin in breast and prostate cancers [65,93]. The mechanism of action underlying the anti-oncogenic activity of melatonin has not been completely established, but the involvement of melatonin in regulation of epigenetic responses through DNA modifications has been suggested [65,91].

Currently, it is well recognized that epigenetics is an important aetiological factor of tumours, including breast cancer. Principally, the genome of cancer tissues presents both global hypomethylation and promoter hypermethylation of tumour suppressor genes [94]. In breast cancer, global hypomethylation is frequently linked with genomic instability and upregulation of oncogenes [95]. Hypomethylation within CpG sites promotes epigenetic chromatin closing and further results in silencing of tumour suppressor genes, cell proliferation and tumour development [96]. Finally, promoter hypermethylation of breast cancer oncogenes has been suggested to silence growth regulatory genes resulting in anomalous cell proliferation, where global hypomethylation stimulates the expression of metastatic genes required for cancer cells dissemination [97]. While these epigenetic aberrations are well documented in tumour processes, little is known about how these DNA methylation abnormalities are initiated and controlled. One proposal envisages a role for melatonin in mediating environmental epigenetic effects.

Epigenetic modifications of malignant processes by melatonin are still unclear. However, melatonin can regulate epigenetic modifications in cancer cells by both DNA methylation and histone protein remodelling. In breast cancer, melatonin is involved in downregulation of related oncogenes either by methylation of the Aromatase gene (CYP19) or deacetylation of CYP19 histones [98]. In melatonin-treated human breast cancer cell lines, the increased DNA methylation corresponded with downregulation of the oncogenes EGR3 and POU4F2/Brn-3b and upregulation of the tumour suppressor gene GPC3 [99]. Furthermore, melatonin treatment can suppresses human breast cancer cell proliferation by deacetylation of oncogenes, resulting in chromatin closing and thus inhibition of the binding of transcriptional factor required for triggering the expression of oncogenes [100].

In 4T1 breast cancer inoculated, short-day acclimated BALB/c female mice, ALAN exposure of short wavelength illumination (450 lux and 469 nm) resulted in significant global DNA hypomethylation and this epigenetic effect was inhibited by exogenous melatonin during the night time when light interference was applied [91]. Therefore, it is of

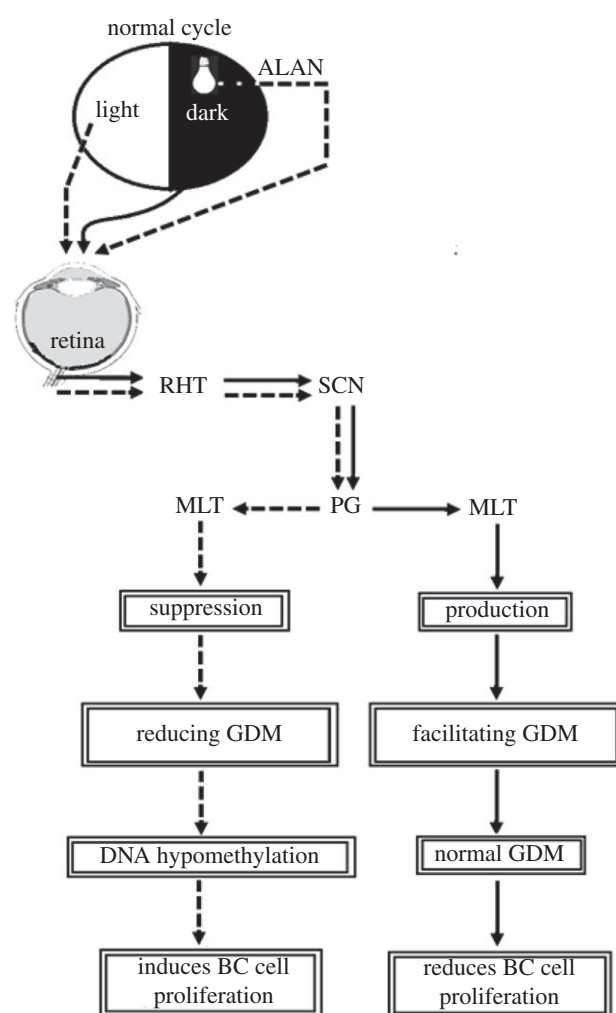


Figure 1. Link between environmental illumination conditions and epigenetic-induced breast cancer (BC). Light signals are the most proximate cues affecting the master circadian clock in the suprachiasmatic nucleus (SCN). Light signals are conveyed from the retina to the SCN through the retino-hypothalamic tract (RHT) and thereafter to the pineal gland (PG). Melatonin (MLT) synthesis takes place in the PG stimulated by darkness during the dark phase and inhibited during both the normal light phase and artificial light at night (ALAN) mainly of short wavelength. MLT regulates epigenetic cancer-related pathways such as global DNA methylation (GDM), in this case preventing the loss of methyl groups.

prime importance to evaluate whether exogenous melatonin can counteract blue ALAN-induced aberrant DNA methylation and moderate epigenetic cancer development. Taken together, the association between epigenetic effects of melatonin, tumorigenesis and the suppressive action of ALAN on nocturnal melatonin production by the pineal gland, support the nexus between ALAN exposure, melatonin suppression and breast cancer progression. The connection between ALAN and cancer-related epigenetic pathways, particularly global DNA methylation, is presented in figure 1. Accordingly, the light signals generated in retinal non-image-forming photoreceptors that are intrinsically photosensitive [32] regulate melatonin production by the pineal gland which in turn mediates the anti-cancer effect of aberrant epigenetic modifications such as DNA methylation.

Although, several studies have been conducted in human and non-human animals regarding the ecological and physiological impacts of ALAN, the threshold characteristics of ALAN for triggering malignant diseases such as breast

cancer remain to be defined. To assess clinical relevance, initial *in vivo* studies in animal models and *in vitro* human cell lines are warranted to characterize spectral, irradiance and duration thresholds of ALAN from different illumination sources, particularly new lighting technologies such as the blue light-emitting diodes. In these studies, melatonin suppression and epigenetic responses, particularly global and local DNA methylation of oncogenes and cancer suppressor genes, can be used as biomarkers for constructing the threshold exposure to ALAN. In the area of epidemiology, studies should be carried out to examine the relation between ALAN and cancer incidences more fully, in which bedroom light characteristics and habitual sleeping with ALAN should be the main focus. In the area of early detection and treatment, studies should be conducted to explore the role of melatonin and epigenetic modifications as biomarkers for early detection, prevention and treatment of ALAN related cancers. Finally, the combined results from these studies are expected to increase awareness, knowledge and behavioural changes towards developing new outdoor and indoor light pollution standards that would comprise power efficiency, energy saving and, above all, less risk to human health than the current standards.

6. Conclusion

Light pollution is an increasing problem compromising the timing of pivotal biological activities. Cancer incidence,

particularly breast cancer, is among the most challenging health problems resulting from light pollution in our modern lifestyle. Epigenetic modifications are imperative for gene regulation and expression, and have robust effects on development of diseases such as tumorigenesis. Melatonin can provide the missing link between environmental disruption of biological rhythms and the epigenetic molecular machinery which regulates global DNA hypomethylation in oncogenes and local DNA hypermethylation in tumour suppressor genes. Although substantial and significant progress has been made in understanding the molecular basis of epigenetic-induced tumorigenesis, more research is still warranted, particularly for characterizing the spectral and irradiance sensitivity of the biological clock to ALAN, a novel source of pollution. Furthermore, the exact relation between circadian disruption, melatonin suppression, and aberrant DNA methylation and histone acetylation requires further research. Understanding the interplay between environmental factors and epigenetic remodelling of certain oncogenes would be of great interest for both establishing sustainable illumination and discovering novel biomarkers for cancer. DNA methylation and melatonin level profiling in high risk groups, particularly night shift workers, are important for the prevention, early detection and treatment of developing cancers.

Conflict of interests. We have no competing interests.

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