# We are IntechOpen,
# the world's leading publisher of
# Open Access books
# Built by scientists, for scientists

## 6,900
Open access books available

## 186,000
International authors and editors

## 200M
Downloads

## 154
Countries delivered to

Our authors are among the

## TOP 1%
most cited scientists

## 12.2%
Contributors from top 500 universities

**CLARIVATE ANALYTICS**
**BOOK CITATION INDEX**
**INDEXED**

**WEB OF SCIENCE**™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

## Interested in publishing with us?
## Contact book.department@intechopen.com

**Chapter**

# Consequences of Artificial Light at Night: The Linkage between Chasing Darkness Away and Epigenetic Modifications

*Abraham Haim, Sinam Boynao and Abed Elsalam Zubidat*

## Abstract

Epigenetics is an important tool for understanding the relation between environmental exposures and cellular functions, including metabolic and proliferative responses. At our research center, we have devolved a mouse model for characterizing the relation between exposure to artificial light at night (ALAN) and both global DNA methylation (GDM) and breast cancer. Generally, the model describes a close association between ALAN and cancer responses. Cancer responses are eminent at all light spectra, with the prevalent manifestation at the shorter end of the visible spectrum. ALAN-induced pineal melatonin suppression is the principal candidate mechanism mediating the environmental exposure at the molecular level by eliciting aberrant GDM modifications. The carcinogenic potential of ALAN can be ameliorated in mice by exogenous melatonin treatment. In contrast to BALB/c mice, humans are diurnal species, and thus, it is of great interest to evaluate the ALAN-melatonin-GDM nexus also in a diurnal mouse model. The fat sand rat (*Psammomys obesus*) provides an appropriate model as its responses to photoperiod are comparable to humans. Interestingly, melatonin and thyroxin have opposite effects on GDM levels in *P. obesus*. Melatonin, GDM levels, and even thyroxin may be utilized as novel biomarkers for detection, staging, therapy, and prevention of breast cancer progression.

**Keywords:** melatonin, thyroxin, light-at-night, global DNA methylation, diurnal species, breast cancer, biomarkers

## 1. Introduction

Since the invention of electrical light in 1879 by Thomas Alva Edison, artificial light at night (ALAN) has become a definitive feature of human development with accelerated increase concurrent with urbanization and industrialization. The light emitted from the original bulb of Edison known as incandescent bulb was weak, with a dominant long wavelength emission above 560 nm. Most of the incandescent electrical energy is dissipated as heat energy, thus making this type of illumination energetically inefficient. Therefore, new illumination technologies were developed, in order to discover efficient bulbs that transfer most of the electrical energy into light. White fluorescent and light-emitting diodes (LED) are examples of energy efficient bulbs developed to decrease carbon dioxide production from electric power plants, thus lessening the greenhouse effect. One of the adverse outcomes of using efficient

illumination at night time is the emission of shorter wavelengths (SWLs) that further exacerbate the health and ecological problems associated with a new source of environmental pollution currently known as ALAN [1–3]. Light pollution is increasing rapidly, resulting in a more illuminated world, where outdoor and indoor illumination sources are increasing ALAN in developed and developing countries [4, 5].

From an anthropological perspective, electric light has brought pronounced benefits including advancing urbanization and industrialization by increasing productivity, but we are also increasingly being aware of serious public health and ecological negative impacts emerging from disrupting the adaptive temporal organization of biological responses [6–8]. Certainly, multiple studies have shown the effects of light pollution on social, behavioral, physiological, and molecular responses in many different taxa, including insects [9], fishes [10], amphibians [11], reptiles [12], birds [13], and mammals [14], as well as plants [15]. Some of the most disturbing effects of ALAN on health are metabolic dysfunction and cancer progression [2, 16]. In mice and humans, several lines of evidence suggest a close association between ALAN levels and both obesity and breast cancer progression [17–19]. Here, we focus on ALAN as a novel environmental polluter that disrupts biological timing (temporal organization) and consequently may provoke severe health risk, particularly breast cancer development through epigenetic modifications. First, the mammalian photoperiodic system is reviewed in relation to light perception and downstream endocrine responses for timing biological rhythms. Thereafter, we discuss the sensitivity of the photoperiodic system to the spectral composition of ALAN, particularly SWL illuminations. We further discuss the ALAN signal transduction pathway involved in melatonin suppression and aberrant epigenetic modifications in breast cancer progression. Therefore, melatonin and epigenetics are suggested as new biomarkers for breast cancer prevention. Finally, melatonin and thyroxin treatments in the diurnal fat sand rat (*Psammomys obesus*) are discussed in relation to their potential role in mediating the environmental exposures at the molecular level *via* epigenetic modifications, particularly global DNA methylation (GDM).

## 2. The mammalian photoperiodic system

In an early study, it has been demonstrated that the blind mole rat (*Spalax ehrenbergi*) responded differently to short and long photoperiod manipulations in regard to its capability to cope with low ambient temperature exposure [20]. Results of a more recent study on *S. ehrenbergi* manifested robust and differential responses in metabolism, stress, and melatonin levels to ALAN of different spectral compositions and acclimation duration [21]. These results suggested that the vestigial retina of this species still expresses photoreceptors that are involved mainly in nonvisual response. Currently, the mammalian eye is described as a dual-function organ, expressing photoreceptors for both visual and nonvisual responses [22]. The visual response is mediated by two distinct photoreceptor types, rods and cones, which control scotopic vision and photopic vision, respectively [23]. The nonvisual responses are mainly mediated by intrinsically photosensitive retinal ganglion cells (ipRGCs) that express the photopigment melanopsin. Even though the ipRGCs are connected with rods and cones by bipolar cells, they mediate nonvisual responses including photo-entrainment of biological rhythms [24].

First, photoperiodic signals are perceived by ipRGCs that express the photopigment melanopsin [25]. The detected environmental light signal by the ipRGCs synchronizes the master circadian clock located in the mammalian hypothalamic suprachiasmatic nucleus (SCN) by the retinohypothalamic tract (RHT). The

SCN regulates the synthesis and release of the hormone melatonin by the pineal gland through multiunit sympathetic nerves from the superior cervical ganglion (SCG). The SCG presynaptic sympathetic terminals release noradrenalin that interacts with postsynaptic α- and β-adrenergic receptors to regulate synthesis and release of pineal melatonin [26]. In mammals, the activity of the adrenergic SCG terminals that innervate the pineal gland is stimulated by darkness and inhibited by light [27]. Under dark conditions, stimulation of the pineal adrenergic receptors increases cellular cAMP levels leading to the activation of aryl-alkyl-amine-N-acetyltransferase (AA-NAT), a key enzyme in melatonin synthesis [28]. The nocturnal increase in the enzymatic activity of AA-NAT is strongly inhibited by light exposure, consequently leading to a rapid decrease in nocturnal melatonin levels [29]. The pinealocytes are the primary neuroendocrine cells that synthesis melatonin by sequential hydroxylation and decarboxylation of its precursor tryptophan to serotonin. Thereafter, serotonin is acetylated by the rate-limiting enzyme AA-NAT and methylated by the enzyme hydroxyindole-O-methyltransferase (HIOMT) to the final product of melatonin [28, 30]. Finally, the activity of both AA-NAT and HIOMT is under photoperiodic control at the transcriptional level showing distinct diurnal rhythms with peak levels during night and nadir levels during the day [31].

## 3. Melatonin suppression as an indicator of SWL pollution

In most mammals, no level of light exposure is powerless regarding melatonin suppression and even low intensity and short-term exposures can reduce its production and lead to decreased circulating levels [32, 33]. Nonetheless, melatonin suppression is strongly wavelength- and irradiance-dependent, with faster and more robust response at the SWL end of the visible spectrum below 500 nm [19, 34, 35]. A large-scale study comparing the effect of different light technologies on melatonin production in humans demonstrated that the strongest suppression occurred in response to 4000 and 5000 K LED lights compared with incandescent, halogen, and fluorescent counterpart lightening systems [36]. Narrow bandwidth blue LED exposure (λ = 469 nm, ½ peak bandwidth = 26 nm) decreased melatonin levels in an irradiance dose-dependent manner, and this light was more effective in decreasing the hormone levels compared with that of 4000 K of white fluorescent at twice the energy of the latter [37]. In horses, 1 h exposure of 3 lux SWL blue light (468 nm) administered only to one eye was sufficient to decrease melatonin levels compared with control animals [38].

Furthermore, blue LED pulses (2-s pulse every 1 min for 1 h, λ = 450 nm) administrated through closed human eyelids markedly suppressed nocturnal melatonin levels and delayed the melatonin onset phase [39–41]. While the eyelids can weaken irradiance and wavelength ([42], light signals can still penetrate them, be detected by the retinal photoreceptors, and affect circadian regulation [43]. In humans, blue LED exposure (40 lux, 470 nm) emitted from display screens (tablets and computers), suppressed nocturnal melatonin in a duration-dependent manner [44, 45] and melatonin suppression showed higher sensitivity to wavelength compared with intensity manipulations [46].

Together, it is clear that the adverse effects of light pollution are strongly manifested by the SWL portion of the spectrum. As the LED illumination is becoming ubiquitous in every aspect of our modern life, the expected increase in light pollution may exacerbate the problem since higher irradiance and shorter wavelengths would be emitted by the energy efficient technology [47, 48]. Accordingly, the American Medical Association [49] passed a resolution in 2016 calling upon

communities in the USA to avoid using LED lighting in public domains as it is enriched with SWL [49]. In summary, SWL-ALAN is a source of pollution and should be removed from public spaces through legislation.

## 4. ALAN as an environmental change and a model for studying epigenetic modifications

The flexibility and the sensitivity of the endocrine system play an adaptive role in determining the success and survival of organisms under contentiously changing environmental conditions in their habitat [50]. As the endocrine system regulates several functions, it is expected to be the first system to respond to environmental changes such as ALAN by coordinating body functions to maintain homeostasis during the exposure. The core stimulus-response of the endocrine system to ALAN relies on four main components, including the pineal gland, the hypothalamic-pituitary-gonadal (HPG) axis, the hypothalamic-pituitary-thyroid axis (HPT), and the hypothalamic-pituitary-adrenal (HPA) axis [51]. The elaborated hormonal responses generated by these axes to ALAN exposure might be mediated by transcriptional regulation of gene expression *via* epigenetic modifications [52]. Therefore, epigenetic-elicited alteration in gene expression is a potential transduction pathway by which hormonal responses (e.g., melatonin) may mediate environmental exposures (e.g., ALAN). Conversely, the ALAN-induced alteration in melatonin rhythms may also exert endocrine responses *via* epigenetic modifications [53].

The incidences of breast and prostate cancers show close association with light pollution particularly in urbanized and industrialized regions [2, 54]. Several epidemiological studies have found direct association between light pollution and incidence of breast cancer in women as well as prostate cancer in men [18, 55, 56]. Furthermore, the strong association between light pollution and cancer incidences displays divergent spatial disruption with higher incidences in urban compared with rural regions [57, 58]. Evidence for direct association between ALAN and cancer development comes also from animal studies.

In rats, ALAN exposure accelerated the growth rates of induced-tumors, includ-ing mammary cancer [59–62]. Studies under control conditions demonstrated that 30-min ALAN per midnight emitted from either white fluorescent or blue LED illuminations can accelerate tumor growth and lung metastatic activity in female BALB/c mice inoculated with 4T1 mammary carcinoma [63, 64]. Indeed, the effects of ALAN on tumor growth have been demonstrated at different spectral composi-tions with markedly higher cancer burden in response to lighting exposure lower than 500 nm [19].

These studies have related the increased cancer burden to aberrant epigenetic modifications, particularly advanced global DNA hypo-methylation. Promoter hyper-methylation of cancer suppresser genes and global DNA hypo-methylation are characterizing epigenetic patterns in breast cancer cells [65, 66]. These aber-rant epigenetic modifications may contribute to increase cancer burden by elicit-ing genomic instability and activation of both oncogenes and metastatic related genes, as well as silencing tumor suppressor genes. Generally, prominent decreased methylation in repetitive DAN elements is a common trait in most cancer cells [67]. Demethylation of pro-metastatic genes is normally suppressed by DNA methylation and might advance gene overexpression leading to genetic instability that increases the risk of developing cancer [68, 69]. DNA hypomethylation can be detected at an early stage of breast cancer and is correlated with the degree of tumor differentiation [70, 71]. Altogether, the close association between aberrant

DAN hypomethylation and tumorigenesis, particularly of breast cancer, is well-established, but the underlying mechanism remains poorly understood, especially how the adverse ALAN effects are mediated.

## 5. Melatonin as a mediating signal linking ALAN and epigenetic-induced cancer

Since the melatonin hypothesis was first proposed during the late twentieth century by Stevens [72], multiple studies in human and nonhuman animals have provided direct and indirect evidence that melatonin suppression by ALAN could impose health risks, including metabolic disorders and cancer progression [2, 54]. The importance of melatonin in the regulation of several biological functions depends heavily on its lipophilic and hydrophilic traits that make it omnipresent in all cell compartments, principally in the nucleus [73]. Indeed, low levels of 6-sulfatoxymelatonin (6-SMT), the major metabolites of the hormone in urine [74], have been demonstrated to correlate with increased risk of breast cancer in postmenopausal women [75–77]. Furthermore, women with blindness or long sleep duration (elevated melatonin levels) present reduced breast cancer risk relative to normal women [78, 79].

Physiological blood concentration of melatonin blocked human leiomyosarcoma (soft tissue sarcoma) proliferation by inhibiting tumor metabolic and genetic pathways presumable by suppression of cellular cAMP levels *via* melatonin receptor [80]. In hepatocellular carcinoma-induced mice, melatonin treatment suppressed tumor cell proliferation through arresting the cell cycle [81]. The metastatic activity of oral squamous cell carcinoma was notably reduced by melatonin-mediated inhibition of tumor-associated neutrophils [82], inflammatory cells involved in promoting several solid tumors [83]. Similarly, the anti-oncogenic property of melatonin has been demonstrated also in other cancer types, including lung [84], gastric [85], ovarian [86], and colon [87], as well as breast cancers [88].

Melatonin could mediate its effects of cancer development *via* epigenetic modifications, particularly GDM [89]. Melatonin treatment to MCF-7 cell lines significantly increased DNA methylation that was associated with increased transcriptional levels of the tumor metastasis suppressor gene glypican-3 and decreased expression levels of the oncogenes EGR3 and POU4F2/Brn-3b [90]. In estrogen-receptor-related breast cancer, melatonin may decrease transcriptional levels of the aromatase gene (involved in the regulation of estrogen synthesis) by either methylation of the gene or deacetylation of the promoter gene [91]. Additionally, nocturnal melatonin treatment can rectify the induced DNA demethylation, tumor growth, and metastatic activity by both blue LED and fluorescent ALAN in 4T1 mammary cancer cell-inoculated female BALB/c mice [63, 64]. In a more recent study that evaluated the effects of ALAN and melatonin treatment at different spectral compositions in 4T1-inoculated BALB/c mice, a tissue-specific response in GDM was detected [19]. In this study, the tumor tissue manifested the most prominent changes in GDM showing an inverse wavelength-dependent correlation that was reversed by melatonin. Conversely, other tissues (e.g., lung, liver, and spleen) showed mixed results of positive, negative, or indifferent correlation between methylation levels and both wavelength and melatonin treatments [19]. Largely, melatonin may regulate epigenetic modifications in a number of tumor-related genes mainly by DNA methylation, but other modifications are also possible.

The strong association between ALAN, DNA hypo-methylation, and melatonin suppression may be of significant clinical importance. DNA methylation and melatonin can be utilized as biomarkers for detecting and preventing breast cancer development. The traditional diagnosis method for breast cancer is scanning by

mammography, which is a useful technique to identify the growth of cancer. The mammography cannot predict risk for breast cancer as it indicates its existence, but trends in melatonin suppression and DNA methylation can provide a simple, noninvasive, and reliable tool for predicting cancer risk, particularly among a group of high-risk individuals for developing the disease such as night shift workers. Bearing in mind that epigenetic modifications are reversible [92], early treatment by melatonin or any other analogs [93] for individuals at high risk can be very effective in preventing breast cancer. We are aware today, that genetics factors such as breast cancer genes are not the major causes of the malignancy and other external factors are heavily involved. Therefore, much more attention should be given to environmental changes that link endocrinology with epigenetic modifications.

Collectively, in diurnal humans, circadian disruption enforced by activity impinging on the inactive period during the nighttime is recurrently associated with a number of health problems. However, a direct link between ALAN-induced circadian disruption and health risks is still difficult to clearly establish as most data are derived from epidemiological and nocturnal animal studies [94]. Therefore, integrating diurnal animal models of chronodisruption with epidemiological and nocturnal model studies would add a significant value in defining potential direct signal transduction pathways mediating the environmental exposure impacts on physiology and health. Consequently, we conducted a preliminary study to investigate the effects of hormonal manipulations in diurnal species on physiological and epigenetic regulations. This preliminary study is a first step in a large-scale study using diurnal mouse model to elucidate the association between ALAN-induced circadian disruption and the development of health problems at the behavioral, physiological, and molecular levels.

## 6. Physiological and epigenetic responses to melatonin and thyroxin in diurnal species

Bearing in mind that humans are diurnal, understanding the physiological and epigenetic response to ALAN in human disease can benefit significantly from using a diurnal species such as the fat sand rat (*Psammomys obesus*). This species is a good model because it is a photoperiodic species that responds to photoperiod with robust daily rhythms in a number of physiological functions, including body temperature, melatonin levels, and AA-NAT activity [95, 96]. Furthermore, *P. obesus* is a useful model for studying human health and diseases such as metabolic disorders, obesity, diabetes, inflammation, and cardiovascular impairment [97–100]. Since most previous studies on photoperiodic responses were conducted on nocturnal species, in our research center at the University of Haifa, we use *P. obesus* as a model for studying photoperiodic and hormonal manipulations. In *P. obesus*, melatonin and body temperature rhythms were diminished in response to constant dim blue light exposure, while melatonin treatment restored the disrupted rhythms [63]. Although the previous studies have clearly indicated that as a diurnal species, *P. obesus* can respond to photoperiod and light manipulations, the underling mechanism mediating the effect of the environmental changes remains unknown. An unanswered question is how melatonin and thyroxin interact to mediated environmental-induced epigenetic modifications. To answer this question, male *P. obesus* were acclimated to a long photoperiod cycle of 16L:8D at an ambient temperature of 24 ± 1°C and humidity of 45 ± 2%. Lights during the day were emitted from cool fluorescent lamps at 470 lux and 470 nm. Rats were caged individually and provided with ad libitum tap water and low energy diet. At the end of 3-week acclimation period, rats were either untreated, *i.p.* injected

with melatonin, thyroxin, or melatonin and thyroxin in combination 3 h after the dark period onset (01:00 h). Hormones were daily administered for 3 weeks at a dose of 50 µg/kg for melatonin and 2 mg/kg for thyroxin. During the experimental period, body mass ($W_b$) was monitored every other day and urine samples were collected by a noninvasive method [19] at 4 h intervals over a 28 h period. Urine samples were used to measure the major metabolite of melatonin in urine, 6-SMT [101]. The urinary metabolite concentrations were assayed by enzyme-linked immunosorbent assay utilizing a commercial IBL kit (RE54031) following the manufacture's protocol. Finally, digit tips were collected from rats at the end of urine collection for DNA isolation (High pure PCR Template Preparation Kit, Roche) and subsequently for GDM analysis (MethylFlash™ Methylated DNA Quantification Kit, Epigentek). All experimental procedures were performed with the approval from the Ethics and Animal Care Committee of the University of Haifa.

The results showed that melatonin alone significantly increased $W_b$ from day 1 compared with controls, but with a decreasing magnitude with time (**Figure 1A**). Mass gain on day 1 was approximately 1.5-fold higher compared with that at the last. T4 also increased $W_b$ from day 1 to day 5 compared with controls, but with significantly lesser effect compared with melatonin. Thereafter, mass was decreased showing a moderate mass loss from day 13 to day 21 compared with controls. Thyroxin and melatonin in combination markedly decreased $W_b$ with time compared with all other groups. Mass gain decreased from 0.46 ± 0.88% at day 1 to −20.21 ± 2.56% at day 21. Thyroxin can regulate $W_b$ by increasing heat production through nonshivering thermogenesis by changing membrane permeability to sodium, increasing the pump activity to maintain cell homeostasis in brown adipose tissue, resulting in higher body temperature values and loss in $W_b$ [102].

Melatonin may operate through increasing the amount of brown adipose tissue, thus increasing heat production by increasing energy expenditure. Melatonin and thyroxin in combination provoked considerably more mass loss than melatonin alone, suggesting that melatonin may act synergistically with thyroxin to evoke mass loss in rats, due to the combined effect of increasing energy expenditure.

Body temperature rhythms were notably altered only in response to T4 treatment, while melatonin alone and in combination with thyroxin had no effect on body temperature compared with controls (**Figure 1B**). Furthermore, the significant decrease in body temperature following treatments with thyroxin and melatonin in combination, compared with T4 alone, suggests that melatonin and thyroxin exert a significant antagonistic effect on body temperature.

Thyroxin treatment had no effect on mean 6-SMT levels but altered the daily rhythms with higher amplitude and delayed acrophase by approximately 2 h (**Figure 2A**). Finally, melatonin treatment elicited hypomethylation while thyroxin alone or thyroxin and melatonin in combination exerted comparable effects on GDM levels showing marked hypermethylation compared with control levels (**Figure 2B**). Similar to $W_b$, thyroxin and melatonin may have exerted synergistic effects on promoting DNA hypermethylation, but this effect did not reach statistical significance.

These results suggest that melatonin and thyroxin have a role in the regulation of body temperature and apparently metabolism, in which the former may attenuate metabolism and the latter may accelerate it. Both hormones exerted inverse effects on global DNA levels, suggesting that different transduction pathways are involved in the circadian regulation of body temperature in *P. obesus*. The results suggest also that change in body temperature is more sensitive to thyroxin treatment than melatonin, as the effect of the latter was masked in the combined treatment with the other hormone.
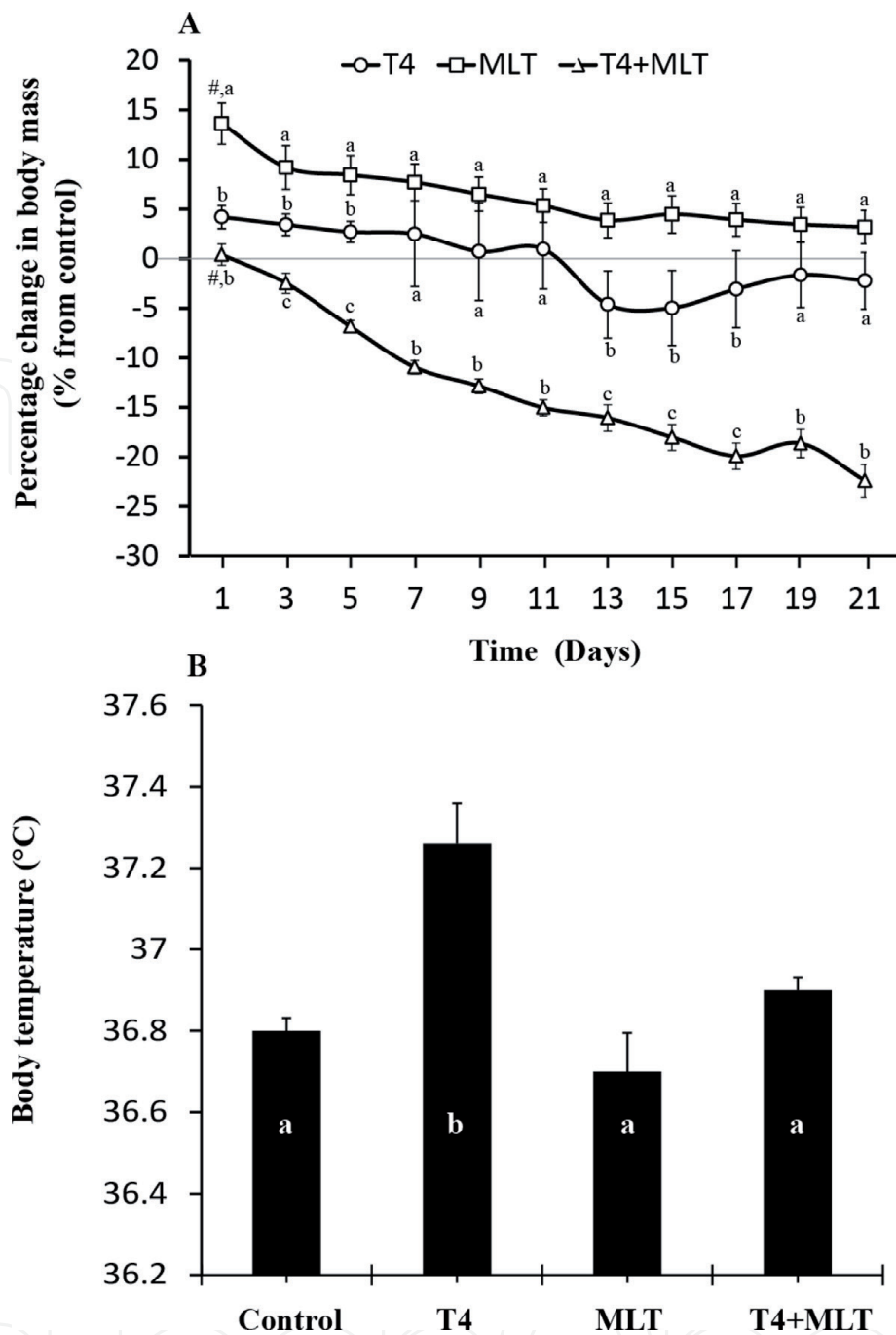
**Figure 1.**
*Percentage change in body mass (A) and body temperature (B) in long-day acclimated P. obesus under four conditions: control no treatments, thyroxin (T4) treatment, melatonin (MLT) treatment, and combined treatment with T4 + MLT. Data are presented as mean ± standard error of nine animals. Different letters represent statistically significant difference among groups (Bonferroni, P < 0.01). # vs. day 21 (Bonferroni, P < 0.02).*

However, in humans, melatonin may interact with the HPT axis to modulate the circadian rhythm of body temperature [104]. In mammals, the HPT axis plays a major role in several adaptive functions such as growth, development, metabolic rate, thermogenesis, heart rate, immune, and reproductive responses [105]. The HPT releasing and stimulating hormones as well as the thyroid hormones (T4 and T3) are under photoperiodic control presumably by the pars tuberalis of the adenohypophysis [106, 107]. In rats, T3 and T4 concentrations exhibit significant circadian rhythms with elevated levels during the dark period compared with the counterpart light period [108]. The nocturnal increase in the thyroid hormones was reported also in the rat pineal gland following an increase in type I 5′-iodothyronine deiodinase activity, which catalyzes the conversion of T4 to T3 [109]. Furthermore, the thyroid hormones are crucial photoperiodic regulators of several physiological
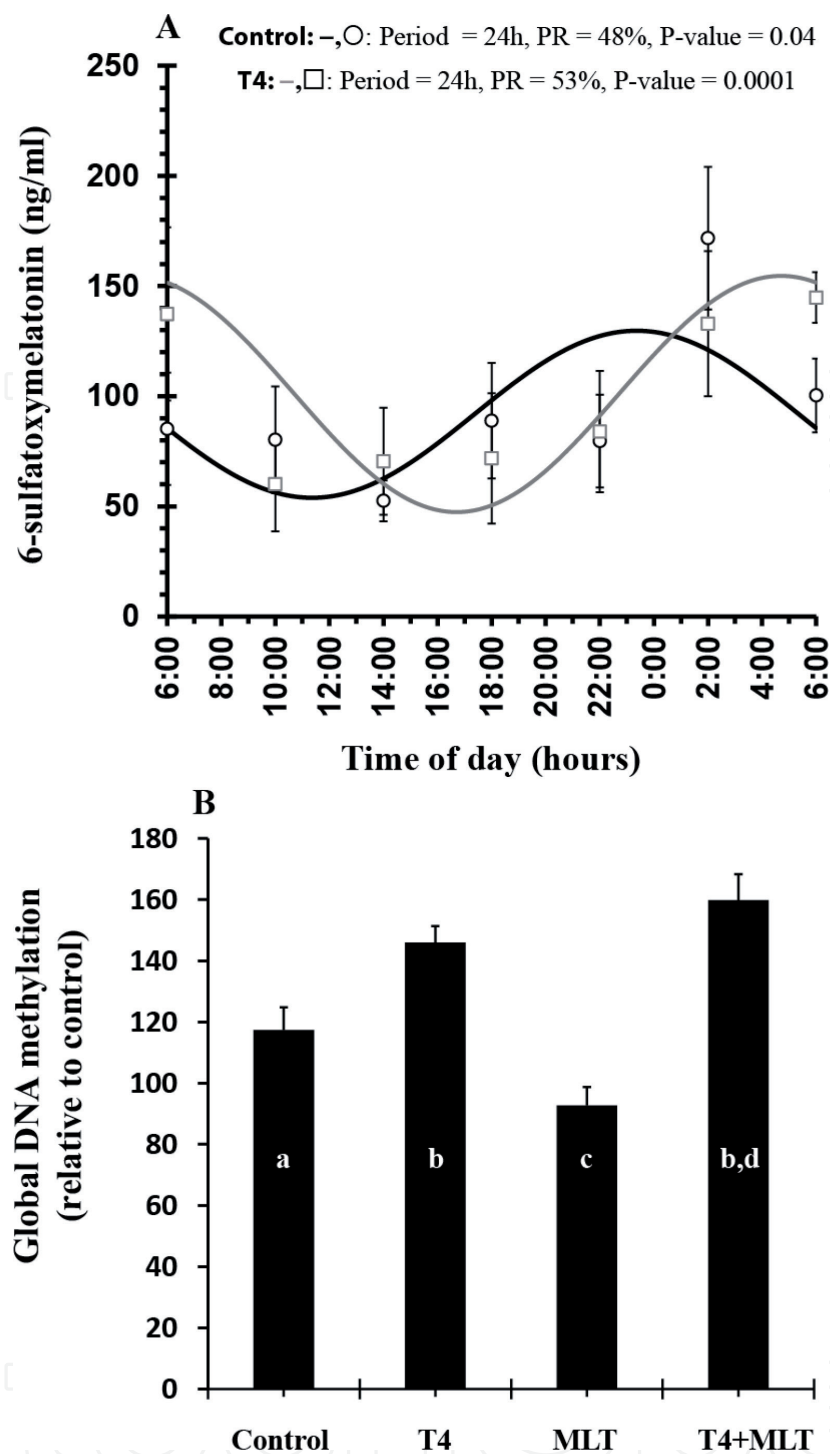
**Figure 2.**
*Daily rhythms of urinary 6-sulfatoxymelatonin (A) and global DNA methylation (B) levels in long-day acclimated P. obesus under four conditions: control no treatments, thyroxin (T4) treatment, melatonin (MLT) treatment, and combined treatment with T4 + MLT. In panel A, the best-fitted cosine curve (black and gray lines) and Cosinor estimates (period, P-value, and percentage of the rhythm [PR]) are depicted [103]. The gray area in each plot represents the length of the dark period. Data are presented as mean ± standard error of seven to nine animals. Different letters represent statistically significant difference among groups (Bonferroni, P < 0.01).*

processes including energy metabolism and reproduction [110, 111]. While the relation between the HPT axis and the photoperiodic system are well-characterized, there are limited studies on the effect of ALAN on the HPT axis. However, due to the link with the photoperiodic system, environmental perturbation of the circadian clock by ALAN is expected to alter the activity of the HPT axis, including the thyroid hormones. In hamsters under short-day photoperiod, low levels of ALAN elevated the levels of thyroid-stimulating-hormone (TSH) receptors causing advanced $W_b$ and gonadal growth [112]. Continuous exposure to ALAN decreased

TSH, but increased both T3 and T4 in mice [113]. In birds, long-term exposure to ALAN increased both the blood levels of the thyroid hormones and $W_b$ [114]. Overall, ALAN may induce aberrant epigenetic modifications by disrupting endocrine axes such as HPT axis that interacts with melatonin to manifest the adverse effects of the environmental exposure. However, the exact mechanism of action by which HPT axis may directly, or *via* melatonin, mediate the disruption effects of ALAN on the circadian system and promote downstream health risk is still unclear, and further efforts are warranted for elucidating it.

## 7. Conclusions

Currently, it is clear that electric light not only has remarkable anthropological advantages, but also severe adverse ecological and public health concerns. One of the most alerting impacts of ALAN on public health is the potential association between SWL exposure and cancer development, particularly in urbanized regions worldwide. ALAN effects are suggested to be mediated at the cellular level by inducing epigenetic modifications *via* nocturnal melatonin suppression. A schematic of ALAN-induced adverse effects is presented in **Figure 3**. Accordingly, light signals including ALAN are detected by ipRGCs and conveyed to the SCN by RHT. During a normal light dark cycle, melatonin is synthesized and secreted to the blood during the night, where it entrains central and peripheral oscillators to regulate normal physiological responses. Conversely, ALAN suppresses melatonin levels causing chronodisruption and misalignment in central and peripheral oscillators resulting in impaired physiological responses. The central and peripheral oscillators can be regulated directly by the melatonin signal or indirectly by modifying the body temperature rhythms [115]. In mice, daily variations in body temperature rhythms have been demonstrated to synchronize circadian gene expressions [116] and these central-controlled variations can be utilized to regulate variant peripheral circadian clocks in mammals [117]. Consequently, in diurnal species, thyroxin as an endocrine pathway is presumably involved in center circadian regulation of peripheral clocks by modifying body temperature daily rhythms.

These effects are presumably mediated by aberrant epigenetic modifications. Therefore, DNA methylations, which are a reversible modification in genes, triggered by melatonin, are a promising mechanism linking between environmental exposures like ALAN and hormonal/cellular pathway mediating carcinogenic activities like metastasis activity, tumor cell proliferation, and estrogen-related responses [89]. Melatonin may affect DNA methylation by modulating the activity of DNA methyltransferases involved in the regulation of gene expression by changing DNA methylation patterns. The well-established fact that different tissues present specific patterns of epigenetic modifications [118] may account for the observed tissue-specific effects of ALAN and melatonin on DNA methyl-transferase activity and GDM levels. Tissue differential effects on the activity of DNA methyl-transferases and GDM levels in response to ALAN exposure may present tissue-specific responses to genes that are involved in circadian regulation of several transduction pathways including cancer cell proliferation and metastatic activity. Since humans are diurnal species and most studies have been conducted on nocturnal animals, a diurnal experimental model should be of a great clinical interest. *P. obesus* may be very useful as a diurnal animal model for understanding the physiological and molecular effects of light pollution on public health. Melatonin suppression, GDM, and even thyroxin levels may present a significant clinical importance as a biomarker for early detection of cancer, particularly in individuals who are at increased risk of developing cancer by circadian disruption induced by excessive ALAN exposures. As epigenetic modifications are revisable, these biomarkers retain therapeutic value
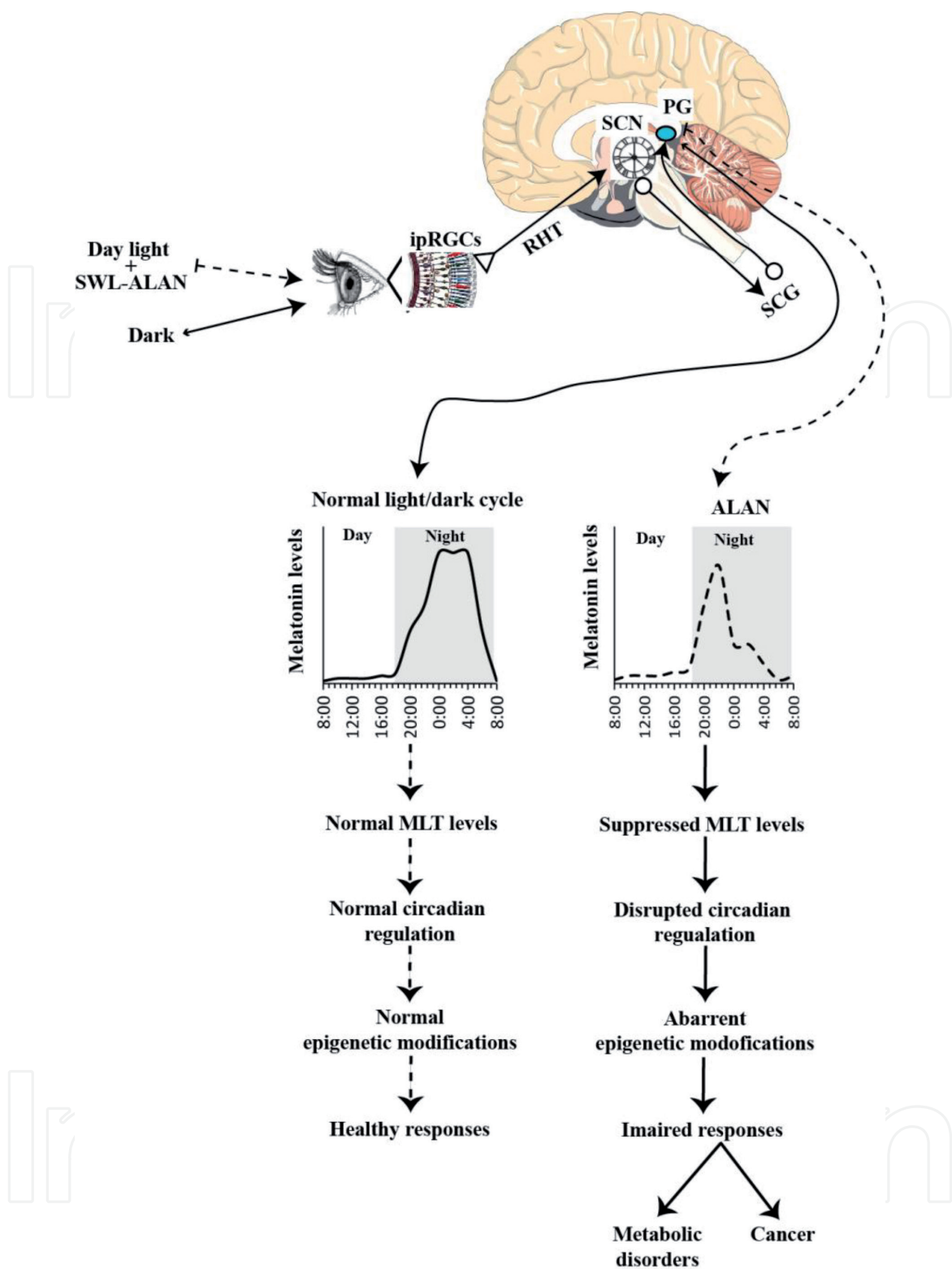
**Figure 3.**
*Schematic representation of the mechanism of ALAN in eliciting adverse health effects. Light signal, including short wavelength ALAN (SWL-ALAN), is detected by intrinsically photosensitive retinal ganglion cells (ipRGCs) that propagate it to the SCN via the retinohypothalamic tract (RHT). Thereafter, the signal is transmitted to the pineal gland (PG) via superior cervical ganglion (SCG). Finally, melatonin is synthesized and secreted to circulation by the PG during the night, where it synchronizes peripheral clocks with the ambient photoperiod. Generally, ALAN suppresses nocturnal melatonin, in which adverse health impacts are generated by inducing aberrant epigenetic modifications.*

for ALAN-induced cancer by gene demethylation. Finally, the accumulating data regarding the adverse effects of light pollution on ecology and heath compel us to take drastic and rapid measures to reduce light pollution by extreme regulation or at least reducing SWL emission by developing safe lightning technology.

## Acknowledgements

## Dedication

This chapter is dedicated to the memory of Professor Abraham Haim, who passed away before publication of this work. His contribution was foremost among the authors of this chapter.

## Abbreviations

| | |
|---|---|
| ALAN | artificial light at night |
| AA-NAT | aryl-alkyl-amine-N-acetyltransferase |
| $W_b$ | body mass |
| GDM | global DNA methylation |
| HIOMT | hydroxyindole-O-methyltransferase |
| SCN | hypothalamic suprachiasmatic nucleus |
| HPA | hypothalamic-pituitary-adrenal |
| HPG | hypothalamic-pituitary-gonadal |
| HPT | hypothalamic-pituitary-thyroid axis |
| ipRGCs | intrinsically photosensitive retinal ganglion cells |
| LED | light-emitting diodes |
| RHT | retinohypothalamic tract |
| SWLs | short wavelengths |
| SCG | superior cervical ganglion |
| TSH | thyroid-stimulating hormone |

## Author details

Abraham Haim, Sinam Boynao and Abed Elsalam Zubidat*
The Israeli Center for Interdisciplinary Research in Chronobiology, University of Haifa, Haifa, Israel

*Address all correspondence to: zubidat3@013.net.il

IntechOpen

## References

[1] Haim A, Portnov BA. LAN and breast cancer risk: Can we see a forest through the trees?—Response to "measurements of light at night (LAN) for a sample of female school teachers" by M. S. Rea, J. A. Brons, and M. G. Figueiro. Chronobiology International. 2011;**28**(8):734-736. DOI: 10.3109/07420528.2011.604591

[2] Zubidat AE, Haim A. Artificial light-at-night—A novel lifestyle risk factor for metabolic disorder and cancer morbidity. Journal of Basic and Clinical Physiology and Pharmacology. 2017;**28**(4):295-313. DOI: 10.1515/jbcpp-2016-0116

[3] Haim A, Scantlebury DM, Zubidat AE. The loss of ecosystem-services emerging from artificial light at night. Chronobiology International. 2018;**19**:1-3. DOI: 10.1080/07420528.2018.1534122

[4] Cinzano P, Falchi F, Elvidge CD. The first world atlas of the artificial night sky brightness. Monthly Notices of the Royal Astronomical Society. 2001;**328**(3):689-707. DOI: 10.1046/j.1365-8711.2001.04882.x

[5] Hölker F, Moss T, Griefahn B, Kloas W, Voigt CC, Henckel D, et al. The dark side of light: A transdisciplinary research agenda for light pollution policy. Ecology and Society. 2010;**15**:13. Available from: http://www.ecologyandsociety.org/vol15/iss4/art13/

[6] Navara KJ, Nelson RJ. The dark side of light at night: Physiological, epidemiological, and ecological consequences. Journal of Pineal Research. 2007;**43**(3):215-224

[7] Dominoni DM, Borniger JC, Nelson RJ. Light at night, clocks and health: From humans to wild organisms. Biological Letters. 2016;**12**(2):20160015. DOI: 10.1098/rsbl.2016.0015

[8] Russart KLG, Nelson RJ. Light at night as an environmental endocrine disruptor. Physiology and Behavior. 2018;**190**:82-89. DOI: 10.1016/j.physbeh.2017.08.029

[9] Owens ACS, Lewis SM. The impact of artificial light at night on nocturnal insects: A review and synthesis. Ecology and Evolution. 2018;**8**(22):11337-11358. DOI: 10.1002/ece3.4557

[10] Pulgar J, Zeballos D, Vargas J, Aldana M, Manriquez PH, Manriquez K, et al. Endogenous cycles, activity patterns and energy expenditure of an intertidal fish is modified by artificial light pollution at night (ALAN). Environmental Pollution. 2019;**244**:361-366. DOI: 10.1016/j.envpol.2018.10.063

[11] Gastón MS, Pereyra LC, Vaira M. Artificial light at night and captivity induces differential effects on leukocyte profile, body condition, and erythrocyte size of a diurnal toad. Journal of Experimental Zoology Part A: Ecological and Integrative Physiology. 2019;**331**(2):93-102. DOI: 10.1002/jez.2240

[12] Hu Z, Hu H, Huang Y. Association between nighttime artificial light pollution and sea turtle nest density along Florida coast: A geospatial study using VIIRS remote sensing data. Environmental Pollution. 2018;**239**:30-42. DOI: 10.1016/j.envpol.2018.04.021

[13] Dominoni DM, de Jong M, Bellingham M, O'Shaughnessy P, van Oers K, Robinson J, et al. Dose-response effects of light at night on the reproductive physiology of great tits (Parus major): Integrating morphological analyses with candidate gene expression. Journal of Experimental Zoology Part A: Ecological and Integrative Physiology. 2018;**329**(8-9):473-487. DOI: 10.1002/jez.2214

[14] Hoffmann J, Palme R, Eccard JA. Long-term dim light during nighttime changes activity patterns and space

use in experimental small mammal populations. Environmental Pollution. 2018l;**238**:844-851. DOI: 10.1016/j. envpol.2018.03.107

[15] Solano-Lamphar HA, Kocifaj M. Numerical research on the effects the skyglow could have in phytochromes and RQE photoreceptors of plants. Journal of Environmental Management. 2018;**209**:484-494. DOI: 10.1016/j. jenvman.2017.12.036

[16] Nelson RJ, Chbeir S. Dark matters: Effects of light at night on metabolism. Proceedings of the Nutrition Society. 2018;**77**(30):223-229. DOI: 10.1017/ S0029665118000198

[17] Abay KA, Amare M. Night light intensity and women's body weight: Evidence from Nigeria. Economics and Human Biology. 2018;**31**:238-248. DOI: 10.1016/j.ehb.2018.09.001

[18] Garcia-Saenz A, Sánchez de Miguel A, Espinosa A, Valentin A, Aragonés N, Llorca J, et al. Evaluating the association between artificial light-at-night exposure and breast and prostate cancer risk in Spain (MCC-Spain Study). Environmental Health Perspectives. 2018;**126**:047011. DOI: 10.1289/ EHP1837

[19] Zubidat AE, Fares B, Fares F, Haim A. Artificial light at night of different spectral compositions differentially affects tumor growth in mice: Interaction with melatonin and epigenetic pathways. Cancer Control. 2018;**25**(1):1073274818812908. DOI: 10.1177/1073274818812908

[20] Haim A, Heth G, Pratt H, Nevo E. Photoperiodic effects on thermoregulation in a 'blind' subterranean mammal. Journal Experimental Biology. 1983; **107**:59-64

[21] Zubidat AE, Nelson RJ, Haim A. Spectral and duration sensitivity to

light-at-night in 'blind' and sighted rodent species. Journal of Experimental Biology. 2011;**214**(Pt 19):3206-3217. DOI: 10.1242/jeb.058883

[22] Matynia A. Blurring the boundaries of vision: Novel functions of intrinsically photosensitive retinal ganglion cells. Journal of Experimental Neuroscience. 2013;7:43-50. DOI: 10.4137/JEN.S11267

[23] Collin SP, Davies WL, Hart NS, Hunt DM. The evolution of early vertebrate photoreceptors. Philosophical Transactions of The Royal Society B Biological Sciences. 2009;**364**(1531):2925-2940. DOI: 10.1098/rstb.2009.0099

[24] Detwiler PB. Phototransduction in retinal ganglion cells. Yale Journal of Biology and Medicine. 2018;**91**(1):49-52

[25] Hannibal J, Christiansen AT, Heegaard S, Fahrenkrug J, Kiilgaard JF. Melanopsin expressing human retinal ganglion cells: Subtypes, distribution, and intraretinal connectivity. Journal of Comparative Neurology. 2017;**525**(8):1934-1961. DOI: 10.1002/ cne.24181

[26] Moore RY. Neural control of the pineal gland. Behavioural Brain Research. 1996;**73**(1-2):125-130

[27] Perreau-Lenz S, Kalsbeek A, Van Der Vliet J, Pévet P, Buijs RM. In vivo evidence for a controlled offset of melatonin synthesis at dawn by the suprachiasmatic nucleus in the rat. Neuroscience. 2005;**130**(3):797-803

[28] Klein DC. Arylalkylamine N-acetyltransferase: "the Timezyme". Journal of Biological Chemistry. 2007;**282**(7):4233-4237

[29] Klein DC, Coon SL, Roseboom PH, Weller JL, Bernard M, Gastel JA, et al. The melatonin rhythm-generating enzyme: Molecular regulation of

serotonin N-acetyltransferase in the pineal gland. Recent Progress in Hormone Research. 1997;**52**:307-357

[30] Maronde E, Stehle JH. The mammalian pineal gland: Known facts, unknown facets. Trends in Endocrinology and Metabolism. 2007;**18**(11):142-149

[31] Ribelayga C, Garidou ML, Malan A, Gauer F, Calgari C, Pévet P, et al. Photoperiodic control of the rat pineal arylalkylamine-N-acetyltransferase and hydroxyindole-O-methyltransferase gene expression and its effect on melatonin synthesis. Journal of Biological Rhythms. 1999;**14**(2):105-115

[32] Thapan K, Arendt J, Skene DJ. An action spectrum for melatonin suppression: Evidence for a novel non-rod, non-cone photoreceptor system in humans. Journal of Physiology. 2001;**535**(Pt 1):261-267

[33] Cajochen C, Münch M, Kobialka S, Kräuchi K, Steiner R, Oelhafen P, et al. High sensitivity of human melatonin, alertness, thermoregulation, and heart rate to short wavelength light. Journal of Clinical Endocrinology and Metabolism. 2005;**90**(3):1311-1316

[34] Brainard GC, Lewy AJ, Menaker M, Fredrickson RH, Miller LS, Weleber RG, et al. Dose-response relationship between light irradiance and the suppression of plasma melatonin in human volunteers. Brain Research. 1988;**454**(1-2):212-218

[35] Falchi F, Cinzano P, Elvidge CD, Keith DM, Haim A. Limiting the impact of light pollution on human health, environment and stellar visibility. Journal of Environmental Management. 2011;**92**(10):2714-2722. DOI: 10.1016/j.jenvman.2011.06.029

[36] Aubé M, Roby J, Kocifaj M. Evaluating potential spectral impacts of various artificial lights on melatonin suppression, photosynthesis, and star visibility. PLoS One. 2013;**8**:e67798. DOI: 10.1371/journal.pone.0067798

[37] West KE, Jablonski MR, Warfield B, Cecil KS, James M, Ayers MA, et al. Blue light from light-emitting diodes elicits a dose-dependent suppression of melatonin in humans. Journal of Applied Physiology. 2011;**110**(3):619-626. DOI: 10.1152/japplphysiol.01413.2009

[38] Walsh CM, Prendergast RL, Sheridan JT, Murphy BA. Blue light from light-emitting diodes directed at a single eye elicits a dose-dependent suppression of melatonin in horses. The Veterinary Journal. 2013;**196**(2):231-235. DOI: 10.1016/j.tvjl.2012.09.003

[39] Figueiro MG, Bierman A, Rea MS. A train of blue light pulses delivered through closed eyelids suppresses melatonin and phase shifts the human circadian system. Nature and Science of Sleep. 2013;**5**:133-141. DOI: 10.2147/NSS.S52203

[40] Figueiro MG, Plitnick B, Rea MS. Pulsing blue light through closed eyelids: Effects on acute melatonin suppression and phase shifting of dim light melatonin onset. Nature and Science of Sleep. 2014;**6**:149-156. DOI: 10.2147/NSS.S73856

[41] Haim A, Portnov BA. Light Pollution as a New Risk Factor for Human Breast and Prostate Cancers. Dordecht: Springer Science + Buisness Media; 2013. DOI: 10.1007/978-94-007-6220-6_1

[42] Ando K, Kripke DF. Light attenuation by the human eyelid. Biological Psychiatry. 1996;**39**(1):22-25

[43] Bierman A, Figueiro MG, Rea MS. Measuring and predicting eyelid spectral transmittance. Journal of Biomedical Optics. 2011;**16**:067011. DOI: 10.1117/1.3593151

[44] Figueiro MG, Wood B, Plitnick B, Rea MS. The impact of light from computer monitors on melatonin levels in college students. Neuro Endocrinology Letters. 2011;**32**(2):158-163

[45] Wood B, Rea MS, Plitnick B, Figueiro MG. Light level and duration of exposure determine the impact of self-luminous tablets on melatonin suppression. Applied Ergonomics. 2013;**44**(2):237-240. DOI: 10.1016/j. apergo.2012.07.008

[46] Green A, Cohen-Zion M, Haim A, Dagan Y. Evening light exposure to computer screens disrupts human sleep, biological rhythms, and attention abilities. Chronobiology International. 2017;**34**(7):855-865. DOI: 10.1080/07420528.2017.1324878

[47] Gaston KJ, Duffy JP, Gaston S, Bennie J, Davies TW. Human alteration of natural light cycles: Causes and ecological consequences. Oecologia. 2014;**76**(4):917-931. DOI: 10.1007/ s00442-014-3088-2

[48] Kyba CCM, Kuester T, Sánchez de Miguel A, Baugh K, Jechow A, Hölker F, et al. Artificially lit surface of Earth at night increasing in radiance and extent. Science Advances. 2017;**3**:e1701528. DOI: 10.1126/sciadv.1701528

[49] AMA. Human and environment effects of light emitting diode (LED). Community Lighting. 2016. Available from: https://circadianlight.com/ images/pdfs/newscience/American-Medical-Association-2016-Health-Effects-of-LED-Street-Lighting [Accessed: 28 December 2019]

[50] Wingfield JC. Environmental endocrinology: Insights into the diversity of regulatory mechanisms in life cycles. Integrative and Comparative Biology. 2018;**58**(4):790-799. DOI: 10.1093/icb/icy081

[51] Ouyang JQ , Davies S, Dominoni D. Hormonally mediated effects of artificial light at night on behavior and fitness: linking endocrine mechanisms with function. Journal of Experimental Biology. 2018;**221**(Pt 6):1-11. pii: jeb156893. DOI: 10.1242/jeb.156893

[52] Zhang X, Ho SM. Epigenetics meets endocrinology. Journal of Molecular Endocrinology. 2011;**46**(1):R11-R32

[53] Fleisch AF, Wright RO, Baccarelli AA. Environmental epigenetics: A role in endocrine disease? Journal of Molecular Endocrinology. 2012;**49**(2):R61-R67. DOI: 10.1530/JME-12-0066

[54] Touitou Y, Reinberg A, Touitou D. Association between light at night, melatonin secretion, sleep deprivation, and the internal clock: Health impacts and mechanisms of circadian disruption. Life Science. 2017;**173**: 94-106. DOI: 10.1016/j.lfs.2017.02.008

[55] Kloog I, Haim A, Stevens RG, Portnov BA. Global co-distribution of light at night (LAN) and cancers of prostate, colon, and lung in men. Chronobiology International. 2009;**26**(1):108-125. DOI: 10.1080/07420520802694020

[56] Kloog I, Stevens RG, Haim A, Portnov BA. Nighttime light level co-distributes with breast cancer incidence worldwide. Cancer Causes & Control. 2010;**21**(12):2059-2068. DOI: 10.1007/s10552-010-9624-4

[57] Kim YJ, Park MS, Lee E, Choi JW. High incidence of breast cancer in light-polluted areas with spatial effects in Korea. Asian Pacific Journal of Cancer Prevention. 2016;**17**(1):361-367

[58] Keshet-Sitton A, Or-Chen K, Yitzhak S, Tzabary I, Haim A. Light and the City: Breast cancer risk factors differ between urban and rural women in Israel. Integrative Cancer Therapies.

2017;**16**(2):176-187. DOI: 10.1177/ 1534735416660194

[59] Anderson LE, Morris JE, Sasser LB, Stevens RG. Effect of constant light on DMBA mammary tumorigenesis in rats. Cancer Letters. 2000;**148**(2):121-126

[60] Blask DE, Dauchy RT, Sauer LA, Krause JA, Brainard GC. Growth and fatty acid metabolism of human breast cancer (MCF-7) xenografts in nude rats: Impact of constant light-induced nocturnal melatonin suppression. Breast Cancer Research and Treatment. 2003;**79**(3):313-320

[61] Cos S, Mediavilla D, Martínez-Campa C, González A, Alonso-González C, Sánchez-Barceló EJ. Exposure to light-at-night increases the growth of DMBA-induced mammary adenocarcinomas in rats. Cancer Letters. 2006;**235**(2):266-271

[62] Vinogradova IA, Anisimov VN, Bukalev AV, Ilyukha VA, Khizhkin EA, Lotosh TA, et al. Circadian disruption induced by light-at-night accelerates aging and promotes tumorigenesis in young but not in old rats. Aging (Albany NY). 2010;**2**(2):82-92

[63] Schwimmer H, Metzer A, Pilosof Y, Szyf M, Machnes ZM, Fares F, et al. Light at night and melatonin have opposite effects on breast cancer tumors in mice assessed by growth rates and global DNA methylation. Chronobiology International. 2014;**31**(1):144-150. DOI: 10.3109/07420528.2013.842925

[64] Zubidat AE, Fares B, Faras F, Haim A. Melatonin functioning through DNA methylation to constrict breast cancer growth accelerated by blue LED light at night in 4T1 tumor bearing mice. Journal of Cancer Biology and Therapeutics. 2015;**1**(2):57-73. DOI: 10.18314/gjct.v1i2.35

[65] Karsli-Ceppioglu S, Dagdemir A, Judes G, Ngollo M, Penault-Llorca F, Pajon A,

et al. Epigenetic mechanisms of breast cancer: An update of the current knowledge. Epigenomics. 2014;**6**(6): 651-664. DOI: 10.2217/epi.14.59

[66] Xiang TX, Yuan Y, Li LL, Wang ZH, Dan LY, Chen Y, et al. Aberrant promoter CpG methylation and its translational applications in breast cancer. Chinse Journal Cancer. 2013;**32**(10):12-20. DOI: 10.5732/ cjc.011.10344

[67] Ross JP, Rand KN, Molloy PL. Hypomethylation of repeated DNA sequences in cancer. Epigenomics. 2010;**2**(2):245-269. DOI: 10.2217/epi.10.2

[68] Ogishima T, Shiina H, Breault JE, Tabatabai L, Bassett WW, Enokida H, et al. Increased heparanase expression is caused by promoter hypomethylation and up-regulation of transcriptional factor early growth response-1 in human prostate cancer. Clinical Cancer Research. 2005;**11**(3):1028-1036

[69] Loriot A, Van Tongelen A, Blanco J, Klaessens S, Cannuyer J, van Baren N, et al. A novel cancer-germline transcript carrying pro-metastatic miR-105 and TET-targeting miR-767 induced by DNA hypomethylation in tumors. Epigenetics. 2014;**9**(8):1163-1171. DOI: 10.4161/epi.29628

[70] Soares J, Pinto AE, Cunha CV, André S, Barão I, Sousa JM, et al. Global DNA hypomethylation in breast carcinoma: Correlation with prognostic factors and tumor progression. Cancer. 1999;**85**(1):112-118

[71] Jackson K, Yu MC, Arakawa K, Fiala E, Youn B, Fiegl H, et al. DNA hypomethylation is prevalent even in low-grade breast cancers. Cancer Biology and Therapy. 2004;**3**(12):1225-1231

[72] Stevens RG. Electric power use and breast cancer: A hypothesis.

American Journal of Epidemiology. 1987;**125**(4):556-561

[73] Reiter RJ. Functional pleiotropy of the neurohormone melatonin: Antioxidant protection and neuroendocrine regulation. Frontiers in Neuroendocrinology. 1995;**16**(4):383-415

[74] Middleton B. Measurement of melatonin and 6-sulphatoxymelatonin. Methods in Molecular Biology. 2013;**1065**:171-199. DOI: 10.1007/978-1-62703-616-0_11

[75] Schernhammer ES, Hankinson SE. Urinary melatonin levels and postmenopausal breast cancer risk in the Nurses' Health Study cohort. Cancer Epidemiology, Biomarkers and Prevention. 2009;**18**(1):74-79. DOI: 10.1158/1055-9965.EPI-08-0637

[76] Basler M, Jetter A, Fink D, Seifert B, Kullak-Ublick GA, Trojan A. Urinary excretion of melatonin and association with breast cancer: Meta-analysis and review of the literature. Breast Care (Basel). 2014;**9**(3):182-187. DOI: 10.1159/000363426

[77] Brown SB, Hankinson SE, Eliassen AH, Reeves KW, Qian J, Arcaro KF, et al. Urinary melatonin concentration and the risk of breast cancer in Nurses' Health Study II. American Journal Epidemiology. 2015;**181**(3):155-162. DOI: 10.1093/aje/kwu261

[78] Kliukiene J, Tynes T, Andersen A. Risk of breast cancer among Norwegian women with visual impairment. British Journal of Cancer. 2001;**84**(3): 397-399

[79] Wu AH, Wang R, Koh WP, Stanczyk FZ, Lee HP, Yu MC. Sleep duration, melatonin and breast cancer among Chinese women in Singapore. Carcinogenesis. 2008;**29**(6): 1244-1248. DOI: 10.1093/carcin/bgn100

[80] Mao L, Dauchy RT, Blask DE, Dauchy EM, Slakey LM, Brimer S, et al. Melatonin suppression of aerobic glycolysis (Warburg effect), survival signalling and metastasis in human leiomyosarcoma. Journal Pineal Research. 2016;**60**(2):167-177. DOI: 10.1111/jpi.12298

[81] Sánchez DI, González-Fernández B, Crespo I, San-Miguel B, Álvarez M, González-Gallego J, et al. Melatonin modulates dysregulated circadian clocks in mice with diethylnitrosamine-induced hepatocellular carcinoma. Jornal of Pineal Research. 2018;**65**(3):e12506. DOI: 10.1111/jpi.12506

[82] Lu H, Wu B, Ma G, Zheng D, Song R, Huang E, Mao M, Lu B. Melatonin represses oral squamous cell carcinoma metastasis by inhibiting tumor-associated neutrophils. American Journal of Translational Research. 2017;**9**:5361-5374

[83] Hurt B, Schulick R, Edil B, El Kasmi KC, Barnett C Jr. Cancer-promoting mechanisms of tumor-associated neutrophils. The American Journal of Surgery. 2017;**214**(5):938-944. DOI: 10.1016/j.amjsurg.2017.08.003

[84] Fan C, Pan Y, Yang Y, Di S, Jiang S, Ma Z, et al. HDAC1 inhibition by melatonin leads to suppression of lung adenocarcinoma cells via induction of oxidative stress and activation of apoptotic pathways. Journal of Pineal Research. 2015;**59**(3):321-333. DOI: 10.1111/jpi.12261

[85] Li W, Fan M, Chen Y, Zhao Q, Song C, Yan Y, et al. Melatonin induces cell apoptosis in AGS cells through the activation of JNK and P38 MAPK and the suppression of nuclear factor-kappa B: A novel therapeutic implication for gastric cancer. Cellular Physiology and Biochemistry. 2015;**37**(6):2323-2338. DOI: 10.1159/000438587

[86] Akbarzadeh M, Movassaghpour AA, Ghanbari H, Kheirandish M, Fathi Maroufi N, Rahbarghazi R, et al. The potential therapeutic effect of melatonin on human ovarian cancer by inhibition of invasion and migration of cancer stem cells. Scientific Reports. 2017;**7**:17062. DOI: 10.1038/s41598-017-16940-y

[87] Bakalova R, Zhelev Z, Shibata S, Nikolova B, Aoki I, Higashi T. Impressive suppression of colon cancer growth by triple combination SN38/EF24/melatonin: "oncogenic" versus "onco-suppressive" reactive oxygen species. Anticancer Research. 2017;**37**(10):5449-5458

[88] Mao L, Summers W, Xiang S, Yuan L, Dauchy RT, Reynolds A, et al. Melatonin represses metastasis in Her2-postive human breast cancer cells by suppressing RSK2 expression. Molecular Cancer Research. 2016;**14**(11):1159-1169

[89] Haim A, Zubidat AE. Artificial light at night: Melatonin as a mediator between the environment and epigenome. Philosophical transactions of the Royal Society of London. Series B, Biological sciences. 2015;**370**(1667):1-7. pii: 20140121. DOI: 10.1098/rstb.2014.0121

[90] Lee SE, Kim SJ, Yoon HJ, Yu SY, Yang H, Jeong SI, et al. Genome-wide profiling in melatonin-exposed human breast cancer cell lines identifies differentially methylated genes involved in the anticancer effect of melatonin. Journal of Pineal Research. 2013;**54**(1):80-88. DOI: 10.1111/j.1600-079X.2012.01027.x

[91] Korkmaz A, Sanchez-Barcelo EJ, Tan DX, Reiter RJ. Role of melatonin in the epigenetic regulation of breast cancer. Breast Cancer Research and Treatment. 2009;**115**(1):13-27. DOI: 10.1007/s10549-008-0103-5

[92] Bennett RL, Licht JD. Targeting epigenetics in cancer. Annual Review of Pharmacology and Toxicology. 2018;**58**:187-207. DOI: 10.1146/annurev-pharmtox-010716-105106

[93] Gatti G, Lucini V, Dugnani S, Calastretti A, Spadoni G, Bedini A, Rivara S, Mor M, Canti G, Scaglione F, Bevilacqua A. Antiproliferative and pro-apoptotic activity of melatonin analogues on melanoma and breast cancer cells. Oncotarget. 2017;**8**:68338-68353. DOI: 10.18632/oncotarget.20124.

[94] Nunez AA, Yan L, Smale L. The cost of activity during the rest phase: Animal models and theoretical perspectives. Frontiers in Endocrinology (Lausanne). 2018;**9**:72. DOI: 10.3389/fendo.2018.00072

[95] Neuman A, Gothilf Y, Haim A, Ben-Aharon G, Zisapel N. Nocturnal patterns and up-regulated excretion of the melatonin metabolite 6-sulfatoxymelatonin in the diurnal rodent *Psammomys obesus* post-weaning under a short photoperiod. Comparative Biochemistry and Physiology Part A: Molecular & Integrative Physiology. 2005;**142**(3):297-307

[96] Schwimmer H, Mursu N, Haim A. Effects of light and melatonin treatment on body temperature and melatonin secretion daily rhythms in a diurnal rodent, the fat sand rat. Chronobiology International. 2010;**27**(7):1401-1419. DOI: 10.3109/07420528.2010.505355

[97] Bouderba S, Sanchez-Martin C, Villanueva GR, Detaille D, Koceïr EA. Beneficial effects of silibinin against the progression of metabolic syndrome, increased oxidative stress, and liver steatosis in *Psammomys obesus*, a relevant animal model of human obesity and diabetes. Journal of Diabetes. 2014;**6**(2):184-192. DOI: 10.1111/1753-0407.12083

[98] Sihali-Beloui O, El-Aoufi S, Maouche B, Marco S. *Psammomys obesus*,

a uniquemodel of metabolic syndrome, inflammation and autophagy in the pathologic development of hepatic steatosis. Comptes Rendus Biologies. 2016;**339**(11-12):475-486. DOI: 10.1016/j.crvi.2016.08.001

[99] Gouaref I, Detaille D, Wiernsperger N, Khan NA, Leverve X, Koceir EA. The desert gerbil *Psammomys obesus* as a model for metformin-sensitive nutritional type 2 diabetes to protect hepatocellular metabolic damage: Impact of mitochondrial redox state. PLoS One. 2017;**12**:e0172053. DOI: 10.1371/journal.pone.0172053

[100] Chaudhary R, Walder KR, Hagemeyer CE, Kanwar JR. *Psammomys obesus*: A atural diet-controlled model for diabetes and cardiovascular diseases. Current Atherosclerosis Reports. 2018;**20**(9):46. DOI: 10.1007/s11883-018-0746-6

[101] de Almeida EA, Di Mascio P, Harumi T, Spence DW, Moscovitch A, Hardeland R, et al. Measurement of melatonin in body fluids: Standards, protocols and procedures. Child's Nervous System. 2011;**27**(6):879-891. DOI: 10.1007/s00381-010-1278-8

[102] Bianco AC, McAninch EA. The role of thyroid hormone and brown adipose tissue in energy homoeostasis. Lancet Diabetes and Endocrinology. 2013;**1**(3):250-258. DOI: 10.1016/S2213-8587(13)70069-X

[103] Nelson W, Tong Y, Lee J, Halberg F. Methods for cosinor-rhythmometry. Chronobiologia. 1979;**6**(4):305-323

[104] Mazzoccoli G, Giuliani A, Carughi S, De Cata A, Puzzolante F, La Viola M, et al. The hypothalamic-pituitary-thyroid axis and melatonin in humans: Possible interactions in the control of body temperature. Neuro Endocrinology Letters. 2004;**25**(5):368-372

[105] Zoeller RT, Tan SW, Tyl RW. General background on the hypothalamic-pituitary-thyroid (HPT) axis. Critical Reviews in Toxicology. 2007;**37**(1-2):11-53

[106] Dardente H, Hazlerigg DG, Ebling FJ. Thyroid hormone and seasonal rhythmicity. Frontiers Endocrinology (Lausanne). 2014;**5**:19. DOI: 10.3389/fendo.2014.00019

[107] Korf HW. Signaling pathways to and from the hypophysial pars tuberalis, an important center for the control of seasonal rhythms. General and Comparative Endocrinology. 2018;**258**:236-243. DOI: 10.1016/j.ygcen.2017.05.011

[108] Campos-Barros A, Musa A, Flechner A, Hessenius C, Gaio U, Meinhold H, et al. Evidence for circadian variations of thyroid hormone concentrations and type II 5′-iodothyronine deiodinase activity in the rat central nervous system. Journal of Neurochemistry. 1997;**68**(2):795-803

[109] Soutto M, Guerrero JM, Osuna C, Molinero P. Nocturnal increases in the triiodothyronine/thyroxine ratio in the rat thymus and pineal gland follow increases of type II 5′-deiodinase activity. The International Journal of Biochemistry and Cell Biology. 1998;**30**(2):235-241

[110] Hut RA. Photoperiodism: Shall EYA compare thee to a summer's day? Current Biology. 2011;**21**(1):R22-R25. DOI: 10.1016/j.cub.2010.11.060

[111] Wood S, Loudon A. Clocks for all seasons: Unwinding the roles and mechanisms of circadian and interval timers in the hypothalamus and pituitary. Journal of Endocrinology. 2014;**222**(2):R39-R59. DOI: 10.1530/JOE-14-0141

[112] Ikeno T, Weil ZM, Nelson RJ. Dim light at night disrupts the short-day

response in Siberian hamsters. General and Comparative Endocrinology. 2014;**197**:56-64. DOI: 10.1016/j. ygcen.2013.12.005

[113] Maroni MJ, Capri KM, Cushman AV, Monteiro De Pina IK, Chasse MH, Seggio JA. Constant light alters serum hormone levels related to thyroid function in male CD-1 mice. Chronobiology International. 2018;**35**(10):1456-1463. DOI: 10.1080/07420528.2018

[114] Yang Y, Yu Y, Yang B, Zhou H, Pan J. Physiological responses to daily light exposure. Scientific Reports. 2016;**6**:24808. DOI: 10.1038/srep24808

[115] Borniger JC, Maurya SK, Periasamy M, Nelson RJ. Acute dim light at night increases body mass, alters metabolism, and shifts core body temperature circadian rhythms. Chronobiology International. 2014;**31**(8):917-925. DOI: 10.3109/07420528.2014.926911

[116] Saini C, Morf J, Stratmann M, Gos P, Schibler U. Simulated body temperature rhythms reveal the phase-shifting behavior and plasticity of mammalian circadian oscillators. Genes and Development. 2012;**26**(6):567-580. DOI: 10.1101/ gad.183251.111

[117] Brown SA, Zumbrunn G, Fleury-Olela F, Preitner N, Schibler U. Rhythms of mammalian body temperature can sustain peripheral circadian clocks. Current Biology. 2002;**12**(18): 1574-1583. Available from: https:// linkinghub.elsevier.com/retrieve/pii/ S0960-9822(02)01145-4

[118] Zhang M, Xu C, von Wettstein D, Liu B. Tissue-specific differences in cytosine methylation and their association with differential gene expression in sorghum. Plant Physiology. 2011;**156**(4):1955-1966. DOI: 10.1104/pp.111.176842