

## **Erasing day/night differences in light intensity and spectrum affect biodiversity and the health of mammals by confusing the circadian clock**

Smazávání rozdílů mezi denní a noční intenzitou světla a jeho spektrem ovlivňuje biologickou diversitu a zdravotní kondici savců dysregulací cirkadiálních hodin

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**Abstract.** The beneficial effect of sunlight on all forms of life has been well-known to human cultures worldwide throughout history. However, the importance of darkness for survival, successful reproduction and the overall fitness of all organisms is fully appreciated only by physiologists and environmental biologists. Seasonal variations in environmental conditions (i.e., rainfall, temperature, barometric pressure, food availability) significantly affect reproduction and survival but they are of little predictive value. In contrast, daily fluctuations in light levels and the light spectrum are less dramatic in their impact on life, but were highly predictable throughout evolution. Natural selection has thus favored a strategy of monitoring a day's length as a predictor of changes in external conditions by the development of the molecular circadian clock, which is sensitive to changes in light/darkness during the day and night. Well-synchronized circadian clockwork ensures that behavioral and physiological processes fluctuate with the daily solar cycle and programs the seasonal changes in physiology via the transduction of the photoperiod into hormonal messages. During the last two decades, energy-efficient lighting technology has shifted from “yellow” high-pressure sodium vapor lamps to new “white” light-emitting diodes (LEDs). As a consequence, nighttime light pollution increased, and the sharp difference between day and night has been erased in many parts of the world, which threatens animal ecology and human health. Studies on humans, laboratory mammals and wildlife suggest that the physiological costs of living under artificial light at night (ALAN) may be due to the disruption of circadian and circannual timing. This overview summarizes the recent findings on the effect of the blurred day/night difference on the circadian clock, nighttime melatonin secretion and photoperiodic changes in mammals and suggests that the gradual decline of fitness due to the increasing ALAN measured in the human population may contribute to the changes in mammalian biodiversity in nature.

**Key words.** Artificial light at night, light pollution, circadian clock, melatonin, photoperiodism, mammals.

### INTRODUCTION

Life on Earth evolved under the sustained influence of regular cycles of natural light and darkness with daily, lunar or seasonal periods. Until the introduction of artificial lighting, the light/dark cycle and changes in the ratio of day and night were highly reliable indicators of incoming environmental changes in temperature, wind patterns or precipitation. The anticipation of such changes that are often remote seemed to benefit the survival of almost all organisms enough

that they evolved biological clocks that are able to anticipate incoming environmental events in advance (BHADRA et al. 2017).

The most potent clocks function with a circa-24-h period that is endogenously generated, innate and persistent in organisms that are maintained in constant environmental conditions. However, its intrinsic phase and period do not match the solar cycle, and, to fulfill their role as the predictor of events, the clocks need to be adjusted to the external time via appropriate environmental cues (*zeitgebers*). The light/dark cycle is a dominant *zeitgeber* for all organisms and accounts for the synchronization of the clock's oscillation to the environment-based time through resetting the speed and phase of the clock (DIBNER et al. 2010, GOLOMBEK & ROSENSTEIN 2010). In birds and mammals, the circadian clock is also essential for measuring changes in day length, triggering seasonal responses and synchronizing circannual rhythms (IKEGAMI & YOSHIMURA 2012). Circadian clocks thus integrate endogenous timekeeping with photic information and generate internal representations of time that are then communicated to every organ and cell in the body. The temporal coordination of all physiological processes occurs across the molecular and biochemical levels of bodily organization and affect most of the physiological processes, such as metabolism, cell cycle, immune responses, detoxication, reproduction, cardiovascular function, the sleep-wake cycle and cognitive functions (SCHIBLER et al. 2015; Fig. 1). The disruption of temporal coordination throughout the body is associated with an increased risk of cancer, immune deficiencies, metabolic syndrome, type 2 diabetes mellitus, cardiovascular disease, psychiatric diseases and disrupted sleep in human and laboratory animal models (SULLI et al. 2018). Aside from occasional genetic alterations, the main cause of circadian system disruption is compromised photic entrainment due to the high level of light at night (CHO et al. 2015, FONKEN & NELSON 2013, ZUBIDAT & HAIM 2017, LUNN et al. 2017, HATORI et al. 2017, TOUITOU et al. 2017).

In the last century, human society has increased the level of artificial light at night (ALAN), producing changes in the light/dark cycle so quickly that negative effects on wild species were noticed as early as during the 1930s (ROWAN 1938). However, the commercial production of white light-emitting diodes (LEDs) in the 1990s and the widespread switch from high-pressure sodium to LED street lights has been transforming the global nighttime environment dramatically, and the rapid changes in light wavelengths and intensities represent a real threat to all types of ecosystems and to human health. Streets with standard sodium lamps were originally illuminated to about 5 to 10 lux on the walkway. After being replaced with LEDs, illuminance values reach 20 to 80 lux, but it is not uncommon to find illuminance exceeding 100 lux. Although LED technology allows people to select from a range of spectral compositions, currently, the most used type for public lighting is neutral white LEDs with a high portion of biologically active short-wavelength "blue" light. From 2012 to 2016, Earth's artificially lit outdoor area grew by 2.2% per year, with a total radiance growth of 1.8% per year. In most urbanized countries, the increase can even surpass 20% per year (FALCHI et al. 2016, KYBA et al. 2017).

In parallel with rising light pollution worldwide, the number of studies dealing with its negative impact on ecosystems and on the behavior and physiology of individuals has increased. In addition, the discovery of the third type of photoreceptor system in vertebrates, which supplies the circadian clock with photic information, at the beginning of this millennium has inspired many laboratory experiments that have helped uncover the mechanism of light pollution's profound impact on physiology (HATTAR et al. 2002, BERSON et al. 2010, PANDA et al. 2002, TOUITOU 2015). Most studies of light pollution's impact on wildlife have been conducted on nocturnal insects, reptiles and birds. The attraction of nocturnal insects to streetlights (EISENBEIS 2006,

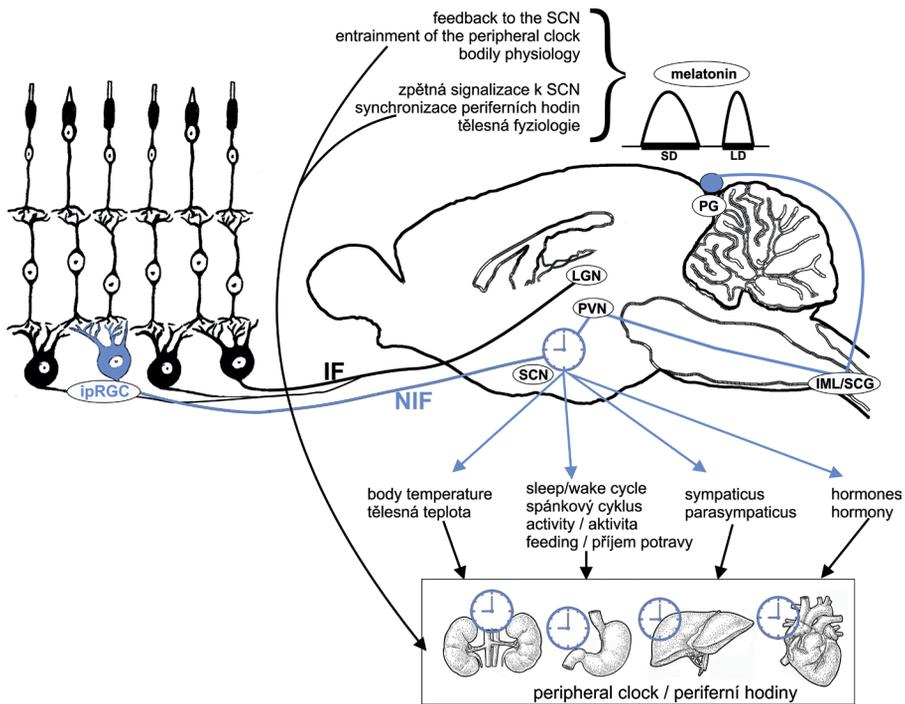


Fig. 1. The circadian system in mammals. The major circadian pacemaker in the suprachiasmatic nucleus (SCN) receives photic information via a non-image-forming pathway (NIF) composed of axons of intrinsic photosensitive retinal ganglion cells (ipRGCs). The NIF differs from image-forming pathway (IF) that leads to the first relay structure in the thalamic lateral geniculate nucleus (LGN) and to visual cortex. The SCN directly regulates several physiological rhythms that subsequently drive a large range of circadian rhythms generated by peripheral clocks in organs and tissue. One of the major outputs from the SCN is the rhythmic regulation of melatonin synthesis. Circadian signals from the SCN are transmitted to the paraventricular nuclei (PVN), the intermediolateral nucleus of the spinal cord (IML), the superior cervical ganglion (SCG) and finally the pineal gland (PG). The melatonin rhythm copies the length of the night and it becomes longer under the short days (SD) and is shorter under the long summer days (LD). It is released into the blood stream and plays various roles in bodily physiology, such as regulation of photoperiodism, sleep-wake timing, immune defence and oncogenic role, neurogenesis or metabolism.

Obr. 1. Cirkadiální systém savců. Hlavní cirkadiální pacemaker v suprachiasmatickém jádře (SCN) přijímá informace o světle prostřednictvím dráhy pro neobrazové vidění (NIF), která je tvořena axony vnitřně fotosenzitivních retinálních gangliových buněk (ipRGC). NIF se liší od dráhy pro obrazové vidění (IF), která vede do talamického laterálního genikulárního jádra (LGN) a do zrakové kůry. SCN přímo reguluje několik fyziologických rytmů, které následně řídí širokou škálu cirkadiálních rytmů generovaných periferními hodinami v orgánech a tkáních. Jedním z hlavních výstupů SCN je rytmická regulace syntézy melatoninu. Cirkadiální signály z SCN jsou přenášeny do paraventrikulárního jádra (PVN), intermediolaterálního jádra míchy (IML), superiorního cervikálního ganglia (SCG) a nakonec do epifyzy (PG). Rytmus melatoninu kopíruje délku noci a během krátkých dnů (SD) se prodlužuje a je kratší na dlouhých letních dnech (LD). Melatonin je uvolněn do krevního oběhu a plní různé funkce v tělesné fyziologii jako je regulace fotoperiodických odpovědí, časování spánku a bdění, imunitní obrana a protirakovinové působení, neurogenese nebo metabolismus.

FRANK 2006, FIREBAUGH & HAYNES 2016), alteration of reproductive behaviors in sea turtles near illuminated beaches (TUXBURY & SALMON 2005) and disorientation of birds near urban sky glow are the best documented impacts of light pollution (GAUTHREUX & BELSER 2006, MONTEVECCHI 2006, RODRÍGUEZ et al. 2015, DOMINONI & PARTECKE 2015, CABRERA-CRUZ et al. 2018, RAAP et al. 2015, 2017, LA SORTE et al. 2017, OUYANG et al. 2017). In mammals, several biological and ecological processes affected by ALAN that can be divided into two groups have been identified: a) circadian rhythms, photoperiodism and health and b) visual perception, spatial orientation and niche partitioning. Although both groups can be viewed as highly interconnected, for the purpose of this overview, we focus mainly on ALAN's effect on circadian rhythmicity and downstream physiology.

### Circadian clock and mechanisms of photoperiodism

In mammals, the circadian system is hierarchical with master circadian clock residing in the suprachiasmatic nucleus (SCN) of the hypothalamus. This clock is capable of generating of self-sustained rhythms in gene expression and electrical activity that oscillate with a circadian period of approximately 24 h and produce the humoral or electrical timing signals that are distributed throughout the body (DIBNER et al. 2010). The clockwork mechanism underlying this endogenous periodicity is based on the transcriptional/translational negative and positive feedback loops of clock genes – such as *Period 1, 2, Clock, Bmal1, Cryptochromes, Rev-erba, casein kinase 1 epsilon* and other – that are mutually interconnected with the membrane's electrical properties (TAKAHASHI 2016). The feedback loops of the clock genes are not specific to SCN neurons but exist in almost all cells of an organism (YAMAZAKI et al. 2000, BALSALOBRE 2002, SCHIBLER et al. 2015). The SCN is nevertheless necessary for the synchronization of phases between individual peripheral oscillators (SAKAMOTO et al. 1998, YAMAZAKI et al. 2000). This circadian system regulates more than 43% of all protein-coding genes with tissue-specific functions, and 32% of conserved noncoding RNAs oscillate with a circadian period (ZHANG et al. 2014). The circadian clock thus participates significantly in the regulation of organ physiology and metabolism (LI & ZHANG 2015).

The ways the SCN transmits timing information includes the regulation of the autonomic nervous system, temperature and humoral signaling (SAKAMOTO et al. 1998, KALSBECK et al. 2010, 2011). Glucocorticoids and melatonin are two of the key hormones whose synthesis is controlled by the SCN. Receptors for these hormones are widespread throughout the body, which enables them to function as the SCN's “extended hands” and allows them to set a peripheral clock in peripheral organs with the phase of the master clock (PEVET 2014, LELIAVSKI et al. 2015).

Although the SCN generates circadian rhythms even in complete darkness, its precise 24-h periodicity requires perpetual resetting by the solar light/dark cycle. The photic entrainment is an important adaptive feature of all organisms that keeps them synchronized with the latitude and season. As such, the circadian clock is programmed to process the gradual changes in day length via the morning and evening light. During the summer and winter months, the middle of the night defines the period of darkness required for body growth, memory consolidation, peripheral organ regeneration and immune system activity. The high contrast between day and night is necessary for proper entrainment of the circadian clock in nocturnal and diurnal animals (MARTINEZ-NICOLAS et al. 2014). Continuous exposure to light causes desynchronization of SCN neurons and, subsequently, of the peripheral clock in bodily tissues (OHTA et al. 2005, DIBNER et al. 2010, GOLOMBEK & ROSENSTEIN 2010, COOMANS et al. 2013).

Light information arrives at the SCN by a branch of the visual pathway called the retinohypothalamic tract (RHT). The RHT consists of axons of intrinsic photosensitive retinal ganglion cells (ipRGCs) containing photopigment melanopsin (PROVENCIO et al. 2000, HATTAR et al. 2002, BERSON et al. 2010, PANDA et al. 2002). These photoreceptors measure the intensity of light (irradiance detection) with a maximum sensitivity toward short wavelength (460–480 nm) and have a low spatial resolution and long latencies compared to cone and rod responses. They show the ability to integrate photic energy over long periods and form so-called the “non-image forming system” (NIF) that modulates all light-responsive physiological functions except vision. These NIF effects can be long-lasting and include circadian entrainment and shifting the timing of circadian rhythms in hormone secretion, heart rate, body temperature and the sleep-wake cycle (HATORI & PANDA 2010), or they can be acute and mediate melatonin suppression, pupillary constriction, alertness and performance improvement, as well as cognitive brain responses (GOOLEY et al. 2003). Sixteen years after its discovery, the ipRGC has been described not only in human (PROVENCIO et al. 2000) and traditional laboratory rodents (HANNIBAL et al. 2002a) but in *Spalax* (HANNIBAL et al. 2002b), Nile grass rats (LANGEL et al. 2015), marmosets (JUSUF et al. 2007), macaques (HANNIBAL et al. 2014), Mongolian gerbils (JEONG & JEON 2015) and bats (JEONG et al. 2018) Its sequence similarity with the opsin of non-mammalian vertebrates provides the reasonable assumption that sensing blue light via NIF is an integral property of all vertebral species (BELLINGHAM et al. 2006).

Many experiments conducted since the mid-1970s have shown that the change in the level of neurohormone melatonin is responsible for seasonal changes in behavior and physiology (e.g., reproduction, molt, appetite and fattening and migration or hibernation) in mammals and birds (TUREK et al. 1975, TAMARKIN et al. 1976, CUTTY et al. 1981, HOFFMANN et al. 1981, BARTNESS & WADE 1985, VANĚČEK & ILLNEROVÁ 1982). The daily timing of melatonin secretion is highly conserved across all vertebrates (REITER et al. 2014). Melatonin is synthesized by the pineal gland at night and in the darkness. Natural melatonin synthesis is completely dependent on nighttime SCN signaling, and the melatonin rhythm changes its amplitude and peak duration in response to the change of the length of the night (KLEIN & WELLER 1970, ILLNEROVÁ et al. 1979, KLEIN et al. 1983, 1985, PERREAU-LENZ et al. 2003, 2004). Many experiments have shown that a variety of mammals, including photoperiodic hamsters and non-photoperiodic rats adapted to the long summer photoperiod, have a significantly shorter melatonin signal than mammals adapted to a short winter photoperiod (PRESLOCK 1976, HOFFMANN 1979, VIVIEN-ROELS et al. 1979, ILLNEROVÁ & VANĚČEK 1980). These dynamic changes over the year serve as a reliable signal of the coming season. The length of the melatonin signal negatively correlates with the size of short-breeders’ gonads but positively with the reproductive activity of long-breeding animals, such as sheep (VANĚČEK & ILLNEROVÁ 1982, HOFFMANN et al. 1986, LINCOLN 1994). In recent years, the mechanism of melatonin control of seasonal reproduction has been suggested; a short melatonin signal activates transcription factor *Eya3* in part of the tuberous, which controls the expression of the thyroid-stimulating hormone (TSH). Therefore, the TSH level is high in long photoperiods and low in short photoperiods (DARDENTE et al. 2010). TSH acts on tanycytes, ependymal cells spanning the third ventricle of the brain, which synthesizes deiodinase 2. This enzyme converts metabolically inactive thyroxine (T4) to triiodothyronine (T3) (YOSHIMURA et al. 2003, YASUO et al. 2007, HAZLERIGG & LOUDON 2008). The high level of T3 changes the reproductive physiology and metabolism of mammals and birds (BARRETT et al. 2007, FREEMAN et al. 2007, EBLING 2014). In the long winter, the melatonin signal blocks the *Eya3* expression, which triggers the synthesis of deiodinase 3; this in turn inactivates T3 (WATANABE et al. 2004,

2007, REVEL et al. 2006, WOOD & LOUDON 2014). T3 regulates gonadotropin-releasing hormone neurons through the RF-amide related proteins, kisspeptin (HENNINGSEN et al. 2016). Some species exhibit seasonal cycles that are predominantly controlled by an endogenous circannual clock that is entrained by, but not directly dependent on, changes in photoperiod (HELM et al. 2013). The site of the circannual clock has not yet been fully proven, but all indirect evidence points to the pars tuberalis (WOOD & LOUDON 2018).

Aside from its role in photoperiodism, melatonin plays a variety of modulatory roles in the body. Its immunomodulatory role was first recognized in the 1970s when researchers observed reduced immune capacity following pinealectomy in rats (CSABA & BARATH 1975). Since then, melatonin has been widely studied for its anti-inflammatory and oncostatic properties (CARRILLO-VICO et al. 2013, MARSEGLIA et al. 2014, HARDELAND et al. 2015, FAVERO et al. 2017, LI et al. 2017, SU et al. 2017), for its involvement in the regulation of the sleep–wake cycle (BROWN 1994, GOLOMBEK et al. 2015, POZA et al. in press) or for its use in regard to metabolism and neurogenesis (CIPOLLA-NETO et al. 2014, TAN et al. 2015, SARLAK et al. 2013). Importantly, sudden light at night rapidly suppresses melatonin levels and blocks its synthetic pathway. This effect, mediated via NIF and the activation of the SCN, can be regarded as “waking up” the clock from its nocturnal state and is understood as the primary cause of the adverse effect of ALAN on organismal health and well-being (HAIM & ZUBIDAT 2015).

### The effect of ALAN on the night melatonin levels

Light shining at night has two major effects on circadian physiology that arise from the function of the NIF system. First, ALAN compromises the natural entrainment of the circadian clock by lowering the irradiance contrast between day and night (MARTINEZ-NICOLAS et al. 2014); second, it directly suppresses nocturnal melatonin synthesis (REITER 2002). The extent of melatonin suppression is widely used as a marker of the NIF sensitivity to light, which allows the impact of light to be extrapolated on other NIF-dependent functions. Moreover, chronically diminished melatonin has a direct detrimental effect on photoperiodic responses, immune functions, the metabolism and the sleep–wake cycle of diurnal and nocturnal animals.

The sensitivity of melatonin-synthetic pathways to ALAN may, however, differ between diurnal and nocturnal species. One of the first studies conducted on nocturnal laboratory rodents showed that an 8-min exposure to  $0.186 \mu\text{W}/\text{cm}^2$  (<1 lux) of cool white fluorescent light caused a depression of pineal melatonin in Syrian hamsters to less than 25% of control values. The melatonin level remained low for a couple of hours, even when animals were returned to darkness (BRAINARD et al. 1982, 1984a). These results were similar to research on rats, in which melatonin was depressed for up to 5 h after a 1-min exposure to light (ILLNEROVÁ & VANĚČEK 1979, ILLNEROVÁ et al. 1979). The decline in pineal melatonin content due to light exposure in all tested animals has a half-time of less than 10 min. These data show that very dim light can affect the melatonin level in nocturnal animals within a minute or less. A bright light ( $32,000 \mu\text{W}/\text{cm}^2 \approx 1000$  lux) can similarly effect a hamster’s melatonin level after exposure of 1 sec (REITER et al. 1986). Moreover, LERCHL (1995) published an important study where he demonstrated that a 1-min light pulse suppresses the melatonin in Djungarian hamsters for several consecutive nights, indicating a very effective light memory of the melatonin-generating neuronal network in nocturnal rodents. Finally, Illnerová and Vaněček (1979) and Illnerová et al. (1979) showed that the timing of acute light exposure during a dark period may determine the light’s ability to alter the melatonin level. They found that 1 min of light exposure during late night (after the

middle of the night) was more effective in depressing the melatonin synthesis for a prolonged period than 1 min of light exposure earlier in the dark phase. A similar observation was later made in the eastern chipmunk (*Tamias striatus*) (REITER et al. 1982).

Bats, members of another group of nocturnal animals, are also intensively tested for light sensitivity. Although light-induced melatonin suppression was not tested, it has been shown that even less than a 0.5-msec flash of light is sufficient to reset the circadian clock of Schneider's roundleaf bats (*Hipposideros speoris*). The authors revealed that the light necessary to induce the phase shifts of the circadian clock saturates at 136 lux operating for 0.063 msec (JOSHI & CHANDRASHEKARAN 1984, 1985). The studies in nocturnal rodents have shown that the response of their circadian clock and melatonin to light can be the dose-dependent. However, the saturation level is usually much lower than most of the measured values of ALAN in urban areas and their near surroundings (FALCHI et al. 2016, KYBA et al. 2017).

The studies dealing with diurnal mammals are usually less laborious and usually do not test saturation levels of intensity and the duration of disturbing light. What has been measured, however, suggests that their sensitivity to ALAN is by orders lower compared to nocturnal animals. In guinea pigs, for example, the activity of the rate-limiting enzyme of melatonin synthesis, N-acetyltransferase, was suppressed by 10-min light pulses of 900 lux (VOLLRATH & HUESGEN 1988). In goats, 400 lux suppressed melatonin at night (MAEDA et al. 1984), and in the rhesus monkey, white fluorescent light of 450 lux affecting the animals for 4 h canceled melatonin in cerebrospinal fluid (REPPERT et al. 1981). Finally, 45 min of 200 lux markedly diminished melatonin in the European hedgehog (*Erinaceus europaeus*) (SABOUREAU et al. 1991). Although the light of only 10–30 lux was enough to suppress serum melatonin to near daytime levels (NOZAKI et al. 1990) in the Japanese macaque (*Macaca fuscata*), this irradiance is still an order higher compared to light affecting the nocturnal animals.

A specific category of research about the impact of ALAN on organisms is human studies. Several publications exist whose results are summarized by FIGUEIRO (2017). They suggest that the partial suppression of melatonin in humans can be achieved by exposure to 100–300 lux for 2 h. However, doubts exist about the experimental design of these studies, which mostly do not consider the lowered default melatonin level of the participants who were invited to come to the laboratory only a few hours before the light treatment, and their previous lighting history was not taken into account.

Importantly, the degree of melatonin suppression by ALAN not only depends on the light's intensity but on its spectrum. In human studies, the short wavelengths corresponding to blue light have been shown to elicit a much stronger suppressive effect on melatonin levels than longer wavelengths, such as orange/red light (CAJOCHEN et al. 2005, NAVARA & NELSON 2007, AUBÉ et al. 2013). In the pioneering human study, 1.3 lux of monochromatic light at 460 nm depressed melatonin levels (BRAINARD et al. 2001, 2008), which is more than 10× lower than the intensity of spectrally undefined white light. Similarly, another older study found that 12,000 lux was needed to phase-shift the human circadian rhythm (CZEISLER et al. 1986), but under monochromatic light and in laboratory conditions, this intensity was reduced to 5 lux (LOCKLEY et al. 2003, WRIGHT et al. 2004).

Despite the energetic benefits of LEDs, the spectral power distributions of street LED lights overlay the sensitivity of the melatonin and circadian system (Fig. 2). Similar to the effect in humans, wavelength-dependent effects were also found in Syrian hamsters several years before the discovery of melanopsinergic ipRGC (BRAINARD et al. 1984b) and, relatively recently, in the social voles (*Microtus socialis*) (ZUBIDAT et al. 2011). In several species of nocturnal primates,

housing under blue light at night significantly attenuated their nighttime activity and suppressed their melatonin to half of the level measured in animals housed under red light (FULLER et al. 2016). Also, in horses, the threshold level of blue light required to inhibit melatonin production is quite low and lies between 3 and 10 lux (WELSH et al. 2013). The seminatural study showed that the tamar wallabies (*Macropus eugenii*) exposed to white LED (peak wavelength 448 nm; mean irradiance 2.87 W/m<sup>2</sup>), significantly suppressed nocturnal melatonin compared to those exposed to amber LED (peak wavelength 605 nm; mean irradiance 2.00 W/m<sup>2</sup>) (DIMOVSKI & ROBERT 2018). This study illustrates how the shifting the spectral composition of light to longer wavelengths can mitigate the negative physiological impacts of ALAN. Combined with data on birds (LEWIS et al. 2001, SURBHI & KUMAR 2015) and fishes (OLIVEIRA et al. 2007, ZIV et al. 2007, VERA et al. 2010), it can be concluded that short to middle wavelengths can suppress melatonin levels and shift the circadian rhythms in vertebrates much more efficiently and thus affect circadian physiology to a greater extent than longer wavelengths.

### The effect of ALAN on the seasonal reproduction

A growing collection of data proves that the timing of seasonal reproductive processes differs between vertebrates inhabiting areas with ALAN and their conspecifics inhabiting areas with little or no ALAN (SCHOECH et al. 2013, DOMINONI et al. 2013, IKENO et al. 2014, DE JONG et al. 2015, BRÜNING et al. 2016). Given the central role of melatonin in the regulation of seasonal

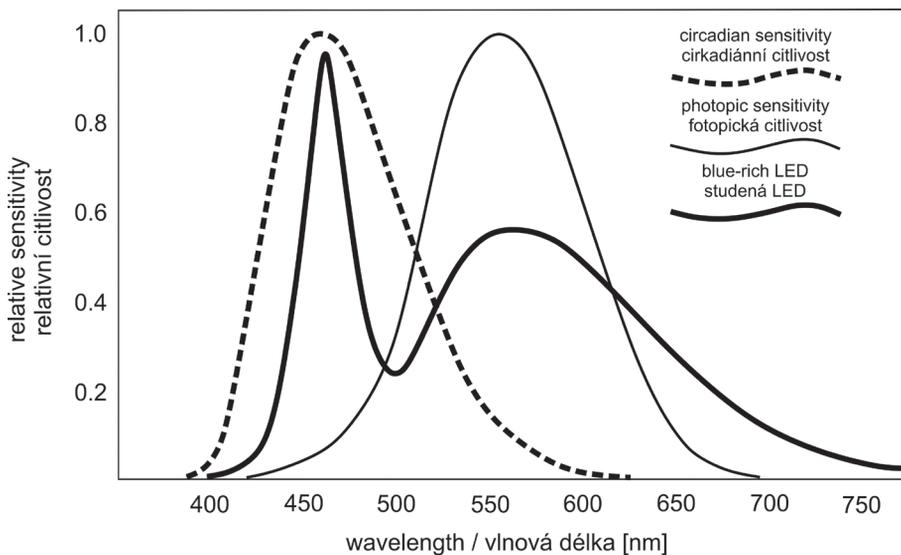


Fig. 2. Spectral distribution of typical blue-rich LED light source displayed against a photopic (IF) and circadian (NIF) sensitivity curve of a mammalian visual system.

Obr. 2. Spektrální distribuce typického světelného zdroje LED s výrazným zastoupením modré složky je zobrazená ve srovnání s křivkou citlivosti savčího fotopického (IF) a cirkadiálního (NIF) zrakového systému.

reproduction, its chronic suppression or masking of changes in natural day length may shift or even inhibit the reproductive maturation and breeding of a large group of animals. The available evidence from studies of free-living vertebrates have focused mainly on birds and have found that birds living in areas with ALAN initiate seasonal reproductive processes earlier than birds in areas lacking ALAN (DE MOLENAAR et al. 2006, KEMPENAERS et al. 2010, RUSS et al. 2015). Laboratory experiments with mammals demonstrated that 5 lux of light during the night phase is sufficient to disrupt the short-day response in Siberian hamsters, such as pelage density, fur color, gonadal activity and body mass, and these animals displayed altered responses to immune challenges. Furthermore, these experiments also clearly demonstrated that this lighting condition disturbs the circadian clockwork and affects photoperiodic responses on a molecular, gene-dependent level (IKENO et al. 2014, AUBRECHT et al. 2015). A similar detrimental effect of dim light at night on gonadal activity in male Syrian hamsters has been previously published (REITER et al. 1982).

In nature, the long-term monitoring of female tammar wallabies (*Macropus eugenii*) living in areas with ALAN showed that the animals gave birth later and the deliveries are less synchronized to a particular season of the year than wallabies living in areas free of ALAN. The authors suggest that ALAN masks the small increase in the darkness following the summer solstice that wallabies use to reactivate the blastocysts (ROBERT et al. 2015). In female gray mouse lemurs (*Microcebus murinus*) exposed to ALAN that simulated the average light intensity and irradiance spectra of streetlights in Brunoy, the first seasonal estrus occurred 2 weeks earlier than in females exposed to moonlight. Moreover, the daily activity rhythms of females exposed to ALAN showed significant changes that mimicked long-day acclimatization (LE TALLEC et al. 2016). These studies demonstrate that ALAN can affect daily rhythms and the timing of seasonal reproduction. The functional changes in the circadian system in wildlife could presumably result in the population declines observed in response to ALAN.

### The adaptation vs. the creeping erosion of health

The natural range of illumination between day and night is not stable; it depends highly on the season, clouds, phase of the moon and the species-specific habitat. Illumination at the forest floor, for example, can be  $10^{-4}$  or  $10^{-5}$  lux, while a full moon usually produces around 0.1–0.3 lux. The daytime illuminance on cloudy days can be around  $10^4$  lux, but with full sunlight, it can exceed  $10^5$  lux. As a consequence of the development under large differences in ambient illumination between day and night, animal species are supposed to show plasticity in their response to light intensity and partial adaptation that may protect them against the negative impact of ALAN. Laboratory tests confirm some extent of adaptation, predominantly in diurnal animals. For example, the exposure of laboratory-raised diurnal Richardson's ground squirrels to an irradiance of  $400 \mu\text{W}/\text{cm}^2$  during the night completely prevented the nocturnal rise in pineal melatonin levels, while the exposure of wild-captured squirrels to the same light irradiance was ineffective (REITER et al. 1983). In nocturnal animals, such an adaptation is not distinguishable; wild-captured hispid cotton rats (*Sigmodon hispidus*) exposed to various, relatively low, illumination (i.e., 5.0, 0.04, 0.03 or  $0.01 \text{ W}/\text{cm}^2$ ) for 32 min diminished melatonin levels to the same extent as laboratory-raised rats (THIELE et al. 1983). The difference in the sensitivity of laboratory-raised and wild-captured ground squirrels may relate to their previous lighting history; in a subsequent study, the same laboratory showed that light irradiance of  $200 \mu\text{W}/\text{cm}^2$  throughout the night did not affect the melatonin level in the Mexican ground squirrel (*Spermophilus mexicanus*) and

the eastern chipmunk (*Tamias striatus*), but exposure of chipmunks to such a light for seven consecutive days did; however, it reduced the evening rise in melatonin (REITER & PETERS 1984). A clinically relevant adaptation to light level has been demonstrated in humans. A significant increase in sensitivity to light at night was observed in humans who were adapted to low light irradiances during the daytime for several days before the measurement was taken (HÉBERT et al. 2002, SMITH ET al. 2004, CHANG et al. 2011).

Such plasticity of the human circadian clock and melatonin synthetic pathway points to the beneficial effect of daytime light and suggests that increasing the contrast between day and night by daylight illumination may attenuate the aversive effect of light at night, at least in diurnal mammals. This hypothesis has been verified, and recent data show that increasing the intensity of morning light enriched by blue light may significantly ameliorate the negative effect of evening light on cognitive function in humans (MÜNCH et al. 2016). However, while the conscious enhancement of irradiance contrast between day and night may be useful to treat clock-derived diseases in human, it is of low value for wildlife and is of no value for highly sensitive nocturnal animals.

When speaking about ALAN, we should consider more than urban areas. A large area of Earth is affected by artificial sky glow, which occurs when artificial light is scattered by atmospheric molecules or aerosols and returned to Earth. Sky glow is an unavoidable consequence of the use of artificial light outdoors and can be dramatically brighter on cloudy nights and can scatter to a large distance from the source. It has been estimated that sky glow can illuminate approximately 23% of Earth's terrestrial ecosystems outside the Arctic and Antarctic. It affects almost 50% of the United States and even influences the forest ecosystems in Brazil (FALCHI et al., 2016, FREITAS et al. 2017). Given the dramatic global increase in ALAN (2–20% per year, depending on geographic region) and the extensive use of blue light sources (HÖLKER et al. 2010, KYBA et al. 2012, KYBA & HÖLKER 2013), sky glow may soon unavoidably abolish the day/night difference to an extent that will fundamentally exceed the degree of adaptability not only of nocturnal animals but of diurnal animals, including humans.

Several epidemiologic and experimental observations in humans have shown that the disruption of circadian coordination and associated melatonin suppression by exterior lighting increases the risk for a variety of pathologies, such as psychiatry disorders and metabolic alterations, and promotes cancer development and progression (GIUDICE et al. 2018, NELSON & CHBEIR 2018, OBAYASHI et al. 2018). Satellite imagery of night lighting correlated with epidemiological indications of variety of diseases suggests that long-term exposure to high levels of ALAN worldwide can be associated with the increase in obesity (McFADDEN et al. 2014, RYBNIKOVA et al. 2016) and incidence of breast cancer (BAUER et al. 2013, HURLEY et al. 2014, KIM et al. 2015, 2016, AL-NAGGAR & ANIL 2016, KESHET-SITTON et al. 2017) and prostate cancer (KLOOG et al. 2009, KIM et al. 2017), depression (MIN & MIN 2017) and neurodegenerative diseases (ROMEO et al. 2013).

Regarding wildlife, living under ALAN conditions has been shown to affect the activity of populations of diurnal and nocturnal species (PERRY et al. 2008, AZAM et al. 2015, LUARTE et al. 2016, SANDERS & GASTON 2018), sexual selection (DE JONG et al. 2018) and the shifts in biological communities to more light-tolerant species (LACOEUILHE et al. 2014, NAVARRO-BARRANCO & HUGHES 2015, GRUBISIC et al. 2018, SPOELSTRA et al. 2018). It has also been shown to impact changes in foraging strategies due to the affected balance between prey behavior and risk of predation (CRAVENS & BOYLES 2018) and changes in migratory traits due to the discontinuation in the territories of nocturnal animals (LA SORTE et al. 2017, CABRERA-CRUZ et al. 2018), but

little attention has been paid to the direct consequences on an individual's health and fitness after long-term living in artificial light conditions.

The fundamental influence on the health of free-living animals can be only derived from laboratory settings that investigate the causation and mechanisms of the health consequences of ALAN on humans. A strong disrupting stimulus, such as the long-term exposure to constant light (105 lux for 24 weeks), has been shown to reduce rhythmicity in the SCN neurons by 70%, to reduce muscle strength and to induce a transient pro-inflammatory state in mice. These animals also had significantly higher blood glucose levels and presented with all the symptoms of osteoporosis (LUCASSEN et al. 2016). Previous studies have already linked constant light conditions with impaired immune function. Nocturnal light exposure reduces natural killer cell responses in rats (OISHI et al. 2006), and mice subjected to a chronic (i.e., 4-week) jet lag protocol with shifting the timing of the light period have an enhanced response to endotoxin-induced inflammation (CASTANON-CERVANTES et al. 2010). Furthermore, exposing rats to constant light increased mortality following endotoxin-induced sepsis (CARLSON & CHIU 2008). A similar study demonstrated that mice housed under constant 180 lux of white light exhibited more than a 50% reduction in the SCN rhythm amplitude, increased food intake, decreased energy expenditure and importantly the complete abolishment of normal circadian variation in insulin sensitivity (COOMANS et al. 2013). These and many other observations demonstrate how detrimental the disruption in environmental lighting rhythm can be, but the high illumination used in these experimental settings is not yet an appropriate model for ALAN conditions. In most of the areas affected by ALAN, the nighttime light intensity has only reduced the day/night difference but has not yet completely erased it.

Unfortunately, the experiments that are focused more on the effect of dim light at night do not show substantially better outcomes for individual health. Chronic exposure (>4 weeks) of mice to dim light at night of 5 lux elicited a significant body mass increase, altered body temperature and activity rhythms compared to mice maintained in the natural darkness of night (BORNIGER et al. 2014). Rhythms in body temperature are directly driven by the SCN and serve as a one of the important entraining cues that enables the synchronization of the peripheral clock (SCHIBLER et al. 2015). The deregulation of its rhythmicity may contribute to the internal desynchrony between the central and peripheral oscillators with health-related consequences. It has been also shown that exposure to dim light at night during early development increases adult anxiety-like responses (BORNIGER et al. 2014). Dim nighttime light also impaired spatial learning and provoked depressive-like symptoms in a diurnal Nile grass rat, as well as in nocturnal mice and hamsters (FONKEN et al. 2012, 2013, BEDROSIAN et al. 2013). The most disconcerting is the data collection concerning the tumor growth in laboratory animal models: rats implanted with mammary adenocarcinoma cells that were exposed to dim light during the darkness phase showed significantly higher rates of tumor growth, lower survival than the controls and lower nocturnal excretion of melatonin (COS et al. 2006). Similar data were observed almost ten years prior to this in mice; DAUCHY et al. (1997) demonstrated that the Morris hepatoma tumors implanted subcutaneously into the mice grew faster under light contamination conditions of only 0.2 lux during an otherwise normal dark phase. A subsequent study concerning rats confirmed this principal finding in mice and showed that exposure of rats bearing xenografts of human breast cancer to dim light at night (0.08 mW/cm<sup>2</sup>; i.e., 0.2 lux) resulted in approximately a 65% suppression of the amplitude of the nocturnal melatonin signal in the blood, significantly stimulated tumor growth and affected the signal transduction and metabolic activity of tumor cells. All these effects were nearly equivalent to that observed in constant bright light-exposed

tumor-bearing rats, suggesting that in nocturnal animals, the saturation light level sufficient for dramatic dysregulation of the immune system is below 1 lux (BLASK et al. 2002, 2005a, 2009). All these studies concurred that light at night may predominantly speed up cancer growth via its ability to suppress the nocturnal production of melatonin by the pineal gland. In support of this hypothesis, melatonin-rich sera collected at night compared to melatonin-depleted sera collected after ALAN significantly suppressed the proliferative activity of human breast cancer xenografts in rats (BLASK et al. 2005b). Alternatively and additionally, the unsteady synchronization of the circadian molecular clockwork that is highly interconnected with the cell cycle and DNA repair mechanism may weaken natural rescue processes and enable tumor cell growth with fewer of the obstacles that are usually made by an activated immune system (UTH & SLEIGH 2014a, b).

## CONCLUSIONS

In conclusion, it is already widely accepted that the anthropogenic light at night alters natural light regimes, which affect the activity and composition of populations of diurnal and nocturnal species. A driving force behind the changing patterns of activity and foraging is understood to likely be light-induced attraction/repulsion of the prey and the subsequent balance between rewards of foraging and risk of predation. In addition, the discontinuities in the territories of nocturnal animals and the interruption of foraging traits have been documented as important ecological aspects of ALAN (LONGCORE & RICH 2004, HÖLKER et al. 2010). The visual pathway that ultimately mediates the effect of light on mammals has two distinct parts. First is the image-forming pathway that leads to conscious “seeing” and is important predominantly in orientation behavior and foraging, and second is the non-image forming pathway that transduces the information about the irradiance level to the circadian clock. Through the clock, this pathway affects all physiological processes in the body. The impact of ALAN in the development of various, so-called “civilization diseases” via the disruption of the circadian system is widely studied in humans, but is less studied in laboratory animals, and only very little is known about its impact on wildlife. Although we are aware of the fact that laboratory findings may have limited relevance in practice, we cannot dismiss potential risks due to exposure to ALAN for the individual health of wild animals. We suggest that in addition to widely discussed ecological aspects, the fitness of individual animals, which reflects the strength of their circadian system, may contribute to the population changes in response to ALAN in wildlife.

## SOUHRN

Příznivý účinek slunečního záření na všechny formy života byl známý lidským kulturám po celém světě od nepaměti. Význam noční tmy pro přežití, úspěšnou reprodukci a celkovou zdatnost všech organismů je však nedocenen. Reprodukce a přežití je významně ovlivněno sezónními výkyvy v přírodních podmínkách (tj. srážkami, změnami teploty, barometrického tlaku, dostupnosti potravy). Tyto výkyvy jsou ale často nepravidelné a dají se obtížně předvídat. Naproti tomu denní změny v osvětlení a světelném spektru mají sice menší vliv na život organismů, byly ale během celé evoluce vysoce předvídatelné. Přírodní výběr tak upřednostnil strategii sledování délky dne k předpovědi jiných změn ve vnějších podmínkách. V každém organismu se tak vyvinuly cirkadiální hodiny, které jsou citlivé na změny světla a tmy v průběhu dne i v noci. Dobře synchronizovaný mechanismus cirkadiálních hodin zajišťuje, že behaviorální a fyziologické procesy rytmují se slunečním cyklem a programuje sezónní změny ve fyziologii transdukci fotoperiody do hormonálních signálů.

Během posledních dvou desetiletí energeticky úsporné technologie osvětlení způsobují plošný přesun ze “žlutých” vysokotlakých sodíkových výbojek na nové “bílé” světelné diody (LED). V důsledku toho

se zvyšuje noční světelné znečištění a v mnoha částech světa je postupně smazáván rozdíl mezi dnem a nocí. Je již obecně přijímáno, že toto antropogenní noční světlo mění přirozené světelné cykly, což ovlivňuje aktivitu a složení populací nočních i denních druhů živočichů. Za hlavní příčinu měnicích se způsobů chování a reprodukce bývá považována změna v dostupnosti potravy, např. v důsledku světlem indukovaného chování hmyzu, a změny ve složení společenstev jsou pak důsledkem hledání rovnováhy mezi výhodami v přísunu potravy a rizikem predace. Kromě toho bývají zdůrazňovány bariéry vytvořené světlem na území nočních zvířat a přerušení migračních tras svícením do oblohy (LONGCORE & RICH 2004, HÖLKER et al. 2010).

Zraková dráha savců má dvě odlišné části; obrazovou dráhu, která vede k vědomému "vidění" a je důležitá převážně pro orientaci v prostoru, a dráhu pro tzv. neobrazové vidění, která přenáší informaci o intenzitě a barvě světla cirkadiánním hodinám. Přes cirkadiánní hodiny tak světlo ovlivňuje všechny fyziologické procesy v těle. Narušením cirkadiánního systému v důsledku světla v noci se významně zvyšuje riziko vzniku různých tzv. "civilizačních nemocí" jako jsou karcinomy, metabolické poruchy, diabetes druhého typu, hypertenze nebo deprese. Podstata vzniku těchto nemocí je intenzivně studována zejména u člověka, méně u laboratorních zvířat a téměř vůbec u volně žijících živočichů. Dostupné studie však naznačují, že cena zdravím za život v umělém nočním světle může být vysoká zejména u nočních živočichů, kteří jsou vysoce citliví jak na intenzitu světla, tak na jeho spektrální složení. Domníváme se však, že pokračující smazávání rozdílů mezi dnem a nocí přesáhne bzy adaptační možnosti i denních živočichů a zdravotní důsledky pro jednotlivá volně žijící zvířata známé z lidské populace mohou, spolu s ekologickými aspekty, také výrazně přispět ke změně biodiverzity savců v přírodě.

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