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Effects of Light at Night on Laboratory Animals and Research Outcomes

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Abstract

Light has substantial influences on the physiology and behavior of most laboratory animals. As such, lighting conditions within animal rooms are potentially significant, and often underappreciated variables within experiments. Disruption of the light/dark cycle, primarily by exposing animals to light at night (LAN), disturbs biological rhythms and has widespread physiological consequences due to mechanisms such as melatonin suppression, sympathetic stimulation, and altered circadian clock gene expression. Thus, attention to the lighting environment of laboratory animals and maintaining consistency of a light/dark cycle is imperative for study reproducibility. Light intensity as well as wavelength, photoperiod, and timing are all important variables. Although modern rodent facilities are designed to facilitate appropriate light cycling, there are simple ways to modify rooms to prevent extraneous light exposure during the dark period. Attention to lighting conditions of laboratory animals by both researchers and research care staff ensures best practices for maintaining animal welfare, as well as reproducibility of research results.

Keywords

light at night; circadian rhythm; melatonin; physiology; laboratory animals

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Introduction

Life on Earth has evolved under light days and dark nights over the course of billions of years; thus, biological systems have evolved in a way that the overall health and well-being of an organism depends on its physiology and behavior following this rhythmic environment. Locomotor activity and sleep are the behaviors with the most obvious circadian patterns, but hormones, core body temperature in endotherms, metabolism, immune function, and several other physiological and behavioral processes critical for survival also have rhythms coordinated by light/dark exposure (Gnocchi & Bruscalupi, 2017; Refinetti & Menaker, 1992; Scheiermann et al., 2013; Wiggins & Legge, 2016; Yang et al., 2006). Strict adherence to this biological schedule is adaptive for wild animals; for example, most rodent species forage under the protection of darkness to reduce the likelihood of predation (Clarke, 1983; Griffin et al., 2005). Chances of survival are significantly increased when a free-living animal's biological clock is synchronized to the environment (Brooks & Canal, 2013; Sharma, 2003; Spoelstra et al., 2016). On the other hand, disruption of an animal's light days or dark nights can disturb these critical survival behaviors as well as indirectly cause harm through misalignment of the circadian clock.

Depending on cloud cover and time of day, the sun provides up to 100,000 lux of light at the Earth's surface, whereas a full moon on a cloudless night casts off less than 2 lux of light (Thorington, 1985; Weaver, 2011; Wright et al., 2013). Until approximately 140 years ago, when electric lighting was introduced, the sun was solely responsible for the demarcation between day and night. Today, >99% of people living in the United States and Europe reside in regions with significant nighttime artificial light pollution (Falchi et al., 2016). Initially astronomers raised the alarms about light pollution, and subsequently nighttime light exposure has been correlated with several concerning physical and mental health trends in humans such as depression, increased risk of cancer, immune suppression, and obesity (Conlon et al., 2007; Erren et al., 2010; Haus & Smolensky, 2013; Kloog et al., 2008; Min & Min, 2017; Obayashi et al., 2013; Obayashi et al., 2017; Schernhammer et al., 2003; Schernhammer et al., 2006; Spiegel et al., 2009). Ecologists have likewise documented physiological and behavioral changes in free-living animals (Dominoni et al., 2013a; Dominoni et al., 2013b; Kempenaers et al., 2010; Miller, 2006; Raap et al., 2016), and researchers studying biological rhythms in wild and laboratory animals have recapitulated and expanded these observations (Bedrosian et al., 2011a; Fonken et al., 2009; Fonken et al., 2012). However, many laboratory-based investigators in other fields do not appear to appreciate the importance of synchronized circadian rhythms for the overall wellbeing of research animals and rigor of laboratory experiments.

Because artificial light has substantial influence on the physiology and behavior of laboratory animals, lighting conditions within animal rooms are a significant, and often underappreciated, variable within experiments. Animals exposed to problematic light intensity, wavelength, or timing are at risk for circadian disruption (Ohta et al., 2005) and subsequent behavioral and physiological alterations. In this paper, we review circadian rhythms and the effects of extraneous light exposure, specifically light at night (LAN), on research animals, and provide simple suggestions for modifying rodent holding rooms to

better control light/dark cycles. This, in turn, should reduce experimental variability and increase reproducibility of laboratory research by keeping biological rhythms aligned.

Circadian Rhythms

Circadian rhythms are endogenous biological rhythms with periods of approximately 24 hours that persist in the absence of environmental cues. In mammals, circadian rhythms are organized by a master biological clock located in the suprachiasmatic nucleus (SCN) of the anterior hypothalamus (Partch et al., 2014; Takahashi, 2016). Lesser circadian pacemakers have been discovered in the pineal gland, and several peripheral organs including retinas and liver, but the SCN synchronizes them (Lamia et al., 2008). In free running conditions (without exogenous cues), circadian rhythms may shift to a slightly shorter or longer period and gradually disengage from the geological cycle (Stephan, 1983; Czeisler et al., 1999). Therefore, environmental cues, such as light, precisely entrain circadian rhythms to the 24-h solar day. This entraining mechanism allows organisms to synchronize their physiology and behavior with the environment for optimal functioning as well as for survival. A circadian clock is present in virtually all flora and fauna (Somers et al., 1998; Tei et al., 1997), suggesting that circadian rhythms are fundamental to overall fitness.

Light at Night (LAN)

Because light plays such a significant role in circadian clock entrainment, the timekeeping system is vulnerable to aberrant lighting outside the solar day. Humans are potentially exposed to light at night during hospital stays, night shift work, nighttime travel, or from artificial light pollution in the environment. Likewise, laboratory animals are potentially subjected to light exposure at night from vivarium light sources. Exposure to constant light can disrupt circadian rhythms by desynchronizing clock neurons, although the ability to generate rhythms remains intact. This may result in “splitting” behavioral rhythms into two bouts of activity and rest within 24-h, phase shifting to shorter or longer periods, or a flattening/complete loss of rhythms (Ohta et al., 2005). For laboratory animals, sources of bright light within vivaria include constant light from malfunctioning light timers or pulses of light from improperly entering animal rooms or working with animals during the dark phase.

Low light intensities during the dark phase (dim light at night, dLAN) are also capable of disrupting biological rhythms. Nocturnal species, including most laboratory rodents, often have poor visual acuity, but remain highly sensitive to light intensity (Baker, 2013). Melanopsin, the photopigment present in ipRGCs, is activated by less than 1 lux of light (Glickman et al., 2002). Thus, it is reasonable to assume that any extraneous light in vivaria could potentially disturb circadian rhythms. Chronic dLAN exposure for laboratory animals can originate from electronics and rack tower screens within the room or hallway light leaking in around doors and through windows.

Physiological Effects of Light at Night

Disrupted circadian rhythms from LAN exposure likely cause extensive physiological effects through three key mechanisms: altered clock gene expression, melatonin suppression, and sympathetic stimulation (Jones et al., 2015; Lee et al., 2010; Takahashi, 2016). Clock genes including *Brain and Muscle ARNT-like Protein 1* (*Bmal1*), *Circadian Locomotor Output Cycles Kaput* (*Clock*), *Cryptochrome* (*Cry 1 and 2*), and *Period* (*Per 1–3*) work intricately together to generate oscillations of clock-controlled gene expression which control tissue function and maintain homeostasis (Partch et al., 2014; Takahashi, 2016). Disruption of these clock genes can create feedback loops that deviate from 24 h, resulting in misalignment of circadian-controlled processes and loss of homeostasis (Mazzoccoli et al., 2012). Exposure of laboratory rodents to light during the dark phase, as short as a 15 minute pulse, can elevate baseline expression of clock genes, phase shift the molecular clock, and increase daytime activity (Daan and Pittendrigh, 1976; Shigeyoshi et al., 1997; Shuboni and Yan, 2010). Even chronic exposure to 5 lux of light, a level approximately equal to a nightlight ~2 meters away, altered circadian clock genes *Bmal1*, *Per1, Per2*, *Cry1* and *Cry2* in central and peripheral tissues in Swiss Webster mice (Fonken et al., 2013) and Siberian hamsters (Bedrosian et al., 2013a). Although altered clock gene expression in laboratory animals is unlikely to affect immediate survival, for example by foraging at the incorrect time and falling prey to a predator, it can alter oscillations of clock-controlled genes throughout the body and disturb homeostasis.

In addition to altering clock gene expression, effects of LAN may occur due to melatonin suppression. Melatonin has a remarkably extensive list of receptor-mediated (e.g. circadian regulation, immune modulation) and receptor-independent (e.g. free radical scavenging, detoxification) physiological functions (Carrillo-Vico, 2005; Reiter, 2009; Reiter 2014). Notably, changes in melatonin disrupt endocrine pathways via alterations in reproductive, adrenal, and thyroid hormone axes (Scheving and Pauly, 1966; Snyder et al., 1965; Torres-Farfan et al., 2008). Accordingly, suppression of melatonin due to aberrant light exposure has the potential for widespread biological consequences due to its diverse functionality.

Melatonin suppression is dependent on light intensity, wavelength, and host species. Studies have demonstrated that dim light at night, as low as 0.25 lux of broad spectrum light in rats (Dauchy et al., 1999), or 0.05 lux of green light in Syrian hamsters (Podolin et al., 1987), can suppress pineal melatonin production. Whereas the majority of mammals have robust melatonin rhythms, melatonin production is highly variable among laboratory rodents. Commonly used laboratory rodents including rats (*Rattus norvegicus*), Syrian hamsters, Siberian hamsters, and Mongolian gerbils all demonstrate a discrete, nocturnal melatonin peak (review Reiter, 1991). On the other hand, melatonin production among laboratory mouse strains is more variable in terms of amount and timing. A considerable melatonin peak 2 h before lights on has been detected by radioimmunoassay in C3H and CBA mouse strains (Goto et al., 1989; Viven-Roels et al., 1998); however, no melatonin peak was detected in other inbred strains including C57BL/6, BALB/c, and AKR mice (Ebihara et al., 1986; Goto et al., 1989; Kennaway et al., 2001). Melatonin production has been debated by other investigators sampling more frequently (every 15–30 min) during the dark cycle who were able to detect a brief but significant melatonin peak in C57BL/6, BALB/c, and AKR

strains (Conti & Maestroni, 1998; Maestroni et al., 1986; Viven-Roels et al., 1998). Mutations in enzymes that catalyze the synthesis of melatonin such as *N*-acetyltransferase (Roseboom et al., 1998) and/or hydroxyindole-*O*-methyltransferase (HIOMT) (Kasahara et al., 2010; Kennaway et al., 2001) may explain the variability in melatonin robustness among laboratory mouse strains. Notably, regardless of the magnitude of melatonin peak, these animals all maintain strong circadian rhythmicity.

Moreover, the SCN generates a strong circadian rhythm in autonomic nervous system signaling (Lee et al., 2010) and, independent of melatonin suppression, sympathetic control has been documented to alter physiological processes following changes in lighting conditions (Bartness et al., 2002). The sympathetic nervous system regulates important cellular processes such as cell cycle control; therefore, circadian dysfunction may promote tumor formation and progression (Lee et al., 2010). This is particularly important for animal tumor studies because of the potential for altered tumor growth rates following LAN exposure (Dauchy et al., 1999; Dauchy et al., 2011).

Metabolism and Obesity

There are compelling data available regarding the relationship between circadian and metabolic disruption. Rodents that lack expression of normal circadian clock genes have abnormal metabolic phenotypes. For example, *Clock* $^{\Delta 19}$ mutant mice are obese and have abnormal lipid and glucose metabolism (Yang et al., 2006). Likewise, *Bmal1* mutant mice have impaired insulin responsiveness and gluconeogenesis (Rudic et al., 2004). These strains demonstrate the importance of an intact molecular clock for normal metabolism.

Similar to mutant mouse models, laboratory animals exposed to dLAN have elevated body mass and body fat (Fonken et al., 2013) and impaired glucose tolerance (Opperhuizen et al., 2017) compared to those with dark nights. Exposing mice to dLAN for just two weeks reduces energy expenditure and increases carbohydrate over fat oxidation, resulting in an overall increase in body mass (Borniger et al., 2014). Administration of exogenous melatonin to obese mice and to jet-lagged mice attenuates circadian disruption in adipose tissue as well as reduces body weight gain (Liu et al., 2017). Additionally, mice exposed to dLAN shift a portion of their normal nocturnal food intake to daytime and increase body mass despite equivalent caloric intake relative to mice in dark nights (Fonken et al., 2010).

The alterations in body fat composition and glucose tolerance observed in obese mice potentially alters research results. Drug administration in obese laboratory animals is difficult because pharmacokinetic data are determined in individuals of healthy body mass. Due to the lower relative lean muscle in obese animals, they are often overdosed when calculating drug dosages based strictly on body mass (Cheymol, 2000). Further, increased incidence of comorbidities in obese animals may impair function of organs involved in drug elimination such as the kidney or liver. Obesity is also associated with chronic, low-grade inflammation, specifically increased TNF-α (Hotamisligil et al., 1993). Thus, exposure to LAN precipitates metabolic disruption, which may cause variability in research results due to inconsistent agent administration, comorbidities, and other systemic effects in laboratory animals.

Immune System

The immune system is vulnerable to circadian disruption due to clock control of immune cell counts and function. Immune cell and cytokine/chemokine levels fluctuate according to the time of day and the sleep-wake cycle (Cermakian et al., 2013). Specifically, rodent studies describe increased levels of lymphocytes, granulocytes, neutrophils, and monocytes during the day compared to at night; however, numbers of NK cells peak at the end of the dark cycle (Hriscu, 2005; Pelegri et al., 2013; Oishi et al., 2006). Rodents that lack expression of normal clock genes demonstrate their importance for the immune system. For example, *Clock* mutant mice display suppressed and phase shifted total white blood cell and lymphocyte counts compared to wild types (Oishi et al., 2006). Similarly, *Per2* mutant mice have suppressed levels of IFN-γ, a critical cytokine that modulates both innate and adaptive immunity, and loss of IFN-γ normal daily rhythmicity (Arjona & Sarkar, 2006).

Immune responses often vary depending on time of day due to these daily oscillations in immune cell activity, therefore circadian disruption from LAN has the potential to alter immune function. For example, allergic diseases exhibit daily variation in symptom severity based on time of day, which can be explained by circadian control of IgE/mast cell-mediated allergic reactions (Nakamura et al., 2011) and T cell-mediated hypersensitivity reactions (Takita et al., 2013). This variation is demonstrated by Siberian hamsters exposed to dLAN that had decreased skin contact hypersensitivity response compared to controls in dark nights (Bedrosian et al., 2011b). Interestingly, offspring of dLAN-exposed hamsters that were housed in standard LD lighting conditions from birth also exhibited differential delayed hypersensitivity reaction than controls (Cisse et al., 2017). Furthermore, mouse models have demonstrated that susceptibility to endotoxic shock is dependent on the time of day when lipopolysaccharide (LPS) is administered (Marpegan et al., 2009). Mice exposed to 4 weeks of dLAN had heightened inflammatory responses to LPS injection compared to mice housed in dark nights (Fonken et al., 2013). In addition to phase shifted immune response, exaggerated reactivity to LPS is likely due to suppression of melatonin and its anti-inflammatory effects (Tan et al., 2002). Several inflammatory cytokines are elevated in a tissue-specific manner following dLAN exposure in mice and Siberian hamsters (Bedrosian et al., 2013b; Fonken et al., 2013).

Altered immune function in laboratory animals potentially affects animal welfare and experimental outcomes. Decreased lymphocyte counts and chronic inflammation following circadian dysfunction damages immune surveillance and precedes various infectious and non-infectious diseases (Landskron et al., 2014; Vojdani, 2014; Wellen and Hotamisligil, 2005). These pathologies not only decrease animal wellbeing, but also have the potential to confound research data. Importantly, immunology research outcomes such as infectious disease testing are directly impacted by any alterations to the immune system. Controlling the timing of immune challenges as well as maintaining circadian rhythm alignment is vital for research reproducibility due to daily variation in immune cell numbers and reactions.

Cancer

Cancer is likely the biomedical field for which the most compelling data exist for an effect of nighttime lighting in both humans and rodents. Cancer rates in industrialized nations are

remarkably higher than elsewhere, and increased LAN exposure is one of the many factors to which this phenomenon has been attributed. Indeed, more than 99% of the US and European populations live in regions with significant nighttime light pollution (Falchi et al., 2016). While controlling for other relevant socioeconomic factors, breast cancer rates were correlated with mean illumination levels at night in 164 countries. There is a strong correlation between levels of light at night and breast cancer rates in these countries (Kloog et al., 2008).

Likewise, night shift work is associated with an increased risk of developing breast, prostate, and colorectal cancer; presumably in part due to exposure to LAN exposure (Schernhammer et al., 2003; Schernhammer et al., 2006; Conlon et al., 2007; Kloog et al., 2008). In fact, recently The International Agency for Research on Cancer listed shift work as “probably carcinogenic to humans” in group 2A (World Health Organization, 2010) and Denmark offers compensation to women who work night shifts and develop breast cancer (Erren et al., 2010).

Laboratory studies utilizing animals also report a positive relationship between exposure to LAN and tumor formation and progression. More than 60 years ago, increased occurrence of spontaneous mammary tumors in mice housed in constant light was first reported (Jöchle 1964). Likewise, induced mammary tumor incidence is increased in rats exposed to constant light beginning *in utero* compared to those in dark nights (Mhatre et al., 1984). Notably, administration of melatonin to these rats in a pattern that simulates nighttime exogenous release reverses the deleterious effects of constant light. Constant lighting conditions may also be favorable for enhanced tumor growth due to increased macrophage recruitment and upregulation of genes involved in lipogenesis, glucose uptake, and tumor growth in the tumor microenvironment (Guerrero-Vargas et al., 2017). Promotion of anabolic metabolism may be necessary to support rapid tumor growth.

Increased tumor incidence and progression are not limited to constant light. Dim light during the dark phase also promotes tumor progression in rats with hepatomas (Dauchy et al., 1999), mice with induced mammary adenocarcinoma (Schwimmer et al., 2014), and rats with human breast cancer xenographs (Blask et al., 2005). Remarkably, these effects were also able to be rescued by the administration of exogenous melatonin during the dark phase.

Whether due to the general disruption of circadian rhythms, reduced melatonin production, or likely a combination of the two, exposure to LAN increases cancer risk. With an increased resurgence in this area of research, beneficial effects of melatonin on tumor initiation and progression have become increasingly clear. Melatonin can reduce estrogen receptor alpha (ERα) mRNA expression/transcriptional activity and decrease aromatase action (Molis et al., 1994; Ram et al., 1998; Blask et al., 2011), both of which play important roles in tumor growth of ER+ breast cancer. Further, melatonin can inhibit cancer cell invasion and metastasis by enhancing the expression of adhesion proteins (e.g. E-cadherin and β1 integrin) and decreasing expression of matrix metalloproteinases (Mao and Hill, 2010; Blask et al., 2011).

The beneficial actions of melatonin are not limited to direct effects on cancer cells. Melatonin can enhance immune surveillance by increasing natural killer cell activity, which is an important mechanism limiting tumor growth (Stevens et al., 1992). Further, melatonin counteracts tumor immune evasion by increasing IL-12, IL-2, and INF-γ production in T cells and monocytes, therefore driving T cells toward a Th1 response (Carrillo-Vico et al., 2005). Importantly, all of the beneficial effects of melatonin on cancer initiation, progression and immune cell activation are absent when animals are exposed to light at night (Blask et al., 2014).

Not only do these data present concern for the health of the animals in non-cancer studies, but also results from studies involving tumor formation and progression may be skewed if LAN is not carefully controlled and reported. For example, Dauchy et al. (2011) describes relocating a cancer laboratory between institutions and finding the new animal room contained light pollution that augmented tumor growth rates along with many other physiologic parameters. Tumor latency-to-onset and proliferation rate increased directly in proportion to light intensity at night experienced by tumor-bearing nude rats. This case undoubtedly emphasizes the real consequences of LAN on animal data for researchers.

Reproduction

The circadian clock system is integrated into the hypothalamic-pituitary-gonadal (HPG) axis, regulating hormone gene expression and secretion as well as biological rhythms within reproductive tissues (Khan et al., 2016). Ovaries of vertebrates, from fish to mammals, have oscillating *Clock* and *Per2* expression, and the light/dark cycle is critical for regulating these clock genes (Karman & Tischkau, 2006; Shimizu et al., 2011; Wiggins and Legge, 2016). Female reproductive cycling, oocyte recruitment, and release of a mature oocyte are directly influenced by ovarian biologic rhythms (Wiggins and Legge, 2016). In fact, both male and female *Bmal1* knock out mice are infertile due to delayed implantation and early embryo loss (Alvarez et al., 2008). Reproductive timing is profoundly influenced by clock genes, and consequently misalignments of the circadian clock can alter or repress reproduction.

Numerous studies have demonstrated that abnormal lighting conditions are capable of disrupting reproductive endocrinology in various animals including humans. In free-living birds, exposure to artificial LAN altered estrone concentrations in female blackbirds (Dominoni et al., 2013b), testosterone in female scrub-jays (Schoech et al., 2013), and luteinizing hormone (LH) in male scrub-jays (Schoech et al., 2013). Furthermore, exposure to constant light has been shown to disrupt ovulation in hamsters (Alleva et al., 1968), and eventually cease ovulation in rats due to LH suppression (Lawton & Schwartz, 1967). In addition to animals, similar observations in human studies show that circadian disruption due to shift work, jet lag, or exposure to LAN can alter female menstrual cycles and ovulation (Mahoney, 2010; Lin et al., 1990; Preston et al., 1973).

Many wild and domestic animals, including some laboratory species, are seasonal breeders, meaning their reproductive status is dependent on duration of light exposure and resulting melatonin production (review Reiter, 2009). Thus, interruption of the dark phase with artificial light can disturb melatonin production and provide animals with incorrect information regarding day length. Artificial light has been shown to perturb seasonal

breeding in various animal species (Baker & Richardson, 2006; Chemineau et al., 1992; Robert et al., 2015). For example, European blackbirds exposed to very low dLAN (0.3 lux) exited their photorefractory period nearly one month earlier than birds exposed to dark nights, and demonstrated no signs of reproductive activity the next year (Dominoni et al., 2013b). Likewise, Siberian hamsters exposed to short day/long night lighting conditions with the addition of dLAN did not display the expected winter phenotype of reduced gonadal and body mass, decreased sperm count, and white pelage (Ikeno et al., 2014). Moreover, male mouse lemurs exposed to 5 weeks of LAN during a short-day lighting regimen had increased testis size and plasma testosterone concentration, indicating premature sexual recrudescence (Le Tallec et al., 2016). Thus, LAN has been shown to disrupt reproduction in a wide range of species.

Reproduction in photoperiodic animals is highly sensitive to aberrant lighting during the dark phase, and the health of breeding colonies is likely improved with increased attention to maintaining dark nights. This is especially noteworthy for principal investigators with rodent breeding colonies. Laboratory purpose-bred rodents generally breed during the night and breeding success is highest with a consistent light/dark cycle due to normal melatonin signaling.

Glucocorticoids

Glucocorticoids modulate numerous biological functions, including maintaining homeostasis and coordinating stress responses; glucocorticoids are often referred to as “stress hormones” but they also serve many critically important physiological functions. Glucocorticoid levels in the blood follow a circadian rhythm, increasing upon waking, peaking within ~30 min, and then slowly declining throughout the animal’s active phase. Within this general pattern, synthesis of glucocorticoids occurs as discrete ultradian pulses, pulsing approximately hourly, due to alternating activation and inhibition of the hypothalamus-pituitary-adrenal (HPA) axis (Lightman et al., 2008).

Studies in laboratory rodents demonstrate that abnormal light cycles are able to eliminate the normal biological rhythm of glucocorticoids and/or increase circulating levels in the blood. For instance, 5 lux of dLAN flattened endogenous cortisol rhythms in hamsters (Bedrosian et al., 2013a) and increased circulating corticosterone levels in mice and grass rats (Fonken et al., 2012; Martynhak et al., 2016). Even 15 min bursts of bright light exposure at night increased glucocorticoid hormones in mice compared to LD controls, and supplementation with exogenous melatonin was able to rescue glucocorticoid levels (Wilson and Downs, 2015).

Glucocorticoids are robust immunomodulatory agents capable of disturbing virtually all physiologic processes including wound healing, blood pressure, growth and development, blood glucose levels, muscle and bone physiology, and mentation (Schacke et al., 2002). Accordingly, alterations in circulating glucocorticoid levels from exposure of laboratory animals to aberrant light has the potential for systemic effects that may interfere with data interpretation by researchers in various disciplines.

Growth

Growth factors including growth hormone (GH) and insulin-dependent growth factor 1 (IGF1) display daily oscillations. Research in the area of LAN and growth is sparse; however, due to circadian control of growth hormones, dLAN exposure during development may disturb expected growth rates and overall wellbeing of animals. This was shown in songbirds exposed to dLAN (3 lux) during development that had reduced gains in body mass compared to control birds (Raap et al., 2016). Another notable consideration is that the response to GH administration is dependent on the time of day. GH administration at various times of day in teleost fish leads to varied activation of the somatotropic axis, with the greatest effect observed when given midway through the dark period (Costa et al., 2015). Attention should be given to a time of day effect when administering growth hormone. Consequently, timing of administration of growth hormones must be controlled during research studies in order to reduce variability between animals.

Considerations for Invertebrates

Lighting conditions are also a concern when housing invertebrates used in research because these animals (and even unicellular organisms) have the same complexity of biological rhythms as mammals (Vitaterna et al., 2001). In fact, the first circadian clock genes were identified in the fruit fly (*Drosophila melanogaster*), and the fruit fly today remains a fundamental model organism for studying genetics, development, and disease (Konopka and Benzer, 1971; Bellen et al., 2010). Constant bright light has been shown to negatively affect fecundity, longevity, and development of *D. melanogaster* (Sheeba et al., 1999; Kouser and Palaksha, 2014). These widespread effects have the potential to alter experimental results utilizing fruit flies. Other less-commonly studied invertebrates are similarly vulnerable to aberrant lighting conditions. Exposure to LAN can dampen immune responses in crickets (Durrant et al., 2015); reduce clutch sizes in ants (Lone and Sharma, 2008); and decrease likelihood of successful mating in moths, fireflies, and aphids (Firebaugh and Haynes, 2016; Sanders et al., 2015; Van Geffen et al., 2015). These findings highlight that the potential effects of LAN on circadian disruption and physiology are highly conserved across phylogeny and appropriate light/dark cycles must be considered when housing invertebrates.

Behavioral Effects of Light at Night

In addition to many physiological functions, LAN also potentially affects animal behaviors under circadian control. Beyond activity and rest, the effects of light at night on affective behaviors, specifically depressive-like and anxiety-like behaviors, remain problematic for research outcomes. For example, Siberian hamsters exposed to dLAN for 8 weeks and mice exposed to constant light for 3 weeks both displayed increased depressive-like behavior compared to control LD animals (Bedrosian et al., 2011a; Fonken et al., 2009). These consequences are not limited to immediate effects as exposure of mouse or hamster pups to dLAN in early post-natal life has been demonstrated to cause anxiety-like behavior that persists into adulthood (Borniger et al., 2014; Cisse et al., 2016). Furthermore, Nile grass rats, a diurnal laboratory rodent, exhibited impaired learning and memory in addition to increased depressive-like behaviors with chronic exposure to dLAN (Fonken et al., 2012).

Together, these studies emphasize the potential for persistent behavioral changes in laboratory animals exposed to aberrant lighting conditions.

These affective-like changes are concerning for more than just researchers who perform behavioral testing, because psychological states affect other organ systems and can influence the outcomes of a multitude of diseases. Neurotransmitters, neuropeptides, and neurohormones altered with mental disorders are common signaling mediators in the immune system, endocrine system, and peripheral nerves (Reiche et al., 2004). This means that psychosocial disorders may have systemic implications. To illustrate, depression has been associated with morbidities such as cardiovascular disease (Perlmutter et al., 2000), hypertension (Meng et al., 2012), and diabetes (Anderson et al., 2001) in humans. Thus, exposure of laboratory animals to LAN can cause depressive- and anxiety-like behaviors with the potential for broad physiological changes.

Lighting Conditions in Animal Rooms

Due to the extensive effects on physiology and behavior, aberrant light in vivaria can broadly affect animal welfare and research outcomes. Therefore, the lighting environment in animal holding rooms is an important variable in animal research. While these principles apply to all species used in research, we will focus on rodents considering mice and rats account for approximately 95% of biomedical research animals in the United States (National Association for Biomedical Research, 2017).

Macroenvironment

The *Guide for the Care and Use of Laboratory Animal,* a publication produced by the NIH, specifies international standards for animal care in biomedical research. The *Guide* recommends that extraneous light exposure during the dark cycle be minimized or eliminated, and that a time-controlled lighting system be used to guarantee regular cycling (National Research Council, 2011). The *Guide* also states that 325 lux, measured approximately 1 m above the floor, appears to be sufficient light for animal care as well as avoiding phototoxic retinopathy in albino rodents (National Research Council, 2011). Despite these recommendations, vivarium lighting is often adjusted to accommodate the needs of both animal care and laboratory personnel. Brighter room lights are commonly used when changing cages to aid in visualization during the light phase. Various photic disturbances, such as entering and exiting animal rooms during the dark phase and housing electronic equipment within the room, also alter light exposure at the room level, and may result in differential exposure of the mice based on room location. Periodically placing data loggers in animal rooms is a good option to check lighting conditions and verify absence of light during the dark cycle. Further, lighting alarms can quickly catch malfunctioning light timers and personnel inappropriately entering animal rooms during the dark phase to protect study animals from aberrant light exposure and the potential disturbance to research data.

Microenvironment

In addition to the macroenvironment, an animal's microenvironment also influences lighting conditions. The microenvironment includes elements such as cage opacity, nesting material,

and enrichment devices. One study found that rats experienced circadian variation as demonstrated by altered phase timing, amplitude, or duration of plasma melatonin and other hormones depending on whether they were housed in clear or tinted cages (Wren et al., 2014). Similarly, altered spectral quality through tinted enrichment devices such as huts or tunnels was sufficient to cause circadian disruption in rats (Wren-Dail et al., 2016). Along with spectral variation, rodent enrichment also potentially influences the light intensity experienced by the animal. Nesting material and opaque huts provide a physical barrier between the animal and light source, thereby reducing light exposure. Because of the potential variation in light exposure, cage type along with the amount and type of enrichment should be standardized within a study and reported in publications.

Cage Location

For laboratory animals housed on racks, the rack location in the room and the cage location on the rack also potentially influence lighting environment. In a rodent room, light intensity is typically greater towards the top of the rack, near the ceiling light source. Remarkably, light intensity can differ as much as 80-fold within clear cages located on the same rack (Schlingmann et al., 1993). This is a substantial amount of variation, with the potential for significant animal variability. In fact, differences in retinal morphology and ocular lesions among BALB/c mice and Fischer 344 rats in chronic toxicity studies have been attributed to cage location (Greenman et al., 1982; Rao, 1991). Cage location and corresponding light intensity has also been found to influence rates of spontaneous and induced neoplasia in mice (Greenman et al., 1984). These studies demonstrate that cage location can significantly affect animal data and lead to experimental variability. Options for controlling light variation include utilizing similar location for all cages on study, rotating cage position on the rack, or using specially-designed cabinets that deliver consistent lighting to all cages.

Light Spectrum

Many studies involving circadian disruption by light utilize white light, but it is important to recognize that biological effects can vary with different wavelengths of light. Intrinsically photosensitive retinal ganglion cells (ipRGCs) are maximally responsive when exposed to wavelengths of light around 480 nm, corresponding to blue light, and least responsive to longer wavelengths of light, which appear red (Lucas et al., 2001; Berson et al., 2002; Dacey et al., 2005). The specific wavelengths of light that maximally activate ipRGCs can vary between species. For example, in chicks light of 560 nm elicited the strongest response, corresponding to green light (Jiang et al., 2017). Nonetheless, in general long wavelengths of light in the red spectrum elicit the least response from ipRGCs, whereas shorter wavelengths of light in the blue spectrum elicit the greatest response.

Physiological changes can occur depending on the wavelength of light utilized in an animal's housing environment. Rats exposed to daytime LED lighting with high blue emissions had significantly different food and water intake, melatonin peaks, and plasma circadian markers than rats exposed to daytime white-light LEDs (Dauchy et al., 2016). Likewise, the physiological responses to light at night exposure can also vary with the wavelength. Melatonin in Syrian hamsters was differentially suppressed following exposure to light of different wavelengths at night, with the greatest suppression from blue

wavelengths (Brainard et al., 1984). Additionally, pulses of blue or white light, but not red light, were shown to activate neural activity in the SCN of Siberian hamsters and alter results of depressive-like behavioral testing (Bedrosian et al., 2013b).

Eliminating all light exposure at night in vivaria is best for both animal welfare and experimental data, but when necessary, utilizing dim red light is an effective alternative to maintain circadian organization in laboratory species. It is important to recognize, however, that light bulbs appearing red do not necessarily emit light solely in the red spectrum. Some red-appearing bulbs may not block all shorter wavelengths of light; therefore, emitted wavelengths must always be confirmed by a photometer before use around animals.

Bulb Type

Fluorescent lighting is the conventional source of general illumination in most buildings. Traditionally vivaria utilize cool white fluorescent (CWF) or full spectrum fluorescent lighting (FSFL), which mimic natural light due to broad spectral distribution. A topic currently under discussion among individuals in lab animal management is switching from fluorescent to light-emitting diode (LED) lighting for vivarium illumination. LED lighting is attractive because it is energy efficient, produces less heat, and bulbs are changed less frequently. Preliminarily work found no significant difference in melatonin suppression, ocular pathology, or retinal physiology between CWF and broad-spectrum LED lighting in rats (Heeke et al., 1999). However, as mentioned above, high blue emission LEDs in animal rooms can greatly enhance nighttime melatonin levels, and so the LED spectrum is critical (Dauchy et al., 2016). At this time, little to no information is available regarding chronic LED exposure in animals. What we do know is that bulb type determines spectral quality and therefore it has the potential to influence biological rhythms.

Solutions to Light Pollution During the Dark Cycle

Pollution of the housing environment by LAN is a common problem, even in modern animal facilities, which could inadvertently lead to increased variation in research results. There are, however, simple remedies for many common sources of light pollution. Light pollution can originate from within the room itself, often from seemingly innocuous indicator lights. Lights on ventilated rack control tower screens, biosafety hoods, and small electronics such as power strips and lab equipment give off continuous light during the dark phase. The IVC control tower screens in night mode (red screen background) we measured emitted 35 lux of light (Mavolux 5032C, Gossen, Nurnberg, Germany). This light source is present for the full duration of the dark phase every night and cages may be located directly next to it. These screen lights are easily covered by small, removable sheets. For example, laminated black cardstock adhered with Velcro is an inexpensive, minimally invasive covering for equipment screens and lights that can be removed when needed.

Additionally, animal holding room doors often contain viewing windows for quick visualization. Covering these windows with a light-impenetrable material or red acetates reduces light pollution from hallway illumination. If left uncovered, racks near the door potentially experience appreciably increased light levels. Light that measured 234 lux in the hallway outside of the animal room door radiated 170 lux through a clear glass door

window. The light was reduced to 4.1 lux when adding a red acetate window covering and 0 lux when using a light-impenetrable vinyl material (Mavolux 5032C, Gossen, Nurnberg, Germany). Hallway light also leaks around incompletely sealed doors. Adding supplementary seals such as door sweeps or weather stripping can reduce this light intrusion.

Another important source of LAN exposure for laboratory animals is personnel entering and exiting animal rooms during the dark phase. This may cause brief, high intensity bursts of light, which, as described above, can have physiological consequences. Prevention is the best option for correcting this exposure route; restricting animal room entrance after lights out and educating staff of its importance is essential. An alternative, more flexible, approach is to add red filters over hallway lights. Red light, as discussed previously, is less disruptive to circadian rhythms of rodents. If entering the animal room during the dark phase is required, designing the room to include an anteroom to act as a light trap would be ideal. One research lab installed a lightproof curtain outside the exterior door, which dropped their light pollution down to undetectable levels within the rodent room (Dauchy et al., 2011). Inexpensive and relatively easy modifications to animal rooms can significantly reduce light pollution during the dark cycle.

Conclusions and Perspectives

Data collected from a wide array of species in both natural habitats and laboratories indicate that there are widespread effects of aberrant light, specifically light at night, on physiology and behavior. Clock gene disruption and melatonin suppression from light exposure during the dark phase are two thoroughly characterized mechanisms of action causing these effects (Jones et al., 2015; Takahashi, 2016). To ensure maintenance of complete darkness, animal holding rooms must be inspected for sources of light pollution and room entrance during the dark phase should be controlled in a way that prevents light intrusion. To do this, cover light sources within the room including electronic indicator lights and ventilated tower screens, and prevent light from entering around doors and through windows. Using data loggers to monitor light intensity and installing light alarms in animal rooms is helpful to catch malfunctioning light timers and inappropriate room entrance during the dark phase. If entering an animal room after dark, use only dim red lights and red acetates that have been properly checked for spectral quality in order to minimize circadian disturbance. Both research care staff and investigators are stakeholders in making this a priority for quality data and animal welfare. All experiments are different and so there cannot be one set of recommendations that will be optimal for all animal users, but these considerations provide a good starting point for discussion.

Because of the potential for unintended alterations in research findings, reporting detailed lighting conditions along with the timing of experimental manipulations is critical for reproducibility. Standardizing and reporting experimental times such as when samples are taken, agents are administered, and surgeries are performed (both circadian time and zeitgeber time) properly accounts for the well-documented daily oscillation of many hormones such as glucocorticoids, melatonin, growth hormone, gonadal steroids, and thyroid hormone (Gnocchi & Bruscalupi, 2017). Likewise, behavioral testing may yield different results when performed during the light versus dark phase due to regular active and

sleep phases. For instance, there is a 50% increase in withdrawal threshold in response to mechanical stimulation of the paw when mice are tested during the light phase versus the dark phase (Minett et al. 2014). Testing animals during the light (their inactive) phase may produce significantly different results due to reduced motivation to complete the tasks, sleep deprivation, increased stress, or associated cognitive deficits (Hawkins and Golledge, 2017).

Under most circumstances, interruptions in the light/dark cycle should be avoided for laboratory animals; however, intentional LAN research continues to be an area of interest to investigate potential effects on human health and well-being. Night shift workers, frequent travelers experiencing jet lag, the ill/elderly, and other people with nighttime light exposure are at increased risk for many physical and mental disorders (Conlon et al., 2007; Erren et al., 2010; Haus & Smolensky, 2013; Kloog et al., 2008; Min & Min, 2017; Obayashi et al., 2013; Obayashi et al., 2017; Schernhammer et al., 2003; Schernhammer et al., 2006; Spiegel et al., 2009). As more of the developing world begins to reside in areas with significant artificial nighttime light pollution, these animal models help us understand the potential risks that come along with a 24/7 society. Whether it be humans or other animals, consistent, controlled photoperiods are of the utmost importance in maintaining normal biological rhythms and overall well-being.

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References

Alleva JJ, Waleski MV, Alleva FR, Umberger EJ. Synchronizing effects of photoperiodicity on ovulation in hamsters. Endocrinology. 1968; 82:1227–1235. [PubMed: 5647603]

Alvarez JD, Hansen A, Ord T, Bebas P, Chappell PE, Giebultowicz JM, Williams C, Moss S, Sehgal A. The Circadian Clock Protein *BMAL1* is Necessary for Fertility and Proper Testosterone Production in Mice. Journal of Biological Rhythms. 2008; 23:26–36. DOI: 10.1177/0748730407311254 [PubMed: 18258755]

Anderson RJ, Freedland KE, Clouse RE, Lustman PJ. The prevalence of comorbid depression in adults with diabetes: A meta-analysis. Diabetes Care. 2001; 24:1069–1078. [PubMed: 11375373]

Arjona A, Sarkar DK. The Circadian Gene *mPer2* Regulates the Daily Rhythm of IFN-g. Journal of Interferon & Cytokine Research. 2006; 26:645–649. [PubMed: 16978068]

Baker M. Neuroscience: through the eyes of a mouse. Nature. 2013; 502:156–158. [PubMed: 24108031]

Baker BJ, Richardson JML. The effect of artificial light on male breeding-season behavior in green frogs, *Rana clamitans melanota*. Canadian Journal of Zoology. 2006; 84:1528–1532.

Bartness TJ, Demas GE, Song CK. Seasonal changes in adiposity: the roles of the photoperiod, melatonin, and other hormones, and sympathetic nervous system. Experimental Biology and Medicine. 2002; 227:363–376. [PubMed: 12037125]

Bedrosian TA, Fonken LK, Walton JC, Haim A, Nelson RJ. Dim light at night provokes depression-like behaviors and reduced CA1 dendritic spine density in female hamsters. Psychoneuroendocrinology. 2011a; 36:1062–1069. [PubMed: 21292405]

Bedrosian TA, Fonken LK, Walton JC, Nelson RJ. Chronic exposure to dim light at night suppresses immune responses in Siberian hamsters. Biology Letters. 2011b; 7:469–471.

Bedrosian TA, Galan A, Vaughn CA, Weil ZM, Nelson RJ. Light at night alters daily patterns of cortisol and clock proteins in female Siberian hamsters. Journal of Neuroendocrinology. 2013a; 25:590–596. [PubMed: 23489976]

Bedrosian TA, Vaughn CA, Galan A, Daye G, Weil ZM, Nelson RJ. Nocturnal light exposure impairs affective responses in a wavelength-dependent manner. Journal of Neuroscience. 2013b; 33:13081–13087. [PubMed: 23926261]

Bellen HJ, Tong C, Tsuda H. 100 years of *Drosophila* research and its impact on vertebrate neuroscience: a history lesson for the future. Nature Reviews Neuroscience. 2010; 11:514–522. [PubMed: 20383202]

Berson DM, Dunn FA, Takao M. Phototransduction by retinal ganglion cells that set the circadian clock. Science. 2002; 8:1070–1073.

Blask DE, Brainard GC, Dauchy RT, Hanifin JP, Davidson LK, Krause JA, Sauer LA, Rivera-Bermudez MA, Dubocovich ML, Jasser SA, Lynch DT, Rollag MD, Zalatan F. Melatonin-depleted blood from premenopausal woman exposed to light at night stimulates growth of human breast cancer xenografts in nude rats. Cancer Research. 2005; 65:11174–11184. [PubMed: 16322268]

Blask DE, Dauchy RT, Dauchy EM, Mao L, Hill SM, Greene MW, Belancio VP, Sauer LA, Davidson L. Light Exposure at Night Disrupts Host/Cancer Circadian Regulatory Dynamics: Impact on the Warburg Effect, Lipid Signaling and Tumor Growth Prevention. PLoS ONE. 2014; 9:e102776.doi: 10.1371/journal.pone.0102776 [PubMed: 25099274]

Blask DE, Hill SM, Dauchy RT, Xiang S, Yuan L, Duplessis T, Mao L, Dauchy E, Sauer LA. Circadian regulation of molecular, dietary, and metabolic signaling mechanisms of human breast cancer growth by the nocturnal melatonin signal and the consequences of its disruption by light at night. Journal of Pineal Research. 2011; 51:259–269. [PubMed: 21605163]

Borniger JC, McHenry ZD, Salloum BA, Nelson RJ. Exposure to dim light at night during early development increases adult anxiety-like responses. Physiology & Behavior. 2014; 133:99–106. [PubMed: 24857721]

Brainard GC, Richardson BA, King TS, Reiter RJ. The Influence of Different Light Spectra on the Suppression of Pineal Melatonin Content in the Syrian Hamster. Brain Research. 1984; 294:333–339. [PubMed: 6704731]

Brooks E, Canal MM. Development of circadian rhythms: role of postnatal light environment. Neuroscience & Biobehavioral Reviews. 2013; 37:551–560. [PubMed: 23454636]

Carrillo-Vico A, Guerrero JM, Lardone PJ, Reiter RJ. A Review of the Multiple Actions of Melatonin on the Immune System. Endocrine. 2005; 27:189–200. [PubMed: 16217132]

Cermakian N, Lange T, Golombek D, Sarkar D, Nakao A, Shibata S, Mazzoccoli G. Crosstalk between the circadian clock circuitry and the immune system. Chronobiology International. 2013; 30:870–888. [PubMed: 23697902]

Chemineau P, Malpaux B, Delgadillo JA, Guerin Y, Ravault JP, Thimonier J, Pelletier J. Control of sheep and goat reproduction: use of light and melatonin. Animal Reproduction Science. 1992; 30:157–184.

Cheymol G. Effects of Obesity on Pharmacokinetics. Clinical Pharmacokinetics. 2000; 39:215–231. [PubMed: 11020136]

Cisse YM, Russart KLG, Nelson RJ. Parental exposure to dim light at night prior to mating alters offspring adaptive immunity. Scientific Reports. 2017; 7:45497.doi: 10.1038/srep45497 [PubMed: 28361901]

Cisse YM, Peng J, Nelson RJ. Dim light at night prior to adolescence increases adult anxiety-like behaviors. Chronobiology International. 2016; 33:1473–1480. [PubMed: 27592634]

Clarke J. Moonlight's influence on predator-prey interactions between short-eared owls (*Asio flammeus*) and deer mice (*Peromyscus maniculatus*). Behavioral Ecology and Sociobiology. 1983; 13:205–209.

Conlon M, Lightfoot N, Kreiger N. Rotating shift work and risk of prostate cancer. Epidemiology. 2007; 18:182–183. [PubMed: 17179764]

Conti A, Maestroni GJM. Melatonin Rhythms in Mice: Role in Autoimmune and Lymphoproliferative Diseases. Annals of the New York Academy of Sciences. 1998; 840:395–410. [PubMed: 9629266]

Costa LS, Rosa PV, Fortes-Silva R, Sanchez-Vazquez FJ, Lopez-Olmeda JF. Daily rhythms of the expression of genes from the somatotropic axis: The influence on tilapia (*Oreochromis niloticus*) of feeding and growth hormone administration at different times. Comparative Biochemistry and Physiology Part C Toxicology & Pharmacology. 2015; 181–182:27–34.

Czeisler C, Duffy J, Shanahan T, Brown E, Mitchell J, Rimmer D, Ronda J, Silva E, Allan J, Emens J, Dijk D, Kronauer R. Stability, precision, and near-24-hour period of the human circadian pacemaker. Science. 1999; 284:5423.

Daan S, Pittendrigh C. A functional analysis of circadian pacemakers in nocturnal rodents. Journal of Comparative Physiology. 1976; 106:253–266.

Dacey DM, Liao HW, Peterson BB, Robinson FR, Smith VC, Pokorny J, Yau KW, Gamlin PD. Melanopsin-expressing ganglion cells in primate retina signal colour and irradiance and project to the LGN. Nature. 2005; 17:749–754.

Dauchy RT, Blask DE, Sauer LA, Brainard GC, Krause JA. Dim light during darkness stimulates tumor progression by enhancing tumor fatty acid uptake and metabolism. Cancer Letters. 1999; 144:131–136. [PubMed: 10529012]

Dauchy RT, Dupepe LM, Ooms TG, Dauchy EM, Hill CR, Mao L, Belancio VP, Slakey LM, Hill SM, Blask DE. Eliminating animal facility light-at-night contamination and its effect on circadian regulation of rodent physiology, tumor growth, and metabolism: A Challenge in the relocation of a cancer research laboratory. Journal of the American Association for Laboratory Animal Science. 2011; 50:326–336. [PubMed: 21640027]

Dauchy RT, Wren-Dail MA, Hoffman AE, Hanifin JP, Warfield B, Brainard GC, Hill SM, Belancio VP, Dauchy EM, Blask DE. Effects of Daytime Exposure to Light from Blue-Enriched Light-Emitting Diodes on the Nighttime Melatonin Amplitude and Circadian Regulation of Rodent Metabolism and Physiology. Comparative Medicine. 2016; 66:373–383. [PubMed: 27780004]

Dominoni DM, Quetting M, Partecke J. Artificial light at night advances avian reproductive physiology. Proceedings of the Royal Society B. 2013a; 280:20123017.doi: 10.1098/rspb.2012.3017 [PubMed: 23407836]

Dominoni DM, Quetting M, Partecke J. Long-term effects of chronic light pollution on seasonal functions of European blackbirds (*Turdus merula*). PLoS ONE. 2013b; 8:e85069.doi: 10.1371/journal.pone.0085069 [PubMed: 24376865]

Durrant J, Michaelides EB, Rupasinghe T, Tull D, Green MP, Jones TM. Constant illumination reduces circulating melatonin and impairs immune function in the cricket *Teleogryllus commodus*. PeerJ. 2015; 3:e1075.doi: 10.7717/peerj.1075 [PubMed: 26339535]

Ebihara S, Marks T, Hudson DJ, Menaker M. Genetic control of melatonin synthesis in the pineal gland of the mouse. Science. 1986; 231:491–493. [PubMed: 3941912]

Erren TC, Falaturi P, Morfeld P, Knauth P, Reiter RJ, Piekarski C. Shift Work and Cancer. Deutsches Arzteblatt International. 2010; 107:657–662. [PubMed: 20953253]

Falchi F, Cinzano P, Duriscoe D, Kyba CCM, Elvidge CD, Baugh K, Portnov BA, Rybnikova, Furgoni R. The new world atlas of artificial night sky brightness. Science Advances. 2016; 2:e1600377.doi: 10.1126/sciadv.1600377 [PubMed: 27386582]

Firebaugh A, Haynes KJ. Experimental tests of light-pollution impacts on nocturnal insect courtship and dispersal. Oecologia. 2016; 182:1203–1211. [PubMed: 27646716]

Fonken LK, Finy MS, Walton JC, Weil ZM, Workman JL, Ross J, Nelson RJ. Influence of light at night on murine anxiety- and depressive-like responses. Behavioural Brain Research. 2009; 205:349–354. [PubMed: 19591880]

Fonken LK, Workman JL, Walton JC, Weil ZM, Morris JS, Haim A, Nelson RJ. Light at night increases body mass by shifting the time of food intake. Proceedings of the National Academy of Sciences. 2010; 107:18664–18669.

Fonken LK, Kitsmiller E, Smale L, Nelson RJ. Dim nighttime light impairs cognition and provokes depressive-like responses in a diurnal rodent. Journal of Biological Rhythms. 2012; 27:319–327. [PubMed: 22855576]

Fonken LK, Aubrecht TG, Melendez-Fernandez OH, Weil ZM, Nelson RJ. Dim light at night disrupts molecular circadian rhythms and increases body weight. Journal of Biological Rhythm. 2013; 28:262–271.

Glickman G, Levin R, Brainard GC. Ocular input for human melatonin regulation: relevance to breast cancer. Neuroendocrinology Letters. 2002; 23(suppl 2):14–22.

Gnocchi D, Bruscalupi G. Circadian Rhythms and Hormonal Homeostasis: Pathophysiological Implications. Biology. 2017; 6doi: 10.3390/biology6010010

Goto M, Oshima I, Tomita T, Ebihara S. Melatonin content of the pineal gland in different mouse strains. Journal of Pineal Research. 1989; 7:195–204. [PubMed: 2769571]

Greenman DL, Bryant P, Kodell RL, Sheldon W. Influence of cage shelf level on retinal atrophy in mice. Laboratory Animal Science. 1982; 32:353–356. [PubMed: 7144107]

Greenman DL, Kodell RL, Sheldon WG. Association between cage shelf level and spontaneous and induced neoplasms in mice. Journal of the National Cancer Institute. 1984; 73:107–113. [PubMed: 6376903]

Griffin P, Griffin S, Waroquiers C, Mills C, Scott L. Mortality by moonlight: predator risk and the showshoe hare. Behavioral Ecology. 2005; 16:938–944.

Guerrero-Vargas NN, Navarro-Espindola R, Guzman-Ruiz MA, Basualdo MC, Espitia-Bautista E, Lopez-Bago A, Lascurain R, Cordoba-Manilla C, Buijs RM, Escobar C. Circadian disruption promotes tumor growth by anabolic host metabolism; experimental evidence in a rat model. BMC Cancer. 2017; 17:625. [PubMed: 28874144]

Haus EL, Smolensky MH. Shift work and cancer risk: Potential mechanistic roles of circadian disruption, light at night, and sleep deprivation. Sleep Medicine Reviews. 2013; 17:273–284. [PubMed: 23137527]

Hawkins P, Golledge HDR. The 9 to 5 Rodent – Time to change? Scientific and welfare implications of circadian and light effects on laboratory mice and rats. Journal of Neuroscience Methods. 2017 in press.

Heeke SD, White MP, Mele GD, Hanifin JP, Brainard GC, Rollag MD, Winget CM, Holley DC. Light-emitting diodes and cool white fluorescent light similarly suppress pineal gland melatonin and maintain retinal function and morphology in the rat. Laboratory Animal Science. 1999; 49:297–304. [PubMed: 10403445]

Hotamisligil GS, Shargill NS, Spiegelman BM. Adipose expression of tumor necrosis factor-alpha: direct role in obesity-linked insulin resistance. Science. 1993; 259:87–91. [PubMed: 7678183]

Hriscu ML. Modulatory factors of circadian phagocytic activity. Annals of the New York Academy of Science. 2005; 1057:403–430.

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. [PubMed: 24362257]

Jiang N, Wang Z, Cao J, Dong Y, Chen Y. Effect of monochromatic light on circadian rhythmic expression of clock genes in the hypothalamus of chick. Journal of Photochemistry and Photobiology B: Biology. 2017; 173:476–484.

Jöchle W. Trends in photophysiologic concepts. Annals of the New York Academy of Sciences. 1964; 117:88–104. [PubMed: 14196671]

Jones TM, Durrant J, Michaelides EB, Green MP. Melatonin: a possible link between the presence of artificial light at night and reductions in biological fitness. Philosophical Transactions of the Royal Society B. 2015; 310:20140122.doi: 10.1098/rstb.2014.0122

Karman BN, Tischkau SA. Circadian clock gene expression in the ovary: Effects of luteinizing hormone. Biology of Reproduction. 2006; 75:624–632. [PubMed: 16807384]

Kasahara T, Abe K, Mekada K, Yoshiki A, Kato T. Genetic variation of melatonin productivity in laboratory mice under domestication. Proceedings of the National Academy of Sciences. 2010; 107:6412–6417.

Kempenaers B, Borgstrom P, Loes P, Schlicht E, Valcu M. Artificial Night Lighting Affects Dawn Song, Extra-Pair Siring Success, and Lay Date in Songbirds. Current Biology. 2010; 20:1735–1739. [PubMed: 20850324]

Kennaway DJ, Voultsios A, Varcoe TJ, Moyer RW. Melatonin in mice: rhythms, response to light, adrenergic stimulation, and metabolism. American Journal of Physiology: Regulatory, Integrative, & Comparative Physiology. 2001; 282:352–365.

Khan ZA, Yumnamcha T, Rajiv C, Sanjita Devi H, Mondal G, Devi SD, Bharali R, Chattoraj A. Melatonin biosynthesizing enzyme genes and clock genes in ovary and whole brain of zebrafish (*Danio rerio*): Differential expression and a possible interplay. General and Comparative Endocrinology. 2016; 233:16–31. [PubMed: 27179881]

Kloog I, Haim A, Stevens RG, Barchana M, Portnov BA. Light at night Co-distributes with incident breast but not lung cancer in the female population of Israel. Chronobiology International. 2008; 25:65–81. [PubMed: 18293150]

Konopka RJ, Benzer S. Clock mutant of *Drosophila melanogaster*. Proceedings of the National Academy of Sciences. 1971; 68:2112–2116.

Kouser S, Palaksha, Shakunthala V. Study on fitness of *Drosophila melanogaster* in different light regimes. Biological Rhythm Research. 2013; 45:293–300.

Lamia KA, Storch K, Weitz CJ. Physiological significance of a peripheral tissue circadian clock. Proceedings of the National Academy of Sciences. 2008; 105:15172–15177.

Landskron G, De la Fuente M, Thuwajit P, Thuwajit C, Hermoso MA. Chronic Inflammation and Cytokines in the Tumor Microenvironment. Journal of Immunology Research. 2014; 2014:149185.doi: 10.1155/2014/149185 [PubMed: 24901008]

Lawton IE, Schwartz NB. Pituitary-ovarian function in rats exposed to constant light: a chronological study. Endocrinology. 1967; 81:497–508. [PubMed: 6067908]

Lee S, Donehower LA, Herron AJ, Moore DD, Fu L. Disrupting Circadian Homeostasis of Sympathetic Signaling Promotes Tumor Development in Mice. PLoS ONE. 2010; 5:e10995.doi: 10.1371/journal.pone.0010995 [PubMed: 20539819]

Le Tallec T, Thery M, Perret M. Melatonin concentrations and timing of seasonal reproduction in male mouse lemurs (*Microcebus murinus*) exposed to light pollution. Journal of Mammalogy. 2016; 97:753–760.

Lightman SL, Wiles CC, Atkinson HC, Henley DE, Russell GM, Leendertz JA, McKenna MA, Spiga F, Wood SA, Conway-Campbell BL. The significance of glucocorticoid pulsatility. European Journal of Pharmacology. 2008; 583:255–262. [PubMed: 18339373]

Lin MC, Kripke DF, Parry BL, Berga SL. Night Light Alters Menstrual Cycles. Psychiatry Research. 1990; 33:135–138. [PubMed: 2243890]

Liu Z, Gan L, Luo D, Sun C. Melatonin promotes circadian rhythm-induced proliferation through Clock/histone deacetylase 3/c-Myc interaction in mouse adipose tissue. Journal of Pineal Research. 2017; 62:e12383.doi: 10.1111/jpi.12383

Lone SR, Sharma VK. Exposure to light enhances pre-adult fitness in two dark-dwelling sympatric species of ants. BMC Developmental Biology. 2008; 8:113. [PubMed: 19046462]

Lucas RJ, Douglas RH, Foster RG. Characterization of an ocular photopigment capable of driving pupillary constriction in mice. Nature Neuroscience. 2001; 4:621–626. [PubMed: 11369943]

Maestroni GJM, Conti A, Pierpaoli W. Role of the Pineal Gland in Immunity: Circadian synthesis and release of melatonin modulates the antibody response and antagonizes the immunosuppressive effect of corticosterone. Journal of Neuroimmunology. 1986; 13:19–30. [PubMed: 2944914]

Mahoney MM. Shift Work, Jet Lag, and Female Reproduction. International Journal of Endocrinology. 2010; 2010 article ID 813764.

Mao L, Hill SM. Inhibition of cell proliferation and blockade of cell invasion by melatonin in human breast cancer cells mediated through multiple signaling pathways. Breast Cancer Research. 2010; 12:1–14.

Marpegan L, Leone MJ, Katz ME, Sobrero PM, Bekinstein TA, Golombek DA. Diurnal variation in endotoxic-induced mortality in mice: correlation with proinflammatory factors. Chronobiology International. 2009; 26:1430–1442. [PubMed: 19916840]

Martynhak BJ, Hogben AL, Zanos P, Georgiou P, Andreatini R, Kitchen I, Archer SN, von Schantz M, Bailey A, van der Veen DR. Transient anhedonia phenotype and altered circadian timing of behavior during night-time dim light exposure in *Per3*$^{-/-}$ mice, but not wildtype mice. Scientific Reports. 2016; 7:40399.doi: 10.1038/srep40399

Mazzoccoli G, Pazienza V, Vinciguerra M. Clock genes and clock-controlled genes in the regulation of metabolic rhythms. Chronobiology International. 2012; 29:227–251. [PubMed: 22390237]

Meng L, Chen D, Yang Y, Zheng Y, Hui R. Depression increases the risk of hypertension incidence: a meta-analysis of prospective cohort studies. Journal of Hypertension. 2012; 30:842–851. [PubMed: 22343537]

Mhatre MC, Shah PN, Juneja HS. Effect of varying photoperiods on mammary morphology, DNA synthesis, and hormone profile in female rats. Journal of the National Cancer Institute. 1984; 72:1411–1416. [PubMed: 6427503]

Miller M. Apparent Effects of Light Pollution on Singing Behavior of American Robins. The Condor. 2006; 108:130–139.

Min JY, Min KB. Outdoor light at night and the prevalence of depressive symptoms and suicidal behaviors: A cross-sectional study in a nationally representative sample of Korean adults. Journal of Affective Disorders. 2017; 227:199–205. [PubMed: 29100153]

Molis TM, Spriggs LL, Hill SM. Modulation of estrogen receptor mRNA expression by melatonin in MCF-7 human breast cancer cells. Molecular Endocrinology. 1994; 8:1681–1690. [PubMed: 7708056]

Nakamura Y, Harama D, Shimokawa N, Hara M, Suzuki R, Tahara Y, Ishimaru K, Katoh R, Okumura K, Ogawa H, Shibata S, Nakao A. Circadian clock gene Period2 regulates a time-of-day-dependent variation in cutaneous anaphylactic reaction. The Journal of Allergy and Clinical Immunology. 2011; 127:1038–1045. [PubMed: 21458659]

National Association of Biomedical Research. Mice and Rats2017http://www.nabr.org/biomedical-research/laboratory-animals/species-in-research/mice-and-rats

National Research CouncilGuide for the Care and Use of Laboratory Animals: Eighth EditionWashington, DC: The National Academic Press; 2011

Obayashi K, Saeki K, Iwamoto J, Ikada Y, Kurumatani N. Exposure to light at night and risk of depression in the elderly. Journal of Affective Disorders. 2013; 151:331–336. [PubMed: 23856285]

ObayashiK, , SaekiK, , KurumataniN. Bedroom Light Exposure at Night and the incidence of Depressive Symptoms: A longitudinal Study of the HEIJO-KYO Cohort. American Journal of Epidemiology2017in press.

Ohta H, Yamazaki S, McMahon DG. Constant light desynchronizes mammalian clock neurons. Nature Neuroscience. 2005; 8:267–269. [PubMed: 15746913]

Oishi K, Ohkura N, Kadota K, Kasamatsu M, Shibusawa K, Matsuda J, Machida K, Horie S, Ishida N. Clock mutation affects circadian regulation of circulating blood cells. Journal of Circadian Rhythms. 2006; 4:13.doi: 10.1186/1740-3391-4-13 [PubMed: 17014730]

Opperhuizen AL, Stenvers DJ, Jansen RD, Foppen E, Fliers E, Kalsbeek A. Light at night acutely impairs glucose tolerance in a time-, intensity- and wavelength-dependent manner in rats. Diabetologia. 2017; 60:1333–1343. [PubMed: 28374068]

Partch CL, Green CB, Takahashi JS. Molecular architecture of the mammalian circadian clock. Trends in Cell Biology. 2014; 24:90–99. [PubMed: 23916625]

Pelegri C, Vilaplana J, Castellote C, Rabanal M, Franch A, Castell M. Circadian rhythms in surface molecules of rat blood lymphocytes. American Journal of Physiology: Cell Physiology. 2003; 284:67–76.

Perlmutter JB, Frishman WH, Feinstein RE. Major depression as a risk factor for cardiovascular disease: Therapeutic implications. Heart Disease. 2000; 2:75–82. [PubMed: 11728243]

Podolin PC, Rollag MD, Brainard GC. The suppression of nocturnal pineal melatonin in the Syrian hamster: Dose-response curves at 500 nm and 360 nm. Endocrinology. 1987; 121:266–270. [PubMed: 3595519]

Preston FS, Bateman SC, Short RV, Wilkinson RT. Effects of flying and of time changes on menstrual cycle length and on performance in airline stewardesses. Aerospace Medicine. 1973; 44:438–443. [PubMed: 4694855]

Raap T, Casasole G, Costantini D, AbdElgawad H, Asard H, Pinxten R, Eens M. Artificial light at night affects body mass but not oxidative status in free-living nestling songbirds: an experimental study. Scientific Reports. 2016; 6:35626.doi: 10.1038/srep/35626 [PubMed: 27759087]

Ram PT, Kiefer T, Silverman M, Song Y, Brown GM, Hill SM. Estrogen receptor transactivation in MCF-7 breast cancer cells by melatonin and growth factors. Molecular and Cellular Endocrinology. 1998; 141:53–64. [PubMed: 9723886]

Rao GN. Light intensity-associated eye lesions of Fischer 344 rats in long term studies. Toxicologic Pathology. 1991; 19:148–155. [PubMed: 1663269]

Refinetti R, Menaker M. The circadian rhythm of body temperature. Physiology & Behavior. 1992; 51:613–637. DOI: 10.1016/0031-9384(92)90188-8 [PubMed: 1523238]

Reiche EMV, Nunes SOV, Morimoto K. Stress, depression, the immune system, and cancer. Oncology. 2004; 10:617–625.

Reiter RJ. Pineal Melatonin: Cell Biology of Its Synthesis and of Its Physiological Interactions. Endocrine Reviews. 1991; 12:151–180. [PubMed: 1649044]

Reiter RJ. Melatonin and Reproduction Revisited. Biology of Reproduction. 2009; 81:445–456. [PubMed: 19439728]

Reiter RJ, Paredes SD, Manchester LC, Tan DX. Reducing oxidative/nitrosative stress: a newly-discovered genre for melatonin. Critical Reviews in Biochemistry and Molecular Biology. 2009; 44:175–200. [PubMed: 19635037]

Reiter RJ, Tan DX, Galano A. Melatonin: Exceeding Expectations. Physiology. 2014; 29:325–333. [PubMed: 25180262]

Robert KA, Lesku JA, Partecke J, Chambers B. Artificial light at night desynchronizes strictly seasonal reproduction in a wild mammal. Proceedings of the Royal Society of London B. 2015; 282:20151745.doi: 10.1098/rspb.2015.1745

Roseboom PH, Namboodiri MA, Zimonjic DB, Popescu NC, Rodriguez IR, Gastel JA, Klein DC. Natural melatonin 'knockdown' in C57BL/6J mice: rare mechanism truncates serotonin N-acetyltransferase. Brain Research Molecular Brain Research. 1998; 63:189–197. [PubMed: 9838107]

Rudic RD, McNamara P, Curtis A, Boston RC, Panda S, Hogenesch JB, FitzGerald GA. BMAL and CLOCK, Two Essential Components of the Circadian Clock, Are Involved in Glucose Homeostasis. PLoS Biology. 2004; 2:e377.doi: 10.1371/journal.pbio.0020377 [PubMed: 15523558]

Sanders D, Kehoe R, Tiley K, Bennie J, Cruse D, Davies TW, van Veen FJF, Gaston KJ. Artificial nighttime light changes aphid-parasitoid population dynamics. Scientific Reports. 2015; 5:15232.doi: 10.1038/srep15232 [PubMed: 26472251]

Schacke H, Docke WD, Asadullah K. Mechanisms involved in the side effects of glucocorticoids. Pharmacology & Therapeutics. 2002; 96:23–43. [PubMed: 12441176]

Scheiermann C, Kunisaki Y, Frenette PS. Circadian control of the immune system. Nature Reviews Immunology. 2013; 13:190–198. DOI: 10.1038/nri3386

Schernhammer ES, Kroenke CH, Laden F, Hankinson SE. Night work and risk of breast cancer. Epidemiology. 2006; 17:108–111. [PubMed: 16357603]

Schernhammer ES, Laden F, Speizer FE, Willett WC, Hunter DJ, Kawachi I, Fuchs CS, Colditz GA. Night-shift work and risk of colorectal cancer in the nurses' health study. Journal of the National Cancer Institute. 2003; 95:825–828. [PubMed: 12783938]

Scheving LE, Pauly JE. Effect of light on corticosterone levels in plasma of rats. American Journal of Physiology. 1966; 210:1112–1117. [PubMed: 5947258]

Schlingmann F, DeRijk SHLM, Pereboom WJ, Remie R. Avoidance as a behavioral parameter in the determination of distress amongst albino and pigmented rats at various light intensities. Animal Technology. 1993; 44:71–85.

Schoech SJ, Bowman R, Hahn TP, Goymann W, Schwabl I, Bridge ES. The effects of low levels of light at night upon the endocrine physiology of western scrub-jays (*Aphelocoma californica*). Journal of Experimental Zoology Part A Ecological Genetics and Physiology. 2013; 319:527–538.

Schwimmer H, Metzer A, Pilosof Y, Szyf M, Machnes ZM, Fares F, Harel O, Haim A. 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; 31:144–150. [PubMed: 24131150]

Sharma VK. Adaptive Significance of Circadian Clocks. Chronobiology International. 2003; 20:901–919. DOI: 10.1081/CBI-120026099 [PubMed: 14680135]

Sheeba V, Sharma VK, Chandrashekaran MK, Joshi A. Persistence of eclosion rhythm in *Drosophila melanogaster* after 600 generations in an aperiodic environment. Naturwissenschaften. 1999; 86:448–449. [PubMed: 10501695]

Shigeyoshi Y, Taguchi K, Yamamoto S, Takekida S, Yan L, Tei H. Light-induced resetting of a mammalian circadian clock is associated with rapid induction of the mPer1 transcript. Cell. 1997; 91:1043–1053. [PubMed: 9428526]

Shimizu T, Hirai Y, Murayama C, Miyamoto A, Miyazaki H, Miyazaki K. Circadian clock genes *Per2* and *clock* regulate steroid production, cell proliferation, and luteinizing hormone receptor transcription in ovarian granulosa cells. Biochemical and Biophysiology Research Communications. 2011; 412:132–135.

Shuboni L, Yan L. Nighttime dim light exposure alters the response of the circadian system. Neuroscience. 2010; 170:1172–1178. [PubMed: 20705120]

Snyder SH, Zweig M, Axelrod M, Fischer JE. Control of the circadian rhythm in serotonin content of the rat pineal gland. Proceedings of the National Academy of Sciences. 1965; 53:301–305.

Somers DE, Devlin PF, Kay SA. Phytochromes and Crytochromes in the Entrainment of the *Arabidopsis* Circadian Clock. Science. 1998; 282:1488–1490. [PubMed: 9822379]

Spiegel K, Tasali E, Leproult R, Van Cauter E. Effects of poor and short sleep on glucose metabolism and obesity risk. Nature Reviews Endocrinology. 2009; 5:253–261.

Spoelstra K, Wikelski M, Daan S, Loudon A, Hau M. Natural selection against a circadian clock gene mutation in mice. Proceedings of the National Academy of Sciences. 2016; 113:686–691.

Stephan F. Circadian rhythms in the rat: constant darkness, entrainment to T cycles and to skeleton photoperiods. Physiology & Behavior. 1983; 30:451–462. [PubMed: 6683413]

Stevens RG, Davis S, Thomas DB, Anderson LE, Wilson BW. Electric power, pineal function, and the risk of breast cancer. The FASEB Journal. 1992; 6:853–860. [PubMed: 1740235]

TakahashiJS. Molecular Architecture of the Circadian Clock in Mammals. In: Sassone-CorsiP, , ChristenY, editorsA time for Metabolism and HormonesSpringer; Cham, Switzerland: 2016

Takita E, Yokota S, Tahara Y, Hirao A, Nakamura Y, Nakao A, Shibata S. Biological clock dysfunction exacerbates contact hypersensitivity in mice. The British Journal of Dermatology. 2013; 168:39–46. [PubMed: 22834538]

Tan DX, Reiter RJ, Manchester LC, Yan MT, El-Sawi M, Sainz RM, Mayo JC, Kohen R, Allegra M, Hardeland R. Chemical and physical properties and potential mechanisms: melatonin as a broad spectrum antioxidant and free radical scavenger. Current Topics in Medicinal Chemistry. 2002; 2:181–197. [PubMed: 11899100]

Tei H, Okamura H, Shigeyoshi Y, Fukuhara C, Ozawa R, Hirose M, Sakaki Y. Circadian oscillation of a mammalian homologue of the *Drosophila period* gene. Nature. 1997; 389:512–516. [PubMed: 9333243]

Thorington L. Spectral, irradiance, and temporal aspects of natural and artificial light. Annals of the New York Academt of Science. 1985; 453:28–54.

Torres-Faran C, Richter HG, Rojas-Garcia P, Vergara M, Forcelledo ML, Valladares LE, Torrealba F, Valenzuela GJ, Seron-Ferre M. Melatonin receptor in the primate adrenal gland: inhibition of adrenocorticotropin-stimulated cortisol by melatonin. The Journal of Clinical Endocrinology & Metabolism. 2003; 88:450–458. [PubMed: 12519889]

Van Geffen KG, Groot AT, Van Grunsven RHA, Donners M, Berendse F, Veenendaal EM. Artificial night lighting disrupts sex pheromone in a noctuid moth. Ecological Entomology. 2015; 40:401–408.

Vitaterna MH, Takahashi JS, Turek FW. Overview of circadian rhythms. Alcohol Research and Health. 2001; 25:85–93. [PubMed: 11584554]

Vivien-Roels B, Malan A, Rettori M, Delagrange P, Jeanniot J, Pevet P. Daily variations in pineal melatonin concentrations in inbred and outbred mice. Journal of Biological Rhythms. 1998; 13:403–409. [PubMed: 9783231]

Vojdani A. A Potential Link between Environmental Triggers and Autoimmunity. Autoimmune Disease. 2014; 2014 article ID 437231.

Weaver R. Effects of stimulated moonlight on activity in the desert nightsnake (*Hypsiglena chlorophaea*). Northwest Science. 2011; 85:497–500.

Wellen KE, Hotamisligil GS. Inflammation, stress, and diabetes. Journal of Clinical Investigation. 2005; 115:1111–1119. [PubMed: 15864338]

Wiggins G, Legge M. Cyclic variation of cellular clock proteins in the mouse estrous ovary. Journal of Reproduction & Infertility. 2016; 17:192–198. [PubMed: 27920997]

Wilson AL, Downs CT. Light interference and melatonin affects digestion and glucocorticoid metabolites in striped mouse. Biological Rhythm Research. 2015; 6:929–939.

World Health OrganizationIARC Monographs on the Evaluation of Carcinogenic Risks to Humans: Painting, Firefighting, and ShiftworkInternational Agency for Research on Cancer; Lyon, France: 2010

Wren MA, Dauchy RT, Hanifin JP, Jablonski MR, Warfield B, Brainard GC, Blask DE, Hill SH, Ooms TG, Bohm RP. Effect of different spectral transmittances through tinted animal cages on circadian metabolism and physiology in Sprague-Dawley rats. Journal of the American Association for Laboratory Animal Science. 2014; 53:44–51. [PubMed: 24411779]

Wren-Dail MA, Dauchy RT, Ooms TG, Baker KC, GC, Blask DE, Hill SH, Dupepe LM, Bohm RP. Effects of colored enrichment devices on circadian metabolism and physiology in male Sprague-Dawley rats. Comparative Medicine. 2016; 66:384–391. [PubMed: 27780005]

Wright KP, McHill AW, Birks R, Griffin BR, Rusterholz TR, Chinoy ED. Entrainment of the human circadian clock to the natural light-dark cycle. Current Biology. 2013; 23:1554–1558. [PubMed: 23910656]

Yang X, Downes M, Yu RT, Bookout AL, He W, Straume M, Mangelsdorf DJ, Evans RM. Nuclear receptor expression links the circadian clock to metabolism. Cell. 2006; 126:801–810. [PubMed: 16923398]