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Endocrine Effects of Circadian Disruption

Tracy A. Bedrosian,[1] Laura K. Fonken,[2] and Randy J. Nelson[3]

[1]Laboratory of Genetics, Salk Institute for Biological Studies, La Jolla, California 92037

[2]Department of Psychology and Neuroscience, University of Colorado, Boulder, Colorado 80309

[3]Department of Neuroscience and Behavioral Neuroendocrinology Group, The Ohio State University, Columbus, Ohio 43210; email: Randy.Nelson@osumc.edu

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Abstract

Disruption of circadian rhythms, provoked by artificial lighting at night, inconsistent sleep-wake schedules, and transmeridian air travel, is increasingly prevalent in modern society. Desynchrony of biological rhythms from environmental light cycles has dramatic consequences for human health. In particular, disrupting homeostatic oscillations in endocrine tissues and the hormones that these tissues regulate can have cascading effects on physiology and behavior. Accumulating evidence suggests that chronic disruption of circadian organization of endocrine function may lead to metabolic, reproductive, sleep, and mood disorders. This review discusses circadian control of endocrine systems and the consequences of distorting rhythmicity of these systems.

1. INTRODUCTION: CIRCADIAN RHYTHMS

The Earth rotates on its axis once every 24 h, generating a consistent pattern of light and dark. In turn, this day-night cycle predicts a host of environmental changes, including temperature fluctuations, predation risk, and food availability. Endogenous biological clocks are present in virtually all organisms, including cyanobacteria, plants, rodents, and humans. This mechanism allows organisms to anticipate these daily environmental changes. Synchronizing internal biological processes to the external world is crucial for reproduction and survival, as well as for maintaining temporal homeostasis with the environment. Examples of this synchrony are apparent at behavioral, physiological, and molecular levels of analysis. For instance, nocturnal rodents confine their foraging and reproductive activities to the nighttime, when presumably predation risk by visual hunters is reduced and survival odds are thus enhanced. In most mammals, blood pressure fluctuates according to the time of day, with a nadir occurring during sleep (1). At the molecular level, DNA repair pathways are most active during the daytime, when genotoxic stress due to UV light is highest (2). The circadian system, a hierarchical collection of biological timekeepers, is responsible for maintaining this exquisite tuning of physiological processes to the daily light cycle. Endocrine rhythms are an essential part of physiological timekeeping, and their disruption leads to a variety of consequences for health and disease. This article discusses circadian disruption with regard to its effects on endocrine systems, with a focus on mammalian physiology.

1.1. Circadian Timekeeping

Rhythms generated by the circadian system are distinguished from other cyclic processes in the body by several criteria. For one, circadian rhythms are generated endogenously and persist in the absence of environmental cues. In 1962, Michael Siffre, a French scientist, spent two months living in an underground cave, devoid of all natural light and temperature variation, to determine whether humans possess a natural body clock. Indeed, during his time underground, Siffre's sleep-wake habits and mealtimes followed a near-24-h pattern. His experiment, along with others that followed, established that humans maintain 24-h biological rhythms even in the absence of any apparent environmental cues (3, 4). This endogenous production of rhythms is a defining feature of the circadian system. Siffre and others reported that, although isolated individuals followed a near-24-h rhythm in sleep-wake activities, the period was not precisely 24 h. Indeed, the rhythm lasted slightly longer than 24 h, meaning that isolated subjects tended to go to sleep and wake up a little later each day, with some individual variations in the degree. Subsequent experiments confirmed that humans have a free-running period of 24–25 h on average (5), whereas nocturnal creatures, such as laboratory mice, typically have a free-running period of less than 24 h. Despite these slight variations in period, organisms use environmental cues to synchronize their endogenous rhythms to the 24-h solar day. This ability to entrain is another defining feature of the circadian system. Each entraining stimulus is termed a zeitgeber, meaning time giver, and the most salient of these zeitgebers is light.

In mammals, the circadian system comprises a hierarchy of biological timekeepers. The master biological clock is located in the ventral hypothalamus of the brain, within a paired structure termed the suprachiasmatic nuclei (SCN). The SCN contains approximately 20,000 neurons, which are capable of acting as an autonomous pacemaker. Notably, cultured SCN explants maintain near-24-h rhythms in gene expression for at least 32 days in vitro (6). The mechanism of the clock arises from a transcriptional autoregulatory feedback loop, generated from a defined set of genes, including those encoding Circadian Locomotor Output Cycles Kaput (CLOCK), Brain and Muscle ARNT-like Protein 1 (BMAL1), Period (PER), and Cryptochrome (CRY), among others. The clock

mechanism has been reviewed in detail elsewhere (7). In brief, at the beginning of the circadian day, CLOCK and BMAL1 proteins form a heterodimer that acts as a transcription factor to induce expression of *Per*, *Cry*, and other clock genes. PER and CRY protein products accumulate over the course of the day and, upon reaching a critical threshold, feed back to the nucleus, where they repress transcription of *Clock* and *Bmal1*. The feedback cycle takes approximately 24 h, thus driving the circadian cycle. In addition to this primary feedback loop, several other regulatory loops are involved in the precise generation of circadian rhythms. Furthermore, growing evidence suggests that transcriptional loops may not be the only factor driving the circadian pacemaker. Other mechanisms, including posttranslational modifications, appear to be essential for molecular clock function; phosphorylation, sumoylation, methylation, and other modifications determine the activity, degradation, and localization of components essential to the molecular timing loop (8). Even cellular cAMP signaling is rhythmic and may sustain the basic circadian transcriptional loop (9). More recent evidence has demonstrated that circadian rhythms can persist in the absence of transcription in a unicellular green alga, via a highly conserved redox-related mechanism (10). Rhythms in these peroxiredoxin oxidation cycles are apparent even in nonnucleated human red blood cells and can be entrained, implying that circadian time can be maintained independently of gene transcription in at least some examples (11).

Entrainment of the circadian clock to the environment is essential. The molecular clock in the SCN is highly sensitive to light information, which it receives via the retinohypothalamic tract. Specialized retinal ganglion cells [intrinsically photosensitive RGCs (ipRGCs)] depolarize in response to light and synapse directly onto SCN neurons. Depending on circadian phase, a brief light stimulus can transiently induce expression of *Per1* and phase shift the molecular clock (12, 13). Time-of-day information determined on the basis of light intensity is then relayed from the SCN to cells and tissues throughout the body. Although the circadian system is entrained primarily by light, other zeitgebers, such as feeding and social cues, are capable of entraining biological rhythms as well.

1.2. Sources of Circadian Disruption

The circadian clock evolved under discrete periods of light and dark driven by the solar day. But the modern world now functions on a 24-h schedule; people can shop, work, eat, and socialize at all hours of the day and night. The invention of electrical lights and subsequent adoption of electricity generation and distribution systems significantly changed the lifestyle of human beings through the extension of activity into the night. Shift workers often come to mind as an example of individuals experiencing circadian disruption; however, most of society is now exposed to environmental elements that can disrupt the circadian system. Below we discuss several common sources of circadian disruption and the mechanisms by which they alter the circadian clock.

1.2.1. Environmental lighting. Exposure to light at night is pervasive in the modern world. A recent large-scale study investigating worldwide patterns of light pollution demonstrated that anthropogenic sky glow dominated over celestial light in more than 80% of the locations evaluated (including rural sites). Furthermore, at 7 out of 22 measuring sites, the sky was at least 10 times brighter than natural levels 95% of the time (14). Sky glow has permanently removed dark nights in many areas, which has widespread ecological consequences.

In addition to altering outdoor lighting, the use of electric light at night has rapidly increased in the home environment since the turn of the twentieth century. Furthermore, the more recent invention of light-emitting diodes (LEDs) has increased exposure to short (blue) wavelengths of light, which are most disruptive to circadian timekeeping. In the United States, it is estimated

that 90% of adults use some form of electronic device within 1 h of bedtime (15). These changes in environmental lighting are often unappreciated factors leading to circadian system disruption (16).

Exposure to electric light at night affects the circadian system through several mechanisms: (*a*) Light exposure of sufficient intensity and duration can potently suppress melatonin (discussed below in Section 2.1); (*b*) changes in lighting environment alter rhythms in glucocorticoids (discussed in Section 2.2); and (*c*) brief pulses of light can induce *Per1* expression in the SCN, and chronic exposure to disruptive light cycles alters rhythms in several core circadian clock genes (17). One important caveat for studies investigating exposure to light at night is the extent to which results collected in the laboratory translate to the real world (18). Significantly, prior photic history affects the sensitivity of the circadian system to light exposure (19, 20). This highlights the importance of not focusing just on nighttime light exposure as a potential source of circadian disruption. Exposure to a low level of daytime lighting is similarly implicated in disturbing circadian rhythms and the sleep-wake cycle. Indeed, a recent pilot study on lighting environment in the workplace demonstrated that workers in windowless environments experience poorer sleep quality, shorter sleep duration, and more frequent sleep disturbances as assessed by self-report and actigraphy recordings (21).

1.2.2. Shift work. In industrialized societies, substantial portions of the population do not fit the traditional 9-to-5, 40-h workweek. For example, up to 30% of the US workforce engages in flexible work schedules (including working weekends and nontraditional hours), and 20% of the population is involved in some form of night shift work (22). Shift work encompasses a variety of schedules and is defined as any work that occurs from 6:00 PM to 6:00 AM. Shift workers suffer from disturbed circadian and sleep rhythms for most of their occupational lives due to exposure to abnormal light cycles and the interference of work hours with traditional sleep timing. Ailments that disproportionately plague the shift working population are frequently used as a barometer of physiological consequences of circadian disruption.

1.2.3. Transmeridian travel and social jet lag. Long-distance longitudinal travel requires the biological clock to gradually realign to a new time zone. The transient mismatch that occurs between internal timing and external conditions produces symptoms termed jet lag. These symptoms can last for days to weeks, depending on several factors, including the magnitude of the shift, the direction of travel, the chronotype of the individual, and the individual's age (23). On average, the circadian system requires one day to adjust per time zone crossed (24).

Although jet lag due to transmeridian travel is typically a merely temporary inconvenience affecting a small portion of the population, social jet lag is estimated to affect as much as 70% of the population in the United States (25). Social jet lag describes the differences that arise between an individual's circadian clock and their social clock. In modern society, alarm clocks and/or medication may be used to align an individual's sleep-wake schedule with work, school, and social obligations. Discrepancies between preferred and actual sleep schedules are apparent when timing and duration of an individual's work and free day sleep are compared (26).

1.2.4. Sleep disorders. As noted above, the circadian clock functions at close to, but not exactly, 24 h in most humans. Typically, the period of the circadian clock is sufficiently close to 24 h (within 1 h) that it is easily entrained to the light-dark cycle. However, blind individuals who do not experience light-entraining cues display circadian rhythms that may slowly drift and become misaligned to the environmental light cycle, causing atypical sleep-wake patterns. Misaligned sleep schedules do not occur in every case of blindness, however, because there may be nonphotic cues

sufficient to synchronize rhythms, individual differences in the period of the circadian clock, or an intact photoreception system that is capable of maintaining rhythmicity (27, 28).

Failure of circadian entrainment also occurs in sighted individuals. Non-24-h sleep-wake syndrome, which consists of both delayed-phase sleep disorders (DPSDs) and advanced-phase sleep disorders (APSDs), is characterized by a misalignment between biological time and the conventional sleep-wake schedule. This misalignment may be related to age in some instances, as circadian rhythms significantly vary across the course of the life span. APSD occurs more frequently in older individuals who habitually go to sleep early and wake up early (29). In contrast, DPSD patients are often adolescents or young adults who habitually go to sleep late and wake up late (30). The genetic and endocrine components of these disorders are discussed in a following section.

2. ENDOCRINE SYSTEMS IN ORDER AND DISORDER

The SCN serves as the dominant biological clock, but endogenous oscillators consisting of the same conserved molecular mechanism have been observed in cells and tissues throughout the body. These peripheral clocks are organized in a hierarchical manner, receiving neural and humoral input from the SCN that integrates the entire body circadian system. In addition to SCN input, specific tissues are sensitive to local inputs relevant to their function. For example, the liver clock receives sympathetic input from the SCN, but it is also sensitive to phase resetting in response to feeding cues. In mice, restricting food intake to the daytime phase shifts the liver clock without affecting the central SCN clock, representing an uncoupling of the oscillators (31). Here we provide an overview of circadian entrainment of some of the major endocrine systems that are sensitive to circadian control, in addition to discussing how these systems are perturbed by circadian misalignment.

2.1. Central Endocrine Glands

A variety of hormones are produced in the central nervous system via the pineal gland, hypothalamus, and pituitary gland. Neuroanatomical connections from the SCN mediate the circadian oscillations evident in many of the hormones produced.

2.1.1. Pineal gland. The pineal gland is a small neuroendocrine organ responsible for secreting melatonin into systemic circulation. Its activity is under circadian control via the SCN, as rhythmic melatonin secretion persists in constant darkness conditions, but light is also a potent inhibitor of the melatonin rhythm (32). Pineal activity is strongly driven by light information relayed through the retinohypothalamic tract and sympathetic nervous system. In brief, light depolarizes ipRGCs, stimulating the SCN to project inhibitory signals to the paraventricular nucleus (PVN), thus maintaining a quiescent state of the system. In the dark, this inhibitory pressure is relaxed, and the PVN activates the superior cervical ganglion, which in turn activates adrenergic receptors in pinealocytes. Aralkylamine *N*-acetyltransferase (AANAT) activity increases in darkness and converts serotonin to *N*-acetylserotonin, at which point hydroxyindole-*O*-methyl transferase converts the product to melatonin. AANAT is instrumental in the control of melatonin synthesis; its activity is tightly linked to light. AANAT's regulation varies by species; for example, in mice *AANAT* mRNA increases 100-fold in darkness, whereas in humans *AANAT* transcription is fairly constitutive, with alternate mechanisms contributing to the diurnal variation (33). Despite different regulatory pathways, in both diurnal and nocturnal species, the outcome is a rhythmic secretion of melatonin that peaks during the dark phase. Melatonin released into circulation has many targets throughout the body. Melatonin receptors are located in the brain and peripheral organs, including the heart, liver, adrenal glands, testes, and ovaries. Melatonin has pleiotropic

functions that are not exhaustively covered here; for example, melatonin is believed to influence the immune system, the sleep-wake cycle, mood, and the entrainment of peripheral circadian clocks. Many environmental causes of circadian disruption, as discussed in this review, tend to perturb normal pineal melatonin secretion due to its dependence on darkness. In humans, 100 to 350 lux of light is sufficient to suppress melatonin levels (34, 35), and exposure to just 100 lux in the early night phase delays the melatonin rhythm (36). Use of a tablet computer or e-reader before bed is sufficient to suppress melatonin (15, 37). Sensitivity may be even greater for other species, hinting at the ecological consequences of environmental light pollution. Syrian hamsters significantly suppress melatonin secretion in response to only 0.058 $\mu W/cm^2$ (38). The effects of altered melatonin secretion are varied and are discussed below.

2.1.2. Pituitary gland. The pituitary gland is a small structure connected to the base of the hypothalamus; its activity is regulated by projections from cell bodies located in the PVN. The pituitary is divided into anterior, intermediate, and posterior lobes. Parvocellular neurosecretory cells in the PVN project to the anterior pituitary, which is responsible for secreting growth hormone, thyroid-stimulating hormone, corticotropins, lactotropins, and gonadotropins. Magnocellular neurons in the PVN project to the posterior pituitary gland, which secretes vasopressin and oxytocin. The SCN sends direct anatomical connections to the PVN, resulting in a circadian component to many of the hormones secreted through the pituitary. An interesting feature of the pituitary is that many of its hormonal outputs are releasing factors, meaning that they stimulate the secretion of hormones downstream of peripheral endocrine organs. One example of particular interest to the topic of this review is adrenocorticotropin-releasing hormone (ACTH), which plays a role in the hypothalamic-pituitary-adrenal (HPA) axis. Corticotropin-releasing hormone (CRH) release from the PVN is controlled by direct and indirect SCN inputs. CRH mRNA levels in the PVN oscillate with a diurnal rhythm, even in the absence of corticosteroids (39). At its peak levels, CRH stimulates the anterior pituitary to release ACTH, which in turn controls release of cortisol from the adrenal glands. Thus, the pituitary functions as an important intermediary in the diurnal cortisol rhythm.

2.2. Peripheral Endocrine Glands

Many hormones are produced by the peripheral endocrine glands, which exhibit varying degrees of circadian control. In particular, the adrenal, metabolic, and reproductive systems demonstrate strong evidence of circadian rhythmicity. This list is not exhaustive but instead represents a few systems with a well-studied circadian component.

2.2.1. Adrenal glands. The adrenal glands, which rest atop the kidneys, consist of an outer cortex that secretes corticosteroids and an inner medulla that produces the catecholamines epinephrine and norepinephrine. Besides hormonal input from the pituitary gland, the adrenal gland also receives neural input from the SCN via a projection through the PVN and the intermediolateral column of the spinal cord (40). Glucocorticoids are particularly important in considering circadian disruption because they are both a primary output of, and a feedback signal for, the circadian system. Glucocorticoids—primarily cortisol in humans and corticosterone in most rodents—are released from the zona fasciculata of the adrenal cortex in a rhythmic fashion under nonstressed conditions. The robust rhythmicity of this hormone relies on the SCN; glucocorticoid rhythmicity persists in constant conditions, but only when the SCN is intact (41, 42). Glucocorticoid receptors are expressed throughout the brain (notably, except for the SCN), and glucocorticoids entrain local oscillations in several peripheral tissues in rodents and humans (43, 44).

The adrenal medulla expresses some circadian clock genes (45), but only the adrenal cortex exhibits strong rhythmic expression of all canonical clock genes (46), consistent with the observation that glucocorticoid secretion from the adrenal cortex occurs rhythmically over 24-h periods. The adrenal cortex appears to possess a functional clock because adrenal slice cultures continue to rhythmically produce corticoids in the absence of SCN input. Furthermore, wild-type adrenal glands transplanted into Per2/Cry1 mutant mice generate rhythmic glucocorticoid secretions despite lacking a properly functioning SCN (46). This effect requires a light-dark cycle; once the host is released into constant darkness, the rhythmic secretion is abolished, suggesting that light input is essential to adrenal gland entrainment. The pattern of corticosteroid secretion follows the light-dark cycle. In humans, plasma cortisol levels peak in the early morning, within 30 min of rising, and reach their nadir near midnight. By peaking prior to or at the onset of the active phase, this catabolic hormone is believed to help prepare the body for waking and activity. Importantly, not only do glucocorticoids fluctuate throughout the day, but the responsiveness of the tissues and cells that they target also fluctuates likely due to rhythmic repression of the glucocorticoid receptor (47). Glucocorticoid and mineralocorticoid receptors are localized throughout the body, where they influence the immune system, metabolism, reproduction, the brain, and even their own production via a negative feedback loop in the HPA axis.

Disruptions to the circadian system modulate glucocorticoids in a variety of ways. For example, the effect of exposure to light at night depends on the species (see table 1 in Reference 48). Diurnal Nile grass rats increase serum corticosterone concentrations after chronic exposure to dim light at night (49). In contrast, cortisol and corticosterone concentrations are unchanged in nocturnal hamsters and mice exposed to dim light at night (50, 51). The different glucocorticoid responses of these species following nighttime light exposure may relate to diurnal versus nocturnal activity patterns, but additional examples are needed to test this conjecture.

Exposure to constant light, which typically abolishes circadian rhythms in locomotor activity, can reduce or conversely increase corticosterone concentrations in mice (52–54). This discrepancy may be related to the loss of rhythmicity observed in constant light conditions. In humans, exposure to light pulses can both phase shift and alter the amplitude of cortisol rhythms (55–57). Furthermore, daytime light levels in the workplace are negatively correlated with cortisol concentrations; workers exposed to lower levels of light in offices without windows have elevated nighttime cortisol concentrations (58).

Shift work is also associated with disrupted cortisol rhythms. Surgeons experience circadian rhythm disruptions while on call and significantly suppress morning salivary cortisol concentrations compared with pre- and postcall levels (59). Moreover, cortisol concentrations in night shift workers are higher during the day and lower during the night compared with cortisol concentrations in day shift workers (60). Exposure to non-24-h light cycles also suppresses cortisol concentrations, further supporting the idea that shift work may dampen the rhythm in cortisol secretion (61). However, hair cortisol levels have been reported to be higher in young adult but not older shift workers compared with levels in age-matched conspecifics, suggesting that there may be an interaction between age and shift work with regard to cortisol response (62). In contrast to shift work, sleep deprivation typically elevates cortisol in humans (61, 63, 64; but see Reference 65). Social jet lag is also associated with higher cortisol concentrations (66), pointing to nuances in the timing of disruption and characteristics of the individual that require further study.

2.2.2. Energy homeostasis. The circadian system regulates energy homeostasis by imposing a 24-h temporal structure on multiple metabolic processes. It is estimated that 10% of the mammalian transcriptome is regulated in a circadian fashion, and circadian regulation of the metabolome may be even higher. One recent study reported that more than 30% of liver

metabolites display diurnal differences in expression (67). Metabolic tissues have some degree of autonomy; for instance, in the absence of SCN input, the kidney and liver maintain circadian oscillations, although the amplitude is decreased or individual tissues desynchronized (68, 69).

Multiple metabolically related hormones, including leptin, ghrelin, insulin, adiponectin, and glucagon, are released in a diurnal fashion (70–73). Importantly, the rhythmic pattern of nutrient-sensitive hormones varies in part in response to environmental and behavioral factors such as timing of food intake. For example, insulin is released from β cells in the pancreas in response to food intake and promotes the absorption of glucose from the blood. However, in experiments clamping glucose concentrations in humans, insulin is still released rhythmically, supporting the concept of an intrinsic circadian mechanism regulating insulin (74). Indeed, in nondiabetic patients, insulin is reported to rise just prior to dawn and thereby help restrain hepatic glucose production and prevent hyperglycemia (75).

Rhythmic expression of several metabolic hormones is abolished in mice with disruptions in core clock genes. Serum ghrelin concentrations oscillate depending on time of day, but the rhythm is lost in Clock mutant mice (76). Furthermore, rhythmic insulin sensitivity is abolished in mice lacking Bmal1 (77). The above experiments demonstrate the effects of whole-animal knockouts on metabolism; however, tissue-specific knockouts have been extensively used to clarify the role of local circadian oscillations in endocrine organ function. Expression of core clock genes and tissue-specific clock-controlled genes are observed in the liver (78, 79), pancreas (80), stomach (81), and kidney (82). The molecular clock mechanism within these tissues may be important to the diurnal expression of hormone rhythms. For example, when brain Bmal1 expression is rescued in Bmal1 knockout mice, behavioral rhythms are restored, but changes in metabolic regulation are not (83). Liver-specific knockout of Bmal1 impairs glucose regulation and abolishes rhythmic expression of glucose-regulatory genes in the liver (84). Also, adipocyte-specific deletion of Bmal1 (but not hepatocyte or pancreatic deletion) disrupts the daily feeding rhythm (85).

Extensive evidence shows that circadian disruption alters metabolically related hormones (86). The effects of circadian disturbances on metabolism are discussed in Section 3.4 in relation to how these hormonal changes leave individuals susceptible to obesity and other metabolically related disorders.

2.2.3. Reproductive system. In rodents, the circadian system is closely tied to reproductive processes, whereas in humans the link is less obvious. Both human menstrual cycles and rodent estrous cycles consist of distinct timed hormonal events. As follicles mature in the ovary, estradiol concentrations increase, signaling a surge of gonadotropin-releasing hormone (GnRH) from the hypothalamus. This surge triggers secretion of luteinizing hormone (LH) from the anterior pituitary, culminating in ovulation by the ovary. After ovulation, progesterone levels increase, and the follicles are luteinized. In rodents, these events are tied to the light-dark cycle by input from the SCN. GnRH neurons become active and the LH surge occurs just before night (87, 88), coinciding with the timing of mating behavior, which occurs during the dark phase in rodents. Lesioning the SCN abolishes reproductive hormonal and behavioral rhythms (89). In humans, the preovulatory LH surge occurs before the onset of activity, between midnight and 8:00 AM (90, 91). But humans do not display circadian rhythms in mating behaviors, and the extent of circadian control over reproductive processes may require further study. In support of a circadian-reproduction link in humans, shift workers tend to suffer reproductive dysfunction.

Among seasonally breeding mammals that depend on day length to determine the optimal time of year for reproduction, circadian misalignment or aberrant light signals in the environment can have devastating results for offspring survival. The same holds true for humans and other nonseasonal breeders, in which circadian disruption affects reproductive success by interfering with

typical hormonal reproductive processes. For one, altering the environmental light cycle instigates reproductive disruption in birds, humans, and other mammals. For example, rats exposed to a constant bright-light environment develop anovulatory persistent estrus (92). Wild birds exposed to light pollution develop their reproductive systems up to a month earlier than those exposed to dark nights (93), with potential detriments for reproductive fitness. A parallel can be drawn to shift-working women, who are chronically exposed to light at night at work and tend to develop irregular menstrual cycles (94).

Pregnancy outcome may also be compromised by circadian disruption, as shift work and frequent travel across time zones have been associated with reduced fertility and poor pregnancy outcome (95, 96). Pregnant women on rotating shifts have greater risk of preterm births and low-birth-weight infants (97). Animal studies have confirmed these associations to some extent. Mice assigned to repeated phase shifts experienced approximately 40–70% decreases in pregnancy success compared with control mice on a constant light-dark cycle (98). Clock-deficient *Drosophila* produce fewer progeny due to a combination of both male and female deficiencies: decreased eggs laid and fertilized and decreased quantity of sperm (99). Importantly, rescuing clock gene expression restores fertility, confirming a role for the circadian clock in reproductive fitness.

Rodents are certainly the best-studied model in terms of circadian control of reproduction. Evidence from rodents confirms that the central biological clock plays a role in reproductive disruption associated with circadian misalignment. In mice, the SCN mediates the timing of estrous cycle events. Lesions of the SCN abolish ovarian cyclicity and the preovulatory LH surge (89, 100). Transplanting a functional SCN to a lesioned animal restores some behavioral rhythms, but not estrous rhythms, suggesting that neural inputs from the clock are necessary for mediating those reproductive cycles (101). Mice lacking functional clocks have varying degrees of reproductive deficiencies. Female mice lacking *Bmal1* have prolonged, irregular estrous cycles and low serum progesterone levels, which lead to implantation failure and infertility (102, 103). Clock mutation results in similarly prolonged estrous cycles accompanied by an irregular LH surge on the day of proestrus and by a high rate of failed pregnancies (104).

3. CONSEQUENCES OF DISRUPTED ENDOCRINE RHYTHMS

As discussed above, a number of hormones are regulated by the circadian system. Endocrine factors are important for maintaining homeostasis in mammals, and the 24-h fluctuations in these factors have likely evolved to anticipate predictable daily events. So what are the pathological consequences of disrupting these oscillations?

3.1. Inflammatory Disorders and Cancer

The immune system is highly regulated by the circadian system in mammals. There are circadian rhythms in multiple aspects of immune function, including immune cell trafficking, antigen presentation, Toll-like receptor function, cytokine gene expression, and lymphocyte proliferation. Inflammatory challenges can result in vastly different outcomes depending on the time at which they occur. For example, sickness behavior and cytokine production vary depending on the time of endotoxic challenge in both humans and rodents (105–107). Furthermore, several inflammatory diseases, including asthma and rheumatoid arthritis, fluctuate in severity over the course of the day, implicating circadian regulation of inflammatory processes (108, 109).

Rhythms in immune activity are both directly and indirectly dependent on circadian rhythms in endocrine factors. Diurnal rhythms in melatonin and glucocorticoids can directly affect immune responses through their potent anti-inflammatory actions (110, 111). However, these hormones

also indirectly affect the immune system via their entraining properties on peripheral cells (106, 112). Exposure to light at night and to non-24-h light cycles alters inflammatory responses in the peripheral and central nervous systems (113–115). Environmental circadian disruption is similarly associated with changes in immune response (116–118). In humans, even acute circadian misalignment reduces circulating cortisol levels and increases inflammatory cytokines (61), and shift work is associated with increased risk for several inflammatory pathologies (119).

The association between nighttime light exposure and cancer is the most extensively studied connection between circadian system disruption and an inflammatory condition (120). A link between cancer and circadian disruption is supported by epidemiological, clinical, and basic research. This research has led the World Health Organization to declare shift work a probable carcinogen (class 2A, International Agency for Research on Cancer). Epidemiological studies indicate that breast cancer risk is significantly elevated in industrialized societies and that this risk increases as countries become more westernized. Misalignment of bedtime on a daily basis, which is an indication of social jetlag and circadian disruption, is associated with more rapid breast cancer development (121). Nighttime light levels also codistribute with breast cancer incidents (122). Furthermore, there is a moderate increase in risk of developing breast cancer among shift workers, with the incidence of breast cancer increasing with the number of years spent working nights (123). In patients with cancer, prognosis is poorer in those who suffer from circadian disturbances. Finally, administering chemotherapeutic agents at specific times of day (an idea termed chronotherapy) improves effectiveness and reduces negative side effects (124).

Exposure to light at night and the subsequent suppression in nocturnal melatonin are thought to underlie the effects of circadian disruption on cancer risk (125). However, other effects of circadian disruption such as changes in cell cycle regulation, genetic mutations in core circadian clock genes, and DNA damage likely contribute (reviewed in Reference 126).

3.2. Sleep

The sleep-wake cycle may be one of the most prominent outward manifestations of the circadian system and is related to pineal melatonin secretion. Sleep is controlled by both genetic and environmental factors; perturbations of circadian timekeeping at either of these levels can lead to sleep disorders. Heritable disorders of sleep phase have been directly linked to mutations of circadian clock genes. Even individual variability in morningness or eveningness tendencies can be attributed, at least in part, to clock gene variants within the population. Familial APSD is a heritable condition characterized by an overall advance of the sleep-wake rhythm, where the individual tends to fall asleep and then rise much earlier than average. Melatonin onset and body temperature rhythm in these patients tend to be advanced. The disorder is fairly heterogeneous in etiology, but at least in some families, a shortened period length of less than 24 h coincides with a missense mutation in the *hPer2* clock gene. In contrast, haplotype variants of the *hPer3* gene, the *AANAT* gene, and other genes are associated with DPSD, in which the affected individual goes to sleep and rises much later than normal. Other, less common sleep disorders, such as free-running rhythm disorder and irregular sleep-wake rhythm, likely originate with a deficiency in the circadian pacemaker (127). Melatonin has long been believed to play a role in promoting sleep onset in diurnal mammals on the basis of the results of exogenous melatonin treatment; a recent study demonstrates that endogenous melatonin is involved in sleep initiation and maintenance in diurnal zebrafish, which share many conserved components of sleep regulation with mammals (128).

Circadian disruption caused by underlying disease pathology may also contribute to disordered sleep. Deterioration of the SCN is common in Alzheimer's disease and dementia, leading to reduced stability and amplitude of endogenous rhythms (129). These changes coincide with general

age-related decline in pineal melatonin production and reduced visual sensitivity, which disrupt normal entrainment to light. Because of these changes, dementia patients frequently suffer from altered sleep phase, altered sleep duration, fragmented sleep, and sleep-related behavioral changes such as sundowning and parasomnias. Mental disorders, such as major depression, are associated with circadian perturbations that include altered gene expression rhythms throughout the brain; such perturbations may be related to a disrupted HPA axis. Clinically depressed patients frequently experience changes in sleep duration. Seasonal affective disorder (SAD) is a subtype of depression that recurs in winter. It is believed to be related to circadian desynchrony caused by short day lengths and difficulty entraining the melatonin rhythm under conditions of low daylight intensity. Morning bright-light therapy that phase shifts the melatonin rhythm is an effective treatment for some individuals.

Circadian disruption caused by environmental causes can affect the sleep-wake cycle too. For example, exposure to artificial light at night suppresses secretion of pineal melatonin when administered exogenously. Chronic exposure to light at night may cause more pronounced dysregulation of the circadian system. For example, night shift workers may experience shift work sleep disorder, resulting in difficulty sleeping or excessive sleepiness during the waking hours. Because the working hours directly conflict with the body's natural circadian rhythms, and the individual changes schedules frequently for rotating work hours or weekends, the internal clock is constantly in disequilibrium with the environment. Jet lag syndrome is another example of this desynchrony of internal and external time. The circadian clock cannot immediately adjust to rapid travel across time zones; approximately one day is needed per time zone crossed. Thus, jet lag results in desynchrony of the internal biological and hormonal rhythms to the external time of day, resulting in excessive daytime sleepiness, difficulty sleeping at night, and interrupted sleep until the internal clock has adjusted. Exogenous melatonin administration is thought to improve sleep disruption associated with shift work or jet lag, but whether suppressed melatonin causes the sleep problems remains unknown. There are no studies of which we are aware that show any sleep disturbances in pinealectomized animals. Another important point is that sleep disruption is just one of many consequences of exposure to light at night. Nocturnal rodents exposed to light at night (i.e., during their waking phase) incur deleterious metabolic, immune, and behavioral consequences.

3.3. Mood Disorders

Circadian disruption has been associated with several mood disorders, including major depression, manic-depressive disorder, and SAD. The genetic and environmental underpinnings, as related to the circadian system, have been discussed in several excellent reviews (130, 131). Here we specifically discuss mood disorders as they pertain to circadian disruption of endocrine function.

Disruption of the daily melatonin rhythm has been linked to SAD (132). In winter, SAD is characterized by recurrent depressive symptoms that remit during spring and summer. The disorder is believed to be related to the short winter day length because the incidence is greater at higher latitudes (133). Some SAD patients may experience a phase shift in the daily melatonin rhythm such that melatonin secretion persists well into the morning (134). The phase-shifted melatonin rhythm may be caused by reduced sunlight exposure during the winter months. Morning bright-light therapy is effective at phase correcting the melatonin rhythm and relieving some symptoms of the disorder (135). Melatonin administration, however, does not reliably reverse the therapeutic effect of light, suggesting that melatonin disturbance is not the only factor contributing to SAD (136).

In contrast, a general suppression of melatonin may also contribute to depressive disorders. Night shift workers who are chronically exposed to nighttime illumination experienced suppressed

melatonin secretion. This population has an increased incidence of mood disorders, including major depressive disorder (MDD) (137). In nocturnal and diurnal animal models of chronic nighttime light exposure in which melatonin concentrations are suppressed, depression-like symptoms are evident (49, 138). Interestingly, chronic exposure to red light at night, which does not suppress melatonin secretion, does not elicit depressive symptoms in hamsters (139). A recent analysis of 516 elderly individuals in Japan found a significant association between nighttime light exposure and depressed mood (140). In recent years, drugs that act as agonists of melatonin receptors have been approved for the treatment of depression (141).

Depressive disorders are also associated with disruption of stress-related hormones, particularly glucocorticoids. One facet is disruption of the diurnal cortisol rhythm. Depressed patients display a flattened amplitude of the diurnal cortisol rhythm and altered HPA axis functioning (142), whereas combat veterans with posttraumatic stress disorder (PTSD) maintain a cortisol rhythm but display lower overall concentrations (143). This difference in cortisol patterns may reflect a difference in the underlying mechanism of the disorder, whereby PTSD subjects are sensitized to cortisol and depressed patients are desensitized or experience dysregulation of the HPA axis. Interestingly, these endocrine changes may persist long after the depressive episode. Two recent large cohort studies showed flattened cortisol rhythms or elevated cortisol levels even in remitted individuals who had experienced MDD in the past (144, 145). The changes in the cortisol rhythm associated with MDD may be related to impaired negative feedback within the HPA axis, leading to chronically elevated CRH secretion. In turn, loss of the cortisol rhythm may be related to some of the cognitive deficits associated with MDD, as an intact glucocorticoid rhythm is essential for learning-induced dendritic spine plasticity (146). Using transcranial two-photon microscopy to follow dendritic spine formation in mice, this experiment demonstrated that disrupting the diurnal corticosterone rhythm impairs normal spine remodeling required for learning and memory.

3.4. Obesity and Metabolic Disorders

Here we provide an overview of the most recent findings linking circadian disruption and metabolism (for a more extensive overview of this topic, see Reference 48). Increases in electric light at night parallel increases in obesity and metabolic syndrome worldwide. A direct association between exposure to aberrant light cycles and weight gain has been established in rodents (51–53, 147). Moreover, exposure to light at night in an uncontrolled home setting is associated with a higher odds ratio for obesity in humans (140). Several large-scale epidemiological studies demonstrate that social jet lag and shift work may contribute to metabolic dysfunction and increases in BMI (25, 148).

Melatonin suppression is one potential mechanism through which exposure to light at night affects metabolism. As discussed above, nighttime light exposure suppresses endogenous melatonin release. Low nocturnal melatonin secretion is associated with an increased risk of developing type 2 diabetes in humans (149). Genome-wide association studies further support a link between noncoding variants in the melatonin receptor B1 and elevated blood glucose and increased risk for developing diabetes (150). Melatonin may improve glucose homeostasis via its protective effects against glucose toxicity in pancreatic β cells (151). However, acute melatonin administration impairs glucose tolerance in both the morning and evening (152). Melatonin treatment improves glucose homeostasis in both genetic and diet-induced rodent obesity models (153, 154), and melatonin treatment reduces body weight in rats fed a high-fat diet (155). Melatonin may partially reduce body weight by altering activity (156).

The temporal pattern of light exposure also appears important for weight regulation. Reid and colleagues recently demonstrated that having a majority of the average daily light exposure occur

earlier in the day was associated with a lower BMI (157). This finding suggests that, in addition to altering metabolism via melatonin, circadian disruption may influence body weight through the regulation of other metabolic hormones. Indeed, a 10-day in-patient study demonstrated that forced circadian misalignment altered levels of several metabolic hormones, including leptin, glucose, and insulin. By the end of the study, some of the healthy volunteers demonstrated glucose levels consistent with those of a prediabetic state (158). A study using a comparable 6-day in-patient simulated shift work protocol demonstrated that shiftwork may also affect metabolism by reducing energy expenditure and altering thermic responses following mealtimes (159). Changes in metabolism induced by circadian misalignment may be long lasting, as a 1-month in-patient protocol demonstrated that circadian misalignment reduced levels of the satiety hormone leptin (160).

Circadian disruption causes several lifestyle and behavioral changes that may further affect metabolism. Most notably, circadian disruption can result in a mismatch between the biological clock and timing of food intake. Unconventional mealtimes due to shift workers' schedules and social jet lag may contribute to metabolic disturbances (161). Indeed, timing of food intake is associated with both weight gain and the effectiveness of a weight loss strategy in humans (162, 163). Late-night eating is associated with a blunted cortisol rhythm, with decreases in glucose tolerance, and with changes in energy expenditure and body temperature (164).

Another mechanism through which circadian disruption alters metabolism is through changes in gut microbiome. Intestinal microbiota of both mice and humans have diurnal oscillations in composition and function. Both genetic and behavioral circadian clock disruptions produce microbial dysbiosis, promoting glucose intolerance and obesity (165, 166). This relationship also appears to be bidirectional, as diet and feeding patterns can alter the gut microbiome (167).

Finally, large epidemiological studies have pointed to a direct relationship between obesity and light at night. For example, in one study of 100,000 women in the United Kingdom, the odds of obesity as assessed by BMI, waist-hip ratio, and waist circumference increased with elevated exposure to light at night (168). This correlation was related only to exposure to light at night and was not related to sleep duration, alcohol intake, cigarette smoking, or physical activity.

4. REMAINING QUESTIONS AND FUTURE DIRECTIONS

Circadian rhythm disruption is increasingly common in modern society, but our understanding of its physiological consequences is still fairly limited. It is clear that disruption of endocrine rhythms is an important factor leading to negative health effects. Strategies to overcome the deleterious effects of circadian disruption will be an important focus of future research.

4.1. Environmental Considerations

A major source of circadian disruption is environmental light pollution that originates from buildings, streetlights, and vehicles. These sources of light are obviously required for human purposes, but better design and updated technology could minimize the unintended consequences for both humans and wildlife. For one, streetlights typically allow light to diffuse horizontally and upward, significantly contributing to sky glow and brightening adjacent unlit areas. This light should be directed downward toward the intended target—streets and sidewalks—to minimize scatter and wasted energy. This goal can be accomplished by using hooded luminaire designs that focus light downward or by narrowing the beam of light emitted. A recently described design uses a cluster of LEDs fitted with a lens to focus beams parallel to one another. The LEDs are mounted inside a reflective box to facilitate light recycling, ensuring that a majority of light reaches the target.

Conventional streetlights lose up to 20% of their energy through horizontal or upward diffusion; in contrast, this design would contribute only 2% of its energy to light pollution (169). Designs such as this one could be considered by individual communities and implemented where needed.

Considerations related to spectral composition are equally important. In mammals, the sensitivity of the circadian system is tuned toward shorter wavelengths, specifically in the range of 460–480 nm. Sunlight reaching Earth is composed mostly of short wavelengths during midday, but those wavelengths become scattered at dusk, when the sun approaches the horizon, causing red wavelengths to predominate. Artificial lighting systems produce different spectrums, depending on the type. Incandescent bulbs emit more peaks in the red spectrum than in the green and blue spectra, whereas gas discharge lamps emit peaks in the shorter wavelengths. Choosing a lighting system with an appropriate spectral distribution, or filtering light to achieve such a distribution, can minimize disruption to the circadian system. For example, using redshifted lighting at night may be beneficial for humans and other mammals, whereas broad-spectrum light is appropriate for daytime indoor lighting. Humans who wore lenses to filter out blue wavelengths during simulated shift work maintained a more normal melatonin rhythm than did humans without the lenses (170). Even in the home, spectral exposure can now be conveniently managed using products designed for this purpose. For example, "smart" LED lightbulbs can be programmed to adjust intensity and wavelength on the basis of time of day. In addition, there are free apps for smartphones and tablets that adjust the light emitted from the screens to red in the evening. Adolescents who wore blue-light-blocking lenses while using electronic media before bedtime were protected from the melatonin suppression and increased alertness associated with these activities (171). Of course, in the ideal scenario, daytime light exposure includes bright, natural light, and nighttime light exposure is minimized altogether.

4.2. Chronotherapeutic Strategies

Among the popular chronotherapeutic strategies for ameliorating circadian rhythm disturbances include improving sleep hygiene, bright-light therapy, exogenous melatonin treatment, and considering timing of exercise and meals. First, improving sleep timing by setting a consistent bedtime is recommended by the American Academy of Sleep Medicine, although human studies on this strategy are lacking (29). Because the circadian system has reciprocal interactions with brain regions that regulate arousal and sleep, improving the sleep cycle is believed to improve circadian rhythms.

Because light is the most potent environmental cue for synchronizing the circadian clock, targeting light is another widespread chronotherapeutic approach. Bright light is well established to phase shift circadian rhythms (172). Light therapy—consisting of bright light in the morning—was first demonstrated to improve circadian rhythms in patients with delayed sleep phase syndrome (173). Furthermore, bright-light therapy alone, or in combination with other chronotherapeutic agents, improves sleep and circadian entrainment in patients with non-24-h sleep disorders; in the elderly; and even in young, healthy individuals (174–176). Importantly, timing, light intensity, spectrum, duration, and distance from the source are key variables to consider when light therapy is implemented.

Exogenous melatonin treatment has also been extensively used to treat circadian rhythm disorders (although, as mentioned above, evidence that endogenous melatonin influences sleep is lacking) (177). For example, melatonin has been used to treat jet lag (178), sleep disorders (179), and circadian rhythm disturbances in the elderly (180) and shift workers (however, see Reference 181). Melatonin may be particularly effective when combined with other chronotherapeutic

approaches (182). Key considerations for melatonin treatment should include timing and dose (183).

Exercise contributes to a healthy lifestyle and can facilitate sleep. Exercise may also be used to assist with shifting or strengthening the circadian clock. Timed exercise can adjust circadian rhythms in both aged and young adults (184). In particular, morning exercise can improve sleep architecture and other health outcomes (185).

Finally, shift work represents a unique form of circadian disruption. Shift workers have less flexibility in implementing the behavioral chronotherapeutic approaches listed above because of the need to adhere to unusual and fluctuating schedules. It has therefore been proposed that, for shift workers, taking factors such as chronotype into consideration could prove to be critical in alleviating circadian disruption and improving sleep (186).

Implementing some of these simple solutions may help to overcome the negative effects of circadian disruption on health and physiology. Further research into the mechanisms whereby aberrant circadian schedules affect endocrine physiology, and in turn overall health, will provide additional strategies with which to overcome the circadian effects of the modern environment.

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