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1

Introduction to Circadian Rhythms

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1.1 Introduction

For the past 3–4 billion years, life on Earth evolved under the predictable pattern of solar days; that is, exposure to light during the day and dark at night. Temporal constraints are obvious when considering the "rules of life." That is, individuals cannot do everything all the time. For instance, energetic requirements are somewhat continuous, whereas energy production or consumption is somewhat sporadic. All organisms partition temporal energetic activities. Indeed, temporal partitioning of photosynthesis, metabolism, gene expression, reproduction, defense, growth, activity, and inactivity is universal among plants and animals. During the evolution of life, organisms internalized the temporal rhythm of Earth's rotation and eventually developed self-sustaining biological clocks. These internal rhythms with periods of approximately 24 hours are called circadian rhythms, and the structures that generate them are called circadian clocks. A human's primary circadian biological clock is a paired cluster of about 20,000 nerve cells in the hypothalamus at the base of the brain, called the suprachiasmatic nucleus (SCN). The period of a circadian clock is approximately 24 hours, but daily light exposure sets it to precisely 24 hours. Having our clocks set closer to our environment's light–dark rhythms optimizes how our bodies function and how we behave.

Circadian clocks are a nearly universal feature of life on this planet, yet over the past century and a half we have managed to manipulate the amount of light in the environment so much that we are disrupting them. As we will learn throughout this book, either too much light exposure at night or too little light exposure during the day can disrupt central and peripheral timing mechanisms, how internal rhythms are entrained to the external environment, and the typical and optimal 24-hour physiological and behavioral functioning of individuals.

1.1.1 Central Pacemaker in the Suprachiasmatic Nucleus

Circadian rhythms in mammals are ubiquitously expressed throughout the body and are regulated by a hierarchy of independent self-sustaining molecular and cellular

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clocks. This hierarchy is entrained by external Zeitgebers ("time givers") including light (primary), food, exercise, and even social cues. Rhythms throughout the body are subsequently maintained in a synchronized manner via intermediary neural and humoral cues. But where are these signals initiated? The primary pacemakers in mammals are the paired suprachiasmatic nuclei (SCN) that govern rhythms throughout the brain and body. The SCN are located directly above the optic chiasm in the anterior hypothalamus and contain a diverse cellular make-up. SCN neurons produce the inhibitory neurotransmitter gamma aminobutyric acid (GABA) and various neuropeptides including arginine vasopressin (AVP), cholecystokinin (CCK), gastrin-releasing peptide (GRP), prokineticin 2 (Prok2), and vasoactive intestinal polypeptide (VIP) (reviewed in Moore et al., 2002; Patton & Hastings, 2018). The SCN comprise two distinct regions with unique neuropeptide expression: the ventrolateral "core" contains neurons that express VIP and GRP, whereas the dorsal shell contains neurons that express AVP and CCK.

SCN neuron firing is tightly synchronized in "core" and "shell" regions through neural connections and timed release of these key neuropeptides (Patton & Hastings, 2018). VIP is an important synchronizer of neuronal networks in the SCN (Abrahamson & Moore, 2001); mice lacking VIP or VIP receptor 2 (VPAC2) exhibit attenuated behavioral rhythms and desynchronized circadian rhythms in cultured neurons from the SCN (Aton et al., 2005; Colwell et al., 2003; Harmar et al., 2002). Interestingly, in SCN neurons with the VIP or VPAC2 genes knocked out, circadian rhythms are restored by co-culture with neurons from a wild-type SCN, suggesting that other molecules such as AVP also synchronize rhythms in the SCN (Maywood et al., 2011). Indeed, an AVP receptor antagonist prevents restoration of rhythms in VPAC2 knockout SCN neurons (Maywood et al., 2011).

Rhythms in the SCN are primarily entrained by light information that is communicated directly from the retina through the retinohypothalamic tract to the SCN (Beier et al., 2021; Hattar et al., 2006; Moore & Qavi, 1971). In addition to retinal input, the SCN core receives input from the thalamus and raphe nucleus and the shell receives input from the hypothalamus, neocortex, and brainstem (Fernandez et al., 2016; Leak & Moore, 2001).

The SCN have unique circadian-focused properties that define them as the primary pacemaker: they receive direct retinal light input; neurons in the SCN have topographically organized coupling mechanisms, which allow them to remain synchronized in the absence of light input (Aton & Herzog, 2005); The SCN are protected from feedback by systemic clock-modifying factors such as glucocorticoids or feeding (Schibler et al., 2015); SCN lesions abolish circadian rhythms throughout the body (Moore & Eichler, 1972; Stephan & Zucker, 1972; Weaver, 1998); electrical and chemical stimulation of the SCN induce phase shifts (Albers et al., 1984; Rusak & Groos, 1982); and transplanting an SCN into an SCN-ablated animal restores circadian activity (Silver et al., 1996). Furthermore, cultured SCN tissue will maintain

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long-term (>1 month) oscillations in the absence of external stimulation (Welsh et al., 1995; Yamazaki et al., 2000; Yoo et al., 2004). Thus, the SCN features direct retinal input, synchronized output, and few peripheral feedback mechanisms, thereby optimizing this brain region to act as the primary circadian oscillator. Additional details about the central clock dynamics are provided in Chapter 2.

1.2 Molecular Mechanisms of the Circadian Clock

At the molecular level, cellular circadian rhythms are formed from interlocking transcriptional–translational feedback loops (TTFL) that drive spontaneous oscillations of gene and protein expression with an approximately 24 hour period. Remarkably, the molecular clock components are expressed rhythmically in nearly every cell of the body and are entrained by signals from the primary clock. The core components of this loop involve the induction of Period (*Per1*, *Per2*, and *Per3*) and Cryptochrome (*Cry1* and *Cry2*) gene expression through E-box enhancers by the transcriptional activators circadian locomotor output cycles kaput (*CLOCK*) and brain and muscle arnt-like protein 1 (*BMAL1*) (Gekakis et al., 1998; Hogenesch et al., 1998; Jin et al., 1999). Per and Cry proteins accumulate in the cytoplasm and then form large multimeric complexes which translocate back to the nucleus to interact with CLOCK and BMAL1 and repress their own transcription (Griffin et al., 1999; Kume et al., 1999; Lee et al., 2001). Progressive degradation of the existing inhibitory complexes then occurs, ultimately leading to renewed transcription of *Per* and *Cry*. This feedback loop takes approximately 24 hours to complete a cycle. There are additional feedback loops interlocked with the CLOCK-BMAL1/Per-Cry loop. A prominent loop involves the activation of the retinoic acid receptor-related orphan receptor (ROR) and REV-ERB by the CLOCK-BMAL1 complex which feeds back on BMAL1 to stabilize rhythms (Preitner et al., 2002). Deletion of "core clock genes" (or, in some cases, 2+ paralogs of clock genes) reveals their requirement for rhythms in activity (Bunger et al., 2000; Cox & Takahashi, 2019; Vitaterna et al., 1994).

1.2.1 The Circadian System Is Synchronized to the Environment

Circadian rhythms oscillate at approximately but not exactly 24 hours. Variations in rhythm period occur at the whole organism level down to the individual cellular level (Czeisler et al., 1999). For example, humans display different "chronotypes," meaning some people are early risers or "larks" and others prefer to stay up later and are known as "night owls." These variations in preferred sleep and wake time are associated with distinct endogenous circadian periods: morning larks tend to have circadian rhythms that are shorter than night owls (Roenneberg et al., 2003). A number of genetic factors are associated with distinct chronotypes that include genes related to circadian regulation, as well as glutamate and insulin signaling

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pathways (Jones et al., 2019). Input to the circadian system is essential for maintaining everyone on the same 24 hour schedule.

1.2.2 Light Is the Dominant Entrainment Factor for the SCN

Light is the primary entrainment factor for synchronizing circadian rhythms to the 24 hour day. The major neural route of light entrainment occurs via activation of specialized cells in the retina called intrinsically photosensitive retinal ganglion cells (ipRGCs) (Berson et al., 2002; Provencio et al., 2002). ipRGCs are a population of non-vision forming cells that are critical in transducing light information via the retinohypothalamic tract to the SCN (Beier et al., 2021; Hattar et al., 2006; Moore & Qavi, 1971). Prior to the discovery of ipRGCs approximately 20 years ago, the existence of a non-vision forming cell was suspected as some individuals that lacked visual awareness maintained circadian rhythmicity and melatonin responses to light (Czeisler et al., 1995). Moreover, responses to light in animals were poorly explained by the properties of rods and cones (e.g., Brainard et al., 2001; Mrosovsky et al., 2001; Takahashi et al., 1984).

ipRGCs have extensive arbors and are activated by short (blue to humans) wavelengths of light due to their expression of the photopigment melanopsin (Do, 2019). Light activates melanopsin to trigger a G protein cascade, causing membrane depolarization and the release of glutamate and the neuropeptide pituitary adenylate cyclase activating peptide (PACAP) (Hannibal et al., 2002). Although the number of ipRGCs in the mammalian retina is limited, they display remarkable heterogeneity with six different morphological subtypes, M1–M6 (reviewed in Do, 2019). The distinct subtypes of ipRGCs are thought to regulate specific light intensity or times of day responses. The sensitivity of ipRGCs specifically to blue light has led to an interest in regulating the circadian system by manipulating the wavelength of light environment. Studies in humans have shown that high intensity blue light can be disruptive to the circadian system, resulting in melatonin suppression and sleep loss (Chang et al., 2015; Hanifin et al., 2019; West et al., 2011). This has led to blue light filters in technology (e.g., laptops and smartphones) that eliminate these wavelengths of light at night. However, it is important to note that filtering out blue light is not a cure all: ipRGCs also receive input from rods and cones. Melanopsin knockout mice maintain some circadian responses to light, but mice lacking melanopsin coupled with disabled rod and cone phototransduction do not (Hattar et al., 2003).

Light input is transduced from an electrical signal – via propagation along the retinohypothalamic tract – to a chemical signal when the tract terminates in the SCN with the release of glutamate. Glutamate acts on NMDA receptors to increase calcium release in SCN neurons (Ding et al., 1997). This increased calcium activates the transcription factor CREB to increase Per transcription (Gau et al., 2002; Ginty et al., 1993; Schurov et al., 1999). For instance, a brief flash of light during the inactive

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phase induces *de novo* expression of *Per* (Albrecht et al., 1997). Through these mechanisms, the SCN are optimized in mammals to link light timing in the environment with physiologic function.

1.2.3 Food, Exercise, and Other Factors Regulate Peripheral Circadian Rhythms

Although most strongly synchronized by light, the circadian system is also entrained by other factors. Early observations by Richter (1922) characterized anticipatory activity in response to timed feeding: rats fed one meal per day increase wheel running several hours prior to food availability. Indeed, both feeding (Boulos et al., 1980) and exercise (Edgar & Dement, 1991) can entrain circadian rhythms in locomotor activity. Moreover, when maintained in constant lighting conditions, rodents will also synchronize activity rhythms based on social cues (Paul et al., 2015). As discussed in Section 1.3, non-photic entrainment factors are typically more salient for extra-SCN clocks.

1.3 Circadian Rhythms Occur Throughout the Body: Extra-SCN Tissue-Specific Clocks

In addition to the central clock in the SCN, individual organs and cells outside the SCN rhythmically express core clock genes. These are termed peripheral or extra-SCN tissue-specific clocks. Individual cells contain autonomous clocks; importantly, all cells work in concert to time the occurrence of physiological events optimally. The SCN regulates peripheral clocks both through indirect and direct means. Direct regulation of peripheral processes by the SCN are evoked by neural or humoral signaling (e.g., Mohawk et al., 2012; Ramanathan et al., 2018). Indirectly, the SCN regulates the peripheral clocks via neural and humoral signaling factors, as well as by modulating the expression of circadian clock genes. For example, the SCN regulates secretion of hormonal cues that synchronize extra-SCN clocks, such as melatonin and glucocorticoids. Glucocorticoids are hormones released by the adrenal gland, and act via the glucocorticoid receptor in nearly all cells to regulate gene expression. Upon binding the cytosolic glucocorticoid receptor, the ligand-receptor complex enters the nucleus and binds to glucocorticoid response elements on DNA to activate or repress gene expression. Importantly, at baseline there are circadian rhythms in glucocorticoid levels and several circadian genes have glucocorticoid response elements in their regulatory regions (Reddy et al., 2007). Application of glucocorticoids to isolated cells can induce Per gene expression and thus serves as an important factor for regulating extra-SCN clocks (Balsalobre et al., 2000; Fonken et al., 2015).

In addition, physiologic cues coordinate or amplify circadian rhythms in extra-SCN cells; these cues include body temperature, feeding, and activity (Schibler et al.,

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2015). These neural, humoral, and physiologic factors are sensitive to entrainment by the SCN – but they are also regulated by other systemic factors (S. Zhang et al., 2020).

External events, such as food intake (Damiola et al., 2000) and physical exercise (Ripperger & Schibler, 2001), can indirectly reset peripheral clock rhythms in the liver and elsewhere (Chen et al., 2019; Landgraf et al., 2015). For example, restricting food intake to certain times of day (time-restricted feeding or TRF) can uncouple the SCN and extra-SCN clocks (Damiola et al., 2000). Indeed, timing of food intake strongly regulates the liver clock (Hatori et al., 2012) as well as cardiovascular function (see Chapter 11). Another mechanism of SCN-mediated peripheral clock regulation is by direct modulation of the autonomic nervous system, as described in Section 1.4.

Importantly, synchronizing clock gene expression in these extra-SCN tissues coordinates transcriptional programming of clock-controlled genes (Mavroudis et al., 2018). This means that myriad cellular functions are governed by the clock in peripheral tissues and also suggests that, during pathology, these intermediary circadian synchronizers may be susceptible to harmful perturbation that could desynchronize circadian oscillators. The remainder of this chapter will introduce circadian regulation of several major body systems; specific chapters in this book will then review clock disruption-elicited pathology in these systems.

1.4 Circadian Regulation of CNS Function

Central nervous system (CNS) function of animals displays distinct and overlapping circadian rhythms (Chapter 6). Indeed examples of circadian fluctuations in learning and memory, sensation and perception, attention, food intake, mating behaviors, maternal behaviors, aggression, drug and alcohol seeking behaviors, as well as regulation of locomotor activity have been reported (Nelson et al., 2021). These temporal variations are often overlooked and can significantly affect experimental outcomes. In this section we review some common examples of circadian regulation of CNS function. Notably, disrupted circadian rhythms negatively affect CNS function.

1.4.1 Locomotor Behavior

Early research on circadian rhythms focused on behavior as an output, especially locomotor behavior (Richter, 1922). Monitoring of activity cycles is adapted to the species under investigation. For example, small mammals are kept in a cage equipped with a running wheel connected to a counting device that automatically produces a continuous record of the individual's locomotor activity. The locomotor activity of small birds can be determined by monitoring perch-hopping activities around the

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clock. Humans can be equipped with electronic smart devices that transmit their locomotor activities to a central monitoring station.

Individuals of species are typically either diurnal or nocturnal in their locomotor activities. As noted, internal clocks display a period of about 24 hours and are set to precisely 24 hours by exposure to light. In the presence of constant lighting conditions (i.e., dim light, bright light, or darkness), locomotor rhythms display a temporal drift from 24 hours that mirrors the internal period (tau) of the circadian clock and is out of phase with the solar day.

Indeed, observing the locomotor activity of a colony of Syrian hamsters (*Mesocricetus auratus*) led to the discovery of an individual male with a very short tau (~22 hours) when housed in constant dark conditions (Ralph & Menaker, 1988). After a return to typical light–dark conditions, this individual displayed aberrant entrainment properties, beginning its locomotor activity about four hours prior to lights out, when hamsters typically begin their activities. This male was mated with three wild-type females with typical taus and, via standard cross-breeding studies, it was revealed that hamsters heterozygous for the mutation displayed periods of about 22 hours, whereas homozygous hamsters displayed locomotor rhythms with taus of about 20 hours. The tau mutant is encoded by casein kinase I epsilon (CKIε) and was the first gene identified that was associated with mammalian circadian rhythms (Lowrey et al., 2000). Animals display species-specific times of locomotor activity onset that are often linked to the timing of food intake, water consumption, and reproductive behavior, and have been a critical tool for understanding the genetics and other properties of circadian rhythms. Gene expression patterns are temporally similar in both nocturnal and diurnal animals (Challet, 2007).

1.4.2 Cognition

There are strong daily rhythms in all aspects of cognition (Fisk et al., 2018; Schmidt et al., 2007; Smarr et al., 2014) (Chapter 6). Generally, memory formation peaks during individuals' active periods. Thus, rats and mice tend to display optimal memory for performance in the Morris water maze during the night, whereas diurnal grass rats display best memory performance during the day (Krishnan & Lyons, 2015; Martin-Fairey & Nunez, 2014).

In rodents, both sensory sensation and perception vary across the day. For example, visual sensation and perception and auditory sensation and perception change across the day in humans and nocturnal rodents (e.g., Basinou et al., 2017; Finlay & Sengelaub, 1981; Meltser et al., 2014). Tasks requiring attention display significant circadian fluctuations in both humans (van der Heijden et al., 2010) and rodents (Gritton et al., 2012). These fluctuations appear to reflect circadian changes in cholinergic activities (Hut & Van der Zee, 2011).

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1.5 Circadian Regulation of Cardiac Function

Cardiac function is regulated by circadian rhythms (Liu et al., 2021; Melendez-Fernandez et al., 2021; Thosar et al., 2018) (Chapter 13). Cardiovascular regulation is associated with sleep–wake patterns (Bastianini et al., 2012; Smolensky et al., 2007) that are linked to underlying circadian rhythms. The circadian regulation of sympathetic and parasympathetic activation modulates heart rate, heart rate variability, blood pressure, vascular tone, and endothelial function (reviewed in Melendez-Fernandez et al., 2021). This temporal organization allows the vascular system to produce the necessary factors and mediators, such as prothrombotic and antithrombotic factors, and nitric oxide, at the appropriate time of the day to support activity during the active phase or support recovery and replenishment during the inactive phase. Dysregulation of these circadian fluctuations in cardiac function has been associated with cardiovascular pathology including myocardial infarction, ventricular tachycardia, and sudden cardiac death, which all peak during the early morning (Khan & Ahmad, 2003; Manfredini et al., 2013; Muller, 1999; Muller et al., 1987).

Cells comprising cardiovascular tissue display robust circadian oscillations including vascular smooth muscle, fibroblasts, cardiomyocytes, and cardiac progenitor-like cells, all of which regulate physiological functions including endothelial function, blood pressure, and heart rate (Paschos & FitzGerald, 2010). Disruption of these rhythms is associated with misalignment of cardiovascular dynamics, including endothelial (Etsuda et al., 1999), prothrombotic (Takeda et al., 2007), and clotting (Dalby et al., 2000) factors, which can provoke a pathological response (Rana et al., 2020).

Taken together, the available data indicate circadian regulation of the cardiovascular system. Indeed, peripheral clocks and clock genes are expressed in these tissues (Davidson et al., 2005; Storch et al., 2002). Rhythms in vascular function are also observed at the molecular level. RNA sequencing data indicate that 6 percent and 4 percent of protein-coding genes in the heart and aorta, respectively, are transcribed in a circadian fashion (Zhang et al., 2014). At the cellular level, the core clock genes, including *Bmal1*, *Clock*, *Per*, *Cry*, and *Rev-Erb*, serve an important role in maintaining physiological homeostasis of the cardiovascular system. For example, mice with *Per2* mutations display reduced nitric oxide production and decreased vasodilatory prostaglandins and elevated vasoconstrictors (Curtis et al., 2007). *Cry1/2* deletion leads to salt-sensitive hypertension and increased baroreflex sensitivity in mice (Stow et al., 2012). Given the importance of circadian organization for typical cardiovascular function, the potential of disrupted circadian rhythms for cardiovascular health is dramatic (see Chapter 13).

1.6 Circadian Regulation of Metabolism

Energy acquisition, storage, and utilization are critical for life. Metabolism regulates chemical changes in a cell or organism in order to generate energy or materials

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needed to grow, reproduce, and function appropriately. The circadian system helps optimize metabolic processes based on distinct metabolic requirements throughout the day to maintain homeostasis. Circadian rhythms in metabolism persist at multiple levels from the function of cellular mitochondria, to hormonal release, to behavioral rhythms in food intake.

Humans and other organisms face distinct metabolic demands based on time of day. A critical aspect of this is that daily behavior is partitioned into an active (wakefulness) and rest (sleep) phase. For understandable reasons, the majority of food intake occurs during an animals active phase, with circadian fluctuations in hunger and appetite contributing to this time of day difference in feeding (Scheer et al., 2013). There are also differences in cravings for specific foods based on time of day, with an increased preference for higher caloric foods as the onset of the sleep phase approaches (Scheer et al., 2013). This is thought to contribute to the increased risk for obesity and metabolic disorders that occurs in night shift workers – night shift workers are awake and active at a time where their bodies are primed for higher calorie food intake (Bouillon-Minois et al., 2022).

Importantly, metabolic regulation is not simply an output of the circadian system. Food intake feeds back on the clock to reinforce rhythms and to adapt physiology to tissue-specific needs. Along with changes in food intake, there are also time-of-day differences in whole body energy expenditure: metabolic rate is reduced during sleep compared to wakefulness (Fraser et al., 1989). Increases in energy expenditure occur during sleep restriction (although increases in energy expenditure are often countered by increased food intake) (Markwald et al., 2013; McHill et al., 2014). However, when humans are sleep restricted and maintained on bed rest, energy expenditure during the typical sleep phase is still lower than during the early active phase (Jung et al., 2011), suggesting the presence of an underlying endogenous rhythm.

Because of the differences in energy intake and expenditure that occur with predictable daily rhythm, there are also rhythms in the underlying hormonal and cellular processes associated with metabolism. Regulation of key metabolic hormones varies throughout the day both due to circadian regulation and as a direct consequence of timing of food intake. For example, because food intake occurs primarily during the active phase, there are increases in most intermediary metabolites including glucose, amino acids, and lipids in the blood during the active phase (reviewed in Reinke & Asher, 2019). The circadian clock, however, is critical for buffering against excessive fluctuations in metabolic factors. For example, blood glucose is regulated by the circadian system; glucose transporters oscillate in a circadian manner, presumably in anticipation of relative nutrient abundance during the active compared to the inactive phase (Reinke & Asher, 2019). Circadian function in key tissues and cells that mediate blood glucose are critical. Indeed, disrupting clock function in the liver and pancreas impacts glucose regulation (Lamia et al., 2008; Marcheva et al., 2010).

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Given this tight regulation between the circadian system and metabolism, it follows that disruption of the circadian clock by genetic or environmental means results in metabolic disruption. Susceptibility to diet-induced obesity in a genetic circadian model was first shown in clock mutant mice (Turek et al., 2005). Subsequently, mutations in many clock linked genes have been associated with metabolic dysfunction (see table 2 in Fonken & Nelson, 2014). Environmental circadian disruption in rodent models, including exposure to light at night (Fonken, Aubrecht, et al., 2013; Fonken et al., 2010; Fonken & Nelson, 2013; Fonken, Weil, et al., 2013), constant light (Coomans et al., 2013; Fonken et al., 2010), simulated shift-work protocols (Barclay et al., 2012; Salgado-Delgado et al., 2013), and non-24 hour light cycles (Karatsoreos et al., 2011), are also associated with metabolic dysfunction. Furthermore, humans that are at risk for circadian disruption by engaging in activities such as shift work are at increased risk for developing metabolic syndrome (Pietroiusti et al., 2010). Perhaps not coincidental, the global obesity epidemic parallels rapid increases in disruptive nighttime light exposure in recent decades. This work is reviewed in Chapter 10. Overall, metabolism and the circadian system are integrally associated.

1.7 Circadian Regulation of Immune Function

The diverse activities in which humans and other animals engage throughout the day come with different risks for encountering pathogens, toxins, and injuries. This suggests that coordinating responses to such threats would also be adaptive, with the immune system representing a major responder. Under healthy conditions, the immune systems may promote a state of anticipation and enhanced vigilance prior to the onset of the active phase, and repair and rejuvenation at the end of the active phase (Curtis et al., 2014).

The immune system differentially responds to challenges based on time of day (Haspel et al., 2020). For example, exposure to the same *E. coli* endotoxin challenge during the active versus inactive phase produces striking differences in mortality: rats that receive *E. coli* endotoxin during their inactive phase exhibit approximately 10 percent mortality versus approximately 80 percent mortality to the exact same dose during the active phase (Halberg et al., 1960). Similarly, humans with rheumatoid arthritis show increased pain and inflammatory markers during the nighttime (rest phase) and early morning (Gibbs & Ray, 2013; Ingpen, 1968; Perry et al., 2009). These changes in immune function are associated with direct circadian regulation of immune cells as well as due to circadian regulation of hormones that gate immune responses (e.g., glucocorticoids).

Recent work has illuminated how the circadian system drives healthy daily rhythms in immune responsivity and migration. Every immune cell examined expresses the circadian clockwork necessary for approximately 24 hour rhythms entrained by intermediary oscillators, and these clock genes refine expression of

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