Ageing Research Reviews xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Ageing Research Reviews

journal homepage: www.elsevier.com/locate/arr

Review

Circadian rhythms, time-restricted feeding, and healthy aging

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ARTICLE INFO

Article history:
Received 3 September 2016
Received in revised form
16 December 2016
Accepted 18 December 2016
Available online xxx

Keywords:
Circadian rhythms
Metabolism
Time-restricted feeding
Aging
Health

ABSTRACT

Circadian rhythms optimize physiology and health by temporally coordinating cellular function, tissue function, and behavior. These endogenous rhythms dampen with age and thus compromise temporal coordination. Feeding-fasting patterns are an external cue that profoundly influence the robustness of daily biological rhythms. Erratic eating patterns can disrupt the temporal coordination of metabolism and physiology leading to chronic diseases that are also characteristic of aging. However, sustaining a robust feeding-fasting cycle, even without altering nutrition quality or quantity, can prevent or reverse these chronic diseases in experimental models. In humans, epidemiological studies have shown erratic eating patterns increase the risk of disease, whereas sustained feeding-fasting cycles, or prolonged overnight fasting, is correlated with protection from breast cancer. Therefore, optimizing the timing of external cues with defined eating patterns can sustain a robust circadian clock, which may prevent disease and improve prognosis.

Contents

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http://dx.doi.org/10.1016/j.arr.2016.12.006
1568-1637/

1. Introduction

Nearly all living organisms ranging from archaea to mammals display circadian rhythms. Circadian (circa – approximately; dian – day) rhythms are approximately 24 h oscillations that can be found at the molecular, physiological, and behavioral level (Bell-Pedersen et al., 2005; Edgar et al., 2012; Loudon, 2012; Whitehead et al., 2009). The daily rhythms of sleep and activity and the associated rhythms in metabolic states emerge from a complex interplay of endogenous cell autonomous circadian oscillators, daily exposure to light and darkness, and daily patterns of feeding and fasting. These seemingly simple daily behavioral rhythms tune the function of almost all organ systems: digestive system, metabolic organs, immune system, reproductive system, endocrine systems, cardiovascular system, and several brain regions. The cell autonomous circadian oscillator in mammals is based on interlocked transcription-translation feedback loops. This molecular clock reciprocally regulates the cell's internal environment including, but not limited to, redox state, NAD+ levels, energy state (ATP/AMP ratio), and Ca2+ levels (Peek et al., 2013).

Oscillators modulate the function of a large number of gene products in a tissue specific manner so that the major function of almost every organ is rhythmic (Dibner et al., 2010). A number of signaling molecules produced from different neuroendocrine tissues display a circadian rhythm in their abundance and/or their cognate receptors show circadian modulation of activity (Gamble et al., 2015; Hastings et al., 2007). Consequently, synchrony within and between tissues demonstrate daily rhythms. The cell autonomous oscillator itself and a significant portion of the genome in each tissue also indirectly respond to food intake and light/dark cycles in a time of the day specific manner (Asher and Sassone-Corsi, 2015; Rusak et al., 1990). As a result, the circadian system is a master integrator of both the internal state of the organism and the organism's interaction with nutrition and ambient light. Daily oscillations, from individual cells to the whole organism, likely sub-serve a few central purposes. Oscillations temporally separate incompatible biochemical or physiological processes, optimize energy expenditure (as tonic production of several proteins can be costly), and synchronize function of metabolic pathways to reduce the build-up of toxic intermediates. While the circadian system's plasticity towards change in ambient lighting or food availability has been an advantage in nature to adapt to different seasons, such plasticity can become a liability in modern society where both light and food are available around the clock.

After the invention of electrical lighting, almost all modern humans voluntarily override this natural mechanism of diurnal rhythm by self-selecting a sleep-wake pattern that suits their schedule, which leads to associated alterations in feeding and fasting. Such chronic disruption of diurnal rhythms can compromise health through multiple discrete mechanisms. Reduced sleep can disrupt metabolic homeostasis by mechanisms that are yet to fully understood (Huang et al., 2011; Sharma and Kavuru, 2010). Light at night suppresses sleep and promotes extended wakefulness, thus allowing ingestive behavior to continue late into the night. This extended period of eating may contribute to increased caloric intake that often correlates with modern human lifestyle. Furthermore, eating at a sub-optimal time of the 24 h day can promote excessive energy storage instead of expenditure. Nutrition quality can also impact hunger, satiety, and hedonic drive for food intake and thereby affect daily eating pattern, which in turn can impact the robustness of circadian oscillators in various organs. Chronic circadian disruption due to erratic lifestyle or shift work compromises health and increase the risk of several chronic diseases that are associated with aging (Castanon-Cervantes et al., 2010; Maywood et al., 2006; Qian and Scheer, 2016; Scheer et al., 2009). Conversely, recent work has shown maintaining a defined daily feeding-fasting rhythm, as in time-restricted feeding (TRF), can prevent or attenuate several of these chronic diseases (Chaix et al., 2014). In this review we will discuss the general organization of the circadian system, its role in physiology and metabolism, how these rhythms change with age, and how eating pattern affects circadian regulation. For most of the article, we will focus our discussion largely on rodent models with occasional examples from other model organisms and humans.

2. Circadian clock machinery

Almost every cell in the body has a clock, each with an approximately 24 h period. However, in the absence of a coordinating signal, small period differences between oscillators leads to desynchrony (Welsh et al., 1995). The suprachiasmatic nucleus (SCN) in the hypothalamus acts as a master clock to coordinate these independent oscillators throughout the body and determine the period of the organism (Guo et al., 2006; Ralph et al., 1990). Unlike peripheral oscillators, the SCN is composed of a network of neurons with intricate intercellular communication (Welsh et al., 2010) to produce robust outputs through both neural and humoral cues (LeSauter and Silver, 1998).

In addition to this internal regulation, the SCN also receives external input, such as light, to help an organism coordinate with their environment. Nutrient consumption also has a large influence on biological rhythms, but has a more direct effect on peripheral oscillators than the SCN. Together, light and nutrients coordinate internal biological rhythms with the environment (Castillo et al., 2004; Daan and Pittendrigh, 1976; Damiola et al., 2000; Emery et al., 1998; Rusak et al., 1990; Schibler et al., 2003; Stokkan et al., 2001).

2.1. The molecular clock and transcriptional regulation

The mammalian molecular clock is comprised of interlocked transcriptional and translational feedback loops. BMAL1 and CLOCK (or NPAS2) heterodimerize and bind to an E-box motif of *Period1* (*Per1*), *Per2*, *Cryptochrome1* (*Cry1*), *Cry2*, *Rev-Erbα*, *RORα* (Retinoic acid-related orphan nuclear receptors), and other clock controlled genes to drive transcription. As the protein levels of PER and CRY rise, they form heterodimers that deactivate the CLOCK/BMAL1 complex, thus inhibiting their own transcription. REV-ERBα and RORα provide additional regulation by acting on RORE (or RRE, retinoic acid related orphan receptor response element) in the Bmal1 promoter to respectively repress or activate the transcription of Bmal1. Additional layers of post-translational regulation, such as CK1ε/δ and AMPK phosphorylation of PER and CRY, respectively, also play a large role in determining the period the clock (Lamia et al., 2009; Lee et al., 2001). The duration of one full loop is the period of the clock.

2.2. Clock controlled genes

The molecular clock also regulates the transcription of thousands of clock controlled genes (CCGs) either directly by the CLOCK/BMAL complex binding to an E-box of a promoter and REV-ERB or ROR binding to an RRE of a promotor, or indirectly through other clock output proteins (Bozek et al., 2009; Hirayama and Sassone-Corsi, 2005; Hunt and Sassone-Corsi, 2007). 7–13% of genes are under circadian control (Martino et al., 2004; McCarthy et al., 2007; Storch et al., 2002; Zhang et al., 2014). Additionally, a large number of proteins show daily rhythms, while their respective mRNAs do not (Neufeld-Cohen et al., 2016; Reddy et al., 2006; Robles et al., 2014). These clock controlled genes are involved in a wide range of cellular processes including cell cycle control, inflammation, and metabolism.

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Cell cycle regulators c-Myc, Cyclin-D1, and Wee-1 are rhythmically expressed. Wee-1 encodes a kinase that phosphorylates the CDC2/Cyclin-B1 complex, which regulates entry into mitosis and is directly regulated by the CLOCK/BMAL complex (Hirayama and Sassone-Corsi, 2005; Hunt and Sassone-Corsi, 2007; Matsuo et al., 2003). Circadian arrhythmic mutant mice demonstrate impaired cell-cycle control in vivo (Matsuo et al., 2003). Thus, through temporal transcriptional control, the clock is able to regulate the timing of the cell cycle. Such circadian gating of cell cycle has practical implication for timing of surgery, radiation therapy, and administration of cell cycle inhibitor drugs for cancer treatments (Dallmann et al., 2016; Levi and Schibler, 2007; Ortiz-Tudela et al., 2016). The clock also regulates inflammation, which is a common cause of metabolic disorders and cancer. CRY regulates the expression of pro-inflammatory cytokines (Narasimamurthy et al., 2012) and chronic behavioral circadian disruption in mice leads to an increase in inflammation (Castanon-Cervantes et al., 2010). Furthermore, mice that lack the circadian gene *Per2* exhibit increased incidence of cancer and tumor growth (Fu et al., 2002). Together these studies demonstrate the interconnected and wide reaching role of the circadian clock.

3. Diurnal regulation of metabolism

Various diseases of aging are associated with metabolic disruption. The anabolic and catabolic metabolism of fat, glucose, cholesterol, and xenobiotics are diurnally regulated by both the endogenous circadian clock and feeding-fasting pattern. These regulatory mechanisms influence metabolism at multiple levels including metabolite concentration, the endocrine system, and the microbiome.

3.1. Metabolites

Metabolite production and regulation are under direct (CLOCK/BMAL transcriptional activation) and indirect (CCGs) circadian regulation. Nicotinamide phosphoribosyltransferase (NAMPT) is a clock controlled gene that acts as a rate limiting enzyme for salvage of nicotinamide adenine dinucleotide (NAD^+), a metabolite involved in ATP synthesis and oxidation-reduction reactions (Ramsey et al., 2009). NAD^+ also modulates activity of protein deacetylases, sirtuins (SIRT), which regulates metabolic enzymes. SIRT1 and NAD both feedback on the core clock to regulate CLOCK/NPAS2, creating an auxiliary feedback loop to further temporally regulate metabolism. SIRT1 feedback plays an important role in clock maintenance as hepatocytes from SIRT1 deficient mice exhibit dysregulated circadian rhythms similar to aged WT mice (Wang et al., 2016). Multiple mitochondrial rate limiting enzymes that are critical parts of the pyruvate metabolism and fatty acid uptake and oxidation are also rhythmically expressed. In circadian mutant mice, enforced feeding-fasting patterns are able to reinstate rhythmic expression of some of these metabolites, such as Acylcarnitine carrier protein and Acyl CoA Dehydrogenase, yet were insufficient to restore rhythms in other enzymes (carnitine palmitoyl transferase 1 and the pyruvate dehydrogenase complex; Manoogian and Panda, 2016; Neufeld-Cohen et al., 2016). These studies illustrate the interaction of nutrient input and circadian control.

3.2. The endocrine system

3.2.1. Insulin and glucagon

The pancreas regulates blood glucose by producing and secreting insulin and glucagon to control release of glucose from the liver when blood glucose levels are too high or too low, respectively. Insulin is produced from β-islet cells in the pancreas, with peak production around 1700 h and a nadir ~0400 h in humans (Goel et al., 2009). Temporal control of hormonal production and release is controlled by both feeding-fasting patterns and circadian rhythms. Eating patterns greatly alter nutrient levels in the blood and can therefore act as an acute overriding signal. The circadian system modulates both insulin and glucagon by controlling production and secretion at the cellular level as well as SCN signaling the autonomic nervous system (Kalsbeek et al., 2008; Sadacca et al., 2011; Vieira et al., 2015). In vitro, β-islet cells exhibit robust rhythms of both *Bmal1* and *Per1* (Mühlbauer et al., 2004; Sadacca et al., 2011). *Bmal1*$^{-/-}$ in the pancreas had disrupted glucose homeostasis and insulin release despite displaying normal activity and feeding-fasting rhythms (Sadacca et al., 2011). This demonstrates how the molecular clock at the cellular and tissue levels can have significant effects on physiology.

Insulin sensitivity is also influenced by both nutrient state and the clock through SIRT1 (Bass and Takahashi, 2010; Civitarese et al., 2007). Research in both animals and humans has shown that caloric restriction increases levels of SIRT1 (Civitarese et al., 2007). Moreover, mice on an ab lib high-fat diet display decreased SIRT1 levels and impaired insulin sensitivity (Sun et al., 2007).The SCN further regulates blood glucose through the autonomic nervous system. β-islet cells of the pancreas receive parasympathetic input from the ventral PVN, which are circadianly controlled by GABAergic projections from the SCN. Similarly, the SCN has both Glutamatergic and GABAergic projections to the dorsal PVN to modulate sympathetic output to the liver to influence glucose production (Kalsbeek et al., 2008).

3.2.2. Cortisol

Cortisol is a steroid hormone in the glucocorticoid family that is involved in metabolism and stress response. Production and secretion of cortisol are rhythmic and regulated by the hypothalamic pituitary axis (HPA) and the autonomic nervous system (ANS). In the HPA axis, corticotropin releasing hormone (CRH) and arginine vasopressin (AVP) are produced in the paraventricular nucleus (PVN) of the hypothalamus. CRH is released from the median eminence and travels to the to the anterior pituitary through the hypophyseal portal system. Hypothalamic AVP neurons project axons directly to the posterior pituitary and release AVP into the circulation. In the anterior pituitary, both CRH and AVP stimulate the release of adrenocorticotropic hormone (ACTH) into the blood. AVP in the adrenal medulla also increases adrenal gland production of ACTH. ACTH acts on the adrenal cortex to stimulate cortisol release. This system is negatively regulated by cortisol in the hypothalamus and the pituitary (Matthews and Challis, 1997). The PVN also sends ANS projections to the intermediolateral column of the spinal cord, which connects to the splanchnic nerve to signal the adrenal gland. Both HPA and ANS regulatory pathways for cortisol are regulated by the SCN at the level of the PVN and upstream in the dorsal medial hypothalamus and the subparaventricular zone. Cells of the adrenal gland also have cellular clocks to temporally influence production and release of cortisol (reviewed in Dickmeis, 2009).

Glucocorticoids are released with both an ultradian (1–2 h) and circadian rhythmicity. Peak levels of glucocorticoids synchronize with the beginning of the active phase to aid in arousal; early morning in diurnal animals and early night in nocturnal animals. Likewise, ACTH exhibits a parallel rhythm as it is also modulated by the SCN (Dickmeis, 2009; Lightman et al., 2008).

Similar to negative feedback on the HPA axis, Glucocorticoids influence circadian rhythms by feeding back on the clock. Glucocorticoids bind to a glucocorticoid response element (GRE) in the *Per1/2* and *Rev-Erbα/β* promoter, to activate and suppress transcription respectively (So et al., 2009; Torra et al., 2000; Yamamoto

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et al., 2005). Conversely, CRY acts as a transcriptional suppressor of glucocorticoid regulated genes (Lamia et al., 2011).

3.3. The microbiome

The microbiome influences metabolism and can contribute to metabolic disorders and obesity. The microbiome is diverse and exhibits daily oscillations in composition. Diet induced obesity and erratic eating patterns can disrupt and dampen these rhythms. Both behavioral and genetically induced circadian disruption have also been shown to decrease the taxonomic diversity and induce intestinal dysbiosis (Voigt et al., 2016, 2014). However, enforced feeding-fasting patterns can restore some of these oscillations (Zarrinpar et al., 2014).

4. Circadian rhythms dampen with age

Circadian rhythms deteriorate with age due to multiple factors. Individual SCN neurons are able to maintain a robust amplitude of core clock gene oscillations in aged mice (Wyse and Coogan, 2010) and in vitro (Welsh et al., 1995), however, there is impaired intercellular coupling within the SCN. Although the total number of neurons within the SCN remains the same in aged rats, the number of neurons that contain vasopressin, a coupling factor for oscillators within the SCN, are decreased (Mieda et al., 2015; Roozendaal et al., 1987). GABA, another important coupling factor within the SCN, also displays impaired signaling with age (Nygård and Palomba, 2006). In response to GABA, aged SCN neurons exhibit a decrease in inhibitory post-synaptic potentials (IPSP) compared to young SCN neurons (Farajnia et al., 2012). This decrease in intercellular communication leads to neuronal desynchrony in the SCN and is a likely cause of the overall decrease in electrical activity of the SCN network (Farajnia et al., 2012; Nygård et al., 2005) and SCN output (Nakamura et al., 2011). The dampening of SCN electrical activity begins a cascade effect. Dampening in both neuronal and humoral outputs results in impaired coordination of peripheral oscillators. Peripheral clocks display a decrease in clock gene amplitude with age. This may be due to disruption of intrinsic molecular clock, impaired temporal coordination of oscillators, or a result of overall impaired physiology associated with aging. The robustness of an organism's biological rhythms is determined by a combination of external cues and internal rhythms. Therefore, as endogenous rhythms dampen with age, the timing of external cues play an increasingly important role in determining the amplitude of an organism's circadian clock.

5. Consequences of circadian disruption

In humans, the most obvious consequence of circadian disruption are observed in activity-rest cycles (Dijk et al., 1999; Farajnia et al., 2012; Huang et al., 2002). Changes are also seen in amplitude and phase of temperature and melatonin rhythms, yet some studies show little to no changes (reviewed by Monk, 2005). Sleep quality and consolidation are also greatly disrupted (Dijk et al., 2001; Farajnia et al., 2012). Genetic, behavioral, and lesion induced circadian disruption or arrhythmicity has been shown to result in a wide range of health consequences including increased risk for cancer, cardiovascular disease, obesity, immune disorders, infertility, and affective disorders (Hastings et al., 2003). Genetically arrhythmic mice (*Bmal1*$^{-/-}$) exhibit symptoms of early onset aging, including a decrease in muscle and subcutaneous fat, cataracts, and organ shrinkage (Kondratov et al., 2006). Circadian disruption caused by shift work in humans is associated with cardiovascular disease, metabolic disorders, and cancer (Kamdar et al., 2013; Proper et al., 2016; Vyas et al., 2012). In rodents, transplanting the SCN from a young hamster, to an old hamster with weak behavioral rhythms, was sufficient to not only reinstate robust behavioral rhythms in the older hamster, but also increased lifespan by 4 months (normal lifespan is ~2 years; Hurd and Ralph, 1998; Viswanathan and Davis, 1995). This indicates that aging of the SCN also dictates aging of behavioral rhythms and physiology.

In addition to an increased risk for disease, circadian disruption can also lead to cognitive deficits. Rodent models have demonstrated that chronic circadian disruption induces deficits in hippocampal learning and memory, but not in fear conditioning (Antoniadis et al., 2000; Craig and McDonald, 2008). Circadian disruption caused by keeping mice in a short photoperiod (20 h, 10 h light:10 h dark) inhibited cognition measured by cognitive flexibility tests (Karatsoreos et al., 2011). Circadian disruption, induced by keeping mice in a short photoperiod (20 h, 10 h light:10 h dark, a period too short for a WT mouse to entrain), inhibited cognition measured by cognitive flexibility tests (Karatsoreos et al., 2011). These mice also showed a decrease in dendrite length and neuronal complexity in the prelimbic prefrontal cortex, a region of the brain involved in executive functions and emotion (Karatsoreos et al., 2011). Observations of airline cabin crews have shown that chronic jet lag is correlated with decreased cognition and temporal atrophy (Cho, 2001; Cho et al., 2000). Rodent models of jet lag demonstrated an inhibition of neurogenesis in the hippocampus and long term cognitive deficits (Gibson et al., 2010) and shorted lifespan (Davidson et al., 2006). Memory deficits may be explained by the circadian control of brain-derived neurotrophic factor (BDNF) expression in the dentate gyrus, but not in CA1 or CA3 of the hippocampus (Schaaf et al., 2000). It is unclear if this control is direct from the SCN or indirect through corticosterone suppression (Schaaf et al., 2000). BDNF modulates cell growth and survival and in the hippocampus plays in important role spatial and contextual learning and memory (Hall et al., 2000; Mizuno et al., 2000). Memory formation is dependent on long-term potentiation (LTP) to alter synaptic connections. Increases in BDNF expression led to increases in LTP and *Bdnf*$^{-/-}$ mice exhibit decreased LTP (Figurov et al., 1996; Korte et al., 1995; Patterson et al., 1996). Deficits in LTP can be rescued in *Bdnf*$^{-/-}$ mice with recombinant BDNF (Patterson et al., 1996). As seen in rodents with circadian disruption, dentate gyrus specific knockdown of neurogenesis in mice impairs spatial memory and object recognition (Jessberger et al., 2009). BDNF is also decreased in the hippocampus of individuals with Alzheimer's Disease (Phillips et al., 1991).

5.1. Circadian disruption and neuro degenerative disease

There many correlations between circadian disruption and neurodegenerative diseases such as Alzheimer's Disease (AD) and Parkinson's Disease. However, the causal relationship is unclear. As circadian rhythms have been shown to play a role in neurogenesis (Borgs et al., 2009; Gibson et al., 2010; Tamai et al., 2008), the dampening of circadian rhythms with age is likely to contribute neurodegenerative diseases such as Alzheimer's disease (AD).

The amyloid hypothesis of AD proposes that excess production and accumulation of amyloid β peptide (Aβ) begins a cascade effect that damages the synapse and neurites and leads to neurofibrillary tangles containing tau protein (Hardy and Selkoe, 2002). Prior to aggregation, there are daily fluctuations in Aβ soluble interstitial fluid (ISF) controlled by the sleep-wake cycle. Levels of Aβ in the ISF correlates with the amount of future Aβ aggregation. After Aβ plaques are formed, diurnal rhythms of both the sleep-wake cycle and fluctuations in ISF Aβ are diminished (Roh et al., 2012). In humans, AD patients exhibit a decreased amplitude in activity patterns and a delay in peak activity and body temperature (Volicer et al., 2001). There was also a correlation between circadian disruptions in locomotor activity and "sundowning" (an exacerbation

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of AD symptoms in the afternoon). This is also associated with a delayed peak of body temperature in the afternoon (Volicer et al., 2001). Further circadian disruption in AD patients can be seen in the SCN. In humans, SCN neurons expressing vasoactive intestinal peptide (VIP; another important intercellular coupling factor in the SCN) were significantly lower in females with AD compared to healthy age-matched controls. Interestingly, this effect was not seen in males. However, young males had more VIP neurons in the SCN compared to older males, whereas young females had less VIP expression compared to healthy older females (Zhou et al., 1995). Although it is unclear if AD leads to circadian disruption or vice versa, some behavioral modifications using bright light exposure have been shown to restore some behavior rhythms in patients with AD and dementia (Ancoli-Israel et al., 2003; Van Someren et al., 1996). These studies indicate that low amplitude circadian rhythms contributes to the AD and dementia pathology.

6. Eating patterns and health in humans

Extensive reciprocal regulation between the circadian clock and nutrient metabolism (reviewed in Asher and Sassone-Corsi, 2015) suggests that daily eating pattern can affect the amplitude and phase of circadian rhythms. There are a variety of eating patterns that concern 'fasting' that are frequently thought of together, including intermittent fasting (IF), periodic fasting (PF), caloric restriction (CR), and time-restricted feeding (TRF). IF, PF, and CR are all based on overtly reducing calories on various timelines. TRF is the only eating pattern that does not require calorie reduction. TRF is based on circadian biology to allow the body a true daily fasting period in which only water is allowed (anything that is more than 5 cal or contains caffeine or artificial sweeteners are excluded).

6.1. Time-restricted feeding in rodents

Laboratory mice with ad libitum access to a standard diet typically consume a majority (60–80%) of their daily food intake at nighttime. "Time-restricted feeding" or "restricted feeding" is a term often used in the field of circadian rhythms to examine the role of timing of food access on the circadian clock. In these experiments timing of food access is restricted to anywhere between 2 and 12 h during the day or night and the effect of this time-restricted access to food on the circadian clock or clock controlled genes are assessed. Within a few days, rodents learn to anticipate the timing of food arrival and consume a large meal during the time-window of food availability. If the period of food access is <6 h, animals cannot eat equivalent amount of food as their ad lib feed (ALF) counterparts. However, with food access of >8 h, they consume an almost equal amount of calories as the ALF cohort. Hence a TRF paradigm, where food access is >8 h is a powerful method to examine the effect of time of food availability independent of nutrition quality or quantity on the circadian clock and animal's health.

TRF paradigm in combination with high-fat diet has been powerful in elucidating the effect of eating pattern on the prevention and treatment of metabolic diseases. Diet induced obesity (DIO) is a widely used experimental model of obesity, diabetes, and several metabolic diseases in which animals have ad lib access to a diet rich in fat (> 11,000 papers in PubMed as of December 2016). After 8–12 weeks, mice on high-fat diet become obese, hence the name. This simple model of obesity without genetic perturbation works well in several strains of mice. Although the metabolic disruption in the DIO model is often ascribed to the high fat diet, the diet also changes the daily eating pattern of mice, such that they continuously snack on the high-fat diet throughout day and night (Pendergast et al., 2013). Such random eating pattern disrupts the circadian oscillator in metabolic organs including the liver. Since genetic and environmental disruption of circadian rhythms, as in shiftwork, perturbs metabolic homeostasis and predisposes to metabolic diseases, disrupted circadian rhythms likely contributes to the disease in the in DIO model. When mice on high-fat diet are granted access to food for 8, 9, 12, or 15 h during the night time, they consume the same amount of total daily calories as the ALF counterparts. However, they are largely protected from several metabolic diseases. Mice with pre-existing obesity due to ALF on a high-fat diet also benefit from the therapeutic effect of TRF (Chaix et al., 2014; Chaix and Zarrinpar, 2015; Sherman et al., 2012).

In mice, TRF exerts pleiotropic effects on multiple organ systems including but not limited to liver, muscle, white adipose tissue, brown adipose tissue, and gut (Zarrinpar et al., 2015). In depth analyses of TRF has largely been done in the liver. Overall TRF exerts profound effect on hepatic gene expression and metabolites (Hatori et al., 2012). Nearly 40% of named metabolites detected in liver change significantly between a DIO and TRF liver. Among them, the largest clusters of metabolites belong to sugar and fat/cholesterol metabolites. Many of these changes correlate with changes in the expression level of corresponding metabolic regulators. In the liver, TRF affects the daily dynamics of major nutrient sensing pathways including CREB, mTOR and AMPK, and thereby impacts their downstream genes or protein products. In DIO liver, the daily rhythm in pCREB and pS6 (readout of mTOR activity) is blunted leading to constitutively elevated pCREB and reduced pS6 levels. In contrast, TRF restores the daytime peak in pCREB and nighttime peak in pS6. The reduction of pCREB in nighttime likely reduces liver gluconeogenesis, while mTOR activation at night can promote glucose utilization in pentose phosphate pathway. Mice on TRF experience extended daily fasting, which likely increases the hepatic AMP levels relative to that seen in the DIO livers. AMP can allosterically activate AMPK, which phosphorylates and deactivates one of the rate-limiting enzymes of fatty acid oxidation, acetyl CoA carboxylase (ACC). Both CREB and AMPK are known to promote the transcription of *Per* genes and degradation of CRY proteins respectively. These functions likely underlie the effect of TRF on improving the amplitude of oscillation of circadian clock components including that of Bmal1 and Rev-erb. Increased Bmal1 levels correlate with increased expression of its target genes Umps and Tk1, which constitute the rate limiting steps in nucleotide metabolism. Accordingly, TRF livers also display increased levels of nucleotides (Hatori et al., 2012).

DIO livers exhibit elevated level of PPARγ, which is known to promote fatty acid synthesis, elongation, and desaturation. TRF reduces PPARγ expression, which parallels a reduction in long chain fatty acid and unsaturated fatty acids. The combined action of increased fatty acid oxidation and reduced fatty acid synthesis leads to >50% reduction in liver fatty acids and nearly complete absence of fat droplets in hepatocytes. This underlies the reduction in fatty liver disease and liver fibrosis in TRF mice. TRF mice also show a mildly elevated level of ketone bodies, which is now linked to several benefits in metabolism and central nervous system function (Akram, 2013; D'Agostino et al., 2013).

Hepatic fatty acid metabolism is closely linked to cholesterol and bile acid homeostasis. Both feeding and the clock component Rev-erbα participate in the daily production of cholesterol and bile acids through transcriptional regulation of the lipid regulator Srebp1c and several rate-limiting enzymes including Hmgcs2 and Cyp7a1 (Cho et al., 2012; Le Martelot et al., 2009). Distinct feeding-fasting rhythms along with improved Rev-erbα rhythms in the livers of TRF mice corrects the phase of expression of Hmgcs2 and Srebp1c, while increasing the peak levels of Cyp7a1. Elevated Cyp7a1 transcript, which encodes the rate-limiting step in bile acid production from cholesterol, increases hepatic bile acids and contributes to a decrease in serum cholesterol levels in the TRF mice. Increased

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bile acids can enter the general circulation and activate uncoupling protein 1 (UCP1) mediated energy expenditure in brown adipose tissue by acting through TGR5. In fact, the BAT of TRF mice increased UCP expression, increased mitochondria content, and TRF mice increased oxygen consumption (Hatori et al., 2012).

TRF also alters WAT function and inflammation. In general, the size of adipocyte, macrophage infiltration of WAT, and inflammatory cytokine production are reduced and mitochondria content is increased in the WAT (Hatori et al., 2012).

Benefits of TRF are also seen in mice on other diets including high fructose diet, high fat + high sucrose diet, or a standard diet (Chaix et al., 2014). Mice on a standard diet do not show much body weight loss, rather they show a significant change in body composition under long term TRF of >26 weeks; increased lean mass, and reduced fat mass. ALF mice on a standard diet develop some liver fibrosis with age, which is prevented by TRF. TRF does not profoundly elevate the basal activity level in rodents, but it has an interesting effect on endurance as measured by running on a treadmill. Even after controlling for body weight, DIO mice run for a significantly shorter duration, while TRF mice with access to high-fat diet for 8 or 9 h run >40% longer than the normal chow ALF controls. However, this added endurance is not present in TRF mice with 12 h access to high-fat diet, even though they have comparable adiposity as mice with 8 h access to food (Chaix et al., 2014).

The timing of TRF with relation to day or night seems to have some effect on metabolism. While TRF mice are always leaner than their ALF DIO counterparts, mice with daytime access to high-fat diet (day TRF) fare worse than the night TRF. The underlying changes in metabolism between day- and night-TRF are an exciting area for future investigation. Such difference between day- and night-TRF is exacerbated with high-fat diet, while no such significant difference is generally reported with standard diet (Chaix et al., 2014).

It is worth noting that many caloric restriction studies in rodents inadvertently involve a component of time-restricted access to diet. While many CR studies in rodents are controlled for time of delivering the control standard diet and the reduced caloric diet at a specific time of the morning or evening, some studies are vague about the timing. Nevertheless, CR studies in rodents, irrespective of when the food was delivered usually report positive health outcomes (Lee and Longo, 2016).

6.2. *Time-restricted feeding in Drosophila*

While rodents are nocturnal animals, Drosophila are diurnal and they also have a circadian oscillator that coordinates metabolism, physiology and behavior around the clock. With short lifespan and well-established genetic resources, Drosophila offer a powerful model to test TRF on age related pathologies. TRF in Drosophila is done with 12 h access to food during the daytime and access to only 1% agar at night to maintain humidity. TRF flies, like their rodent counterparts, consume the same amount of calories as their ALF cohorts, yet they do not gain body weight and their total activity remains equivalent. As flies age, the diurnal pattern of activity and sleep dampens as in humans. Sleeping duration at night is decreased and increased during the day. However, flies on TRF displayed sustained nocturnal sleep, nearly doubling total sleep duration of the ALF controls. Flies, like humans, also exhibit age dependent deterioration of cardiac function as reflected in increased arrhythmia. Flies on a 12 h TRF show reduced rate of cardiac aging as their heart function is roughly equivalent to cardiac function of ALF flies that are 2 weeks younger. Gene expression profiling of head, body, and heart demonstrated that overnight fasting in flies does not trigger a gene expression signature characteristic of caloric restriction (Gill et al., 2015).

Taken together these studies demonstrate the potential for simple behavior modifications to enhance the biological clock and rhythmic gene expression to optimize an individual's health.

7. Conclusion

Circadian rhythms are an integral part of physiology that seem to be essential for health. Erratic lifestyle associated with modern society (aberrant eating and sleep patterns, inappropriate light exposure, jet-lag, and shift work) contribute to circadian rhythm disruption. This disruption compromises multiple levels of physiology (ex. metabolism, inflammation) and increases the risk for non-infectious chronic diseases such as metabolic disorder, diabetes, cardiovascular disease, and cancer. Unfortunately, biological rhythms naturally dampen with age, which may contribute to a wide variety of age related diseases. Although further research is still needed to determine the optimal eating duration and efficacy of time-restricted feeding in humans, research in rodents suggests that maintaining a regular daily feeding-fasting pattern may be sufficient to restore robust circadian rhythms to optimize an individual's physiology and decrease their risk of disease to extend healthspan.

Funding

Research in SP lab is supported in part by funding from the NIH (EY016807, CA014195) Glenn Foundation for Aging Research, American Foundation for Aging Research, Helmsley charitable trust, World Cancer Research.

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Please cite this article in press as: Manoogian, E.N.C., Panda, S., Circadian rhythms, time-restricted feeding, and healthy aging. Ageing Res. Rev. (2016), http://dx.doi.org/10.1016/j.arr.2016.12.006

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Please cite this article in press as: Manoogian, E.N.C., Panda, S., Circadian rhythms, time-restricted feeding, and healthy aging. Ageing Res. Rev. (2016), http://dx.doi.org/10.1016/j.arr.2016.12.006

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Please cite this article in press as: Manoogian, E.N.C., Panda, S., Circadian rhythms, time-restricted feeding, and healthy aging. Ageing Res. Rev. (2016), http://dx.doi.org/10.1016/j.arr.2016.12.006

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Please cite this article in press as: Manoogian, E.N.C., Panda, S., Circadian rhythms, time-restricted feeding, and healthy aging. Ageing Res. Rev. (2016), http://dx.doi.org/10.1016/j.arr.2016.12.006