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## The endogenous circadian clock programs animals to eat at certain times of the 24-hour day: what if we ignore the clock?

Peng Jiang and Fred W. Turek

Center for Sleep & Circadian Biology, Department of Neurobiology, Northwestern University, Evanston, IL 60208, USA

### Abstract

The discovery of the molecular mechanisms underlying the circadian clock, which functions in virtually every cell throughout the body to coordinate biological processes to anticipate and better adapt to daily rhythmic changes in the environment, is one of the major biomedical breakthroughs in the 20<sup>th</sup> century. Twenty years after this breakthrough, the biomedical community is now at a new frontier to incorporate the circadian clock mechanisms into many areas of biomedical research, as studies continue to reveal an important role of the circadian clock in a wide range of biological functions and diseases. A forefront of this exciting area is the research of interactions between the clock and energy metabolism. In this review, we summarize animal and human studies linking disruptions of the circadian clock, either environmental or genetic, to metabolic dysfunctions associated with obesity, diabetes, and other metabolic disorders. We also discuss how these advances in circadian biology may pave the way to revolutionize clinical practice in the era of precision medicine.

### Keywords

circadian clock; energy metabolism; obesity; diabetes

### Introduction

Most living organisms have an internal circadian clock that regulates diverse 24-hour rhythms such as body temperature, sleep/wake, and feed/fast cycles. This central clock in mammals is located in the suprachiasmatic nucleus (SCN) of the anterior hypothalamus [1]. While normally entrained to the 24-hour light/dark cycle as the earth rotates on its axis on a daily basis, the SCN central clock continues to provide endogenous cycles even in the absence of any external light/dark or other diurnal 24-hour environmental signals. The endogenously generated rhythms have a period of about a day (e.g. 23~25-hour cycles), and thus the internal clock is referred to as a “circadian” (about a day) clock. Many organisms are programmed to be active and thus feed during the night (nocturnal) while others are

\*Corresponding author at: Dr. Peng Jiang, 2205 Tech Drive, Hogan 2-160, Evanston, IL 60208.

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active during the light portion of the 24-hour day (diurnal). Humans are by nature diurnal, and an evolutionary history over millions of years have led humans and their humanoid ancestors to be active during the light (day) and inactive or asleep during the dark (night) portion of the day. Alas, with the ability to make light at night, especially with the invention and use of the electric light bulb 100+ years ago, humans often decide to ignore Mother Nature and to become a diurnal/nocturnal organism with many individuals in modern society being active (and eating) during the dark as well as the day. In many cases, we even reverse our natural diurnality by being active (and eating) all night long and sleeping (or at least attempting to sleep) in the light portion of the day (e.g., shift workers).

While disrupted circadian rhythms, as in shift work, have been associated with adverse health effects for many years, our understanding of the mechanisms by which disrupted circadian regulation could impact health took a giant leap forward with the identification and cloning of circadian clock genes, first in flies and later in mice [2–7]. This led to the discovery of the core molecular mechanism of circadian clocks, a transcriptional/translational feedback loop, in which transcriptional suppressors PER and CRY repress the activity of transcriptional activators CLOCK and BMAL1, shutting down their own transcription and generating ~24-hour rhythms in the expression levels of clock genes as well as clock-controlled genes [8]. Equally important, and quite unexpected was the discovery that the molecular clock was soon found in almost all the cells of the body [9–11] and this molecular timing system was regulating the rhythmic expression of about 10% of all expressed genes in a given tissue in a tissue-specific fashion and collectively over 50% of the genome [12–15]. The significance of this discovery has likely contributed greatly to the awarding of the 2017 Nobel Prize in Physiology or Medicine to the trio of circadian biologists who cloned the first circadian clock gene, *period (per)*, in fruit flies in 1984 (Michael Young, Michael Rosbash, and Jeff Hall). The fact that the circadian clock is operating in every tissue implies that “for many tissues correct timing is important enough to warrant keeping track of it locally”, as Young noted in his article published by *Scientific American* in 2000 [16]. Observations in many areas of biomedical research have since supported this prediction and elucidated molecular cascades that link the molecular clock to metabolism, endocrine regulation, immune functions, cell proliferation/differentiation, sleep/wake, psychiatric/cognitive functions, and many other biological processes in various organs and tissues [17, 18]. These advances have led to new frontiers of circadian biomedical research, where we are beginning to understand how circadian programs are coordinated within and across tissues/organs in health and dis-coordinated in disease.

In this review, we present findings from studies in animals and humans demonstrating effects of disrupted circadian rhythms on metabolic balance and body weight regulation. This area of physiology is perhaps the most “mature” area for understanding how circadian clock genes interact with other gene networks of cellular functions. We then expand our focus and briefly summarize the links between disrupted circadian clocks and other diseases. We conclude by discussing the challenges and opportunities that have been made available by the exciting scientific breakthroughs over the past few decades to incorporate circadian mechanisms into standard clinical practice for improved clinical outcomes and overall human health.

## Animal models

An early significant finding to support a role of the molecular clock in body weight regulation and metabolic disorders came from our study of the *Clock*<sup>19</sup> mutant mice [19]. *Clock*<sup>19</sup> is a dominant-negative mutant allele identified in a mutagenesis screen in mice [5], which led to the discovery of the positive arm of the transcriptional/translational core clock machinery. *Clock*<sup>19</sup> mice have a much weakened clock (low rhythmic output) with a long circadian period, and this mouse model has been used extensively over the past two decades as a primary genetic model that has directly linked the molecular clock machinery to many aspects of physiology. In 2005, we found that homozygous *Clock*<sup>19</sup> mutant mice were obese and showed signs of metabolic syndrome, including hyperleptinemia, hyperlipidemia, hepatic steatosis, hyperglycemia, and hypoinsulinemia [19]. This finding directly linked the circadian machinery to metabolic functions and body weight regulation. Importantly, feeding rhythms in these animals are blunted: mutant animals eat roughly the same amount during the day and night, while the wildtype animals eat more (~70–80% of the daily food consumption) during the night as is typical for nocturnal animals, implying that disruptions of the circadian feeding rhythm and eating during the wrong time of the day are associated with obesity [19]. The finding that a genetic mutation in a core circadian clock gene leads to obesity and metabolic dysfunction has allowed the biomedical community to quickly tie the clock machinery with metabolic pathways, revealing highly intertwined clock-metabolic networks [20] particularly in metabolic tissues and organs. For example, accumulating evidence has now highlighted a role of the circadian clock machinery in the differentiation and function of the adipose tissue, providing a mechanistic view of the circadian metabolic program (for a review, see [21]). Together, these advances represent a key step towards “a unified ‘systems’ map of metabolic disease” [22].

The relationships between the functioning of the circadian clock and body weight regulation are bidirectional. Mice that are obese due to feeding on a high-fat diet show altered diurnal patterns of locomotor and feeding rhythms such that a significant portion of locomotor activity and food intake occur during the light portion of the day (i.e., the “wrong” time for nocturnal animals) [23, 24]. This association between obesity and eating at the wrong time of the day in mice fed a high fat diet makes a striking resemblance to that observed in the *Clock*<sup>19</sup> mice. Similar observations have been made in genetic models of obesity. Mice genetically deficient in leptin (i.e., *ob/ob* mice) or its receptor (i.e., *db/db* mice) are obese and diabetic, and intriguingly, both models show significantly attenuated diurnal rhythms in the locomotor activity [25, 26]. Leptin indeed appears to be a central link between circadian food intake and body weight regulation. As a hormone important for the regulation of food intake and energy homeostasis, circulating levels of leptin in humans exhibit diurnal variations [27], which is independent of the sleep/wake and fasting/feeding cycles as it persisted under a constant routine protocol [28]. Animal studies have demonstrated that the leptin rhythms are dependent on the SCN [29] and the transcription of the *leptin* gene in adipocytes are under direct control of the circadian clock machinery [30]. More recent data suggest that leptin modulates gastric vagal afferent (VGA) mechanosensitivity in a circadian fashion [31]. Obesity induced by a high-fat diet blunts the circadian variation in the leptin modulation of VGA signaling, which may contribute to arrhythmic eating behavior seen in

the high-fat diet fed mice [31]. Furthermore, circadian disruptions due to clock gene deficiency or chronic repetitive shifts of the light/dark cycle lead to leptin resistance in mice [30]. Together, these findings have important implications for body weight regulation since obesity and disruptions in circadian rhythms may be reciprocally contributing to dysfunctions in both regulatory systems and exacerbate the negative health consequences.

The findings from a number of different animal models indicate that the time of day at which feeding occurs may be important for body weight regulation. Indeed, when comparing mice fed on a high-fat diet only during the light phase of the day (i.e., the “wrong” time) to those fed on the same diet but only during the dark phase (i.e., the “right” time) of day, we found that the wrong-time-fed mice gained weight at a faster pace and the differences became significant in only 2 weeks [32]. Importantly, the amount of daily food intake and the activity levels were not significantly different between the two groups of animals [32]. These observations have provided early implications that when to eat, in addition to what and how much, is important for body weight regulation. It is interesting to note that, unlike the master circadian clock in the SCN, peripheral clocks in metabolic organs, such as the fat body in flies and the liver in mammals, can be entrained to feeding schedules [33–35]. Hence, wrong-time feeding creates a conflict between the transcriptional output of the local clock and systemic neuroendocrine signals from the master clock, which may contribute to a modulated metabolic output that can be reflected by a reprogrammed circadian transcriptome [33, 36].

Follow up studies by Panda and colleagues further demonstrated that mice fed on a time-restricted schedule during the dark phase of the day were protected from obesity, glucose intolerance, hyperinsulinemia, leptin resistance, and steatohepatitis that occur in mice fed on high-fat or high-sugar diets [37, 38]. Mice on time-restricted feeding showed these metabolic benefits without reducing the total amount of caloric intake, but exhibited changes in the liver and serum metabolome that suggested an improved energy expenditure [37, 38]. Remarkably, by switching to time-restricted dark-phase feeding, mice with diet-induced obesity and type 2 diabetes showed reduced body weight and reversed progression of metabolic diseases [38]. These observations are similar to earlier findings that time-restricted feeding during the dark reduced weight gain in obese rats with deficient leptin receptors without changing their total caloric intake [39]. Together, these findings in different animal models suggest restricting feeding to the right time of the day is both preventive and therapeutic to metabolic insults induced by unhealthy diet and genetic deficiency.

## Studies in humans

The importance of feeding time in body weight regulation suggested by animal studies has led to studies in humans to understand the effects on body weight when calories are consumed at different times of the day. Garaulet, Scheer, and colleagues have studied the effects of mealtime in 420 subjects (49.5% female) participating in a 20-week weight-loss treatment program and found that subjects who ate their daily main meal at earlier times of the day showed a more rapid loss of body weight [40]. Remarkably, similar to what has been observed in animal models, early eaters and late eaters showed similar energy intake, dietary

composition, and estimated energy expenditure [40], suggesting a better metabolic balance in early eaters. Importantly, associations between a late mealtime and reduced effectiveness of bariatric surgery in the treatment of severe obesity have been reported in a group of 270 patients [41]. Furthermore, a later “chronotype” (i.e., habitual timing of sleep/wake and fast/feed) has been associated with higher body mass index and body fat content in the general population [42, 43], providing further support for a link between the late eating time and an adverse outcome in body weight regulation in normal as well as obese subjects. It is important to note that, due to individual differences in circadian timing in humans, eating at a late clock time in individuals whose circadian timing is significantly later than normal does not necessarily equal to eating at a “wrong time” of the day. A recent study addressed this particular issue by using the timing of melatonin release as a marker of the endogenous circadian time, and showed that increased body fat content was associated with the circadian timing, rather than the clock time, of food intake [44].

From a historical perspective, it is interesting to note that, in the 1950s, taking a large portion of the daily caloric intake (>25%) at a time much later than normal had been described in a group of obese individuals seeking weight loss treatment [45]. This abnormal eating pattern, termed night eating disorder (NED), is characterized by recurrent episodes of night eating, either consuming a large number of calories after dinnertime or eating after awakening from sleep at night. NED is estimated to occur in ~1.5% of the U.S. population, and the prevalence is significantly increased in obese patients, particularly during times of life stress and weight gain [46]. It is interesting to note that non-obese NED patients are overall very similar to obese NED patients in the self-reported eating behaviors, sleep quality, and mood, but are strikingly younger (by ~9 years) [47], implying that NED may contribute to the risk of obesity later in life. Future longitudinal studies are needed to test this intriguing hypothesis.

While associations between mealtime and body weight observed in the above-mentioned studies do not establish causality, recent studies have directly tested metabolic outcomes of distributing caloric intake at different times of the day. In an elegant study, Jakubowicz and colleagues compared obese women who were randomly assigned into two isocaloric weight-loss groups with high caloric intake occurring at either breakfast or dinner for 12 weeks [48]. They found consuming a large breakfast and a small dinner caused greater weight loss and greater improvements in multiple metabolic parameters compared to having a small breakfast and a large dinner [48]. In addition, a randomized, crossover clinical trial found that delaying dinner time close to the habitual bedtime, when circulating melatonin levels are rising, led to impaired glucose tolerance [49]. Interestingly, genetic variations in *MTNR1B*, a gene encoding a melatonin receptor, have been associated with risk of type 2 diabetes [50, 51], and subjects carrying the diabetic risk allele of *MTNR1B* showed augmented impairment of glucose tolerance when the dinner time was delayed close to the time of daily rise of melatonin levels [49]. These findings thus establish a causal role of late mealtime in adverse metabolic consequences and imply a potential underlying mechanism involving the circadian melatonin rhythms.

In addition to eating at a particularly late time of day, wrong-time feeding can result from frequent shifts of activity/rest (and thus feed/fast) schedules due to work and social

demands. According to a 2004 survey by the Bureau of Labor Statistics, 17.7% of US workers usually work alternate shifts that fall at least partially outside the daytime shift range [52]. The irregular work schedule is often associated with eating at a time of the day when a person would normally not be eating [53, 54]. Thus, the frequent occurrence of eating at the wrong time of day, in addition to factors such as unhealthy diets and insufficient sleep, could contribute to the higher risks of obesity, diabetes, and cardiovascular diseases observed in shift workers [53, 55]. In addition to shift work, eating time can be influenced by work and social demands in the form of “social jet lag”, a phrase used to describe weekly circadian phase shifts for an earlier sleep/wake time during workdays to accommodate work/social schedules and a later sleep/wake time during weekends, equivalent to traveling across time zones twice a week [56]. In a large study of Europeans, ~70% of the participants were found to have a social jet lag of at least 1 hour, and a more severe social jet lag was associated with a higher body mass index [57]. Thus, frequent circadian phase shifts may be linked to adverse effects on body weight regulation, similar to what has been found in those eating at the wrong time of day. In rats, adverse metabolic outcomes, including an increased weight gain, can result from a weekly “shift work” scenario, in which the rats are kept awake during the light phase 8 hours a day, 5 days a week, and are allowed to sleep *ad libitum* during the 2-day “weekends” [58]. Interestingly, these deficits were prevented by restricting food availability to the dark phase, suggesting that metabolic dysfunctions associated with chronic circadian phase shifts can be largely attributable to feeding at the wrong time of the day [58]. How much wrong-time eating contributes to the risk of obesity in shift workers and individuals with severe social jet lag remains an interesting topic for future studies.

### Influence of the sleep/wake cycle

In humans, hunger and appetite show circadian rhythms that can be desynchronized from the sleep/wake cycles [59]. Nevertheless, time of feeding is influenced to a large extent by the sleep/wake cycle, since, except for rare parasomnias, we do not eat while asleep. Sleep/wake influences body weight regulation and metabolic outcomes beyond its role in determining the timing of feeding. It has long been noted that insufficient sleep is associated with a higher body mass index and an increased risk of diabetes (for reviews, see [60–63]), similar to the circadian misalignment caused by a late chronotype, shift work, or social jet lag. In many cases, it is difficult to separate out the effects of circadian disruptions and sleep disturbances. Shift work and late sleep timing often lead to insufficient sleep [64, 65], which could be a contributing factor to the risk of obesity and metabolic dysfunction. Conversely, activity and eating can occur at the wrong circadian time when sleep time is restricted to a short window of time [66]. Under such conditions, the circadian phase of awakening (as measured by the time in relation to an endogenous timing marker, the rhythm in circulating melatonin levels) has been correlated with insulin insensitivity, indicating that circadian misalignment contributes to the metabolic challenge induced by restricted sleep time [66]. Interestingly, *Clock*<sup>-19</sup> mice, while overweight, also show a significant reduction in sleep of ~2 hours a day [67]. Indeed, sleep and the circadian clock are deeply embedded with each other at the molecular level, as mutations or deletions in almost all clock genes have been found to altered sleep architecture and/or homeostasis, in addition to changes in sleep timing

[68]. Thus, disruptions in the circadian rhythmicity and sleep often accompany each other, making it difficult to dissect the exact contribution of each process to metabolic health.

More recent studies have attempted to separate out the effects of a disrupted circadian organization from inadequate sleep by scheduling the time of sleep/wake across different circadian phases. Under a so-called “forced desynchrony” protocol in which sleep/wake and feed/fast cycles are scheduled into 28-hour days and thus are decoupled from the endogenous circadian timing system, subjects showed decreased leptin, increased glucose, and increased insulin levels on the days when eating and sleep occurred ~12-hour apart from habitual times [69]. While this study could not rule out the effects of a decreased sleep efficiency (i.e., percent time spent in sleep when in bed) during circadian misalignment, statistical analysis controlling the effects of lower sleep efficiency suggested an independent effect of circadian misalignment [69]. Only recently have sleep-independent contributions of the circadian misalignment to metabolic dysfunctions been directly assessed [70]. In this study by Van Cauter and colleagues, subjects were restricted to only 5 hours of sleep each day, which occurred either during the middle of habitual bedtime (i.e., circadian alignment) or 8.5 hours later during the daytime (i.e., circadian misalignment). Compared to unrestricted nights, 5-hour sleep restriction resulted in a decreased insulin sensitivity in both groups, but the decrease was doubled in circadian misaligned subjects compared to circadian aligned subjects, even though both groups slept almost identical amount during the 5-hour sleep window. This observation demonstrates an augmented metabolic disruption that is induced by circadian misalignment independent of sleep loss [70], providing critical evidence that challenges in metabolic balance and body weight regulation under conditions such as shift work, late chronotype, and social jet lag are likely to result from independent contributions of both insufficient sleep and circadian misalignment. Therefore, strategies that mitigate the impact of both sleep and circadian disruptions are needed in order to combat these health challenges sufficiently.

## Clock and other diseases

Critically, since the clock is functional in tissues across the body in addition to metabolic organs (Figure 1), the impact of circadian organization and disorganization to health and disease reaches far beyond metabolic balance and body weight regulation. Studies in both humans and animal models have linked circadian disruptions, either genetic (e.g., mutations in clock genes) or environmental (e.g., frequent circadian phase shifts), to a range of diseases, including cardiovascular disease, inflammatory bowel disease, other immune-related disorders (e.g., rheumatoid arthritis and asthma), various cancers, neurodegenerative disorders, psychiatric illness, cognitive impairment, and many others [17, 18]. In many cases, the circadian disruption acts as a “second hit” that exacerbates pathological insult. For example, disruptions of the circadian clock worsen toxin-induced colitis [71] and alcohol-induced “gut leakiness”, a deterioration in gastrointestinal barrier integrity [72]. Similarly, mutations in core clock genes promote tumorigenesis of radiation-induced lymphoma [73] as well as genetically induced lung adenoma and adenocarcinoma [74]. These genetic studies, in particular, begin to tie the clock machinery directly to the molecular cascades in the pathogenesis of tissue-specific disease states [18]. Similar to the bidirectional relationships between clock and energy metabolism, many of the links between the circadian

clock and disease-relevant pathways are also bidirectional. For instance, the oncogene *Myc* modulates the expression of a core clock gene, *Bmal1*, and this process is dysregulated in cancer leading to facilitated energy metabolism of tumor cells [75]. In turn, the degradation of MYC protein is regulated by the core clock protein CRY and a circadian clock modulator FBXL3 in a ubiquitin protein ligase complex [76]. Taken together, these findings suggest that the circadian clock is linked to many cellular pathways key to disease pathology.

This new and fast-growing area of research integrating circadian biology as a key component of biomedical research, although still in its infancy, is expected to pave the way for the use of circadian principles for the treatment and prevention of various diseases. Circadian transcriptomic studies have indeed revealed a large number of rhythmically expressed genes that are targets and metabolic enzymes of best-selling drugs [14], providing support to earlier circadian pharmacokinetics observations that an optimal treatment outcome can benefit from drug administration at a certain time of the day [77, 78]. In addition, an improved understanding of the interrelationships between the circadian clock and disease pathways could reveal novel treatment targets for drug development, as demonstrated by a recent study showing that treating obese mice with a clock-targeting drug controls body weight and alleviates metabolic dysfunctions in a clock-dependent manner [79]. In addition, a study in flies has demonstrated that caloric-restriction-induced lifespan extension requires an intact clock [80], adding new insights into the long-known bidirectional links between the circadian clock and aging [81–83], a strong risk factor for a wide range of diseases [84]. Thus, from a disease prevention perspective, it is important to further explore how a robust and well-coordinated circadian system may contribute to healthy aging and how a disrupted circadian clock system may contribute to age-related diseases as well as to the process of aging itself.

### Circadian coordination beyond tissues and organs

A critical concept in understanding the role of circadian clock in health and disease is that the circadian synchronization and coordination, which lead to the harmonious timing across molecular pathways within a cell, across cells of related functions in a tissue, and across different tissues and organs throughout our body, are important for maintaining good health. Recent studies have extended this concept of circadian synchronization and coordination beyond the cells of our body. The gut microbiota, the collective community of thousands of microbial species living in the mammalian gastrointestinal tract, has been shown to interact with the digestive, metabolic, immune, and even neuropsychiatric and cognitive functions of the host, and a disrupted microbiota has been linked to a wide range of diseases [85, 86]. Interestingly, disruption of the circadian clock by weekly light-dark inversions results in a deviation from the normal microbiota in mice [87], similar to later findings in animals with genetic defects of clock genes [88–90]. Indeed, the gut microbial composition varies with a diurnal rhythm that is regulated by the host circadian clock and feeding time [89–92]. Conversely, peripheral clocks and the circadian transcriptome are modulated in the absence of gut microbiota [91, 93, 94]. While most of the microbiota studies focused on the intestinal microbiota, studies have demonstrated that altered microbiota at other parts of the gastrointestinal tract, such as the oral cavity, have also been linked to obesity and metabolic dysfunction [95–97]. A recent randomized, crossover study examined microbiota in the



saliva samples from young, healthy women and found that the salivary microbial relative abundance and diversity exhibited circadian rhythms and the timing of the rhythms were influenced by the mealtime [98].

At this time, it is not clear whether at least some microbial species living in the mammalian gastrointestinal tract can endogenously generate their own ~24-hour rhythms in the absence of any timing cue from the host organism [99, 100]. This is a distinct possibility since it is known that the freely living cyanobacteria are capable of generating endogenous circadian rhythms [101]. Whether or not some microbial groups in the gastrointestinal tract have their own internal circadian clocks, these recent observations of interactions between gut microbiota and host circadian rhythms raise an intriguing hypothesis that many of the adverse effects of clock disruption may be due, in part, to the impact of an altered diversity and/or composition of gut microbiota. This is likely true at least for metabolic dysfunctions induced by jet lag, as transplantation of the fecal material from jet-lagged human subjects to germ-free mice leads to obesity and glucose intolerance similar to circadian disrupted mice [89]. Whether the gut microbiota and the pathways through which it interacts with the host can be a point of intervention to mitigate adverse health consequences associated with circadian disruptions, such as in shift work and social jet lag, remains an interesting and important subject for future studies.

## Conclusions

The continuing accumulation of evidence linking the molecular clock machinery to a wide range of cellular pathways that play a central role in many diseases has now raised a new challenge to today's circadian biomedical community: how to take advantage of these enormous advances and utilize them in clinical practice, particularly in the age of precision and personalized medicine. At the forefront of this challenge is the lack of reliable and easily accessible circadian biomarkers. Even in areas where some progress has been made towards using circadian principles in clinical practice, such as in the case of circadian pharmacokinetics [77], the full potential of circadian-timed treatment cannot be achieved without knowing precisely the internal circadian timing of the patient, especially given the diversity in human chorotypes [102]. Although transcriptomic and metabolomic studies have demonstrated in principle that it is possible to infer endogenous timing by accessing the omics at only one time point [103, 104], very limited progress has been made toward developing cost-effective technologies that rely on a smaller set of biomarkers and can be applied in a convenient manner in the clinic on a routine basis. Furthermore, it has not been demonstrated whether such methods can provide useful information regarding the exact nature of circadian disruptions, such as lost or reprogrammed rhythmicity of disease-relevant pathways as well as internal desynchrony among organs, which can be used to aid disease diagnosis or define characteristic subpopulations of certain diseases. Nevertheless, with the rapid advances in systems biology, information technologies, and wearable or implantable biosensors, it can be expected that it will be possible in the near future to continuously monitor an array of circadian biomarkers in real-time to assist medical professionals in many aspects of clinical practice from diagnosis to treatment and patient care. Perhaps the awarding of the Nobel Prize in Physiology or Medicine will inspire circadian researchers to more rapidly advance this new frontier of medicine, circadian medicine, so that it can be

fully integrated into standard clinical practice, a necessity for medicine to be truly precise and personalized.

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### Highlights

- A disrupted the circadian clock is linked to adverse outcomes in energy metabolism.
- Circadian coordination across tissues are important for health and disease.
- Precision medicine may benefit from incorporation of circadian timing.

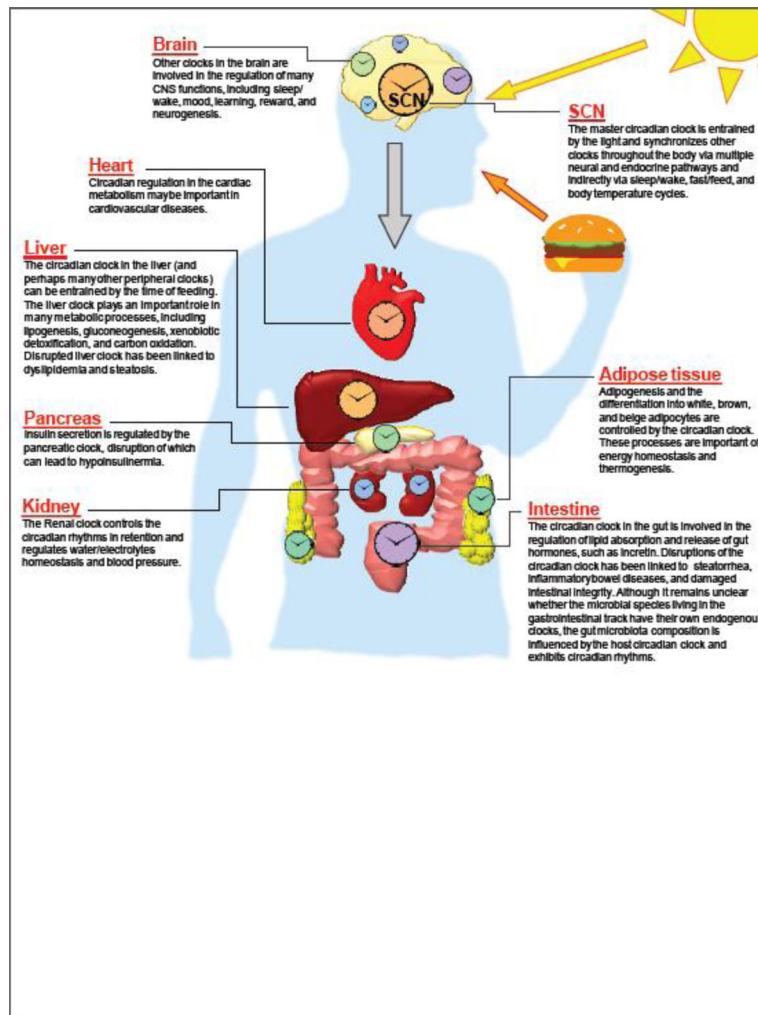
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**Figure 1. Coordinated circadian timing in tissues across the human body**

In humans, a master circadian clock located in the SCN of the brain synchronizes downstream clocks in cells throughout the body, regulating a wide range of tissue-specific functions. Health problems may occur when the synchronization and coordination of the circadian programs among tissues are disrupted.