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NURTURING OUR BIOLOGICAL CLOCKS: WHY TIMING MATTERS

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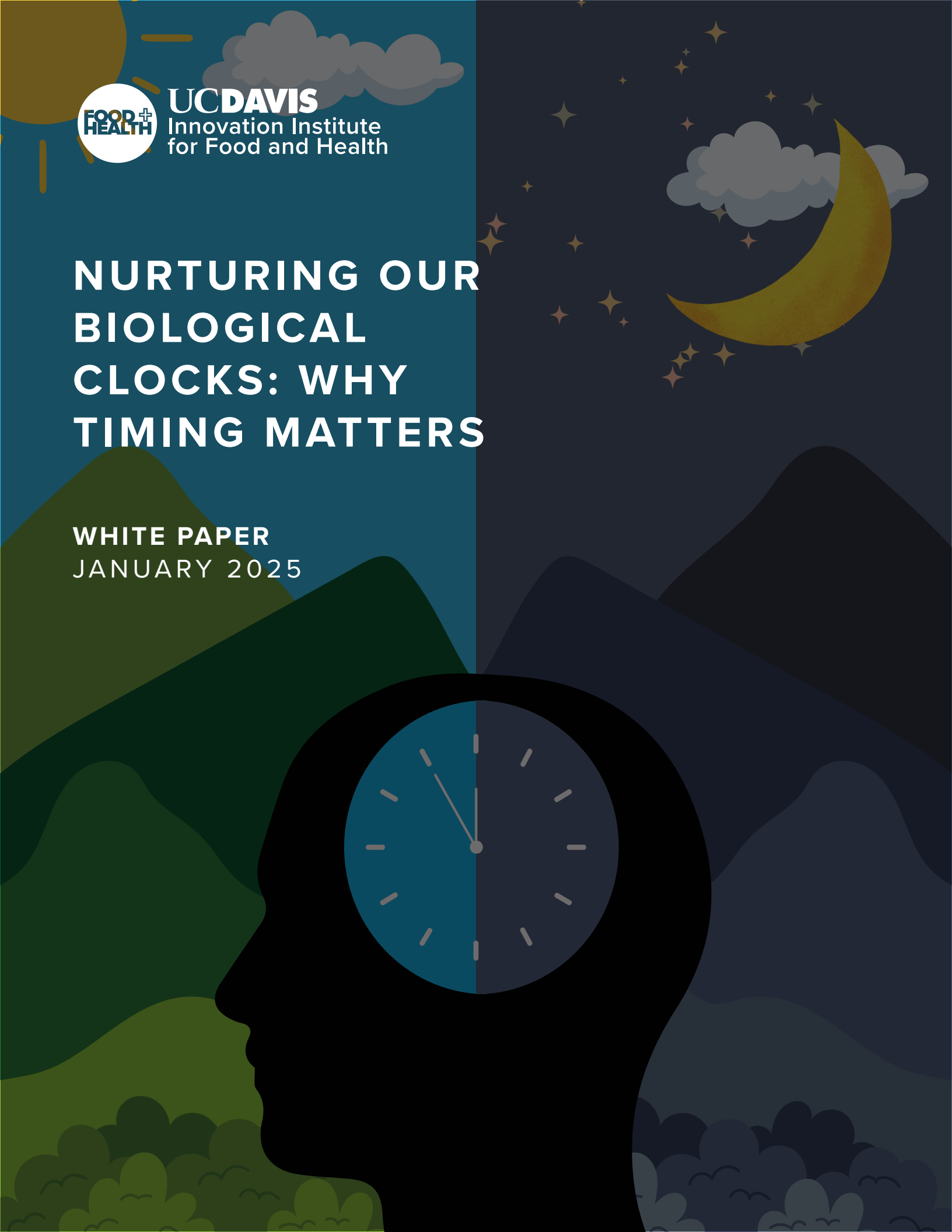

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EXECUTIVE SUMMARY

Nurturing Our Biological Clocks—Why Timing Matters

Circadian rhythms are intrinsic 24-hour cycles that regulate physiological and behavioral processes in almost all organisms, from the simplest bacteria to humans. Governed by internal biological clocks, these rhythms help organisms anticipate and adapt to predictable environmental changes, particularly the day-night cycle. In humans, circadian rhythms influence a wide array of functions, including sleep-wake cycles, hormone secretion, metabolism, digestion, cognitive performance, mood, and overall well-being.

However, modern lifestyles—marked by irregular schedules, shift work, jetlag and constant exposure to artificial lighting—can disrupt these finely tuned rhythms. Such disruptions are linked to various health challenges, including sleep disorders, metabolic imbalances, mental health conditions, and chronic diseases, underscoring the urgent need to realign daily routines with our biological clocks to promote health and overall well-being.

Organization of Biological Clocks

The human body’s internal clock system is organized in a hierarchy, with a "master clock" located in a part of the brain called the suprachiasmatic nucleus (SCN) in the hypothalamus. This master clock synchronizes with external environmental cues, primarily light, received through photoreceptors in the retina. Peripheral clocks exist in nearly every organ and tissue, functioning independently yet in coordination with the SCN. These clocks regulate local physiological processes, ensuring that functions like glucose metabolism, fat storage, and hormone release occur

optimally. At the molecular level, circadian rhythms are controlled by feedback loops involving key clock genes and proteins, such as CLOCK, BMAL1, PER, and CRY. These molecular mechanisms generate rhythmic patterns of gene expression that control downstream pathways affecting various physiological processes.

Circadian Clocks, Nutrition, and Metabolism

The relationship between circadian rhythms and metabolism is complex and bidirectional. Nutritional cues, such as the timing of food intake, can influence the pace of peripheral clocks located throughout our body, resetting processes like blood sugar control and fat metabolism. Conversely, the circadian system regulates metabolism by controlling the daily activity of genes involved in detecting nutrients and balancing energy.

Emerging evidence highlights the health promoting role of lifestyle and dietary interventions in realigning our body with circadian rhythms. Among these, Time-Restricted Eating (TRE) has garnered significant attention. By aligning food intake with periods of peak metabolic efficiency—typically within a consistent 8-10 hour daytime window—TRE can mitigate circadian disruption and enhance metabolic health. Benefits include improved blood sugar regulation, optimized fat metabolism, better energy balance, and reduced risks of obesity, type 2 diabetes, and cardiovascular diseases.

Beyond meal timing, the use of chronobiotics—substances that influence the timing and function of biological clocks—represent an exciting frontier in circadian health optimization. These include nutrients, bioactive compounds, and metabolites capable of resetting or modulating circadian rhythms. Compounds like caffeine, nobiletin (a flavonoid from citrus fruits), and theophylline have been shown to influence clock gene expression, stabilizing or enhancing circadian rhythms. For instance, nobiletin strengthens circadian oscillations and may help manage rhythm-related disorders, such as jet lag and mood disturbances. Therefore, the discovery and characterization of novel food compounds with chronobiotic properties offer promising opportunities to support circadian and overall health.

Measuring and Enhancing Circadian Rhythms

Accurately measuring circadian rhythms is essential for understanding individual biological clocks and tailoring interventions to optimize health outcomes. Traditional methods include tracking sleep-wake cycles, hormonal fluctuations such as melatonin onset (DLMO), core body temperature patterns, and analyzing circadian gene expression profiles. These measures provide insight into an individual's circadian profile, our chronotype — whether we are naturally inclined toward being a "morning person" or a "night owl."

Recent technological advancements have revolutionized the assessment of circadian rhythms. Wearable devices, such as smartwatches and fitness trackers, now offer non-invasive ways to monitor sleep, activity, and heart rate patterns, providing a window into circadian alignment. Additionally, molecular diagnostic tools, including skin and saliva tests, enable the identification of biomarkers associated with circadian phase and gene activity. These innovations allow for real-time, personalized analysis of circadian health, paving the way for tailored chronotherapeutic strategies.

Applications in Circadian Medicine

Leveraging circadian biology principles opens the door to innovative approaches for improving health and well-being. Chronotherapy, which involves synchronizing medical treatments and lifestyle interventions with the body’s natural rhythms, enhances treatment effectiveness while minimizing side effects.

For example, the timing of drug administration significantly influences outcomes. Medications for conditions like hypertension, diabetes, and cancer are more effective and have fewer adverse effects when administered at specific circadian phases.

Similarly, light therapy, a cornerstone of circadian intervention, uses scheduled exposure to bright light to realign disrupted rhythms. It has proven beneficial for individuals with Seasonal Affective Disorder (SAD), circadian rhythm sleep disorders, and cancer patients experiencing chemotherapy-induced fatigue. Melatonin supplementation, when timed appropriately, also offers a potent tool for resetting disrupted circadian rhythms in cases of jet lag or shift work misalignment.

Furthermore, advances in molecular biology are uncovering new opportunities to target the circadian clock directly. The characterization of novel pharmacological agents modulating the activity of clock genes and proteins (e.g., REV-ERBs, RORs, and casein kinases) holds immense potential for developing treatments for circadian-related disorders and enhancing overall well-being.

Conclusion

Understanding and nurturing our circadian rhythms is vital for maintaining health and well-being in an increasingly fast-paced world. As research progresses, integrating circadian biology into healthcare strategies holds tremendous potential to improve the prevention and management of various health conditions. Aligning lifestyle choices, nutritional habits, and therapeutic interventions with our biological clocks can lead to improved metabolic health, mental well-being, and overall quality of life.

INTRODUCTION

Life on Earth has been profoundly shaped by one of the most predictable features of our world: the rhythmic shifts between day and night. Nearly all organisms including plants, animals, and even bacteria exhibit circadian rhythms. These 24-hour endogenous rhythms arise from internal biological clocks, allow organisms to anticipate environmental changes and adapt biological functions to the cyclical nature of our environment.

Circadian rhythms are crucial in our daily routine, impacting nearly every aspect of our lives from sleep to alertness, mood, reproduction, digestion, cognitive performance and beyond. Consider a person who works a traditional 9-to-5 job. Their biological clock naturally prepares them to wake up in the morning by gradually increasing levels of the stress hormone cortisol before dawn, helping them feel alert and ready to start the day. During the day, their body temperature and cognitive functions peak, aligning with work demands. As evening approaches and light decreases, levels of the sleep hormone melatonin rise, signaling that it's time to wind down and prepare for sleep.

Biological clocks not only help us act appropriately at the right times and optimize daily activities but also provide internal temporal organization, coordinating various biological functions to maintain overall health and well-being [1]. Numerous physiological processes exhibit circadian rhythmicity, including body temperature, endocrine signaling, immune response, as well as behavior such as eating/fasting, sleep/wakefulness, cognition and mood [2].

Synchrony of internal biological processes with the external environment is essential for an organism's well-being and survival. Despite their remarkable ability to produce self-sustained oscillations, our biological

clocks must be entrained by environmental time cues to align with local time [3]. In mammals, light, food and physical activity, constitute the most robust synchronizing cues. It is therefore not surprising that numerous factors associated with modern lifestyles, such as artificial lighting, jet lag, shift work, and 24-hour access to energy-dense foods, are now known to disrupt our circadian clocks, and have detrimental effects on our health and well-being.

A red-eye flight from New York City to Paris offers a firsthand experience of the consequences of misalignment between your internal rhythms and the new time zone. Our circadian rhythm becomes out of sync with the local time of our new destination as it is still tuned to our pre-travel time zone. As our body struggles to adjust to the sudden shift (approximately 24 hours for each hour of time zone change), we may find ourselves battling fatigue, having difficulty concentrating, experiencing digestive upsets and anxiety.

Over the long term, misalignment between our internal clocks and our environment is linked to a wide range of pathological conditions including increased risk for cardiovascular disease, metabolic diseases (obesity, type 2 diabetes, etc.), infectious diseases, cognitive and neurodegenerative diseases, infertility, and cancer. This underscores the importance of our internal clocks in maintaining overall health and well-being [4], [5], [6].

So, what can we do to prevent circadian disruption and mitigate the deleterious health consequences associated with it? Is this irreversible? How does the relationship between circadian rhythmicity and nutrition impact our healthspan and lifespan? Can this knowledge be leveraged to establish dietary recommendations that align meal timing with circadian rhythms to prevent obesity and metabolic diseases? Can we even assess our circadian rhythmicity? What are the tools that are currently available? Can we develop personalized chronotherapeutic strategies that consider a person's unique circadian profile to optimize our overall health and well-being?

While answers to these questions are beginning to emerge as we unravel the intricate connections between the circadian clock, nutrition, and metabolism, much remains to be discovered about the inner mechanisms driving these complex interactions. As researchers around the world continue to build on Nobel prize winning discoveries that shape our current understanding of the biological clock, let's examine the central role circadian rhythms have on physiology and explore their potential implications for improving human health.

ORGANIZATION OF THE BIOLOGICAL CLOCKS

Conceptually, a biological clock can be broken down into three key elements:

i. sensors that detect environmental cues like light, temperature, or food
ii. an internal oscillator, made up of genes and proteins that constitute the gears of the clock and drives rhythm
iii. output pathways that allow the clock to regulate downstream molecular processes, influencing behavior and bodily functions [7], [8]

In mammals, including humans, the organization of the circadian clock involves a hierarchical structure with a central oscillator acting as a master clock located in the suprachiasmatic nucleus (SCN) of the hypothalamus [9] (Figure. 1). By receiving direct input about light exposure — mainly through the activation of retinal blue light sensitive photoreceptors named melanopsin [10] — the SCN synchronizes the internal body clock with the external environment.

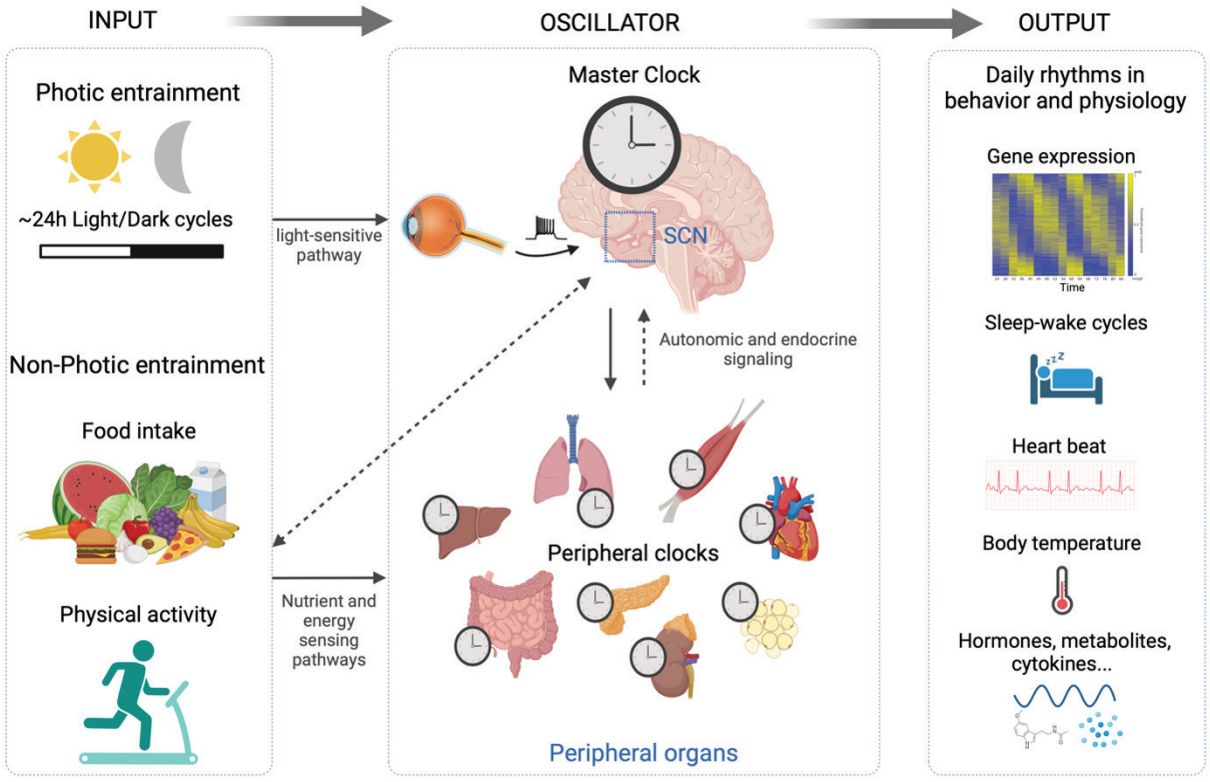

Figure 1. Hierarchical organization of the mammalian circadian system. Each cell of an organ houses its own molecular clock that synchronize through photic and non-photic time cues to drives rhythms in behavior and physiology. Direct projection from the retina transfers information about light and dark cycles (primary Zeitgeber) to the master clock or central pacemaker, located in the suprachiasmatic nuclei (SCN), synchronizing its phase with the external environment. Peripheral oscillators spread across most organs and tissues are entrained and synchronized via i) endocrine and neural signals received from SCN as well as ii) direct and indirect input from non-photic cues including food intake and physical activity. Outputs from peripheral tissues feedback to the master clock in the brain and stabilize circadian synchrony between oscillators. Integration of external signals, collective output of tissue clocks, and rhythmic endocrine and neural signals, ensure the temporal coordination of physiological and behavioral circadian rhythms (adapted from [11]. Created in Biorender.com.)

At the molecular level, the gears of the clock consist of a handful of key genes and proteins that collaborate to drive rhythmic oscillation in gene expression [12] (Figure. 2).

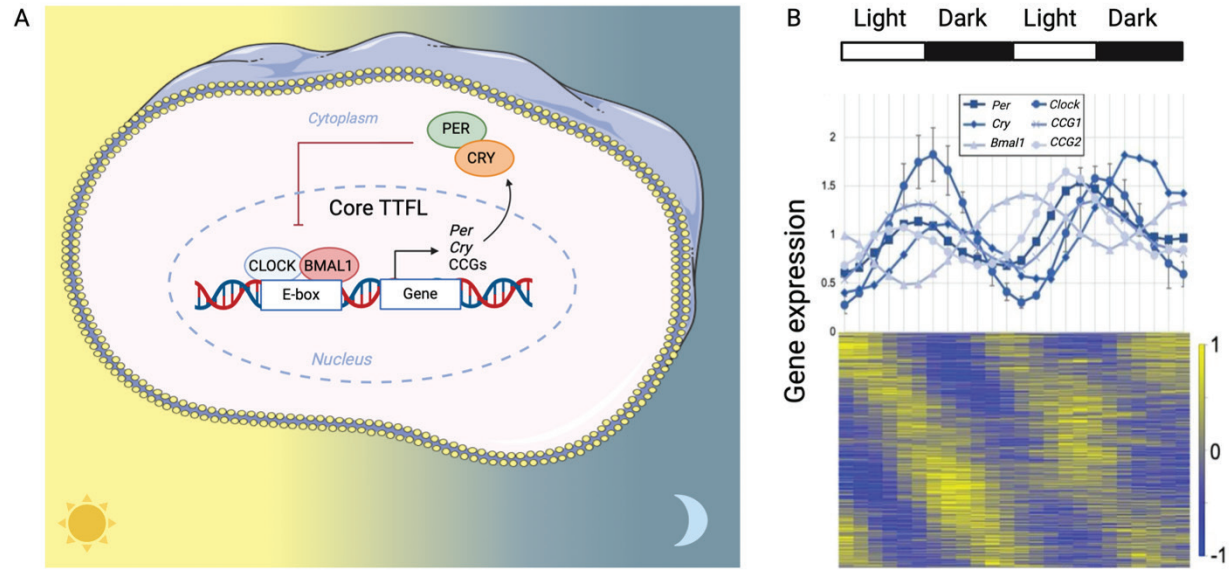

Figure 2. Simplified representation of the molecular circadian clock in mammals. A. The transcriptional-translational feedback loop (TTFL) involves core clock genes and proteins that create a self-sustaining cycle through their synchronization by external time cues. The CLOCK and BMAL1 proteins form a complex that promotes the transcription of Per and Cry genes as well as other clock-controlled genes (CCGs). The resulting PER and CRY proteins accumulate, dimerize, and inhibit CLOCK and BMAL1 activity, reducing their own gene expression. As PER and CRY proteins degrade, the inhibition is lifted, and the cycle restarts. B. Daily oscillation in clock gene expression drives rhythmic expression in CCGs to create organ-specific rhythmic physiological responses. (Adapted from [13], [14], Created in Biorender.com).

This rhythmic pattern in gene expression controls downstream molecular pathways, influencing a wide range of physiological processes such as sleep-wake cycles, hormone release, metabolism, and cell cycle regulation [1], [15]. The precise timing provided by the molecular clock ensures that these biological functions align with the day-night cycle, maintaining homeostasis and promoting overall health [16], [17]. Despite the central role of the master clock in the SCN, circadian gene expression is not confined to the brain; it is pervasive throughout the body. Most peripheral organs and tissues possess their own circadian clocks, generating and maintaining rhythmic oscillations independently [18]. Different tissues' peripheral clocks manage relevant physiological functions, such as glucose production, fat storage, and hormone release [19]. Thus, if each individual cell has its own circadian clock, how do these multiple clocks manage to be entrained by external cues and synchronize effectively? In fact, beyond photic entrainment by the SCN these peripheral clocks can be synchronized

by various environmental factors including food consumption, physical activity, and temperature [20]. This multi-layered organization ensures that physiological processes such as metabolism, hormone release, and cell regeneration are tightly regulated in a coordinated manner, forming a robust yet flexible circadian timing system [21].

CIRCADIAN CLOCK, NUTRITION AND METABOLISM

The circadian system plays an extensive role in the intricate relationship between food and metabolism. In addition to the day-night cycles, it is increasingly recognized that food intake can entrain and reset our peripheral clocks which in turn organizes energy homeostasis, including food intake, fat accumulation, and caloric expenditure [22], [23], [24], [25]. Reciprocal interactions between clock factors and the regulators of intracellular metabolism take place at many levels. First, through the action of clock proteins themselves with components of the molecular clockwork exhibiting metabolic functions [26]. This is the case of the circadian transcription factors 'retinoic acid receptor-related orphan receptors' (RORs) and REV-ERBs (nuclear receptors) that also control the expression of genes involved in lipid metabolism in peripheral tissues. Similarly, the protein 'CLOCK', in addition to its role in the feedback loop, can modify the activity of various proteins including Glucocorticoid receptors. Secondly, many regulators of intracellular metabolism are controlled by clock proteins [26], [27], [28]. Key metabolic and nutrient sensors under circadian regulation include:

- Transcription factors activated by fatty acids, such as peroxisome proliferator-activated receptors (PPARs)

- AMP-activated protein kinase (AMPK), a central regulator of energy balance that responds to changes in cellular energy status, such as low adenosine triphosphate (ATP) levels

- Sirtuins, in particular SIRT1, is a key regulator of several metabolic processes including gluconeogenesis, lipid metabolism, and insulin sensitivity and targets several factors involved in the maintenance of nutrient flux

- Nuclear Factor Erythroid 2-Related Factor 2 (NRF2) that regulates the expression of antioxidant and detoxification genes, protecting cells from oxidative stress

- Mammalian Target of Rapamycin (mTOR) signaling coordinating nutrient availability with cellular growth and metabolism

Some of these metabolic regulators can also send feedback to the molecular clock, adjusting its rhythmic patterns both positively and negatively [29], [30]. Targeting these nutrient-sensing pathways remains challenging given their many roles and wide variety of functions. However, evidence is accumulating regarding the role of specific nutrients, bioactive food compounds and metabolites harboring chronobiotic effect, on circadian rhythm and clock gene expression [31]. Results from in vitro and animal studies suggest that single nutrients such as sodium, amino acids, caffeine, cinnamic acid, nobiletin, palmitate, theophylline, thiamine, ethanol, and retinoic acid can reset or phase-shift circadian rhythms [32], [33]. Whether these findings can translate to humans remains to be determined but they surely open the way to more advanced strategies in precision nutrition to enhance circadian and metabolic health. For example, nobiletin (NOB), a polymethoxy flavone (a type of flavonoid) commonly found in citrus fruits, helps regulate circadian rhythms by enhancing the amplitude of clock gene rhythms within cells. As a result, foods rich in polymethoxy flavones like NOB may offer benefits for managing circadian rhythm disorders, alleviating symptoms of jet lag, and potentially aiding in the treatment of mood disorders.

While the master clock in the SCN is primarily driven by light and less directly responsive to food intake compared to the peripheral clocks, it still plays a significant role in regulating eating behavior and metabolic processes indirectly through feedback mechanisms. The SCN helps to establish the timing of eating behaviors, largely through its regulation of hormones and neurotransmitters that signal hunger and satiety. For example, it coordinates the release of ghrelin (a hunger hormone) and

leptin (a satiety hormone) in a circadian manner. This synchronization between the central and the peripheral clocks ensures that eating patterns occur during periods when the body is most prepared to process food efficiently. Additionally, the SCN can influence the timing of insulin and amylin release, hormones essential for glucose metabolism and energy storage, by sending signals to peripheral clocks [34], [35], [36]. Through these feedback mechanisms, the SCN essentially helps coordinate the body's anticipation of food and prepares the metabolic system to process nutrients at optimal times thus maintaining energy balance and overall metabolic health [4], [15], [16], [17].

This intricate relationship between the circadian machinery, nutrition, and metabolism implies that the dysregulation of one system can impact the others, instigating a vicious cycle. Multiple lines of evidence have demonstrated a reciprocal association between circadian disruption, obesity, insulin resistance and type 2 diabetes [36], [38]. Then, what can we do about it? Can this reciprocal relationship linking the circadian system to metabolism be leveraged to implement dietary recommendations that enhance circadian health and prevent metabolic diseases?

The regularity and timing of food intake are essential not only to maintain a balanced metabolism but also to reinforce its circadian rhythmicity. Emerging behavioral interventions, such TRE, involve limiting calorie intake to an 8 to 10-hour window during the daytime. This approach helps reduce circadian disruption and its related diseases by improving coordination between the body's main clock and other internal clocks, ensuring processes like blood sugar control and fat production happen at the right times [21], [22], [23], [24]. Studies in both animals and humans have demonstrated the benefits of TRE. For instance, research in mice has shown that restricting food intake to specific periods can prevent obesity and metabolic diseases, even when the total calorie intake remains unchanged [21], [23], [25]. Similarly, in humans, on-going clinical studies including cohorts subject to chronic circadian disruption such as shift-workers, indicate that TRE can lead to weight loss, improved insulin sensitivity, and better overall metabolic health [25].

On the pharmacological side, targeting Glucagon-like peptide-1 (GLP-1) pathway holds significant potential in chronotherapy for diabetes given its role in the regulation of blood glucose levels and interaction with the circadian system. Recent research suggests that GLP-1 secretion and receptor sensitivity exhibit circadian variations, which could be leveraged to optimize the timing of GLP-1-based therapies [39]. Administering GLP-1 receptor agonists in alignment with patient circadian rhythms may improve glycemic control and reduce the risk of side effects. This approach could be particularly beneficial in managing diabetes by synchronizing medication with the body's natural metabolic cycles, ultimately leading to more personalized and effective treatment regimens. Furthermore, the development of individual Circadian Rhythm (CR) profiling to monitor and better understand the timing of GLP-1 activity is expected to help the design of meal plans and lifestyle interventions that support circadian health. Thereby improving overall metabolic outcomes for diabetic patients.

An additional growing area of research resides in understanding the effects that our microbiome exerts on the timing of our physiological processes and overall health. Diurnal (i.e., 24-hour) oscillations in the composition of gut microbial communities, their localization across the digestive tract as well as in the release of secondary metabolites produced by gut microbes, have been described in various species including mice and humans [40], [41], [42]. These oscillations are thought to be driven by both eating patterns and endogenous action of the host’s circadian system mediated by intestinal epithelial cells. Conversely, recent studies show that our gut microbiome plays an important role in the entrainment of intestinal and hepatic circadian rhythms that may contribute to the health benefits provided by TRE [43], [44]. The development of food products designed to promote gut health and enhance the production of metabolites that support circadian regulation holds untapped potential for improving overall well-being and optimizing metabolic functions.

CIRCADIAN DISRUPTION AND CONSEQUENCES ON HUMAN HEALTH

As mentioned earlier, lifestyle and environmental factors of modern societies such as artificial lighting, jet lag, shift work, irregular sleep patterns and 24-hour access to energy-dense foods, can disrupt our circadian clocks by creating conditions in which the feedback loops that regulate clock genes and proteins become desynchronized from the experienced light–dark cycle. This desynchrony results in irregular expression of output genes controlling essential physiological processes and leads to a host of adverse effect including, sleep disruption, increased susceptibility to stress and immune challenges, increased risk of cardiovascular and metabolic disease, and increased risk of cancer [5], [45], [46], [47]. Recognizing the significance of circadian rhythms in the prevalence of a wide range of conditions is expected to facilitate the development of effective and actionable measures to improve overall health and well-being. Although chronotherapeutic interventions offer significant potential to address a variety of conditions, their effectiveness depends on a thorough understanding of individual circadian rhythms to accurately time their application.

Implication in Stress and Anxiety

Circadian disruption affects how well we sleep, when we sleep and how we function while awake, translating to a wide range of circadian rhythm sleep disorders (CRSD). According to The International Classification of Sleep Disorders [48], CRSD could be classified into six distinct types including, delayed sleep phase type, advanced sleep phase type, irregular sleep wake phase type, free-running type, jet lag type, and shift work type. Depending on the type and severity of the disorder, individuals may experience impaired cognitive abilities, mood disturbances, increased stress levels and other symptoms characteristic of insomnia [49]. Circadian disruption due to

reduced sunlight exposure during fall and winter and alteration in melatonin levels also constitute one of the leading factors of Seasonal Affective Disorder (SAD) and its associated symptoms such as depression, anxiety, changes in appetite and/or weight gain [50].

Stress and anxiety are increasingly taking a toll on our daily lives, affecting our physical health, mental well-being, and overall quality of life. Integrating circadian biology into stress and anxiety management offers a novel approach to enhancing treatment efficacy. For instance, tailoring therapeutic interventions, such as cognitive-behavioral therapy, to times of day when patients are most receptive can improve outcomes. Similarly, optimizing the timing of pharmacological interventions including anxiolytic or antidepressant administration to align with the body's natural rhythms, can improve absorption and reduce side effects [51]. Melatonin supplementation and light therapy, particularly effective for conditions like SAD, can be used to reset the body’s internal clock, leading to more consistent sleep-wake cycles. These approaches not only improve mood by stabilizing serotonin and melatonin levels but also significantly reduces anxiety and other stress-related symptoms [52].

Implication in Women’s Fertility

The adverse effects of circadian misalignment on sleep extend way beyond its impact on mental and metabolic health and can have dramatic consequences on women’s reproductive function and outcome. The circadian system significantly influences women’s fertility, offering potential for chronotherapeutic interventions that may enhance female reproductive health. Pathologic sleep patterns are closely linked to menstrual irregularity, polycystic ovarian syndrome, premature ovarian insufficiency, sub/infertility, and early pregnancy loss. Additionally, shift work has been associated with lower rate of success in assisted reproductive technology as well as complication in pregnancy, including gestational diabetes and hypertensive disorders [53], [54], [55]. Interventions enhancing the circadian rhythmicity of reproductive hormones like estrogen and

progesterone can optimize the timing for conception, increasing the chances of success. Mitigating the circadian disruptions caused by shift work, consistent sleep patterns, light therapy and precision nutrition can help balance reproductive hormones, address irregularities in menstrual cycles and improve fertility [56]. In-vitro fertilization (IVF) treatments can be more effective when egg retrieval, embryo transfer, and hormone administration are aligned with natural rhythms. For instance, timely administration of exogenous melatonin can enhance egg quality by protecting oocytes from oxidative stress, thereby increasing the likelihood of successful fertilization and embryo development [57]. Moreover, maintaining stable circadian rhythms during pregnancy supports fetal development and reduces complications, highlighting the comprehensive role of circadian biology in women's fertility.

MEASURING CIRCADIAN RHYTHM

The measure of circadian rhythmicity, provide invaluable insights into the timing, strength, and regularity of a person's biological clock. These measurements help assess how well a person's internal rhythms align with the 24-hour day-night cycle and diagnose circadian rhythm disorders. It is increasingly recognized that circadian rhythms vary significantly between individuals, which can result in notable differences in the effectiveness of chronotherapeutic strategies. Understanding our chronotype — whether we are a morning or evening person — is essential for enhancing personalized chronotherapy.For instance, morning types may respond better to circadian-based interventions scheduled earlier in the day, while evening types might find later interventions more effective.

In humans, the measurement of circadian rhythms typically focuses on several key parameters including sleep-wake patterns, Dim-Light Melatonin Onset (DMLO), core body temperature, heart rate, blood pressure and gene expression.

Rest-activity cycles, which track periods of sleep and wakefulness, are crucial indicators of the circadian system's alignment with the day-night cycle [58]. One common method for assessing rest-activity cycles relies on actigraphy, which involves wearable devices equipped with accelerometers to monitor movement patterns. These non-invasive tools record periods of activity and inactivity, providing valuable data on sleep patterns and activity levels. Additionally, questionnaires such as the Morningness-Eveningness Questionnaire or the Munich Chronotype Questionnaire (MCTQ) are used to assess an individual's preferred sleep-wake times and chronotype, by reflecting their natural tendency for morning or evening activity [59], [60].

Complementary measurements of heart rate, blood pressure, body temperature, and hormone secretion offer further insights into circadian functions [61]. Among these, DMLO is considered the gold standard for evaluating circadian phase, as it provides a precise measure of the timing of melatonin secretion in response to low-light conditions [62]. By integrating these various methods, researchers and clinicians can gain a comprehensive understanding of an individual's circadian rhythm and its impact on overall health and well-being.

The phase, amplitude, and period of the circadian system can then be determined from variations in the levels of the output rhythms measured to detect potential abnormalities in rhythmicity informing us on the degree of circadian disruption or misalignment with the external environment [63]. Amplitude, which refers to the strength or magnitude of the circadian rhythm, can be assessed by evaluating fluctuations in body temperature or activity levels over a 24-hour period. For example, an increased amplitude in body temperature may reflect a robust circadian rhythm, while a reduced amplitude could signal a weakened rhythm [64], [65]. The period, or the length of one complete circadian cycle, is typically measured by observing patterns in rest-activity cycles or rhythm in hormone secretion, such as cortisol. Changes such as lengthening or shortening in the period of circadian outputs, can indicate disruptions in the circadian system. Similarly, the phase of circadian outputs, which refers to the specific timing of a biological process or physiological function within the 24-hour circadian cycle, is a major sign of circadian disruptions. For example, individuals experiencing jet lag or shift work may show significant shifts (advance or delay), desynchronization, and irregularities in the phase of their circadian outputs [22], [61], [66], [67] (Figure 3).

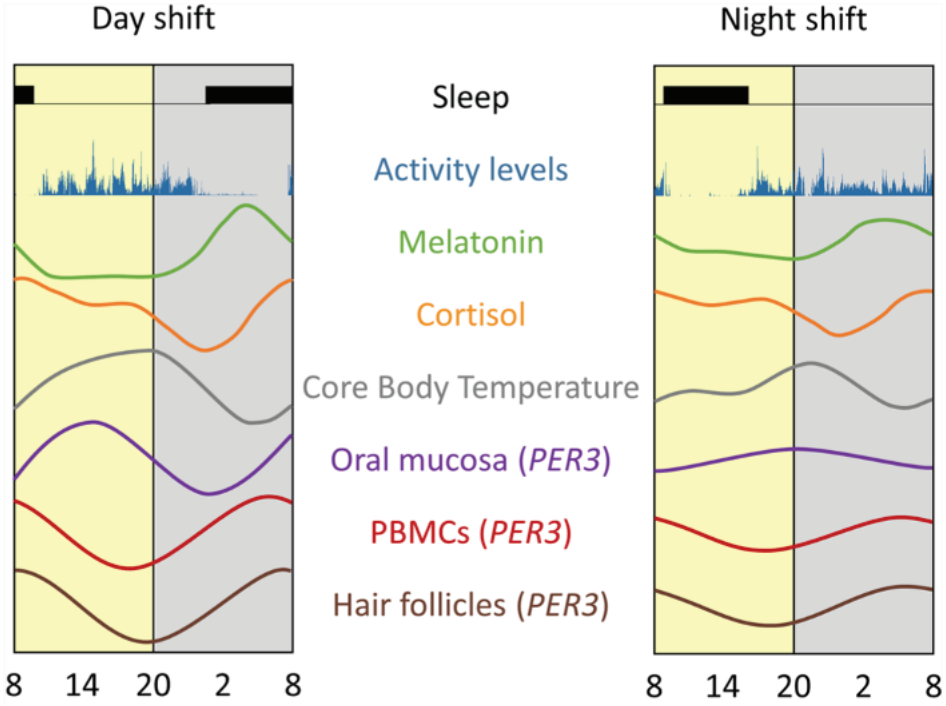

Figure 3. Disruption of central and peripheral rhythms by night-shift work. Under a night-oriented schedule, group rhythms are mis-aligned relative to the shifted rest-activity cycle and dampened in amplitude. yellow and gray rectangles represent the environmental light and dark cycles, respectively. from [68]

Assessment of circadian rhythmicity is not only expected to facilitate diagnosis of circadian disorders but is also critical to improve their treatment efficacy and long-term management through the implementation of appropriate interventions that realign the internal clock with the external environment. For those with circadian rhythm sleep-wake disorders, bright light therapy or melatonin administration can be used to achieve appropriate phase advances or delays. For example, evening light exposure, before the body's core temperature reaches its lowest point, causes phase delays, while morning light, after the temperature minimum, causes phase advances [69]. Light therapy can be used not only to treat circadian rhythm sleep-wake disorders but also as an adjunctive treatment for various medical conditions. For instance, scheduled bright light exposure has been shown to improve outcomes in cancer patients, particularly in reducing circadian disruption and fatigue during chemotherapy [70]. Additionally, in the ICU, patients typically experience low light exposure, which may affect their recovery. Increasing daytime

light exposure in this setting could potentially improve patient outcomes [71]. Similarly, melatonin can also be used to help reset the circadian clock. When given approximately 5 hours before DLMO, exogenous melatonin has been demonstrated to advance the circadian clock, while melatonin in the early morning can delay the circadian clock [72].

Precise circadian rhythm measurement also provides valuable insights in understanding the pathophysiology of circadian rhythm disorders. Clinicians commonly schedule circadian-based treatments based on rest-activity cycle, assuming a consistent phase relationship with other circadian outputs such as melatonin onset and core body temperature minimum. However, the absence of a delayed melatonin rhythm in some patients with delayed sleep-wake phase disorder can complicate the timing of treatments and lead to inconsistent outcomes highlighting the need for more robust and reliable circadian biomarkers [61].

In recent years there has been a surge in the development of emerging technologies designed to track and analyze circadian outputs in order to enhance our circadian rhythmicity [73]. Although the assessment of circadian outputs such as core body temperature, heart rate, blood pressure or activity levels have been facilitated by the development of more sophisticated wearable devices (smartwatch, ring, etc.), other approaches like DLMO profiling or more advanced sleep testing can be expensive, time-consuming and often require an overnight stay at the clinic which may interfere with the sleep time of the test person.

While these techniques remain helpful as they provide constant and accurate capture of circadian outputs over time, they are missing the underlying factor that generates these circa 24-hour rhythms: the circadian gene, transcript and protein network itself. Modeling circadian rhythms based on core-clock gene expression is inherently complex, expensive, and typically requires laboratory analysis and sampling methods that could be invasive. However, with the progress of omics technology and computational techniques, ongoing research is likely to yield more user-friendly and practicable methods for circadian rhythm profiling such as

those developed by SkinPhaser or Timeteller® platforms [74], [75], [76]. SkinPhaser is an open source and user-friendly application leveraging supervised learning technique to predict the molecular clock phase using expression values of 12 biomarker genes from a user's skin sample. With indication that the clock phase in the skin is a reliable predictor of the clock phase in other tissues, including the liver — a crucial organ involved in drug absorption, distribution, metabolism, and excretion — SkinPhaser holds significant potential for advancing circadian medicine. TimeTeller® is an diagnostic tool that allows it to profile individual circadian rhythm in a noninvasive and user-friendly way. It is based on the molecular characterization of the expression of core-clock genes and computational modeling of circadian time series from saliva samples to deliver personalized recommendations on lifestyle adjustment for optimizing health and treatment efficacy. Such approaches are expected to facilitate the validation of robust circadian biomarkers in relation to specific physiological functions, disease states and experimental designs. Moreover, inter-individual variations in circadian rhythmicity, influenced by personal lifestyle factors like mealtimes, light exposure, and exercise, as well as endogenous factors such as genetics, age, or sex, can now be identified with unparalleled precision. The ability to generate personalized circadian profiles based on molecular and computational analysis of circadian gene expression is anticipated to enhance the development of innovative approaches in preventive health and precision medicine.

APPLICATIONS IN CIRCADIAN MEDICINE

The identification of circadian biomarkers to assess rhythmicity may have a significant impact on the management of a wide range of medical conditions including allergies, arthritis, asthma, hyperlipidemia, hypertension, cancer, and neurodegenerative diseases [77], [78], [79]. This approach known as *chronotherapy* or *circadian medicine*, leverages the circadian rhythmicity of cellular processes to optimize treatment effectiveness and minimize side effects in drug development and administration. For instance, studies show that cancer cells exhibit different circadian rhythms compared to normal cells and that drug delivery can then be tailored to precise time windows when cancer cells are the most vulnerable and healthy cells are least sensitive, thereby reducing toxicity and enhancing efficacy [13], [80].

The validation of robust circadian biomarkers to predict clock phase in different tissues also holds major implications in drug development and therapeutic planning. Considering the influence of circadian rhythms on drug pharmacokinetics and pharmacodynamics, the timing of drug administration can have a significant impact on its absorption, distribution, metabolism, and excretion. Therefore, by aligning drug delivery with circadian peaks in metabolic activity, it may be possible to enhance drug efficacy and reduce toxicity [81]. The development of time-release formulations and more advanced programmable drug delivery devices such as chronomodulating infusion pumps and controlled-release microchip, enable precise control over when and how much medication is released into the body. By optimizing the timing of drug release, chronotherapeutic systems can not only enhance the effectiveness of treatments, but also improve patient adherence and reduce the risk of adverse effects, paving the way for more effective and individualized healthcare solutions.

Given the broad impact of circadian rhythms on physiology, another dimension of circadian medicine consists in directly targeting the circadian machinery itself. The choice of targets and the types of small molecule effectors can modify the clock in various ways, necessitating strategies tailored to the desired outcome. For instance, amplitudes of circadian rhythms tend to weaken in the elderly [82] and targeting pathways enhancing the amplitude of the circadian rhythm could promote better health as we age. Conversely, for sleep disorders caused by an extended circadian rhythm, drugs that advance the clock would be beneficial [83]. Additionally, in certain cancers such as glioblastoma, inhibiting the circadian clock may prevent the proliferation of cancer stem cells [84]. Several pathways involved in a wide range of diseases are being investigated, revealing drug candidates that show significant potential for manipulating core clock components. These include molecules targeting the activator of the TTFL, CLOCK and BMAL1 or its repressor PER and CRY. Other clock components forming part of the auxiliary circadian loop such as REV-ERBα/β, RORα/β/γ, and Casein kinase 1 (CK1) and CK2 have been identified and constitute promising candidates due to their key role in the regulation of circadian amplitude [78], [79], [83].

The pace of circadian clocks depends on the subcellular localization, transcriptional activity and stability of the clock proteins. These processes are mediated through post-translational modification consisting in a wide variety of small changes in proteins such as phosphorylation, acetylation, lipidation or glycosylation to name a few. Through their influence on the stability, structure, interaction and regulatory functions of the clock proteins, these modifications play a critical role in controlling the core mechanism of the circadian clock itself and constitute promising targets to fine-tune circadian oscillators [85], [86].

While these approaches show great promise, significant challenges lie in the specificity of these treatments. Considering the ubiquitous nature

of circadian regulation and the increasing evidence for inter-organ communication within the clock system, it is essential to investigate the functional effects, mechanistic pathways, and interventional strategies in an integrative manner to prevent unintended clock disruption in non-targeted tissues.

CONCLUSION

Harnessing the power of timing to enhance human health and well-being represents not just an exciting challenge but a critical frontier in modern science and medicine. The intricate interplay between central and peripheral clocks, shaped by both internal and external cues, is revealing a dynamic field with far-reaching implications for mitigating the widespread impact of circadian misalignment on metabolism, chronic disease, and overall health.

As we continue to unravel the complex relationships between circadian rhythms and the multitude of factors that influence them—such as metabolism, dietary patterns, nutrient composition, exercise, and pharmacology—addressing the significant knowledge gaps in these areas becomes ever more urgent. Understanding the precise mechanisms by which these elements interact with circadian clock components across various tissues holds the key to developing targeted nutritional, behavioral, and pharmacological strategies that could dramatically reduce the growing prevalence of metabolic disorders tied to circadian disruption.

Although animal models have provided critical insights into the molecular underpinnings of circadian biology, translating these findings into human biology remains paramount. Differences in activity patterns, metabolic rates, and physiological responses in nocturnal animals, such as mice, underscore the need for robust human studies to bridge the gap between basic research and clinical application. While emerging techniques for assessing circadian rhythms in humans hold great promise, they are still underutilized in clinical practice. Developing accessible, non-invasive, and cost-effective tools to monitor and assess circadian rhythms will be essential for unlocking the potential of circadian medicine and personalizing interventions for optimal health outcomes.

As these breakthroughs move closer to real-world application, the integration of user-friendly technologies to monitor our circadian biology offers individuals a powerful opportunity to take control of their health. By aligning our lifestyles with our body's natural rhythms, we can not only enhance personal well-being but also drive a paradigm shift in how we approach health and disease prevention on a broader scale.

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