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Circadian regulation of glucose, lipid, and energy metabolism in humans

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ABSTRACT

The circadian system orchestrates metabolism in daily 24-hour cycles. Such rhythms organize metabolism by temporally separating opposing metabolic processes and by anticipating recurring feeding-fasting cycles to increase metabolic efficiency. Although animal studies demonstrate that the circadian system plays a pervasive role in regulating metabolism, it is unclear how, and to what degree, circadian research in rodents translates into humans. Here, we review evidence that the circadian system regulates glucose, lipid, and energy metabolism in humans. Using a range of experimental protocols, studies in humans report circadian rhythms in glucose, insulin, glucose tolerance, lipid levels, energy expenditure, and appetite. Several of these rhythms peak in the biological morning or around noon, implicating earlier in the daytime is optimal for food intake. Importantly, disruptions in these rhythms impair metabolism and influence the pathogenesis of metabolic diseases. We therefore also review evidence that circadian misalignment induced by mistimed light exposure, sleep, or food intake adversely affects metabolic health in humans. These interconnections among the circadian system, metabolism, and behavior underscore the importance of chronobiology for preventing and treating type 2 diabetes, obesity, and hyperlipidemia.

1. Introduction

The circadian system organizes metabolism, physiology, and behavior in a daily cycle of *circadian rhythms*. *Circadian* derives from the Latin roots *circa* meaning *around* and *diēm* meaning *day*, and like all daily or *diurnal* rhythms, circadian rhythms are periodic patterns that repeat themselves approximately every 24 h. However, unlike diurnal rhythms, circadian rhythms are generated endogenously within the organism and perpetuate themselves even in the absence of external time cues (Fig. 1). Such circadian rhythms have evolved over hundreds of millions of years to orchestrate metabolism by temporally separating opposing metabolic processes (such as anabolism and catabolism) and by anticipating recurring feeding-fasting cycles to optimize metabolic efficiency [1–3].

The circadian system comprises a central pacemaker in the brain and a series of clocks in peripheral tissues throughout the body, including liver, muscle, and adipose

Abbreviations: CREB, cAMP response element binding protein; AMPK, adenosine monophosphate-activated protein kinase; SCN, suprachiasmatic nucleus; TTFL, transcriptional-translational feedback loop; CR, constant routine; FD, forced desynchrony; CA/M, circadian alignment/misalignment; h, hour; AUC, area under the curve; IRS-1, insulin receptor substrate-1; FFAs, free fatty acids; RQ, respiratory quotient; TEF, thermic effect of food; RCTs, randomized controlled trials; BMI, body mass index.

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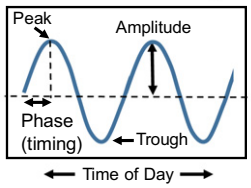
Diurnal Rhythms Glossary.

- **Diurnal Rhythm**: Any physiologic, behavioral, or other biological rhythm that repeats itself approximately every 24 hours.
- **Circadian Rhythm**: Any diurnal rhythm that is endogenously generated by an organism and that sustains itself even in the absence of light and other external cues.
- **Mesor**: The midline or mean of a rhythm.
- **Peak**: The highest value of a rhythm.
- **Trough or Nadir**: The lowest value of a rhythm.
- **Amplitude**: The magnitude or strength of a rhythm. This can be expressed as either a peak-to-mesor amplitude (as shown below) or a peak-to-trough amplitude. (In this review, we report amplitudes predominantly as peak-to-trough amplitudes.)
- **Phase**: The timing of a rhythm, which is defined relative to a key point in the rhythm (typically the peak or trough).
- **Acrophase**: The time at which a rhythm peaks.
- **Period**: The length of time that it takes a rhythm to repeat itself. Circadian rhythms have approximately 24-hour periods.

Structure of a Diurnal Rhythm



- **Entrainment**: The synchronization of a rhythm to an external or environmental cue.
- **Zietgeber**: An external cue that entrains or influences the phase of a rhythm.
- **Phase Advance**: A shift in the timing of a rhythm such that it begins earlier.
- **Phase Delay**: A shift in the timing of a rhythm such that it begins later.
- **Alignment:** The difference in phases between any two rhythms.
- **Misalignment** or **desynchrony**: The state of having an abnormal alignment or difference in phases between two rhythms. The two rhythms are said to be *misaligned* or mistimed.
- **Transcriptional-Translational Feedback Loop (TTFL):** A series of feedback loops among circadian clock genes and proteins that maintain the ~24 hour rhythms in nearly every cell of the body.

Fig. 1 – Diurnal rhythms glossary.

tissue. This system of clocks collectively modulates a wide array of metabolic targets, such as glucocorticoids [4], the master energy sensor AMPK [5], rate-limiting steps in fatty acid and cholesterol synthesis [6,7], and hepatic CREB to modulate gluconeogenesis [8]. The aggregate effect is that an array of metabolic processes—including insulin sensitivity, insulin secretion, cholesterol synthesis, fat oxidation, and energy expenditure—all follow a rhythm across the 24-hour day [2,3,9].

In addition to evidence of circadian rhythms in metabolism, data increasingly suggest that disruption of the circadian system increases the risk of metabolic diseases [9–12]. In rodent studies, clock gene mutants often display obese or diabetic phenotypes and possess defects in core metabolic pathways such as insulin secretion and gluconeogenesis [3,13–17]. Moreover, *misalignment* of circadian rhythms in rodents often makes them hyperphagic, insulin resistant, and hyperlipidemic [9–12]. In human trials, circadian misalignment similarly elevates glucose, insulin, and triglyceride levels [18–20] and lowers energy expenditure [21]. Therefore, understanding these rhythms is important for timing when to eat, sleep, be exposed to bright light, be physically active, and even when to take medications to reduce the risk of metabolic diseases [22–24].

While there is ample mechanistic data in animal models demonstrating the wide-sweeping role of the circadian system in metabolism, there are comparatively fewer trials in humans. Given that rodents differ in several key ways from humans—such as being nocturnal, polyphasic (sleeping more than once per day), and having high metabolic rates per body weight—it is unclear how, and to what degree, circadian and diurnal research in rodents translates into humans. In this review, we synthesize evidence for circadian regulation of metabolism in humans. In Section 2, we provide an overview of the architecture of the circadian system and protocols for measuring circadian rhythms in humans. In Section 3, we summarize the evidence for circadian and diurnal rhythms in glucose, lipid, and energy metabolism in humans. In Section 4, we conclude by discussing how circadian alignment or misalignment with three external factors—light, sleep, and food intake—affects metabolism and the risk of metabolic diseases.

2. Circadian Biology

2.1. *Architecture of the Circadian System*

The circadian system consists of two parts: (1) a central clock located in the suprachiasmatic nucleus (SCN) of the hypothalamus and (2) a series of peripheral clocks located in

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