CellPress

Review

Circadian Metabolism: From Mechanisms to Metabolomics and Medicine

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The circadian clock directs nearly all aspects of diurnal physiology, including metabolism. Current research identifies several major axes by which it exerts these effects, including systemic signals as well as direct control of cellular processes by local clocks. This redundant network can transmit metabolic and timing information bidirectionally for optimal synchrony of metabolic processes. Recent advances in cellular profiling and metabolomics technologies have yielded unprecedented insights into the mechanisms behind this control. They have also helped to illuminate individual variation in these mechanisms that could prove important in personalized therapy for metabolic disease. Finally, these technologies have provided platforms with which to screen for the first potential drugs affecting clock-modulated metabolic function.

Trends

Bidirectional molecular relationships link the circadian clock to energy homeostasis.

These links occur at both cellular and systemic levels.

Metabolomics, transcriptomics, and cellular assays have illuminated mechanisms and interindividual differences in this control.

Cellular circadian assays have provided screening platforms for clock-specific drugs that could be useful for metabolic disorders.

Circadian Metabolism: An Overview

Nearly all aspects of metabolism vary with time of day, at both cellular and systemic levels. These regular daily oscillations persist even in constant environmental conditions, making them 'circadian'. Food intake is circadian, digestion and detoxication are circadian, and cycles of breakdown and storage of fats and sugars are circadian. Even within cells, individual metabolic pathways are circadian. The first reports of circadian transcriptomics suggested that at least 10% of all transcripts are regulated in circadian fashion in most tissues [1,2], and for circadian metabolomics this fraction approaches 20% [3–5] (Box 1). Importantly, many of these rhythms are not merely a consequence of rhythmic food intake and behavior but persist even in constant conditions. Others appear 'driven' by feeding and fasting cycles [6] or by sleep and wake [7,8].

Metabolic Dysfunction from Clock Disruption

Since the publication of the observation that mice deficient for the circadian gene *CLOCK* have metabolic disorder [9], an explosion of research has occurred into the complex relationship between circadian dysfunction, obesity, diabetes, and **metabolic syndrome** (see Glossary). Numerous excellent and detailed reviews exist on this subject [10–12] and we introduce circadian clock mechanisms in Box 2. In brief, it is clear that model organisms with defects engineered into circadian clocks show many features of metabolic syndrome. These include obesity, diabetes, steatosis, cardiomyopathy, and atherosclerosis, not only in mammalian models [13] but also recently in flies [14,15].

These abnormalities emerge from various tissue-specific defects. For example, loss of circadian clock function in liver resulted in hypoglycemia during the fasting phase, implying a role for the circadian clock in buffering circulating glucose [16]. Loss of pancreatic clocks caused glucose intolerance [17,18]. Muscle-specific clock ablation resulted in increased oxidative fibers and muscle fibrosis [19] and is likely to be necessary for proper substrate utilization [20]. Arterial transplantation from clock-deficient to wild-type mice resulted in early atherosclerosis in transplanted pieces [21].

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Box 1. The Power of Metabolomics

Metabolomics has furnished significant insights into the complexity of metabolic dysfunction. By profiling how sugars, FAs, simple carbohydrates, and hormones vary both in solid tissues and in circulation, it has been possible to characterize in great detail broad-spectrum metabolic disorders. Along with these observations, knowledge of human genetic variation has permitted the identification of novel factors leading to susceptibility to these disorders [122], and transcriptomics has provided glimpses into their underlying causes. The increased throughput and reduced cost of RNA profiling and mass spectrometry have recently made it possible to conduct metabolomics and transcriptomics studies using samples collected at many different times of day, in different matrices. However, the application of human circadian profiling in this fashion is a very young science and its clinical potential remains mostly unrealized.

Box 2. An Introduction to Basic Clock Mechanisms

Mammalian circadian physiology relies on a partly centralized and redundant network of circadian clocks throughout the body. A 'master clock' resides in the SCN of the hypothalamus, comprising 20,000 neurons and associated glia, each of which has a cell-autonomous circadian clock within. These independent clocks are coupled together via neuropeptidergic signaling, gap junctions, and standard synaptic connections, resulting in a clock network that is precise, robust, and flexible to light-entrained seasonal changes [123].

Peripheral circadian clocks of similar molecular mechanism exist in nearly all cells of the body and are kept synchronized via timing cues from the SCN. These timing cues include direct nervous signals from the autonomic nervous system (ANS), hormones, and indirect behavior-related signals derived from the timing of food and the daily fluctuation of body temperature. As a result, global circadian physiology in any given tissue is likely to be driven by a mixture of local and systemic signals. Under normal circumstances, direct signals from the SCN are in concordance with indirect behavior-driven signals like food timing. However, under duress these signals can become uncoupled; for example, repeated abnormal meal timing can resynchronize peripheral oscillators independently of SCN-driven timing signals [124].

At the cellular level, the molecular mechanism of the circadian clock in any cell is thought to rely primarily on coupled feedback loops of the transcription and translation of dedicated clock genes and proteins [125]. In one loop, the circadian transcriptional activators CLOCK and BMAL1 bind to *cis*-acting E-box elements to drive transcription of the repressors *Cry1/2*, *Per1/2/3*, and *Rev-Erbα/β*. Subsequently, CRY and PER proteins multimerize, return to the nucleus, and repress their own transcription. In a second linked loop, the activators RORα/β/γ compete with the REV-ERBα/β repressors at *cis*-acting RRE elements to drive circadian transcription of *Bmal1*. The proper function and timing of this network of transcription factors is governed by a wealth of post-translational modifications controlling their stability and/or targeting their degradation [126], as well as RNA-binding proteins and chromatin-modifying factors aiding in their transcriptional activities [127]. In addition, another redox-related circadian oscillation based entirely on post-translational mechanisms may also exist in most cells, completely independent of the 'canonical' transcription/translation-based clock circuitry [128,129].

Glossary

Breath metabolomics: sampling of metabolites from deep lung alveoli via real-time analysis of breath.
Caloric restriction: reduction of the total number of calories consumed during the day.
Chronopharmacology: the timing of medications for optimal efficacy and minimal side effects.
Lipidomics: metabolomics-based determination of lipid species.
Melatonin: circadian hormone released by the pineal gland with soporific and other effects.
Metabolic syndrome: according to the International Diabetes Federation, the cluster of physiological risk factors, like high blood pressure, obesity, and high blood sugar and cholesterol, that increases the risk of heart disease, stroke, and diabetes.
Time-restricted feeding: scheduled mealtimes that limit the intake of food to a particular period within the 24-h day without reducing its amount.

The mechanisms behind these phenotypes vary considerably. Generally, however, they can be classed into two categories: phenotypes resulting from circadian regulation of organ-specific functions necessary for metabolic homeostasis at the level of the whole organism; and circadian control of basic metabolic pathways at a cellular level. We consider these causes in further detail separately below.

Axes of Metabolic–Circadian Interaction: The Whole Body

Considering first the entire body, these signals are likely to represent a complex interplay between: (i) glucocorticoid hormones, which govern conversion of sugar, fat, and proteins into glucose; (ii) insulin, promoting the absorption of glucose from the blood and the storage of fat; and (iii) appetite hormones like leptin and ghrelin, governing food intake. At a macroscopic level, it has been postulated that the circadian clock contributes to metabolic homeostasis by acting as a type of rheostat [12], orchestrating shifts in metabolic patterns to accompany changes in activity and food consumption. The proper function of this rheostat depends at least in part on local circadian clocks to direct circadian control of individual metabolic hormones or the cellular response to them. For example, pancreatic beta-cell-specific clock function is necessary for the rhythmic secretion of insulin [17,18] and multiple aspects of metabolic homeostasis are dependent on circadian function of the adrenal gland, which secretes glucocorticoid hormones [22]. Complementing this control, tissue-specific action of glucocorticoids is dependent on local cooperation with cryptochrome proteins from the circadian clock [23].