Review

MOLECULAR METABOLISM

Interdependence of nutrient metabolism and the circadian clock system: Importance for metabolic health

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ABSTRACT

Background: While additional research is needed, a number of large epidemiological studies show an association between circadian disruption and metabolic disorders. Specifically, obesity, insulin resistance, cardiovascular disease, and other signs of metabolic syndrome all have been linked to circadian disruption in humans. Studies in other species support this association and generally reveal that feeding that is not in phase with the external light/dark cycle, as often occurs with night or rotating shift workers, is disadvantageous in terms of energy balance. As food is a strong driver of circadian rhythms in the periphery, understanding how nutrient metabolism drives clocks across the body is important for dissecting out why circadian misalignment may produce such metabolic effects. A number of circadian clock proteins as well as their accessory proteins (such as nuclear receptors) are highly sensitive to nutrient metabolism. Macronutrients and micronutrients can function as zeitgebers for the clock in a tissue-specific way and can thus impair synchrony between clocks across the body, or potentially restore synchrony in the case of circadian misalignment. Circadian nuclear receptors are particularly sensitive to nutrient metabolism and can alter tissue-specific rhythms in response to changes in the diet. Finally, SNPs in human clock genes appear to be correlated with diet-specific responses and along with chronotype eventually may provide valuable information from a clinical perspective on how to use diet and nutrition to treat metabolic disorders.
Scope of review: This article presents a background of the circadian clock components and their interrelated metabolic and transcriptional feedback loops, followed by a review of some recent studies in humans and rodents that address the effects of nutrient metabolism on the circadian clock and vice versa. We focus on studies in which results suggest that nutrients provide an opportunity to restore or, alternatively, can destroy synchrony between peripheral clocks and the central pacemaker in the brain as well as between peripheral clocks themselves. In addition, we review several studies looking at clock gene SNPs in humans and the metabolic phenotypes or tendencies associated with particular clock gene mutations.
Major conclusions: Targeted use of specific nutrients based on chronotype has the potential for immense clinical utility in the future. Macronutrients and micronutrients have the ability to function as zeitgebers for the clock by activating or modulating specific clock proteins or accessory proteins (such as nuclear receptors). Circadian clock control by nutrients can be tissue-specific. With a better understanding of the mechanisms that support nutrient-induced circadian control in specific tissues, human chronotype and SNP information might eventually be used to tailor nutritional regimens for metabolic disease treatment and thus be an important part of personalized medicine's future.

Keywords Circadian; Metabolism; Nutrients; Synchrony; Nuclear receptors

1. INTRODUCTION

"You are what you eat" is a phrase often used to describe the compromised metabolic health associated with the excessive intake of food with limited nutrient value. While this association seems obvious, less obvious is that our endogenous circadian clocks may reflect what we eat. In fact, our ability to adjust to jet lag, recover from a sleepless night, or respond to and metabolize medicines prescribed may heavily depend on what we eat and when we eat it. Because evidence to date strongly links our internal clock to metabolism and metabolic health, the effect of nutrient intake on our internal 24-h rhythms has taken a spotlight in the field of metabolism research.

Circadian oscillations are naturally recurring rhythms with a periodicity of approximately twenty-four hours. Most organisms display biological circadian rhythms and in humans, they are fundamental to physiology and behavior. The light–dark cycle is considered one of the most potent zeitgebers (or "time-giver") driving behavioral preferences and almost all organisms studied to date respond to this circadian cue. Animal studies indicate that other cues, such as food, also drive our internal clocks to a significant extent. Fundamentally, as a

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Received December 4, 2015 • Revision received December 15, 2015 • Accepted December 29, 2015 • Available online 14 January 2016

http://dx.doi.org/10.1016/j.molmet.2015.12.006

consequence of the Earth's rotation on its axis, seasonal and daily environmental changes occur to which organisms must adapt at the metabolic level. Diurnal species, such as humans, carry out their daily activity during the light cycle, while nocturnal species are active during the dark cycle. This activity-rest cycle requires metabolic and physiological adaptation, producing rhythms in processes as disparate as blood pressure, body temperature, cardiovascular efficiency, muscle strength, hormonal secretion in blood, cognitive ability, etc. [1–4]. While anticipation of the changing environment is controlled to a large extent at the level of the brain, where light activates the central clock (the suprachiasmatic nucleus, or SCN), peripheral clocks also host circadian rhythms [5], but respond predominantly to cues other than light. More specifically, nutrient input is a critical and primary driver of several peripheral clocks, such as the circadian clock in the liver [6–9] and, pending its composition and the timing of administration, can even usurp the local clock, preventing synchronization with the central pacemaker and potentially disrupting synchronization with other peripheral clocks. Becoming more apparent is that nutrient sensing by the clock in different tissues is a powerful mechanism by which tissues maintain or acquire the energy balance necessary to carry out their physiological roles. A large part of this nutrient sensing involves the timing of nutrient input, a topic which has been comprehensively reviewed in several recent reviews [1,10,11]. Thus, the main focus of this review will weigh heavily on some of the most recent studies looking at sensing by the clock of specific nutrients or groups of nutrients as well as some of the epidemiological studies highlighting links between the human circadian clock and nutrient metabolism.

2. MOLECULAR BASIS FOR CIRCADIAN AND METABOLIC INTERACTIONS

Circadian rhythms are supported at the cellular level by a wide range of complex molecular pathways and specific oscillatory enzymes. Nonetheless, from a basic point of view, a circadian clock system is shared among species worldwide [12]. The use of omic technologies has made it possible to ascertain the circadian patterns of a significant number of transcripts, proteins and metabolites that drive cellular rhythmicity. High-throughput transcriptional studies using mouse tissues have revealed that at any given point in time in a single tissue, up to a tenth of all mammalian genes exhibit 24-h variations in mRNA levels (reviewed in Ref. [13]). However, recent studies demonstrate that a much larger percentage of genes oscillate in at least one tissue throughout the body [14], promoting the idea that most genes can oscillate in expression depending on the environment [15]. These transcripts include genes controlling processes as widespread as mitochondrial oxidative phosphorylation, carbohydrate metabolism and transport, lipid biosynthesis, adipocyte differentiation, and cholesterol synthesis and degradation [14,16–21]. Similarly, additional studies looking at protein regulation throughout the circadian cycle reveal that approximately 20% of the proteome in liver and SCN [22,23] is subject to circadian control with some posttranslational modifications also cycling in a circadian manner [24,25]. A significant fraction of the oscillating proteins in a cell is devoid of oscillations at the mRNA level [25]. Thus cellular circadian oscillations take place at several levels of cell function and at several stages in the process of a gene being expressed. Like oscillating gene transcripts, many of the oscillatory proteins within the cell comprise members of various metabolic processes such as urea formation, sugar metabolism and mitochondrial oxidative phosphorylation [22,23]. Metabolite profiling studies have added additional complexity to the picture of circadian clock-controlled metabolic function. Studies in murine animals show that many metabolites involved in amino acid, carbohydrate, lipid, nucleotide and xenobiotic metabolic pathways, oscillate in liver [26], muscle [27] and plasma [28], whereas 15%–70% of the metabolome in humans exhibits circadian variation depending on whether rhythmicity in energy intake and the sleep/wake cycle is maintained [29,30]. Overlapping data from various omic studies demonstrate that circadian rhythms are extremely zeitgeber-responsive and specific. For example, when comparing metabolite or transcript oscillations in the liver of mice with different genetic backgrounds or on different diets, it is revealed that many oscillating events are not shared [15]. Furthermore, comparing oscillations across tissues of the same species reveals that many oscillations are tissue specific [14,15,17,31]. Many of the core clock genes oscillate across tissues or species, but many metabolic oscillations are highly dependent on the environment. Thus, the current understanding of cellular circadian rhythms throughout an organism is that while the core clock genes are oscillating in most tissues and in the midst of enormous environmental pressures, metabolic circadian oscillations are strongly shaped by the environment [14,15].

The core circadian clock system in mammals depends on a central clock located in the hypothalamic suprachiasmatic nucleus (SCN), and on "peripheral" clocks spread throughout the anatomy [32,33]. Rhythmicity at the level of the SCN is extremely complex [34,35] and has two essential functions systemically: integrating direct photic input from the retina through the optic nerve and maintaining the communication among the different clocks through endocrine signals and nerve impulses [36]. As the SCN provides both integration and primary coordination of peripheral clocks throughout the body, it is known as the "master clock", or "pacemaker" in mammals [37]. In most organisms in which the molecular clock mechanism has been investigated, a common model has been observed across cells, be it those of the central pacemaker or those of the periphery: a transcription–translation feedback loop (TTFL) [38]. In mammals, the positive limb of the TTFL is comprised of the transcriptional activators, the circadian locomotor output cycles kaput (CLOCK) and brain and muscle ARNT like protein 1 (BMAL1). These clock core genes encode bHLH-PAS (basic helix–loop–helix; Per-Arnt-Single) proteins that after their own heterodimerization initiate transcription by binding to specific DNA elements like E-boxes (5′-CACGTG-3′) and E'-boxes (5′-CACGTT-3′) in the promoters of target genes. Loss of either BMAL1 or CLOCK and NPAS2 (a paralog of CLOCK), eliminates functionality of the TTFL altogether and thus circadian rhythms in animal physiology and behavior [39–41]. CLOCK:BMAL1 target genes can be metabolic genes which do not directly feed back onto the TTFL or they can be so-called "clock genes", which feed back directly into the clock's TTFL as CLOCK:BMAL1 activity inhibitors or activators [38]. The CLOCK:BMAL1 target genes include the Period (*Per*) and Cryptochrome (*Cry*) genes, which ultimately reach critical protein concentrations, dimerize, and inhibit the subsequent activity of the CLOCK:BMAL1 heterodimer in the nucleus [42]. Degradation of the negative limb proteins PER and CRY is required to initiate of a new cycle of transcription. Casein kinase (CK)1ε and CK1δ phosphorylate the PER proteins, which is necessary for their ubiquitination and degradation by β-transducing-repeat-containing protein (βTrCP) and 26S proteasome respectively [43]. CRY1 is phosphorylated by 5′ AMP-activated protein kinase 1 (AMPK1) [44] and CRY2 by a sequential dual-specificity tyrosine-(Y)-phosphorylation regulated kinase 1A(DYRK1A)/glycogen synthase kinase 3beta (GSK-3β) cascade [45], which targets it for ubiquitination and degradation by F-Box And Leucine-Rich Repeat Protein 3(FBXL3) [46–49]. In addition, the active CLOCK:BMAL1 heterodimer promotes the transcription of the nuclear receptors retinoic acid-related orphan receptor alpha (*Ror*α) and the nuclear receptor subfamily 1, group D (*Nr1d1*), also known as

