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Review

Circadian control of metabolism and pathological consequences of clock perturbations

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A B S T R A C T

Most organisms have developed an autonomous time-keeping system that generates self-sustained daily fluctuations in behavior and physiological processes. These biological clocks are reset every day by light to adjust physiology to the day/night cycle generated by the rotation of the Earth. Clocks present in organs involved in glucose and lipid metabolism such as the liver, muscle, adipose tissue and pancreas are also reset by feeding cues which permits the local integration of systemic and nutritional signals to switch fuel production and utilization according to the feeding/fasting cycle. However, derangements in this finely tuned system can be induced by extended light exposure, 24/7 food availability and altered food intake patterns, repeated jet-lag and shift-working, promoting metabolic imbalances ranging from body weight gain to the development of insulin resistance and liver diseases. Here, we review recent findings on the link between the clock and metabolic fluxes to maintain whole-body homeostasis, and what clock disruption in mice has revealed about the role of the clock in metabolic regulation.

Contents

1. Introduction

Obesity and type 2 diabetes have increased at alarming rates during the past decades with considerable medical and societal costs. During the same period, lifestyles have dramatically changed. The caloric intake has increased, paralleled by a drastic reduction in physical activity. In modern societies, food is available 24/7, and lifestyle patterns have evolved in response to technological advances as well as social and economic demands, so that food intake, physical activity and light exposure are no longer restricted to

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daytime hours. The resulting changes in food intake patterns, light exposure and sleep duration, as well as frequent jet-lag and shift-working have profoundly affected our internal time-keeping systems. The recent development of genetically or environmentally-induced models of circadian disruption has shed light on the link between the biological clock and metabolism, and highlighted the adverse metabolic effects of body clock disarrangement [1].

Organisms rely on a highly conserved biological clock to anticipate predictable changes in the environment generated by the rotation of the Earth about its axis such as the day/night and fasting/feeding cycles. The biological clock is a cell-autonomous molecular circuitry that generates self-sustained oscillations with a period of about a day (circa, around; diem,day) in physiological processes and behavior including body temperature, heart rate, sleep/wake cycles, insulin secretion and metabolism. It operates at different levels, eliciting fluctuations in transcription, translation, post-translational modifications and protein activity as well as metabolite production [2–4].

A so-called central clock is located in the suprachiasmatic nucleus of the hypothalamus and perceives photic cues to adapt the pace of its oscillations to the light/dark cycle [5,6]. Interestingly, clocks exist in virtually all body cells and are synchronized by the central pacemaker in order to create internal alignment. The light/dark cycle is the strongest external signal (zeitgeber) that synchronizes (entrains) biological rhythms with the environment. Noteworthy, while the light entrains the central clock to day/night cycles, the feeding/fasting cycle is also able to entrain peripheral clocks independently of the central clock [7–9]. This allows the clock to sense local variations of energy to control circadian fluctuations in metabolism accordingly [5]. It is now becoming clear that the internal misalignment of body clocks, due to irregular food intake patterns, extended light exposure at night and reduced sleep duration, contributes to the development of obesity, dyslipidemia, insulin resistance and cardiovascular complications [1,10–12].

2. The molecular clock

Circadian rhythms are mastered by a set of core clock genes organized in a positive and a negative limb forming a feedback loop (Fig. 1). The two PAS domain–containing transcription factors Circadian Locomotor Output Cycles Kaput (CLOCK) and Brain and Muscle ARNT like protein 1 (BMAL1) form the positive limb [13–15]. The CLOCK/BMAL1 heterodimer activates *Period* (*Per)* and *Cryptochrome* (*Cry)* genes. PER and CRY are transcription factors which heterodimerize and, once in sufficient concentrations, translocate back to the nucleus to inhibit the activity of the CLOCK:BMAL1 heterodimer. Additionally, the nuclear receptors Rev-erbs (Nr1d1 and Nr1d2), RORα (Nr1f1) and Peroxisome Proliferator-Activated Receptor (PPAR)α (Nr1c1) reinforce this loop. Indeed, CLOCK:BMAL1 induces their expression in a circadian manner. In turn, RORα and PPARα activate BMAL1 gene expression by binding to their response element within the BMAL1 promoter, while Rev-erbα/β compete with RORα and inhibit *Bmal1* transcription [16–18]. These nuclear receptors also integrate metabolic fluxes. Indeed, PPARα can be activated by small molecules derived from metabolism, namely fatty acids and derivatives [19], while Rev-erbα and RORα are able to sense heme and cholesterol-derivatives, respectively [20–23]. Finally, PGC1α, which is crucial for the metabolic adaptation to fasting and contributes to mitochondrial biogenesis, and co-activates Bmal1 gene transcription with RORα [24]. This molecular circuitry thus temporally regulates the expression of gene networks, with widespread effects on metabolism.

Post-translational modifications of the clock components, some of them related to the energetic status of the cells/tissues (see below), affect their stability and thus the pace of the clock, adjusting its phase to the 24-h cycle. For instance, phosphorylation by the casein kinase (CK)Iε or CKII of Per, Cry and BMAL1 destabilizes these proteins and leads to their ubiquitination and subsequent degradation [25–28]. Cry1/2 are also ubiquitinated by F-box/LRR-repeat protein (FBXL)3 [29]. Moreover, Bmal1 activity is regulated by its SUMOylation, which is necessary for its circadian expression [30]. Finally, acetylation of histones leads to chromatin decompaction and participates in the regulation of the transcriptional activity of the clock components [31].

Rev-erbs can be ubiquitinated by Siah2, an E3 ligase, leading to Rev-erb proteasomal degradation [32], whereas it is stabilized by its phosphorylation by glycogen synthase kinase (GSK)3β [33]. In addition to its action on Rev-erbα, GSK3β phosphorylates O-GlcNAc transferase (OGT), the enzyme responsible for O-GlcNacylation of proteins and whose activity depends on the intracellular concentrations of the UDP-GlcNAc donor and hence metabolic fluxes [34]. Indeed, UDP-GlcNAc is formed through the hexosamine pathway from different precursors including glucose, glutamine, acetyl CoA, and UTP, and high concentrations of glucose, free fatty acids and glutamine can drive the synthesis of UDP-GlcNAc. O-GlcNAcylation exhibits diurnal fluctuations in heart due to oscillations in glucose and glutamine metabolism, as well as fluctuations in levels of OGT and the O-GlcNAcase (OGA) which removes the O-GlcNac residue [35]. Interestingly, BMAL1 and CLOCK can be O-GlcNacylated which reduces their ubiquitination and targeting for proteasomal degradation when nutrient levels are high [36,37]. It has also been shown that insulin promotes post-prandial Akt-mediated phosphorylation of BMAL1, resulting in its nuclear exclusion and suppressed transcriptional activity [38].

3. Clock and metabolism: a strong relationship

3.1. Evidence for a direct link between metabolism and the circadian clock

Although ~40% of the genes display 24 h oscillations in transcript abundance throughout the body, the identity of those cyclic genes differs significantly between organs, suggesting organ-specific integration of central cues and local signals to induce cyclic fluctuations relevant to the organ [39]. In the liver, these transcripts encode key or rate-limiting enzymes important for glucose, lipid and bile acid metabolism as well as mitochondrial function [5], anticipating fasting and feeding phases and participating to the partitioning of exclusive metabolic pathways. Interestingly, peripheral clocks can be entrained, independently of the central pacemaker, by the feeding schedule. Indeed, in mice, restriction of the feeding time to the rest period can invert the phase of clock gene expression in peripheral tissues including the liver and pancreas [7], indicating a direct action of nutritional status on the clock.

Several epidemiological studies have highlighted the adverse metabolic consequences of clock disruption in humans. Indeed, shift-working promotes body weight (BW) gain and obesity, and increases the risk of developing insulin resistance, type 2 diabetes and their cardiovascular consequences [10,40]. Imposing chronic jet-lag in mice or light at night disrupts food intake patterns and is associated with higher body weight [41,42], as well as hepatic lipid accumulation [43] and leptin resistance [44]. Food intake at the 'wrong' time (ie during the rest period) and increased snacking are thought to be important drivers of this metabolic imbalance. In mice, high fat diet (HFD)-feeding leads to alterations in the circadian expression of clock genes including *Clock*, *Bmal1*, *Per2* and the *Rev-erbα/RORα* loop in peripheral tissues (such as liver and adipose tissue) as well as in the hypothalamus. This results in altered food intake and locomotor activity patterns with a significantly higher

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