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Review

Circadian disruption in the pathogenesis of metabolic syndrome

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Abstract

Metabolic syndrome is a multifactorial process induced by a combination of genetic and environmental factors and recent evidence has highlighted that circadian disruption and sleep loss contribute to disease pathogenesis. Emerging work in experimental genetic models has provided insight into the mechanistic basis for clock disruption in disease. Indeed, disruption of the clock system perturbs both neuroendocrine pathways within the hypothalamus important in feeding and energetics, in addition to peripheral tissues involved in glucose and lipid metabolism. This review illustrates the impact of molecular clock disruptions at the level of both brain and behavior and peripheral tissues, with a focus on how such dysregulation in turn impacts lipid and glucose homeostasis, inflammation and cardiovascular function. New insight into circadian biology may ultimately lead to improved therapeutics for metabolic syndrome and cardiovascular disease in humans.

Keywords: Metabolism; Circadian rhythm; Cardiovascular disease

1. Metabolic syndrome: etiology

Metabolic syndrome (MetS) is defined by several phenotypic abnormalities, including central (intra-abdominal) obesity, dyslipidemia (elevated triglyceride, and reduced high-density lipoprotein cholesterol), impaired glucose tolerance, and hypertension. Elevated circulating inflammatory and/or thrombotic markers (C-reactive protein, tumor necrosis factor-α, interleukin-6, and plasminogen activator inhibitor type 1) or reduced levels of anti-inflammatory molecules such as adiponectin have also been associated with MetS [1,2]. This syndrome has become a public health challenge worldwide; an estimated 25 to 40% of individuals between the ages of 25 and 64 years of age have MetS (San Antonio Heart Study) [1,3–6]. Moreover, a recent systematic review and meta-analysis, involving over 950,000 patients with MetS, estimated a 2.3 fold increased risk in cardiovascular disease (CVD) and a 2.4 fold increase risk in CVD mortality [7]. Furthermore, in the same report, patients with MetS, but without type 2 diabetes mellitus, maintained a high cardiovascular risk. It is established that body fat distribution rather than adiposity *per se* is a key feature of the syndrome. Excess of intra-abdominal fat rather than subcutaneous (sc) fat (central vs. peripheral obesity) is associated with MetS and CVD [5,8].

The increased adoption of calorically dense (high fat and high carbohydrate) diet, in addition to genetic susceptibility, both contribute to the emergence of the MetS [1]. Consequently, current public health surveys of human nutrition have focused on the macronutrient composition of diet. For instance, recently, Estruch et al. document that provision of extra-virgin olive oil or mixed nuts, in the context of a Mediterranean-style diet, substantially reduced the occurrence of CVD [9]. Such diets are rich in total monounsaturated and polyunsaturated fat and are lower in saturated fat. Another area of recent interest is vitamin D. Increasing evidence indicates that vitamin D deficiency (from sun exposure and/or dietary sources) is associated with multiple parameters of MetS [10–14].

In addition to poor quality of nutrition, excess food intake and physical inactivity, sleep disturbance impacts on metabolism. Indeed, numerous cross-sectional, as well as prospective clinical, studies have demonstrated that short-duration and poor-quality sleep predicts the development of type 2 diabetes and obesity even after age, body mass index and various other confounding variables are taken into account [15–17]. Moreover, shift work is linked to increased risk of type 2 diabetes [18,19] and stroke [20]. Surprisingly, it has been observed that sudden changes in the biologic rhythm can lead to adverse effects on cardiovascular health. For instance, shifts

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to daylight saving time in spring have been associated with an increased incidence of myocardial infarction [21].

Finally, new perspectives into the understanding of MetS pathogenesis can be derived from studies of experimental animal models demonstrating that feeding time also dramatically impacts the development of the MetS [22–28]. When feeding a high-fat diet (HFD) is restricted to the active (dark) phase, mice consumed equivalent calories to those with *ad lib* access and yet are protected against obesity, hyperinsulinemia, hepatic steatosis, and inflammation [23]. Furthermore, other studies showed that the abnormal feeding rhythm corrected by scheduled feeding rescues the onset of obesity in HFD-fed mice [24,29] and as well as in a genetic model of hyperphagia with a dysregulated feeding rhythm, such as in Histamine-H(1)-R knockout mice (H1KO) [25]. Conversely, mice fed a HFD only during the 12-hour light phase gain significantly more weight compared to isocalorically fed mice that were provided food only during the 12-hour dark phase [22]. Similarly, disruption of the normal light/dark cycle (by exposure of mice to light during the night or housing mice in 20-h light/dark cycles), which simulates shift work disruption or jet lag in humans, disrupts the timing of food intake, and results in accelerated weight gain [27,30]. Remarkably, restricting food consumption to the active phase in mice exposed to light during the night prevents body mass gain [27]. Such a relationship between temporal pattern of food intake and the development of metabolic disruptions has been suspected in human, but remains poorly characterized [31]. Nevertheless, a causal link between circadian misalignment and metabolic homeostasis has been described [32]. Indeed, when subjects ate and slept 12 hours out of phase from their habit-

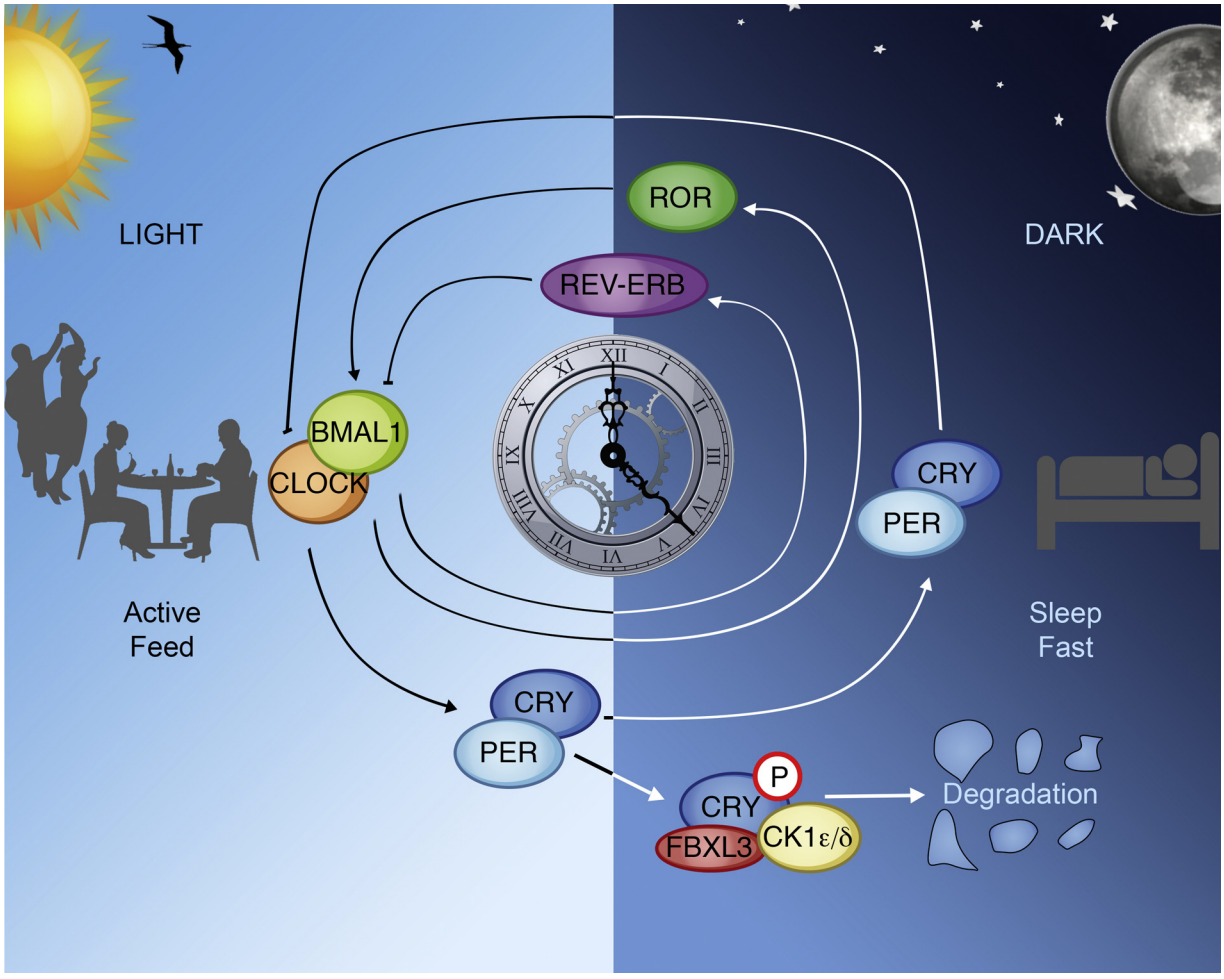

Fig. 1. Core molecular clock. The core molecular clock in mammals is expressed both in brain and peripheral metabolic tissues and coordinates behavioral (i.e. sleep-wake, feeding-fasting), endocrine and metabolic responses with the light/dark cycle. The core molecular clock is composed of a feedback loop involving a series of activators (CLOCK/BMAL1) and repressors (CRYs/PERs) that generate ~24 hours rhythms of gene transcription. CLOCK/BMAL1 activate the rhythmic transcription of downstream target genes that contain E-box cis-regulatory enhancer sequences, including the *Per* and *Cry* genes. The non-phosphorylated proteins PER and CRY heterodimerize, translocate to the nucleus, and inhibit CLOCK/BMAL1. Phosphorylation, in turn, targets PER–CRY for ubiquitin-mediated proteolysis. In addition, CLOCK–BMAL1 activates transcription of the retinoic acid-related orphan nuclear receptors *Rev-erbα* and *Rorα* genes. In turn, REV-ERBα represses, while RORα activates, *Bmal1* transcription. During the dark phase, CK1ε and CK1δ phosphorylate PER and CRY, tagging them for ubiquitylation by FBXL3, and leading to their degradation by the proteosome. BMAL1: brain and muscle aryl-hydrocarbon receptor nuclear translocator-like 1; CLOCK: circadian locomotor output cycles kaput; CK1ε and CK1δ: casein kinase 1ε and –δ; Cry1: cryptochrome 1; FBXL3: F-box and leucine-rich repeat protein 3, Per2: Period 2; ROR: retinoic acid-related orphan receptor.
Adapted from Bass [35].