Acta Pharmaceutica Sinica B 2015;5(2):113–122

HOSTED BY

Chinese Pharmaceutical Association
Institute of Materia Medica, Chinese Academy of Medical Sciences

Acta Pharmaceutica Sinica B

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REVIEW

Circadian rhythms in liver metabolism and disease

Jessica M. Ferrell, John Y.L. Chiang*

Department of Integrative Medical Sciences, Northeast Ohio Medical University, Rootstown OH 44272, USA

Received 21 November 2014; received in revised form 24 December 2014; accepted 4 January 2015

KEY WORDS

Circadian rhythm;
Liver;
Metabolic syndrome;
Type 2 diabetes

Abstract Mounting research evidence demonstrates a significant negative impact of circadian disruption on human health. Shift work, chronic jet lag and sleep disturbances are associated with increased incidence of metabolic syndrome, and consequently result in obesity, type 2 diabetes and dyslipidemia. Here, these associations are reviewed with respect to liver metabolism and disease.

Abbreviations: ARC, arcuate nucleus; BMAL1, brain and muscle ARNT-like 1; CAR, constitutive androstane receptor; CLOCK, circadian locomotor output cycles kaput; CRY, cryptochrome; CYP7A1, cholesterol 7α-hydroxylase; CYPs, cytochrome P450 enzymes; DBP, D-site binding protein; E-box, enhance box; EMT, emergency medical technician; FAA, food anticipatory activity; FASPS, familial advanced sleep-phase syndrome; FEO, food entrainable oscillator; FOXO3, forkhead box O3; FXR, farnesoid-X receptor; GLUT2, glucose transporter 2; HDAC3, histone deacetylase 3; HIP, hypoxia inducing protein; HLF, hepatic leukemia factor; LDL, low-density lipoprotein; LRH1, liver receptor homolog 1; NAD^+, nicotinamide adenine dinucleotide; PER, period; RHT, retinohypothalamic tract; RORα, retinoid-related orphan receptor α; RORE, ROR-response element; SCN, suprachiasmatic nucleus; SHP, small heterodimer partner; SIRT1, sirtuin 1; TEF, thyrotroph embryonic factor; TGR5, G protein-coupled bile acid receptor; TTFL, transcriptional translational feedback loop

*Corresponding author. Tel.: +1 330 3256694; fax: +1 330 3255910.
E-mail address: jchiang@neomed.edu (John Y.L. Chiang).

Peer review under responsibility of Institute of Materia Medica, Chinese Academy of Medical Sciences and Chinese Pharmaceutical Association.

http://dx.doi.org/10.1016/j.apsb.2015.01.003

1. Introduction

Circadian rhythms (Latin, *circa*: "approximate"; *dies*: "day") refer to physiological processes that occur with a repeating period of approximately 24 h and ensure that internal physiology is synchronized with the external environment. Circadian rhythms are ubiquitously present in prokaryotes, fungi, algae, plants and mammals. Temporal organization within an organism is critical for maintenance of homeostasis as well as adaptation to changing environmental conditions. In mammals, this organization is generated and maintained endogenously by the biological clock, the suprachiasmatic nucleus (SCN), a heterogeneous paired cluster of about 20,000 neurons located in the hypothalamus of the brain. Circadian rhythms are defined by three basic properties: 1) they exist endogenously under constant conditions in the absence of resetting cues (for instance, in constant darkness) and oscillate with a period of approximately 24 h, 2) they are temperature-compensated, such that the period of the rhythm remains stable over a physiological range of temperatures, and 3) they are capable of entrainment, or synchronization, by external cues, such that timing of rhythms can be adjusted to match the external environment in a manor favorable to the organism[1,2]. These properties result in endogenous stable rhythms that maintain basic homeostasis and also ensure adaptable physiological responses to the changing environmental photoperiod.

By way of the retinohypothalamic tract that connects the eye to the SCN[3,4], daily light/dark cues (*i.e.*, the rotation of the earth every 24 h) are the main entraining agents, or Zeitgebers (German: "time giver") that synchronize the clock to the external environment. However, non-photic cues such as social interaction, food, or exercise can also serve as Zeitgebers that change or reset the timing of the clock[5]. These Zeitgebers provide input to the SCN, which then processes the information and, through complex neurological pathways, ultimately influences behavioral, hormonal, and biochemical outputs that synchronize peripheral tissues to central timing (Fig. 1A).

At the molecular level, in both brain and peripheral tissues, clock outputs are generated in a cell-autonomous manner by the transcriptional translational feedback loop (TTFL) consisting of clock genes whose protein products oscillate to induce or suppress transcription of other clock genes, resulting in both positive and negative feedback loops[6]. Briefly, protein products of the core clock genes *Clock* (circadian locomotor output cycles kaput) and *Bmal1* (brain and muscle ARNT-like 1) heterodimerize, translocate to the nucleus, and bind to E-box promoter sequences of target core clock genes *Per1* and *2* (Period) and *Cry1* and *2* (Cryptochrome) to initiate transcription. PER and CRY proteins translocate to the nucleus and interact with CLOCK/BMAL1 to inhibit their own transcription. The PER/CRY complex is eventually tagged for degradation *via* phosphorylation by casein kinase, which releases CLOCK/BMAL1 from suppression; this feedback loop takes approximately 24 h to complete. An additional regulatory loop exists whereby the nuclear receptors retinoid-related orphan receptor α (RORα) and REV-ERBα compete for the ROR response element (RORE) binding site in the *Bmal1* promoter to activate or repress its transcription, respectively[7] (Fig. 1B). The TTFL exists in almost all mammalian cells, including heart, liver, pancreas, muscle and white adipose tissue, in whole tissue, tissue explants and even persists in cell culture, and represents a mechanism by which peripheral tissue physiology can be entrained to central timing originating from the SCN.

Central-to-peripheral synchronization provides a means for organs and tissues to function with maximal efficiency (for instance, in preventing metabolic futile cycles during feeding and fasting). It is thought that desynchronization of this timing, due to shift work, chronic jet lag, or mental health disorders that affect sleep quality and timing such as depression and schizophrenia, can contribute to the development of disease conditions. Circadian disruption has been significantly linked to increased incidence of cardiovascular events, gastrointestinal diseases, and metabolic syndrome, and in 2007 the International Agency for Research on Cancer designated shift work as a Class 2A probable human carcinogen[8–19]. Within the liver, approximately 10% of the transcriptome is rhythmically expressed, including genes involved in regulation of glucose, lipid and nutrient homeostasis, and bile acid synthesis and metabolism. Recently, a genome-wide analysis in mouse liver revealed several thousand CLOCK protein binding sites, most of which exhibited day-night variations in CLOCK occupancy, suggesting extensive and wide-reaching metabolic regulatory functions for CLOCK and other clock components[20]. Basic and clinical research continues to provide mounting evidence for a critical link between circadian homeostasis and human

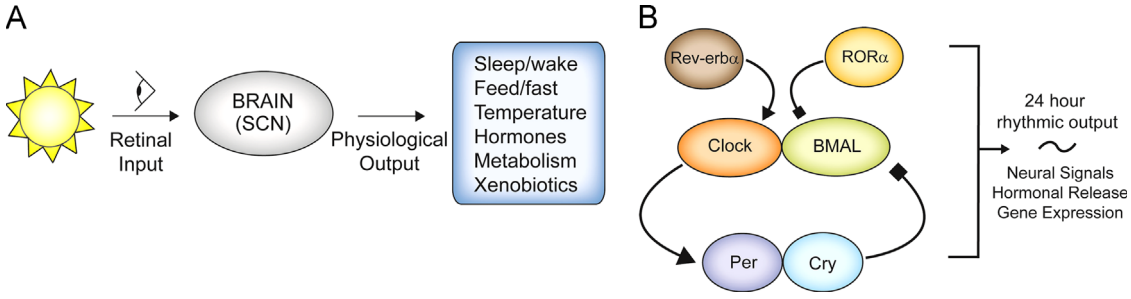

Figure 1 (A) Environmental signals perceived *via* the retinohypothalamic tract (RHT) by the biological clock, the suprachiasmatic nucleus (SCN) are the most prominent clock resetting agents. The SCN integrates photic and nonphotic signals to produce rhythmic outputs resulting in circadian regulation of locomotor activity, food intake, body temperature, hormonal release, and peripheral and xenobiotic metabolism. (B) Diagram depicting the transcriptional translational feedback loop (TTFL) that composes the molecular biological clock in almost all mammalian tissue types. Clock proteins CLOCK and BMAL1 heterodimerize to induce transcription of *PER* and *CRY* genes. PER1/2 and CRY1/2 proteins bind to E-box elements in the *BMAL1* promoter to inhibit *PER*/*CRY* transcription *via* negative feedback. Additional regulatory clock components REV-ERBα and RORα positively and negatively regulate *CLOCK*/*BMAL* transcription, respectively, through binding to ROR-response elements in the *BMAL1* promoter. This feedback loop takes approximately 24 h to complete and is the molecular basis for the mammalian biological clock that produces rhythmic outputs of neural and hormonal signals and gene transcripts.