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The mammalian clock and chronopharmacology

Kristine Griffett, Thomas P. Burris *

130 Scripps Way 2A1, The Scripps Research Institute, Scripps Florida, Jupiter, FL 33458, United States

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ABSTRACT

Increases in our understanding of the molecular control of circadian rhythms and subsequent signaling pathways has allowed for new therapeutic drug targets to be identified as well as for a better understanding of how to more efficaciously and safely utilize current drugs. Here, we review recent advances in targeting components of the molecular clock in mammals for the development of novel therapeutics as well as describe the impact of the circadian rhythm on drug efficacy and toxicity.

Most, if not all light-sensitive organisms, including mammals, possess a master circadian clock that regulates physiological and behavioral processes in alignment with the 24-h day. Recent advances in understanding the molecular control of circadian rhythms and subsequent signaling pathways has allowed for new therapeutic targets to be identified as well as for a better understanding of how to more efficaciously utilize current drugs. In addition to playing a key role in normal physiology and behavior, aberrations in the circadian rhythm are associated with the pathophysiology of diseases including diabetes, cardiovascular disease, psychological disorders and various autoimmune diseases/inflammation.[1–5] Additionally, the potency and efficacy of many drugs is associated with the circadian rhythmicity of expression of their molecular targets and cellular biochemical signals.[4] A significant fraction of genes are expressed in a circadian fashion[6] including many drug targets and drug metabolizing enzymes yielding potential differences in efficacy/side effects based on time of day administration. Applying the knowledge of circadian function and regulation to the relevance of disease has enabled a chronotherapy approach in the timing of administration of conventional drugs in order to synchronize the rhythms in disease activity with the efficacy of the drug. Furthermore, recent advances in targeting the protein components involved in maintenance of the core circadian rhythm have allowed us to examine pharmacological alteration of the core rhythm to examine potential utility for treatment of disease.

Circadian rhythms influence most, if not all of mammalian physiology. Optimizing and coordinating metabolic processes, cellular functions and the organism's behavior including the sleep-wake cycle can be viewed as the main tasks of the circadian timing system (CTS).[2] The CTS is hierarchical in structure with the master pacemaker located in the superchiasmatic nucleus (SCN) of the hypothalamus. This master pacemaker coordinates countless peripheral clocks within various tissue and cell types. In general, the molecular makeup of oscillators within the SCN and the periphery are very similar, with the main difference being how they are synchronized and influenced by various signals. The SCN is entrained by light received by the retina while the peripheral oscillators are often adjusted by chemical signals or by feeding[2,7–9] (Fig. 1).

Feedback regulation on a transcriptional and posttranscriptional level creates and maintains the circadian oscillations in the context of a single cell. Heterodimers of transcription factors, either CLOCK or NPAS2 with BMAL1 bind to DNA E-box elements within enhancer and promoter regions of the *Cryptochrome* (*Cry*) and *Period* (*Per*) genes and stimulate their transcription. CRY and PER protein levels accumulate to form complexes that inhibit the BMAL1-CLOCK/NPAS2 heterodimers, leading to the loss of activation of *Cry* and *Per* genes, and a reduction of CRY and PER protein levels which leads to the next transcriptional cycling event.[2,10,11] Additionally, BMAL1–CLOCK/NPAS2 heterodimers also drive the circadian expression of REV-ERB, an nuclear receptor that represses both *Bmal1* and *Clock* gene transcription by direct binding to their promoters[12–14] (Fig. 2). An additional nuclear receptor, the retinoic acid receptor-related orphan receptor (ROR) also plays an important role activating transcription of the *Bmal1* gene by binding to the identical DNA response element recognized by REV-ERB.[15–17] Other proteins such as the WD40 protein, NONO DNA-binding protein, the WDR5 histone methyl transferase binding platform, and casein kinases (CK1) also play an important role in modulation of the feedback loop ensuring proper circadian function.[2,18] This self-sustained, cell autonomous circadian oscillator is maintained in most, if not all mammalian cells[19] and drives physiological alterations by controlling genes that are responsive to components of the oscillator—clock controlled genes (CCGs).

* Corresponding author. Tel.: +1 561 228 2217.
E-mail address: tburris@scripps.edu (T.P. Burris).

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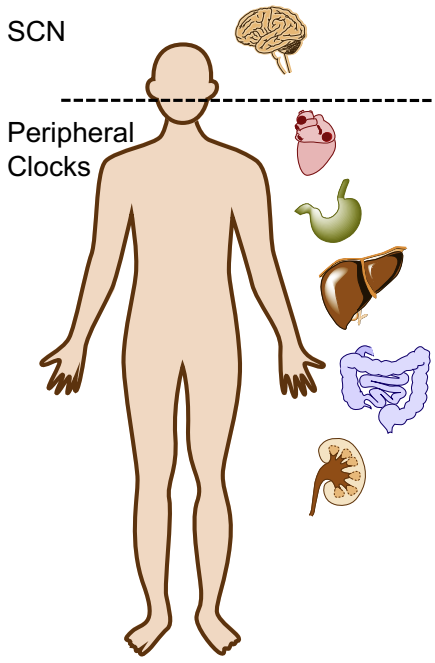

SCN Input	Light
SCN Output	Sleep/Wakefulness Feeding & Energy Expenditure Glucose Homeostasis Hormonal Regulation Body Temperature Regulation Blood Pressure & Respiratory Changes
Peripheral Clocks Input	Feeding/Fasting Signals from SCN
Peripheral Clocks Output	Lipogenesis Insulin Secretion Glucose Clearance Food Absorption Fat Accumulation

Figure 1. Circadian clocks exist both in the central nervous system and in the peripheral tissues. The figure illustrates the master clock (suprachiasmatic nucleus (SCN)) is via light received by the retina. The peripheral clocks of many organs are also illustrated and can be entrained by signals from the SCN as well as other signals such as nutrient availability.

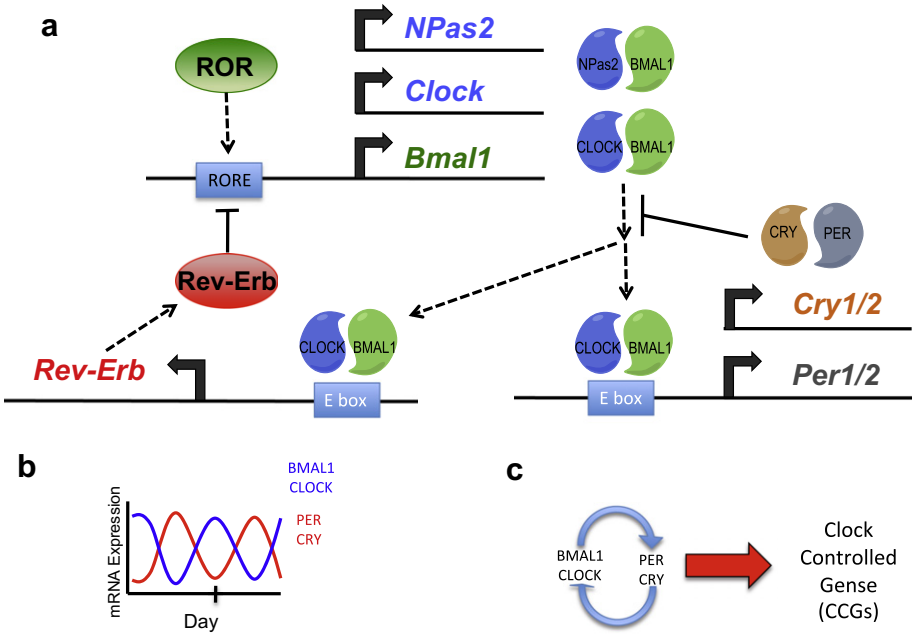

Figure 2. The mammalian circadian clock. (a) The mechanism of the mammalian molecular clock illustrating the feedback loop that maintains 24-h oscillations of BMAL1-CLOCK/NPAS2 and PER-CRY expression. (b) Illustration of antiphase circadian oscillations of BMAL1-CLOCK/NPAS2 and PER-CRY expression. (c) Schematic illustrating the relationship between the core clock and clock-controlled genes.

Some components of the mammalian clock described above are clearly 'druggable' and very recent studies have demonstrated the effects of modulating the activity of these targets on circadian physiology as well as pathological states. The nuclear receptor REV-ERB was recently deorphanized and heme was identified as the physiological ligand[20,21] and these studies clearly suggested that synthetic compounds could directly target this nuclear receptor. Our group recently developed synthetic agonists for REV-ERB, SR9009, that demonstrated the ability to modulate circadian behavior as well as metabolism[3] (Fig. 3). Administration of REV-ERB agonists in mice resulted in alterations in the expression of clock genes both in the SCN and the periphery (liver, adipose and skeletal muscle). Circadian wheel running behavior was altered and interestingly, mice displayed increased energy expenditure with no increase in locomotion or food intake. Additionally, when administered to diet-induced obese mice, REV-ERB agonist SR9009 induced significant weight loss (fat mass) and reduced plasma triglycerides and cholesterol levels. Clearly, these data suggest that