Genetics of Circadian Rhythm Disorders

Anne-Marie Chang, PhD[a,b,*], Phyllis Zee, MD, PhD[c]

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• Advanced sleep phase • Circadian rhythm sleep disorders
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CIRCADIAN RHYTHMS IN MAMMALS

The circadian timing system is ubiquitous to nearly all organisms on earth. The 24-hour cycle of light/dark exhibited by the solar day is reflected in a myriad of circadian rhythms in many living organisms. External environmental changes in the 24-hour day synchronize the various physiologic, biochemical, and behavioral processes in a predictable pattern. The mammalian circadian pacemaker, or biological clock, is located in the suprachiasmatic nucleus (SCN) of the anterior hypothalamus. This circadian clock synchronizes internal biological processes to external time cues and maintains the temporal organization of these processes with each other. This type of circadian organization with respect to the external environment establishes temporal categories in which animals are active or at rest, and may have evolved in response to different needs of organisms (eg, availability of food) and reduced competition for resources. One such circadian rhythm is the timing of the sleep/wake cycle. The daily patterns of light and dark signals entrain the circadian clock as to the appropriate time for sleep.

As a diurnal species, human beings generally prefer to schedule activities during the daytime and sleep at night. Diurnal preference, the proclivity to schedule activity for certain times of the day, varies in the general population. Individuals who prefer to be active in the early part of the day (morning types) are often called larks and those who have a preference for nighttime activity (evening types) are known as owls. Many individuals, if not most, have a neither type diurnal preference. In the past 40 years several questionnaires have been developed and used to subjectively assess diurnal preference. Although they may have been originally developed to identify workers' tolerance of and abilities to adjust to changing work schedules, these questionnaires have become valuable research tools in examining the differences underlying morningness or eveningness and various influences on sleep timing. Morning and evening types have been shown to exhibit differences in circadian phase and phase angle of entrainment of body temperature and hormonal rhythms; in habitual timing of sleep and sleep propensity; and in performance measures. Diurnal preference is influenced by several environmental factors, such as work, school, and social schedules, but has also been shown to have a genetic component.

Numerous animal studies have shown that like diurnal preference, other expressions of circadian behavior have a genetic basis. The investigation of circadian mutants and homologs of circadian genes, originally identified in nonmammalian organisms, led to identification of the genetic components of the mammalian circadian pacemaker. This molecular mechanism consists of autoregulatory feedback loops of genes that regulate circadian timing at the levels of transcription, translation, and posttranslation; and shows remarkable conservation in many species,

[a] Division of Sleep Medicine, Harvard Medical School, 221 Longwood Avenue, Boston, MA 02115, USA
[b] Department of Medicine, Brigham and Women's Hospital, 221 Longwood Avenue, Boston, MA 02115, USA
[c] Department of Neurology, Northwestern University Feinberg School of Medicine, 710 North Lake Shore Drive, Chicago, IL 60611, USA
* Corresponding author. Division of Sleep Medicine, Harvard Medical School, 221 Longwood Avenue, Boston, MA 02115.
E-mail address: amchang@rics.bwh.harvard.edu

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including humans (**Fig. 1**). The genes that make up this mammalian molecular clock are essential to the generation of circadian rhythms, and mutations in these genes have been shown to result in loss of or alterations in these daily rhythms. Genetic components of this clock mechanism are found ubiquitously throughout various tissues suggesting that peripheral clocks play key roles in the maintenance of circadian alignment. Therefore, alterations of the molecular machinery are likely to affect multiple organ systems, in addition to the brain, which has implications for health that go beyond sleep and performance.

CIRCADIAN RHYTHM SLEEP DISORDERS

Sleep is essential for health and performance. As a physiologic and behavioral process, sleep is markedly conserved in numerous species and seems to fulfill multiple functions. Sleep loss, whether the result of insufficiency, disruption, or impairment, has serious implications for general health, mood, behavior, and cognitive performance. Acute and chronic sleep deprivation results in impairment of cardiometabolic function, cognitive performance, and mood.

The timing of sleep is critical to the duration and quality of sleep. For optimal sleep, the major sleep episode should be aligned with the circadian timing of sleep propensity. When the sleep homeostatic process and the circadian pacemaker are misaligned, sleep is disrupted. Habitual misalignment may result in circadian rhythm sleep disorders shown in **Fig. 2**. There are 2 categories of circadian rhythm disorders: those in which the external environment is altered relative to the internal circadian clock, such as jet lag and shift work sleep disorder; and those in which the internal clock is altered relative to the external environment, such as advanced sleep phase (ASP), delayed sleep phase (DSP), irregular sleep/wake, and nonentrained type.

Those in the first category may be temporary, as in the case of jet lag after travel across multiple time zones, which is alleviated once the circadian clock becomes reset to the external time (day/night cycle); or these conditions may be chronic, such as working a rotating shift for months or years, preventing the entrainment of sleep to a stable schedule. It is believed, however, that good sleep can be restored in individuals suffering from jet lag or shift work sleep disorder, once the external source of the misalignment is removed (eg, a shift worker quits their job or begins working a regular stable schedule). Although these disorders are environmentally or behaviorally induced, differences in the genetic regulation of circadian

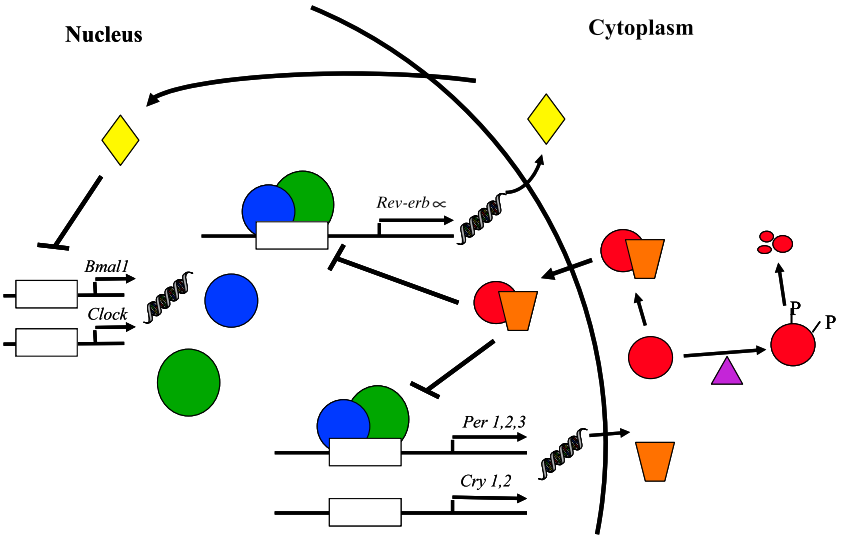

Fig. 1. The putative circadian clock molecular mechanism in mammals. Proteins of several circadian genes are color coded: CLOCK is green, BMAL1 is blue, PER are red, CRYs are orange, CKIε is purple, and REV-ERBα is yellow. CLOCK and BMAL1 are transcription factors that dimerize to initiate transcription of *Period* and *Cryptochrome* genes. PER and CRY proteins dimerize in the cytoplasm, reenter the nucleus, and negatively disrupt the CLOCK-BMAL1 complex to ultimately downregulate their own transcription. Once the transcription, translation, posttranslation, dimerization, and translocation turnover occur, the cycle begins again. The time course is approximately 24 hours. Other feedback loops, positive and negative, interconnect with and regulate this central loop.