Circadian Rhythm Dysfunction in Psychiatric Disorders

What is the Molecular Clock?

Virtually all living creatures have an internal molecular clock that synchronizes biological processes such as sleep/wake cycles, metabolism, and body temperature. The molecular clock oscillates with a period of approximately 24-hours; thus, these biologically processes are described as circadian rhythms. Although the molecular clock is self-sustaining, it needs to be reset daily or else it will drift and be out of sync with environmental cues and resources. Such environmental stimuli include light/dark cycles generated by the movement of the Earth and food availability. There are various factors that can reset the clock, however, light is the most powerful synchronizer. Light entering through the eye is translated via the retinohypothalamic tract to the suprachiasmatic nucleus (SCN) within the hypothalamus. During periods of darkness, the SCN induces release of melatonin from the pineal gland. Interestingly, melatonin can then act on receptors in the SCN to reset the clock (Fig. 1).

Given the sensitivity of the molecular clock to internal and external cues, it is not surprising that the molecular clock may become dysregulated due to many different factors. Social or lifestyle factors, such as shift work, can desynchronize the molecular clock. Mutations in the clock genes that comprise the molecular clock can lead to aberrant regulation of the molecular clock. Impaired neurotransmission, resulting in excessive or insufficient neurotransmitter concentrations can also lead to desynchronization of the molecular clock. As the molecular clock is influenced by neurotransmitters, many of the components of the molecular clock in turn regulate levels of neurotransmitters, including serotonin. A broken molecular clock is cause or effect, many psychiatric disorders, including depression, schizophrenia, and bipolar disorder are associated with disturbances to circadian rhythms.

Pharmacological treatment of psychiatric disorders often entails restoring balance to dysfunctional neurotransmission. Given the sensitivity of the molecular clock to external and internal cues, it is not surprising that the molecular clock may become dysregulated due to many different factors. Social or lifestyle factors, such as shift work, can desynchronize the molecular clock.

Mutations in Clock Genes Linked to Mental Illness

Many psychiatric disorders are associated with sleep disturbances. It is therefore not surprising that polymorphisms in the genes that comprise the molecular clock, CLOCK, CRY, PER, and REV-ERBα have each been associated with various psychiatric disorders, including bipolar disorder, depression, schizophrenia, and seasonal affect disorder.

The Molecular Clock Involves a Cycle of Feedback Inhibition

Heterodimers of CLOCK and BMAL1 bind to the E box promoter regions that regulate transcription of various proteins, including PER and CRY. As PER and CRY accumulate, they heterodimerize to form a complex. Expression of the nuclear receptors, REV-ERBs, is also regulated by binding of the BMAL1:CLOCK complex to an upstream promoter called the ROR/REV-ERBα response element (RRE) (Fig 2A). PER, CRY, and REV-ERBs each provide negative feedback regulation of their own expression. PER and CRY form a complex that inhibits CLOCK:BMAL1-regulated transcription. When REV-ERBα binds the RRE, expression of BMAL1 is blocked (Fig 1B). With expression of PER, CRY, and REV-ERBs inhibited due to the lack of CLOCK:BMAL1, feedback inhibition is no longer an issue. Additionally, RORα binding to the RRE, stimulates expression of BMAL1. Once present, BMAL1 can heterodimerize with CLOCK to begin the cycle of expression and feedback inhibition again (Fig 2C).

Components of the Molecular Clock

At the molecular level, the circadian clock consists of various proteins called transcription factors that work together in a series of negative feedback loops. These transcription factors bind to DNA regions called promoters, which are DNA sequences found near a gene. The binding of a transcription factor to a promoter may turn the gene on or off, thereby controlling production of proteins. In some cases, a heterodimer complex, formed by two different molecules, can act together to regulate transcription. Specifically, the transcription factors that make up the molecular clock include:

- CLOCK
- BMAL1
- PER
- CRY
- REV-ERBα
- RORβ
- RORα

The cycle repeats as BMAL1 and CLOCK proteins accumulate and again turn on transcription of PER and CRY. The cycle can shift due to both internal and external factors, such as changes in sleep/wake cycles and light/dark cycles. Such environmental stimuli are used in the synchronization of the molecular clock.