Circadian abnormalities, molecular clock genes and chronobiological treatments in depression

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Background: A long-standing challenge in the treatment of depression is the development of a rapidly acting antidepressant. Conventional antidepressants typically require 2–8 weeks for clinical remission. In contrast, chronobiological interventions such as sleep deprivation treatment dramatically reduce depressive symptoms within 24–48 h in 40–60% of depressed subjects. It is hypothesized that fast-acting treatments for depression may alter circadian rhythms through chronobiological mechanisms relevant to clock gene function.

Sources of data: A bibliographic review using Entrez PubMed with Boolean search terms ‘circadian’ and ‘depressive’ identified more than 1000 clinical papers published over a 40-year period (1966–present).

Areas of agreement: A large body of clinical data reports that sleep, temperature, hormone and mood changes in depression are consistent with disturbances in circadian-related processes.

Areas of controversy: Consensus has not been achieved in terms of defining underlying chronobiological mechanisms for optimal methods to produce rapid and sustained antidepressant responses to circadian interventions.

Growing points: Chronobiological augmentation using combinations of sleep deprivation with light therapy and/or sleep phase advance in medicated patients supports a clinical strategy for accelerating and sustaining antidepressant responses.

Areas timely for developing research: Advances in technology including improved assays for clock gene expression will facilitate exploring the role of clock genes and may lead to new rapidly acting antidepressant strategies and potential novel drug targets.

Keywords: circadian rhythm/depression/sleep deprivation

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Introduction

A large body of clinical data collected over three decades in a subgroup of depressed patients find sleep, temperature, hormone and mood changes consistent with disturbances in circadian-related processes. Circadian processes regulate daily physiological and biological rhythms to an approximate 24-h cycle. Circadian-related abnormalities are present in virtually all subtypes of depression including seasonal affective disorder (SAD), major depressive disorder (MDD) and bipolar disorder (BPD). This paper focuses on evidence supporting the hypothesis of abnormal clock gene function in mood disorders. Converging data from three areas of clinical research provide consistent evidence for circadian abnormalities in depression. These include physiological and behavioural abnormalities, the rapid (within hours) reversal of depression with circadian manipulations and the effects of antidepressants (e.g. SSRIs, MAOIs, tricyclics) and mood stabilizers (lithium and sodium valproate) on circadian-related mechanisms.

A compelling reason to study circadian effects is the rapid reversal of depressive symptoms that takes place within hours of sleep deprivation. A quick-acting antidepressant is a major advantage in treating depression. The rates of suicidality are significantly increased in the days and weeks following initiating treatment with conventional antidepressant medications while waiting for clinical remission. A rapidly acting antidepressant treatment would alleviate suffering and save lives.

This review presents data supporting the hypothesis that circadian abnormalities are associated with depression. As clock genes play a critical role in maintaining circadian rhythmicity, abnormal function in these genes and their related metabolic processes and pathways are hypothesized to contribute to the core pathophysiology of depression. Selected studies on circadian abnormalities and clock gene research are presented.

Sleep disturbance

Sleep disturbance is one of the predominant circadian abnormalities associated with depression. Approximately 70–80% of depressed patients complain of difficulty in falling asleep, staying asleep or experiencing early morning awakening. Electroencephalographic (EEG) recordings of sleep in depressed patients are suggestive of a dysfunction in several sleep parameters including a more rapid onset of rapid eye movement sleep and a reduction in slow wave sleep (see review).
Temperature dysregulation

Circadian regulation of thermoregulatory function may also be disrupted in depression. Temperature follows a diurnal pattern in healthy individuals. At dawn, temperatures begin to rise, gradually increase over the course into evening and then begin to decline until dawn. Depressed patients have elevated nocturnal core body temperature and higher overall mean temperatures. Remission in depressive symptoms is associated with a normalization of temperature rhythms.

Mood cycle

From a circadian perspective, it is of interest that many depressed patients experience a repetitive pattern of diurnal mood changes. Typically, these patients awaken with a severe depression in the early morning which gradually dissipates by early evening to an almost euthymic state. These cyclic mood patterns can persist for weeks and months through the course of the depressive episode. Such recurrent diurnal changes in mood may be a biomarker (predictor variable) for determining the probability of an antidepressant response to the circadian intervention sleep deprivation.

Hormone abnormalities

Circadian regulation of hormones, melatonin and cortisol may be dysregulated in depression. These hormones play a major role in the regulation of physiological processes.

Melatonin

Melatonin (N-acetyl-5-methoxytryptamine) is secreted at night by the pineal gland and the timing of its release has been used as a marker (zeitgeber) to determine circadian phase. The suprachiasmatic nucleus (SCN) regulates seasonal-dependent changes and controls the release of melatonin from the pineal gland. In depression, dim-light melatonin onset has been used as a test to assess circadian phase delays or advances. Approximately 2 h prior to bedtime, endogenous release of melatonin occurs in dim-light conditions. Many depressed patients have delayed melatonin release suggesting a phase delay in circadian rhythms. Additionally, depressed patients (SAD and BPD) may be supersensitive to light-induced suppression of melatonin.
Newer drugs, such as agomelatine, that target melatonin receptors can restore abnormal circadian rhythms. Clinically, agomelatine is shown to be effective in the treatment of SAD.\textsuperscript{10}

**Cortisol**

As reviewed by Keller \textit{et al.},\textsuperscript{11} up to 40–60\% of depressed patients have disturbances in hypothalamic–pituitary–adrenal (HPA) activity based on abnormalities in diurnal cortisol release as measured by the dexamethasone suppression test and the corticotrophin-releasing hormone (CRH) stimulation test. Bright-light therapy is an effective treatment for some depressed patients. This circadian use of bright-light therapy for depression activates the SCN, inhibiting CRH release and suppressing HPA activity.\textsuperscript{12} Impairment in the normal mechanisms that ‘turn off’ HPA activation can produce behavioural manifestations and neuro-vegetative responses similar to those seen in MDD including changes in sleep, appetite, concentration, motivation, pleasure seeking and psychomotor alterations.\textsuperscript{13} Research suggests that antidepressants may act by reducing HPA activity.\textsuperscript{14}

**Clues from sleep deprivation and bright-light therapy**

Treatment with sleep deprivation may offer valuable clues to the mechanisms that underlie rapid treatment of depression. Sleep deprivation has been used to treat more than 1000 depressed patients worldwide in more than 60 studies and is consistently reported to produce rapid (within 24–48 h) reversal of depressive symptoms in approximately 40–60\% of depressed patients.\textsuperscript{15} Sleep deprivation protocols vary, but essentially, the depressed patient is kept awake all night (total sleep deprivation) or part of the night (partial sleep deprivation). By the next morning, approximately half of depressed patients experience a dramatic improvement in mood which continues throughout the day. Relapse is common following recovery sleep; however, recent studies suggest that the response can be prolonged with adjunctive treatments which include antidepressant medications and mood stabilizers (e.g. lithium) and chronobiological (e.g. light therapy, sleep phase advance) interventions.\textsuperscript{16–19} Even the most-difficult-to-treat patients (treatment-resistant) may respond to sleep deprivation.\textsuperscript{16} Our research demonstrated that sleep deprivation plus adjunctive treatment is more efficacious than medication alone. We combined sleep deprivation with bright-light therapy and sleep phase advance to treat BPD and MDD depressed patients medicated
with antidepressants and lithium. We randomly assigned subjects to either a medication-only group (antidepressants and lithium) or to a chronobiological treatment group (one night of sleep deprivation followed by 3 days of bright-light therapy plus sleep phase advance). The patients treated with the chronobiological therapies showed a robust and faster onset of antidepressant response (within 48 h) than the comparison group. The rapid antidepressant response was maintained for the 7 weeks of the study and patients were significantly less depressed than the medication-only group (Wu et al., in preparation).

Clock genes that regulate circadian rhythms may play a role in depression

The circadian clock rhythmically controls a large number of physiological processes which oscillate with a period close to 24 h. The activities of peripheral and central nervous system clock genes are coordinated by a small area of the brain known as the SCN which is located in the anterior hypothalamus. Clock genes in the SCN maintain rhythmicity throughout the body. A subset of clock genes are responsive to changes in the environment and can be entrained (synchronized) to signals (zeitgebers) such as those related to changes in the day/night cycles (light). Abnormal function in clock genes that are specific to entrainment may lead to depressive disorders following diurnal or seasonal changes (e.g. SAD) in light. Other circadian-regulated clock genes associated with sleep and temperature, for example, may produce the sleep characteristics of SAD or other types of mood changes that may be specific to MDD or BPD.

Current research is focusing on the core clock genes in the SCN that regulate the ‘master clock’. These core clock genes are essential to maintaining circadian rhythmicity and therefore abnormalities in the function of any of these genes could potentially play a role in depression. Several core clock genes have been characterized including the period genes ($per1, per2, per3$) and the cryptochrome genes ($cry1, cry2$) as well as $clock$ and $bmal1$ and their proteins. (Proteins are denoted by capital letters, whereas genes are in italics; see Fig. 1.) There are a number of autoregulatory feedback loops that operate by switching their own gene expressions on and off. These transcriptional/translational feedback loops regulate circadian timing through a series of complex interactions to maintain approximate 24-h rhythms.

Two major circadian regulatory feedback loops are depicted in Figure 1. A negative feedback loop represses clock gene expression for the transcription of its protein products, $PERIOD$ ($PER1$, $PER2$, $PER3$)
and CRYPTOCHROME (CRY1, CRY2). A positive feedback loop drives clock gene expression. The \textit{bmal1} and \textit{clock} genes encode BMAL1 and CLOCK proteins, respectively. BMAL1 and CLOCK form heterodimers (i.e. they bind together to DNA elements in the promoter region of their target genes to activate the transcription of \textit{per} and \textit{cry} genes). In turn, the proteins encoded by \textit{per} and \textit{cry} genes also form heterodimers and enter the nucleus to inhibit their own transcription. The timing of these events is critical to the frequency and amplitude of the circadian generated oscillations. Figure 1 is overly simplified as additional genes and their products function to fine-tune the circadian clock. Newer research focuses on posttranslational processes such as the phosphorylation of clock genes (phosphorylation can either stabilize or destabilize clock gene proteins).

An example of a posttranslational process is chromatin remodelling. Chromatin is the complex of DNA and proteins found in chromosomes and can control cell division and gene expression. Chromatin remodelling takes place at DNA-containing nucleosomes and regulates the activation of gene expression controlled by folding or unfolding chromatin structures. When the chromatin is unfolded, the DNA is exposed and

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\textbf{Fig. 1.} A simplified diagram of the autoregulatory feedback mechanisms involved in the regulation of the mammalian circadian clock in the SCN. The interactions between a negative feedback loop repressing \textit{per} and \textit{cry} gene transcription (blue lines) and a positive feedback loop promoting \textit{Bmal} and \textit{Clock} transcription (red lines) helps maintain circadian rhythmicity.
transcription can be activated. Histone acetyltransferases (HATs) proteins ‘open-up’ chromatin and promotes transcription. Interestingly, the circadian gene clock has been shown to have HAT activity, whereas histone deacetylases ‘close’ chromatin making it inaccessible to transcriptional processes. Chromatin remodelling may play an important role in the phase-shifting effects of light on circadian rhythms.21 (Another posttranslational mechanism is methylation which is not discussed here.)

Clock gene research in depressive illness

Although relatively few studies have been completed and findings need replication, there are interesting clues to implicate abnormal clock gene function in depressive illness, at least in a subgroup of patients.

Seasonal affective disorder

SAD, characterized by recurring fall and winter depressions (with remissions during spring and summer), affects approximately 5% of the population.22 SAD depression is frequently characterized by hypersomnia, overeating and carbohydrate craving and, in some respects, mimics behaviours associated with hibernation in animals. Circadian-related polymorphisms are associated with an increase in susceptibility to SAD. Recent work by Partonen et al.23 focused on changes in clock gene expression in patients suffering from SAD or BPD disorder (with winter depression). One single-nucleotide polymorphism (SNP) was examined for each of three circadian genes, per2, Bmal1 and Npas2 (a gene similar to clock) for association with SAD. According to the investigators, the risk for developing SAD is increased if these genes contain the SNP variations. A separate study on the clock gene 3111C/T polymorphism showed no significant association with SAD.24

Bipolar disorder

BPD is a subtype of major mood disorder. Bipolar patients experience episodes of both depression and mania. A study to examining linkage and association of 10 core clock genes with BPD found a non-significant trend in two of the core clock genes (per3, bmal1).25 In other work, Benedetti et al.26 found that BPD patients who were homozygous carriers for the C alleles of the 3111 SNPs in the 3’ flanking region of the clock gene [3111C/T] were more likely to have a
phase delay in sleep onset, higher rates of insomnia and a diurnal preference for evening activity as compared to controls. They reported that patients homozygous for the C alleles were more active in the evening (before lights were turned off) compared to patients carrying the T alleles. However, there was no difference in the severity of depression in the patient groups according to their allele status. Shiino et al. screened for polymorphisms in the CK1ε region of the human period 2 (hper2) gene and found no association with BPD in a group of Japanese patients. In other work, BPD patients who are homozygous for the SNP (−50T/C) variant in the promoter region of the GSK3β gene show a less severe form and a later onset of bipolar illness and are more likely to respond to one night of total sleep deprivation. The mood stabilizer, lithium, commonly used to treat BPD inhibits GSK3β expression.

**Major depressive disorder**

Serretti et al. reported that polymorphisms in CLOCK protein (homozygous for the C alleles) are related to sleep abnormalities in MDD (and BPD) patients but are not specifically linked to depression. MDD patients having the C alleles had a higher incidence of initial insomnia (BPD patients having the same alleles had insomnia throughout the night and a reduced need for sleep). Antidepressants did not reverse the insomnia. Excessive sleep was not associated with the CLOCK in either BPD or MDD. Allelic differences in CLOCK at the T3111C locus may influence sleep but probably is not linked to MDD or BPD.

**Directions for future research**

A review of the PubMed literature over the past 12 months listed more than 500 papers published on the topic of circadian-related clock genes. The newly identified characteristics of clock genes are beginning to provide intriguing clues to the circadian-related deficits of depressive illness. One example concerns phase analyses. In non-human primates, there is a tendency for clock gene expression to peak at a phase corresponding to the ‘anticipation’ of dawn or dusk. This could imply that dawn and dusk are critical windows for therapeutic interventions. Advances in technology including improved assays for clock gene expression will facilitate exploring the role of clock genes and are likely to lead to new rapidly acting interventions.
References


