The role of the endogenous circadian system is to coordinate the body’s functions with each other and with the external environment. This includes the integration of sensory information and environmental time cues, and of the organism’s physiological and psychological states. When the harmony of this integrative function is perturbed, as could be the case with several mental disorders, disturbances of mood, a disrupted sleep-wake cycle, and changes in levels and/or timing of hormones can occur. Whether these changes precede, follow, or are episodically activated can be associated with depressed mood, anxiety, and other psychiatric symptoms. The study of molecular clock mechanisms in psychiatric disorders is gaining significant interest due to data suggesting that a misalignment between the endogenous circadian system and the sleep-wake cycle might contribute to the clinical status of patients suffering from a variety of psychiatric disorders. Sleep disturbances in major depressive disorder (MDD) are characterized by increased sleep latency, poorer sleep efficiency, reduced latency to the first rapid eye movement (REM) sleep episode, and early-morning awakening, but there is little data to indicate a role of circadian clock genes in MDD. There is also relatively little information regarding the role of clock genes in anxiety. In contrast, a significant amount of evidence gathered in bipolar disorder (BPD) patients suggests a circadian rhythm disorder, namely an advanced circadian rhythm and state-dependent alterations of REM sleep latency. Most research on the role of clock genes in BPD has focused on polymorphisms of CLOCK but the lithium target GSK3 may also play a significant role. A circadian phase shift is also theorized to contribute to the pathophysiology of winter seasonal affective disorder (SAD). Certain allelic combinations of NPAS2, PER3, and BMAL1 appear to contribute to the risk of SAD. In chronic schizophrenia, disturbances of sleep including insomnia and reduced sleep efficiency have been observed. Genetic studies have found associations with CLOCK, PER1, PER3, and TIMELESS. Sleep and circadian changes associated with dementia due to Alzheimer’s disease suggest a functional change in the circadian master clock, which is supported by postmortem studies of clock gene expression in the brain.

Keywords: clock gene; mental disorder; mental health; major depressive disorder; bipolar affective disorder; seasonal affective disorder; schizophrenia; Alzheimer’s disease; sleep-wake cycle; rest-activity cycle; single-nucleotide polymorphism

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nominal to the mental disorders is often difficult to determine with certainty, although several lines of evidence support a role of the endogenous circadian system in the pathophysiology of these disorders. The purpose of this review is to describe sleep and circadian rhythm disturbances in mental disorders and to summarize current research on the role of clock genes in several psychiatric disorders.

Molecular mechanism of circadian rhythmicity

Circadian rhythmicity is a consequence of intracellular molecular mechanisms involving so-called clock genes. The products of some of these clock genes regulate their own expression, and the outcome of this feedback loop is an oscillation in the levels of messenger ribonucleic acids (mRNAs) and proteins. These mRNA and protein rhythms are observed in the suprachiasmatic nucleus (SCN) of the hypothalamus, the master clock, as well as in other brain regions and peripheral tissues. Within the clock, other factors control the phosphorylation, stability, and localization of clock proteins, thereby regulating the oscillation, particularly the period.

In mammals, Clock and Bmal1 encode transcription factors CLOCK and BMAL1 (brain and muscle ARNT-like protein 1; also known as ARNTL or MOP3), which form heterodimers that activate the transcription of three Period genes (PER1, 2 and 3) and two Cryptochrome genes (CRY1 and 2). Rorα and Rev-Erbα act on Bmal1 to activate and repress transcription respectively. NPAS2 is an alternate dimerization partner for BMAL1 that may also regulate circadian rhythmicity in the forebrain, but it has not been consistently found in the SCN. Clock proteins are phosphorylated by casein kinase I epsilon (CKIε) and delta (CKIδ), and possibly also by the Drosophila shaggy homologue glycogen synthase kinase 3 (GSK3). They are targeted for degradation by components of ubiquitin ligase complexes like FBXL3 and β-TRCP1, which together regulate the period of circadian oscillation by controlling the rate of accumulation, association and translocation of PER and CRY.

These genes, protein products, and enzymes work together to control clock functioning, and abnormalities such as clock gene mutations can have profound consequences for the synchronization of emotional, physiological, and behavioral processes with each other and the environment. Examples of the sometimes dramatic effects of clock gene polymorphisms in nonpsychiatric disorders are described, followed by a description of recent research on clock genes in mental disorders.

Figure 1. Simplified schematic diagram of the molecular mechanisms of the circadian clock in mammals. See the main text for details. Positive and negative feedbacks are indicated by arrows with a + and a - sign, respectively. Genes and messenger ribonucleic acid (mRNA) are indicated by italics, proteins are in bold caps. C = CLOCK protein; N = NPAS2 protein; B = BMAL1 protein.
Role of circadian clock genes in disorders of the sleep-wake cycle

The evidence linking mutations of circadian clock genes and nonpsychiatric sleep/circadian related disorders is compelling. In fact, one of the first demonstrations of a disorder directly related to the human molecular clock was a polymorphism of human \( PER2 \) identified in a family diagnosed with familial advance sleep phase disorder (FASPD).\(^{24}\) The resulting amino acid change in the \( PER2 \) protein affects its phosphorylation by \( CKI\delta/\epsilon \), and its stability and intracellular localization, hence the short period and advanced sleep phase of the patients.\(^{25,26}\) Interestingly, in another FASPD family, a mutation was found in the gene encoding \( CKI\delta \).\(^{28}\)

A number of studies have focused on a polymorphism in the human \( PER3 \) gene. In one study, this polymorphism was found to be associated with delayed sleep phase disorder (DSPD).\(^{29,30}\) \( PER3 \) variants have also been associated with morning-evening preference, in this study, possibly through an effect on sleep structure, but not circadian timing. Viola and colleagues\(^{31}\) found that individuals homozygous for the \( PER3 \) allele showed marked differences in sleep compared with those homozygous for \( PER3 \), including greater sleep propensity, increased slow-wave sleep (SWS) and greater susceptibility to the effects of sleep deprivation. However, the circadian rhythms of melatonin, cortisol, and activity were similar in both groups.\(^{31}\) This suggests that different clock genes may affect chronotype, either via direct effects on the clock, or through other mechanisms such as sleep homeostasis.

Polymorphism of the human \( CLOCK \) gene has also been associated with evening preference and delayed timing of the sleep-wake cycle\(^{32,33}\) (but there are also conflicting results\(^{34}\)). Subjects carrying one or two copies of the \( CLOCK \) 3111C allele showed increased eveningness and reduced morningness, while 3111T/T subjects showed higher morningness scores.\(^{32,33}\) Although the 3111C/C genotype is also associated with delayed sleep timing and greater daytime sleepiness in a Japanese population,\(^{33}\) thus far there is insufficient evidence to draw the same conclusions in Caucasians.\(^{32}\) There is currently no evidence to support an association between the 3111C/C genotype and DSPD.\(^{34,35}\)

There is evidence to suggest that evening chronotype could increase the risk of psychiatric disorders.\(^{36}\) Both bipolar disorder (BPD) and schizophrenia/schizoaffective patients show greater eveningness scores than controls. In BPD this observation appears to be correlated with age (ie, younger BPD patients were more extreme “evening types”), while schizophrenia/schizoaffective subjects tended to show greater eveningness at all ages. Being classified as an “evening type” could account for some of the sleep disturbances reported by BPD patients\(^{36}\) and could increase the severity of BPD as evidenced by an earlier age at onset of treatment, greater likelihood of self-reported rapid mood swings, and rapid-cycling mood changes.\(^{36}\)

Some work suggests there may be a relationship between DSPD and personality disorder.\(^{37}\) In one study, 16% of institutionalized mentally ill adolescents were also diagnosed with DSPS,\(^{38}\) as compared with 7.3% of adolescents in Western countries.\(^{37}\) In these adolescents, the diagnoses tended to include an affective component, such as bipolar affective, schizoaffective or borderline personality disorder. Again, this suggests a relationship between circadian and psychiatric disorders, although whether one precedes the other or they co-occur is difficult to determine.

Sleep, circadian clock genes, and mental disorders

Major Depressive Disorder

Sleep disturbances, particularly insomnia, are an important symptom of Major Depressive Disorder (MDD).\(^{39-42}\) Between 80% and 90% of depressed patients report insomnia, and insomnia is also a risk factor for developing depression.\(^{39,41}\) Sleep disturbances are associated with impaired quality of life\(^{43}\) and a greater risk of relapse.\(^{44,45}\) Reduced rapid eye movement (REM) sleep latency (RL), an earlier distribution of REM sleep during the night, and early-morning awakening suggest a possible phase advance of the endogenous circadian system.\(^{46,47}\) This hypothesis is further supported by the therapeutic success of sleep phase advance therapy in depressed patients.\(^{48}\) Higher core body temperature (CBT),\(^{49}\) higher cortisol\(^{50-53}\) and lower melatonin secretion\(^{54,55}\) have been observed in depressed patients, supporting an involvement of the circadian system, although contradictory results exist,\(^{54,56-58}\) (see refs 46 and 47 for reviews). To date there has been no evidence of clock gene mutations associated with MDD. The T3111C polymorphism of \( CLOCK \) was investigated, based on its association...
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with eveningness, but no differences were found in allelic frequencies between a group of 143 people with a history of major depression and 195 controls. However, there has been some recent evidence suggesting that electroconvulsive therapy and antidepressant medications targeting the dopaminergic and serotonergic neurotransmitter systems, including, monoamine oxidase inhibitors (MAOIs), fluoxetine, imipramine, clozapine, risperidone, and haloperidol may have a common mode of action either via the direct inhibition or increased phosphorylation of the GSK3 enzyme. GSK3 is involved in many cellular functions; therefore the therapeutic action may be via a number of possible routes, including regulation of monaminergic signaling, neuroprotection, neuroplasticity, modulation of estrogen and glucocorticoid activity, regulation of brain metabolism, or regulation of the circadian system. This is described in more detail in the section on BPD below.

Anxiety disorders

Individuals suffering from an anxiety disorder frequently experience sleep disturbances such as insomnia. Sleep disorders are common in both generalized anxiety disorder (GAD) and post-traumatic stress disorder (PTSD), and PTSD patients frequently experience nightmares, and reduced REM sleep. There is relatively little evidence suggesting specific circadian disturbances or a role for clock genes in anxiety disorders. This is perhaps not surprising, given the heterogeneity of anxiety disorders and their comorbidity with other disorders such as depression. In contrast to studies in humans, there are a few interesting results from research on animals. One study showed a reduction of Per1 mRNA levels in mouse cerebellum by anxiolytic medications, suggesting that altering circadian clock gene levels could theoretically contribute to the therapeutic action of these drugs. Also of interest is the observed reduction in anxiety observed in mice with a mutation of the Clock gene. For example, Clock mutant animals are much more likely to spend time in open spaces, which normal mice avoid. However, as these mice also showed behaviors associated with mania, it is unclear how to best classify this phenotype.

Bipolar disorder

Sleep disturbances have been observed in BPD and often precede relapses into depression or mania. Insomnia or hypersomnia, early-morning awakenings, reduced sleep efficiency, and reduced RL are the most consistently reported changes. Irregularities in the sleep-wake cycle and daily activities can be important contributing factors in mood disruption. The relationship between the sleep-wake cycle and changes in mood appears to be important in patients with frequent and rapid changes in mood state, so-called “rapid cyclers,” with the switch from mania/hypomania to depression/euthymia occurring during or after sleep, while positive changes in mood from depression to hypomania/mania are more likely to occur after a period of wakefulness. Circadian disturbances have been reported in BPD that suggest a phase advance of the master clock, including a phase advance of the diurnal rhythm of plasma cortisol, although negative results have been reported. Much of the work attempting to link BPD to clock genes has focused on the 3111T/C polymorphism of the human CLOCK gene. The C/C allele of CLOCK has been associated with greater severity of insomnia during antidepressant treatment and a higher recurrence rate of bipolar episodes, and reduced need for sleep. Support for a role of Clock mutation in BPD has recently come from the animal literature, where behavioral studies using CLOCK mutant mice suggest a phenotype similar to mania, with an increase in the reward value of appetitive stimuli and reduced depressive and anxiety-like behaviors. An analysis of 46 single nucleotide polymorphisms (SNP) in eight clock genes (BMAL1, CLOCK, PER 1,2,3, CRY 1,2, TIMELESS) using family-based samples with BPD or schizophrenia has been reported. A Mendelian transmission distortion analysis revealed association of BMAL1 (ARNTL) and TIMELESS with BPD. However, these were modest associations found using a very liberal analysis. Interestingly, an independent study using haplotype analysis seems to confirm the association with BMAL1 (ARNTL) and also finds one with PER3 (TIMELESS was not studied). Studies examining other genes have found negative results; screening for human PER2 mutations at the CKIβ/ε binding site showed no difference in frequency between BPD patients and controls, nor is there any evidence for linkage or association of CRY1. Although it has been known for many years that lithium is effective as a mood stabilizer, its pharmacological mode of action has remained uncertain. However, recent evidence suggests that the therapeutic action of
lithium may be related to direct effects on the circadian clock. For example, lithium has been shown to lengthen the period of circadian rhythms in rodents,\textsuperscript{85} and can lengthen the period of neuronal firing of cultured SCN neurons in a dose-dependent manner.\textsuperscript{82} A delay of the circadian rhythm of temperature and of REM sleep has also been shown in a BPD patient.\textsuperscript{86} This suggests that the therapeutic action of lithium could be due, in part, to correcting a phase advance of the circadian system related to the illness.

One proposed molecular mechanism is via the inhibition of GSK3.\textsuperscript{18,84} Although this enzyme has a number of functions that could potentially mediate the therapeutic effects of lithium,\textsuperscript{85} one likely possibility is via its function as a central regulator of the circadian clock.\textsuperscript{86} Numerous lines of evidence support this idea; both lithium and GSK3 knockdown produce a lengthening of mPer2 period in mouse fibroblasts,\textsuperscript{86} and GSK3 phosphorylates PER2 and REV-ERBα and regulates their localization and stability, respectively.\textsuperscript{18,84} Even more interesting are findings that inhibition of GSK3 may be common to other mood-stabilizing agents such as valproate, and may even be a target of antidepressant therapies, including drugs which target the serotonergic and dopaminergic systems as well as electroconvulsive therapy.\textsuperscript{90} There is also evidence for effects of allelic frequency of the GSK3β -50 T/C SNP. Bipolar patients with the T/T allele of GSK3β show an earlier age on onset of bipolar disorder and enjoy less improvement from lithium therapy than patients with the T/C or C/C alleles.\textsuperscript{87,88} Together these results are persuasive, making GSK3 a promising target for the future development of pharmerapeutic agents.

### Seasonal affective disorder

Seasonal affective disorder (SAD) patients frequently have sleep complaints, particularly hypersomnia, with longer polysomnographically-recorded non-REM (NREM) sleep and greater slow-wave activity per minute of NREM sleep.\textsuperscript{89} A chronobiological hypothesis of SAD has been suggested for a while.\textsuperscript{90-91} The phase shift hypothesis postulates that SAD patients become depressed in winter because there is a season-specific shift in their endogenous circadian system with respect to their sleep-wake cycle.\textsuperscript{90} Bright light exposure and/or exogenous melatonin have been used successfully to correct this phase shift.\textsuperscript{92}

Recent studies suggest that polymorphisms of \textit{PERIOD2}, \textit{NPAS2}, and \textit{BMAL1 (ARNTL)} could be associated with an increased risk for SAD. These three clock genes were analyzed for SNPs in a sample of 189 SAD patients and an equal number of matched controls. Specifically, polymorphisms of \textit{BMAL1}, \textit{PER2}, and \textit{NPAS2} are associated with SAD, but together, certain allelic combinations of SNPs of these three genes have an additive effect, increasing the risk of developing SAD by 4.43 over other genotypes, and 10.67 over the most protective genotype.\textsuperscript{93} An association of the same leucine allele for \textit{NPAS2} 471 had been reported previously.\textsuperscript{94} In addition, this study supported a relationship between the \textit{PER3} 647 Val/Gly genotype and morningness/eveningness, particularly in the SAD group.\textsuperscript{94} This reinforces the suggestion of an association between certain clock gene polymorphisms and chronotype. Also, it suggests that certain abnormalities in the circadian molecular clock increase the susceptibility to SAD.

### Schizophrenia

Sleep abnormalities have been consistently found in schizophrenia, although the results have not been consistent across studies.\textsuperscript{95} These include insomnia, reduced total sleep time (TST), increased sleep latency, poor sleep consolidation and sleep efficiency, and low levels of SWS, with insomnia frequently signaling relapse.\textsuperscript{96} Actigraphic recordings of schizophrenic patients have revealed disturbed rest-activity cycles, showing either phase delays, longer periods of activity, or circadibidian rest-activity patterns.\textsuperscript{97-99} The study of schizophrenic patients by a forced desynchrony experiment revealed an abnormal circadian propensity for sleep suggesting a disturbed circadian regulation of sleep.\textsuperscript{100} Another study reported desynchronization of CBT; pulse and blood pressure rhythms.\textsuperscript{101} The analysis of melatonin secretion demonstrated blunted circadian variation.\textsuperscript{102-104} Others have reported phase advances of prolactin, melatonin and tryptophan.\textsuperscript{105} Evidence linking circadian clock gene polymorphisms or deregulation with schizophrenia is limited. In one study, SNP analysis of the \textit{CLOCK} gene demonstrated that the T3111C polymorphism showed a transmission bias in a sample of 145 Japanese schizophrenic subjects relative to healthy controls.\textsuperscript{106} The authors suggested that this polymorphism, associated with aberrant dopaminergic transmission to the SCN may underlie the pathophysiology of schizophrenia. Since dopaminergic signal-
Dementia

Dementia associated with Alzheimer’s disease (AD) has frequently been associated with psychological disturbances that tend to worsen with the progression of the disease.\textsuperscript{111-113} Disturbances of sleep and the rest-activity cycle are common, including “sundowning,” consisting of increased wandering, aggression, vocalization, and agitation during the evening, as well as polysomnographic sleep measures including increased wake after sleep onset, reduced nocturnal TST, sleep efficiency, and REM sleep, and increased RL, and electroencephalogram (EEG) slowing. In addition, these changes in sleep variables may have diagnostic value as there is some evidence suggesting that sleep disturbances in AD patients correlate with lower cognitive scores.\textsuperscript{114-116} In addition, changes in circadian rhythms of a number of physiological variables have been noted in AD patients including reduced amplitude and increased fragmentation of the circadian rhythm of activity, reduced amplitude and phase delay of the CBT rhythm, and reduced amplitude of the rhythms of melatonin and its metabolite 6-sulfatoxymelatonin.\textsuperscript{117-120} Although AD patients were not significantly different from healthy age-matched controls on all variables, the delay of CBT phase is of particular note because of a tendency toward phase advance of CBT in normal aging.\textsuperscript{121} Anatomical studies suggest that the changes in the circadian organization of the hormonal and sleep-activity cycles observed in AD sufferers are due to fundamental changes in the master clock itself.\textsuperscript{122} Molecular changes in clock gene expression have been identified in the pineal gland, the brain region that produces melatonin in response to timing information from the SCN master clock. Post-mortem pineal tissue from non-demented subjects shows rhythmic circadian fluctuations of BMALI, CRYI, PERI, melatonin, melatonin synthesis, and β\textsubscript{1}-adrenergic receptor mRNA, the receptor responsible for the circadian control of melatonin levels in the pineal. In contrast, AD patients did not show any evidence of day-night differences in clock gene expression, pineal melatonin, melatonin synthesis activity, or β\textsubscript{1}-adrenergic receptor mRNA levels, suggesting malfunction in the circadian signal from the SCN.\textsuperscript{123,124} Based on this evidence, it is possible that a weakening of the signal from the SCN may also be responsible for changes observed in CBT and the sleep-wake cycle of AD patients.

Conclusion

Evidence is mounting for a relationship between BPD and clock genes, particularly with a polymorphism of the gene CLOCK. Also of considerable interest is the relationship between mood-stabilizing and antidepressant treatments and GSK3. Although research linking clock genes and other mental disorders is still in the early stages, the findings to date suggest that this approach may be fruitful, especially in SAD and schizophrenia. Certainly the potential utility of a genetic screening tool for the differential diagnosis of mental disorders can not be underestimated. Clock genes provide a good target for this type of approach. In addition, clock genes could open up a new frontier for genetic therapies, as well as guide the development of new pharmaceuticals. Well-controlled studies in psychiatric populations must be pursued in order to increase our knowledge of sleep and circadian rhythm disturbances in mental disorders and on the genetic basis of these disturbances.\textsuperscript{•}
El papel de los genes del reloj circadiano en la enfermedad mental

El estudio de los mecanismos del reloj molecular en los trastornos psiquiátricos tiene un interés creciente ya que la evidencia sugiere que un desajuste entre el sistema circadiano endógeno y el ciclo sueño-vigilia podría contribuir al estado clínico de pacientes que sufren diversos trastornos psiquiátricos. Las alteraciones del sueño en el trastorno depresivo mayor (TDM) están caracterizadas por un aumento en la latencia de sueño, una pobre eficiencia de sueño, una reducción de la latencia para el primer episodio de sueño de movimientos oculares rápidos (MOR) y un despertar matinal precoz, pero existe escasa evidencia para explicar el papel de los genes del reloj circadiano en el TDM. También es escasa la información sobre los genes del reloj en la ansiedad. En oposición, se ha acumulado una importante cantidad de evidencia en pacientes con trastorno afectivo bipolar (TAB) la que sugiere un trastorno del ritmo circadiano, especialmente un avance de éste y alteraciones de la latencia del sueño MOR estado dependientes. Gran parte de la investigación acerca del papel de los genes del reloj en el TAB se ha centrado en el polimorfismo de CLOCK; pero GSK3, blanco del litio, también puede tener un papel significativo. Además se postula que un cambio de fase circadiana puede contribuir a la fisiopatología del trastorno afectivo estacional invernal (TAE). Al parecer ciertas combinaciones de alelos de genes como NPAS2, PER3, y BMAL1 contribuyen al riesgo de un TAE. En la esquizofrenia crónica se ha observado insomnio y reducción de la eficiencia del sueño. Los estudios genéticos han encontrado asociaciones con genes como CLOCK, PER1, PER3, y TIMELESS. Los cambios circadianos y del sueño asociados con la demencia de la Enfermedad de Alzheimer sugieren un cambio funcional en el reloj maestro circadiano de acuerdo con estudios postmortem de la expresión genética del reloj en el cerebro.

Rôle des gènes de l’horloge circadienne dans la maladie mentale

L’intérêt grandissant de l’étude des mécanismes moléculaires de l’horloge dans les troubles psychiatriques s’explique par les données qui indiquent une mauvaise synchronisation entre le système circadien endogène et le cycle veille-sommeil lors de ces troubles et par l’hypothèse que ceci jouerait un rôle dans l’état clinique des patients. L’allongement du temps d’endormissement, un sommeil moins réparateur, une diminution de la latence du premier épisode de sommeil paradoxal et un réveil matinal précoce sont caractéristiques des perturbations du sommeil dans les troubles dépressifs majeurs (TDM). Le rôle des gènes de l’horloge circadienne reste cependant mal défini dans les TDM et dans l’anxiété. En revanche, un trouble du rythme circadien chez les patients atteints de troubles bipolaires (TB) semble exister, du type d’avance du rythme circadien et d’altérations de la latence du sommeil paradoxal en relation avec l’état pathologique. La recherche sur le rôle des gènes de l’horloge dans les TB a surtout porté sur un polymorphisme du gène CLOCK, mais le GSK3, cible du lithium, pourrait aussi jouer un rôle significatif. La possibilité d’un décalage de phase des rythmes circadiens pourrait également intervenir dans la physiopathologie du trouble affectif saisonnier hivernal (TAS). Certaines combinaisons d’allèles des gènes NPAS2, PER3, et BMAL1 semblent contribuer au risque de TAS. Dans la schizophrénie, des troubles du sommeil comprenant insomnie et diminution de l’efficacité du sommeil sont présents. Des études génétiques ont trouvé des associations avec les gènes CLOCK, PER1, PER3, et TIMELESS. Des études postmortem de l’expression des gènes de l’horloge dans le cerveau soutiennent l’hypothèse d’anomalies fonctionnelles de l’horloge circadienne lors des modifications circadiennes et du sommeil associées à la maladie d’Alzheimer.

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