

Circadian Rhythms and Clock Genes in Psychotic Disorders

Elaine Waddington Lamont, PhD,^{1,2} Daniel L. Coutu, MSc,³ Nicolas Cermakian, PhD,² and Diane B. Boivin, MD, PhD¹

¹ Centre for Study and Treatment of Circadian Rhythms, Douglas Mental Health University Institute, Faculty of Medicine, McGill University, Montreal, QC, Canada

² Laboratory of Molecular Chronobiology, Douglas Mental Health University Institute, Department of Psychiatry, McGill University, Montreal, QC, Canada

³ Lady Davis Institute for Medical Research, McGill University, Montreal, QC, Canada

ABSTRACT

Numerous lines of evidence suggest that a disordered circadian system contributes to the etiology and symptomatology of major psychiatric disorders. Sleep disturbances, particularly rapid eye movement (REM) sleep, have been observed in bipolar affective disorder (BPD) and schizophrenia. Therapies aimed at altering the timing and duration of sleep and realigning circadian rhythms, including sleep scheduling, wake extension, light therapy and drug therapies that alter sleep and circadian rhythms appear beneficial for affective disorders. Interventional studies aiming to correct sleep and circadian disturbances in schizophrenia are scarce, although exogenous melatonin has been shown to improve both sleep structure and psychotic symptoms. The study of molecular clock mechanisms in psychiatric disorders is also gaining interest. Genetics studies have found associations with *CLOCK*, *PERIOD1*, *PERIOD3*, and *TIMELESS* in schizophrenia. Most research on BPD has focused on polymorphisms of *CLOCK*, but the lithium target GSK-3 may also be significant. New research examining the role of circadian rhythms and clock genes in major mental illness is likely to produce rapid advances in circadian-based therapeutics.

orders since misalignment between the endogenous circadian system and the sleep/wake cycle is a critical factor in the clinical status of many psychiatric disorders (2, 3). This review examines the evidence for circadian disturbances in severe psychiatric disorders such as chronic schizophrenia and bipolar affective disorder (BPD), describes circadian-related interventions that have been used successfully to treat these disorders, and discusses current research on the role of clock genes in mental illness.

SLEEP AND CIRCADIAN RHYTHMS IN PSYCHOTIC DISORDER

CIRCADIAN RHYTHMS, SLEEP AND SCHIZOPHRENIA

Kant, Schopenhauer and Hughlings Jackson (4) all underlined the similarity between dreaming experiences and hallucinations. However, it was not until the discovery of rapid-eye movement (REM) sleep by Aserinsky and Kleitman (5) that the study of “dreaming sleep” and, in turn, REM sleep-related disorders became possible. Early studies examining the effects of sleep deprivation in schizophrenia patients (6, 7) were based on the hypothesis that hallucinations may be caused by REM-like intrusions into wakefulness, and by the observation that prolonged sleep deprivation induced hallucinations and psychotic symptoms reminiscent of schizophrenia (8). These pioneering experiments demonstrated an absence of REM sleep rebound after REM sleep specific deprivation, but no other abnormalities specific to this sleep stage. Later studies did not provide a consensus regarding other sleep parameters, presumably because of sampling variability and medication status of the subjects (see below). However, some abnormal polysomno-

INTRODUCTION

The circadian system plays a fundamental role in overall health and longevity (1). This is also true for mental dis-

Address for Correspondence: Diane B. Boivin, MD, PhD, Centre for Study and Treatment of Circadian Rhythms, Douglas Mental Health University Institute, 6875 LaSalle Boulevard, suite F-1127, Montréal, Québec, Canada H4H 1R3. ✉diane.boivin@douglas.mcgill.ca

graphic measures do emerge when drug-free subjects are analyzed, and, importantly, these abnormalities appear to be also present in large numbers of medicated subjects (2, 9, 10). These include poor sleep initiation and consolidation, impaired sleep homeostasis expressed as low levels of slow-wave sleep (SWS), with many subjects showing a total absence of stage 4 sleep, and shortened REM sleep latency with frequent sleep onset REM periods. Taken together, these observations suggest a deficient homeostatic regulation of sleep, although sleep deprivation (SD) can lead to SWS rebound on recovery nights (10). The shortened REM sleep latency, aberrant rest-activity cycles, and blunted melatonin secretion, on the other hand, suggest that abnormalities of the circadian system cannot be completely ruled out.

As with sleep, circadian disturbances have been reported in schizophrenia patients, but the results are inconsistent. One study has measured core body temperature (CBT) variation and reported desynchronization of temperature, pulse and blood pressure rhythms, although this study was conducted under ambulatory conditions and the data influenced by masking effects (11). In some experiments, the analysis of melatonin secretion demonstrated blunted circadian variation, although uncontrolled light exposure prior to data collection may have confounded these results (12-14). Others have reported phase advances of body temperature (15), prolactin and melatonin (16). These advanced rhythms are surprising considering that actigraphic recordings have revealed disturbed rest-activity cycles that are often inconsistent with a phase advance, including phase delays, longer periods of activity or, occasionally, 48 hour rest-activity patterns (17-19). Patients with schizophrenia/schizoaffective disorders also show a greater tendency towards eveningness (later wake and bed times and being most alert later in the day) than controls (20).

The observation that schizophrenia is commonly associated with disturbed sleep/wake cycles supports the hypothesis that these pathologies may emerge from a common underlying neuropathology. Interestingly, atypical antipsychotics can relieve both psychotic and sleep-related abnormalities (9). The dopaminergic hypothesis of schizophrenia postulates that hyperdopaminergic activity from the mesocorticolimbic systems causes positive symptoms. However, because the activity of atypical antipsychotics is associated with serotonergic and cholinergic pathways, a monoaminergic-cholinergic imbalance has also been hypothesized (21). Cholinergic neurons from the basal forebrain, peduncu-

loped tegmentum and laterodorsal tegmentum play key roles in both the arousal and REM sleep systems (22). Importantly, their activity modulates sensory processing and deregulation of these systems (particularly those of the midbrain) could cause hallucinations, as seen in schizophrenia (23). Whereas the role of dopamine in sleep-wake regulation has long been ignored, recent evidence demonstrated that hyperdopaminergic transgenic mice showed REM-like intrusions during wakefulness, an effect that could be blocked by haloperidol (24). These intrusions were exacerbated when the animals were emotionally challenged. Further studies are needed to elucidate the role of the common neurotransmission pathways possibly involved in both schizophrenia and sleep or circadian regulation of sleep-wake states. The lack of consensus across studies on the sleep-related or circadian abnormalities in schizophrenia calls for better controlled studies with standardized experimental protocols. The fact that sleep-wake disorders may play a role in the development of the disease could also lead to novel therapeutic avenues for schizophrenia, including light therapy (25) and melatonin agonists (14, 26).

CIRCADIAN RHYTHMS, SLEEP AND BIPOLAR AFFECTIVE DISORDER

The rhythmic nature of BPD, which is exaggerated in so-called "rapid cyclers" who show rapid mood changes from depression to mania or hypomania, has long invited speculation that the endogenous circadian system may play a role in the etiology of this disorder (27). Circadian disturbances have been observed in BPD such as a phase advance of the diurnal rhythm of plasma melatonin (28) and plasma cortisol (28, 29), although negative results have also been reported (30). Sleep disturbances are a defining symptom of BPD, with insomnia or hypersomnia, early morning awakening, reduced sleep efficiency, and altered REM sleep latency being the most consistently reported (2). The relationship between the sleep-wake cycle and changes in mood appear to be important in BPD, with the switch from mania or hypomania to depression or euthymia often occurring during or after sleep, while positive changes in mood from depression to hypomania or mania are more likely to occur after a period of wakefulness (31, 32). Sleep duration also appears to be critical, as sleep restriction predicts the onset of mania or hypomania the following day (33), while sleep extension is often associated with depression (33, 34).

As with schizophrenia, BPD patients score higher on eveningness scales than controls, although age could

play a role in this association (20). Interestingly, a classification of “evening type” was associated with greater severity of BPD including seeking treatment at an earlier age and a greater likelihood of rapid-cycling mood changes. A major limitation of this study is that mood state at the time of chronotype assessment is unknown (20). Interestingly, phase advance of sleep timing has been found to be effective in the treatment of BPD patients during the depressive phases (35, 36). Further studies will be needed to clarify the association between chronotype and BPD and controversies persist since the therapeutic action of lithium in BPD is associated with lengthening of the circadian period (described below) (37-39).

A number of interventions related to sleep and circadian rhythms have been successfully used to treat BPD. Primary interventions are bright light exposure and SD therapy, either partial or total, scheduled during the depressive phases of the illness. The advantage of these therapies is that they are non-invasive, fast acting, and found to be effective in patients with major depressive disorder and BPD (35, 36, 40-42). The main limitations of SD are a short duration of action, a high relapse rate, and the risk of triggering a manic or hypomanic episode (33, 43). Light therapy has been used to treat BPD, most frequently in combination with mood stabilizers and during the depressive phases, but more studies are needed to clarify its therapeutic utility and caution should be exercised because of the possibility of mood instability and relapses into hypomania (43, 44).

While an improved mood score is unambiguous in a patient with unipolar depression, in BPD it may in fact be an early sign of mania or hypomania (40). One way of achieving the benefits of SD while avoiding the drawbacks is to use it in combination with light or pharmacotherapy (45, 46). For example, Colombo and colleagues (45) found that the acute effects of total SD on mood were sustained when combined with lithium or light therapy, but there were no additive effects when all three treatments were combined. Phase advance of sleep timing has also been found to be effective in BPD patients during the depressive phase of the illness (35, 36). While these results seem promising, both SD and light therapy must be used with caution in BPD because of the potential for mood instability and relapses into hypomania or mania (33, 43). Interestingly, extended periods of sleep/darkness have been used to prevent/treat mania (47, 48). These studies suggest that, as part of a judicious sleep hygiene program, chronotherapeutic interventions such as SD and bright light exposure during depressive phases and

sleep/darkness stabilization during manic/hypomanic phases can be used in BPD (49).

Exogenous melatonin and melatonin agonists have received attention recently as potential treatments for depression, and may also be of benefit in BPD. Lower baseline plasma melatonin levels (50), and greater sensitivity to light-induced melatonin suppression, have been reported in BPD patients compared to controls (51), although some controversies persist (50). Lithium, an effective mood stabilizer for BPD, was shown to reduce melatonin suppression by light in healthy controls (52) and changes in melatonin levels may accompany successful treatment in BPD patients. The few studies to date that have tested the therapeutic effects of exogenous melatonin in BPD have been disappointing as melatonin was not effective (51). However, preliminary results of the effect of the melatonin agonist agomelatine, used with lithium or valproate, seem promising (53), but larger studies are needed.

CLOCK GENES AND PSYCHOTIC DISORDERS

BASIC MOLECULAR MECHANISMS OF CIRCADIAN RHYTHMS

The molecular mechanisms underlying circadian rhythmicity are comprised of positive and negative transcriptional/translational feedback loops and post-transcriptional regulatory elements. The genes *CLOCK* and *BMAL1* encode the transcription factors CLOCK and BMAL1 (54-56), which together activate transcription of three *Period* (*PER*) and two *Cryptochrome* (*CRY*) genes (57-62), *RORA* and *REV-ERB α* (63-65). The proteins PER and CRY combine to inhibit their own transcription, while ROR α and REV-ERB α act on *Bmal1* to activate and inhibit transcription, respectively. Post transcriptional modifications of PERs and CRYs by the enzymes casein kinase I epsilon (CKI ϵ) and delta (CKI δ) (66-68), and possibly the *Drosophila* SHAGGY homologue glycogen synthase kinase-3 (GSK-3) (69) control the rate of accumulation, association and translocation of PER and CRY (70), which can alter the period and phase of the molecular clock. NPAS2 is an alternate dimerization partner for BMAL1 that does not seem to be abundant in the master of the circadian clock, the suprachiasmatic nucleus (SCN), but may be important for circadian function in the forebrain (71, 72). *TIMELESS* (*TIM*) is similar to the fruit fly clock gene *tim*. Although the latter is essential for the fly clock, its role in the mammalian clock has been subject to controversy. Mammalian *TIM* appears to have a role in the clock of the SCN (73), but also in early

embryonic development (74) and DNA replication (75). Mutations of any of these circadian genes can potentially have an impact on the circadian clock, and thus subtly or dramatically alter sleep, mood or behavior in ways that contribute to physical and mental illness.

All these clock genes have been identified in humans, and there is a growing body of literature reporting their expression in human tissues (reviewed in 2). These studies have enabled the tracking of circadian rhythms in peripheral tissues and extra-SCN brain regions under various conditions, including shift work (76), Alzheimer's disease (77, 78) and various lighting manipulations (2, 79, 80).

CLOCK GENES IN NON-PSYCHIATRIC DISORDERS

The first demonstration of the importance of the human molecular clock was related to extreme sleep timing disorders. On one hand, an amino acid substitution was shown to explain the extremely early sleep and wake times (bedtime = 6-9 pm, wake = 1-3 am) of two familial cases of advance sleep phase disorder (FASPD). These mutations were in the *PER2* and *CKIδ* genes (81-84). On the other hand, delayed sleep phase disorder (DSPD; bedtime = 3-6 am, wake = 1-3 pm) was found to be associated with a polymorphism of human *PER3* (85, 86). *PER3* polymorphisms have also been associated with less extreme chronotypes. Individuals with the shorter 4-repeat allele of *PER3* were found more frequently in evening types, while the longer 5-repeat was more frequently seen in morning types, although this association was only significant in younger individuals (18-29 years old) (87). Interestingly, recent data suggest that this polymorphism of *PER3* might impact sleep homeostasis; individuals with the longer allele *PER3*^{5/5} showed increased SWS and electroencephalographic (EEG) slowing, but the circadian rhythms of melatonin, cortisol and peripheral *PER3* expression were not affected (88). In addition, the rhythm of *PER3* expression in white blood cells, but not that of *PER2* or *BMAL1*, is significantly correlated with the timing of the sleep/wake rhythms and rhythms of plasma melatonin and cortisol secretion, indicating *PER3* as a potential genetic marker for circadian mechanisms underlying sleep/wake timing (89).

The *PER* and *CKI* genes are not the only clock genes that have an influence on chronotype. Morningness-eveningness scores have been found to be associated with a single nucleotide polymorphism (SNP) of the human *CLOCK* gene (90, 91). Individuals with the *CLOCK* 3111C/C and C/T alleles showed increased evening-

ness and reduced morningness, while 3111T/T subjects showed higher morningness scores (90, 91), but conflicting results have been reported (92). This may be related to differences in allelic frequencies in different ethnic groups. In a Korean population, there were no individuals carrying the 3111C/C, but individuals with the C/T allele were more likely to show a diurnal preference for eveningness when they also carried a 825C/T SNP of the *GNB3* gene (93). The 3111C/C genotype is also associated with delayed sleep timing and greater daytime sleepiness in a Japanese population (91), but not in Caucasians (92). There is currently no evidence in support of an association between the 3111C/C genotype and DSPD or non-24 hour sleep phase disorder (92, 94).

CLOCK GENES AND SCHIZOPHRENIA

There are few studies demonstrating a link between circadian clock gene polymorphisms or deregulation and schizophrenia. However, the *CLOCK* 3111C/T polymorphism showed a transmission bias in a sample of 145 Japanese schizophrenic subjects relative to healthy controls (95). The authors suggested that this polymorphism, associated with aberrant dopaminergic transmission to the SCN, may underlie the pathophysiology of schizophrenia. Since dopaminergic signalling through D2 receptors is associated with increased *CLOCK:BMAL1* activity (96), this provides an interesting link between the dopaminergic hypothesis of schizophrenia and circadian abnormalities in these patients. Another study used microarray technology to analyze gene expression in the temporal lobe of postmortem brains obtained at autopsy from patients previously diagnosed with schizophrenia (97). The results demonstrated decreased expression of the *PER1* mRNA in schizophrenia patients compared with age-matched normal controls. These findings were also confirmed by RT-PCR. Association of *PER3* and *TIM* with schizophrenia/schizoaffective disorder, as well as with bipolar disorder have also been found (98). The association with *PER3* is interesting, given the evidence of a relationship between *PER3* with delayed sleep phase disorder and evening chronotype. However, the function of *TIM* in mammals is not entirely clear (73), making it difficult to interpret this finding. Finally, the *CRY1* gene was hypothesized to be a candidate gene for schizophrenia based on its location near a linkage hotspot for schizophrenia on chromosome 12q24 (99). The fact that *CRY1* is expressed in dopaminergic cells in the retina (100) and that its expression influences the effects of psychoactive drugs (101) lends further supports to this hypothesis.

CLOCK GENES AND BIPOLAR DISORDER

Of all major mental disorders, the evidence for genetic abnormalities associated with clock genes is strongest in BPD. An analysis of 46 SNPs of eight clock genes (*BMAL1*, *CLOCK*, *PER 1,2,3*, *CRY 1,2*, *TIM*) revealed association of *BMAL1* and *TIM* with BPD using family-based samples with BPD or schizophrenia (98). Even though these were modest associations found using very liberal analyses, the association with *BMAL1* has been independently confirmed using haplotype analysis (102). The same study also demonstrated an association with *PER3*. Studies examining other genes have found negative results: screening for human *PER2* mutations at the CKI δ/ϵ binding site showed no difference in frequency between BPD patients and controls (103), nor was there any evidence for linkage or association of *CRY1* with BPD (104). Interestingly, a recent study pointed to a general reduction in the amplitude of clock gene mRNAs in fibroblasts taken from BPD patients (105).

One group has published numerous studies on the association of the *CLOCK 3111T/C* polymorphism with BPD (106-109). The C/C allele has been associated with greater severity of insomnia during antidepressant treatment (109) and a higher recurrence rate of bipolar episodes (107), reduced need for sleep (108), and a tendency to increased activity during the later part of the day prior to sleep (all C allele carriers, (110)). There is even some suggestion for differential activation in the cingulate cortex during a moral decision-making task, dependent on the C/T genotype of major depressive disorder and BPD patients who underwent fMRI and testing during a depressive episode (110). Support for a role of *CLOCK* mutation in bipolar disorder has recently come from the animal literature, with evidence that the *Clock* mutant mouse might constitute an animal model of mania (111).

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 (39), and can lengthen the period of neuronal firing of cultured SCN neurons in a dose dependent manner (37). A delay in the circadian phase markers, body temperature and REM sleep has also been shown in a BPD patient (38).

One proposed mechanism of the therapeutic action of lithium is via the inhibition of GSK-3 (69, 112). Although this enzyme has a number of functions that could potentially mediate the therapeutic effects of lithium (113), one possibility is via its function as a central regulator of the circadian clock (112). Numerous lines of evidence

support this idea. For example, both lithium and GSK-3 knockdown produce lengthening of the period of *PER2* mRNA transcription rhythms in mouse fibroblasts (114) and GSK-3 β affects the entry of *PER2* into the nucleus (69). REV-ERBA protein expression is dramatically reduced by lithium, via the inhibition of GSK-3 β , but *REV-ERBA* RNA is unaffected (115). This suggests that the inhibition of GSK-3 by lithium has multiple effects on key clock components. Even more interesting are findings that inhibition of GSK-3 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 (112). The above-mentioned study examining circadian gene expression in fibroblasts from BPD patients also identified group differences in GSK-3 β (105). This makes GSK-3 a promising target for future development of pharmacotherapeutic agents.

CONCLUSION

The study of psychiatric populations is difficult and the literature is rife with inconsistencies. Lack of replication, or even contradiction in results between studies may be due to a number of factors, including heterogeneous patient populations, differences in diagnostic criteria, use of medications, insufficient withdrawal periods from medications before testing, and lack of control for variations in light-dark cycles. In spite of these difficulties, well-controlled studies in psychiatric populations must be pursued in order to increase our knowledge of the clinical repercussions of sleep and circadian rhythms disturbances in these populations. Health care professionals should be better trained on the potential diagnostic utility and consequences of changes in sleep-wake patterns for their psychiatric patients. Interventions aimed at correcting disturbed circadian rhythms and/or rest-activity cycles have resulted in effective, well-tolerated therapies used either alone or in conjunction with traditional pharmacotherapies (116). Finally, advances in the circadian genetics of mental illness are likely to open a new frontier of genetic therapies, as well as guide the development of new pharmaceuticals.

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