Published in final edited form as:
Pharmacol Ther. 2007 May ; 114(2): 222–232.

Circadian Genes, Rhythms and the Biology of Mood Disorders

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Abstract

For many years, researchers have suggested that abnormalities in circadian rhythms may underlie the development of mood disorders such as bipolar disorder, major depression and seasonal affective disorder. Furthermore, some of the treatments that are currently employed to treat mood disorders are thought to act by shifting or "resetting" the circadian clock, including total sleep deprivation and bright light therapy. There is also reason to suspect that many of the mood stabilizers and antidepressants used to treat these disorders may derive at least some of their therapeutic efficacy by affecting the circadian clock. Recent genetic, molecular and behavioral studies implicate individual genes that make up the clock in mood regulation. As well, important functions of these genes in brain regions and neurotransmitter systems associated with mood regulation is becoming apparent. In this review, the evidence linking circadian rhythms and mood disorders, and what is known about the underlying biology of this association, is presented.

Keywords

circadian; mood; bipolar; depression; seasonal affective disorder; sleep deprivation; light therapy

1. Introduction

Daily rhythms are prominent in everything from sleep/wake cycles, body temperature, hormone levels, and even cognition, attention and mood (Bunney and Bunney, 2000;Reppert and Weaver, 2001). Disruptions in biological rhythms are known to be strongly associated with mood disorders. Indeed some of the major hallmarks of diseases like major depressive disorder (MDD) and bipolar disorder (BPD) are abnormal sleep/wake, appetite, and social rhythms (Boivin, 2000;Bunney and Bunney, 2000;Lenox et al., 2002;Grandin et al., 2006). Depression symptoms are also diurnal with the most severe symptoms occurring typically in the morning (Rusting and Larsen, 1998), and depression is more prevalent in areas of the world that receive little sunlight for extended periods of time (Booker et al., 1991). In addition, one of the most common mood disorders, affecting some 2–5% of the population in temperate climates, is seasonal affective disorder (SAD), a syndrome where depressive symptoms occur only in the winter months when there are shorter days and a later dawn (Lam and Levitan, 2000;Magnusson and Boivin, 2003). Thus, it has long been hypothesized that abnormalities in the molecular clock underlie the development of these disorders. In addition, nearly all of the successful treatments for mood disorders seem to affect circadian rhythms, and it appears that the shifts, resetting and stabilization of these rhythms produced by these treatments are important for therapeutic efficacy. Though these associations have been known for many years,

we are only now starting to understand the biology that underlies this connection. With the cloning and characterization of the individual genes that make up the molecular clock, researchers now have the opportunity to explore the molecular mechanisms that underlie this association, and determine the importance of circadian rhythms in mood disorders.

2. The molecular clock

The primary molecular clock is located in the suprachiasmatic nucleus (SCN) in the hypothalamus, and consists of a transcriptional feedback loop which cycles over the course of approximately twenty-four hours in the absence of environmental input (Reppert and Weaver, 2001;Ko and Takahashi, 2006). The major transcriptional activator consists of a dimer between the Circadian Locomotor Output Cycles Kaput Protein (CLOCK) and Brain and Muscle ARNT-like Protein 1 (BMAL1, also known as ARNTL or MOP3). This complex binds to E-box sequences in the promoters of many genes including the *Period (Per)* and *Cryptochrome (Cry)* genes. The PER and CRY proteins are translated in the cytoplasm, and are phosphorylated by Casein Kinase I ε and δ (CK1) and Glycogen Synthase Kinase 3β (GSK3β), leading to changes in their stability, association, and nuclear entry (Harms et al., 2003;Iitaka et al., 2005;Knippschild et al., 2005;Kurabayashi et al., 2006). Upon entering the nucleus, they can repress the actions of CLOCK/BMAL1, thus creating a negative feedback loop. In addition, there is an adjoining loop in which CLOCK/BMAL1 activates the transcription of *Rev-erbα* and *Rorα* (Sato et al., 2004;Guillaumond et al., 2005). Once translated, these proteins can bind to the promoter of the *BMAL1* gene and both positively and negatively affect its transcription. Selectively in forebrain regions, Neuronal PAS Domain Protein 2 (NPAS2), a protein very similar to CLOCK, can bind BMAL1 and induce *Per* and *Cry* gene expression (Reick et al., 2001). NPAS2 may also function in the place of CLOCK in the SCN if the CLOCK protein is genetically disrupted (Debruyne et al., 2006). Though the central circadian pacemaker is located in the SCN, all of these genes are expressed throughout the brain and in other organs where they function as peripheral clocks that respond to nonphotic stimuli, and likely in other processes unrelated to circadian rhythms (Abe et al., 2001;Stokkan et al., 2001;Iijima et al., 2002;Granados-Fuentes et al., 2006;McDearmon et al., 2006;Mieda et al., 2006).

3. A circadian basis of mood disorders?

3.1 A generally disrupted clock

Mood disorders such as MDD and BPD may be more prevalent in individuals that are born with an abnormally shifted or arrhythmic clock. Indeed, blunted or abnormal circadian rhythms in a variety of bodily functions including body temperature, plasma cortisol, norepinephrine, thyroid stimulating hormone, blood pressure, pulse, and melatonin have been found in depressed and bipolar patients (Atkinson et al., 1975;Kripke et al., 1978;Souetre et al., 1989). Interestingly, these rhythms seem to return to normal with antidepressant or mood stabilizer treatment and patient recovery. Furthermore, genetic sleep disorders such as familial advanced phase sleep syndrome (FASPS) in which individuals have shifted circadian rhythms where they fall asleep and wake up much earlier than desired, or delayed sleep phase syndrome (DSPS) which has the opposite phenotype, are both highly co-morbid with depression and anxiety (Shirayama et al., 2003;Xu et al., 2005;Hamet and Tremblay, 2006). Even individuals that are genetically predisposed towards “eveningness” (a preference for the evening) versus “morningness” (a preference for the morning) are more likely to develop depression (Drennan et al., 1991;Chelminski et al., 1999). Genetic variations in the circadian genes have been found to associate with these sleep disorders and diurnal preference measures including an association between certain variants of *Per2*, and *CK1δ* with FASPS; *Per3*, *CLOCK*, and *CK1ε* with DSPS; and *Per1*, *Per2*, *Per3* and *CLOCK* with diurnal preference (Katzenberg et al., 1998;Iwase et al., 2002;Archer et al., 2003;Johansson et al., 2003;Takano et al., 2004;Carpen et al.,

2005;Mishima et al., 2005;Xu et al., 2005;Carpen et al., 2006;Vanselow et al., 2006). This suggests a connection between proper mood regulation and a normal functioning circadian clock. Indeed, nearly all individuals that suffer from mood disorders benefit greatly from a strict sleep/wake cycle where they rise in the morning and go to sleep at night at the same time every day (Leibenluft and Suppes, 1999).

3.2 The inability to properly adapt

Though the central molecular clock and peripheral clocks are pre-set and have an endogenous rhythm, the timing of these rhythms can be altered due to environmental influences. For example, locomotor activity rhythms and molecular rhythms in mice change with alterations in the light/dark cycle (Redlin, 2001). Animals also shift their activity rhythms and sleep/wake cycle in response to restricted food availability at a certain time of day (Stephan, 2002). This entrainment to food, or other non-photic stimuli, is controlled by SCN-independent pacemakers located in various regions of the brain and other organs (Stokkan et al., 2001;Stephan, 2002;Mieda et al., 2006). The ability of these clocks to adapt to the environment is highly beneficial for the survival of many species, including our own. The effect of having a clock that is out of sync with the environment is evident to anyone who has experienced jet lag after traveling (Herxheimer, 2005). Indeed, the ability of these clocks to adapt may be important in the regulation of mood in response to changes in seasons, stress levels, sleep schedules, and time zones. For some individuals, these types of changes bring on severe depressive or manic episodes. This is seen in shift workers where often a certain population of them will develop mood disorders over time (Scott, 2000). This development of mood disturbances in response to circadian disruptions is called the social zeitgeber theory. This theory proposes that depressive or manic episodes are brought on by life stresses because they disrupt normal social routines and the sleep/wake cycle, in turn leading to changes in biological rhythms and mood (Grandin et al., 2006). Thus it is possible that individuals that suffer from these types of mood disorders have a molecular clock that is not able to properly adapt to certain types of environmental or other changes.

3.3 Seasonal affective disorder

Seasonal affective disorder (SAD) is perhaps the most common disorder that arises from a failure to properly adapt to changes in the environment. SAD is characterized by depressive symptoms that occur only in the winter months (Magnusson and Boivin, 2003). It has been hypothesized that the circadian hormone, melatonin, is centrally involved in the development of SAD (Pandi-Perumal et al., 2006). Melatonin is released primarily by the pineal gland and can bind to the G-protein coupled receptors, MT_1 and MT_2 (Pandi-Perumal et al., 2006). These receptors are expressed at high levels in the SCN, and upon stimulation, modulate SCN transmission and circadian activity. Melatonin is suppressed by light, participates in sleep, and varies seasonally in many mammals (Pandi-Perumal et al., 2006). In some studies, SAD sufferers have been found to have either a pronounced seasonal melatonin rhythm, or more daytime melatonin specifically in the winter, while healthy control subjects have no seasonal alterations in their melatonin rhythms (Danilenko et al., 1994;Wehr et al., 2001). However, other studies have found significant seasonal alterations in melatonin rhythms in healthy, non-affected individuals, or even melatonin levels that are greater in the summer than the winter (Touitou et al., 1984;Kivela et al., 1988;Honma et al., 1992;Morera and Abreu, 2006). Much of this variability in melatonin measurements likely comes from the variations in seasonal differences between different areas of the world in which these studies were conducted. For example, studies done in the arctic which have extreme seasonal differences in day/night light intensity and duration find strong seasonal rhythms in melatonin (Yoneyama et al., 1999). Studies done in areas of the world where there are less extreme seasonal differences may not find pronounced seasonal rhythms, particularly in individuals who are exposed to self-selected cycles of artificial light. Additional abnormalities in melatonin secretion in SAD patients, such

as phase delays over twenty-four hours, have also been reported; however, other studies have reported no differences in circadian melatonin levels or rhythms in SAD patients (Checkley et al., 1993;Srinivasan et al., 2006). Therefore the link between abnormal or exaggerated melatonin rhythms and SAD is still up for debate.

Similar to the melatonin hypothesis, another one of the central hypotheses put forth to explain SAD is called the circadian phase shift hypothesis. The idea behind this hypothesis is that the later dawn in winter leads to a delay in circadian rhythms and a disconnect between the molecular rhythms of the SCN and the sleep/wake cycle in SAD patients. This hypothesis is largely based on research demonstrating that early morning bright light therapy is the most effective in treating SAD while evening light therapy is often not effective (Lewy et al., 1998b;Terman and Terman, 2005). Therefore, the early morning light is leading to a phase advance in the circadian system putting it back on track with the sleep/wake cycle. In addition, there have been reports that melatonin therapy in the evening can also be effective in producing this same phase advance and may help with the treatment of SAD (Lewy et al., 1998a;Lewy et al., 2006). Though this theory has a lot of support, it still remains controversial. If this hypothesis is true, then evening light exposure should make symptoms worse by further delaying the circadian rhythm. However, in some studies, evening light exposure has an equally strong antidepressant effect as morning exposure and several studies find no therapeutic effects of melatonin treatment (Wirz-Justice et al., 1990;Wirz-Justice et al., 1993;Terman et al., 2001). Other theories suggest that SAD patients actually fall into two categories, some with a phase delay in rhythms and some with a phase advance in rhythms (Boivin, 2000;Lewy et al., 2006). The timing of light therapy and perhaps melatonin therapy would then need to be adjusted for each group separately to produce the desired shift in rhythms and therapeutic effects.

3.4 Influence of the molecular clock on mood-related neurotransmitter systems

The biology that underlies the association between circadian rhythms and mood disorders is still unknown, but may come from the influence of the molecular clock on certain neurotransmitters and their receptors. Indeed some of the major neurotransmitters that have been implicated in mood regulation, including serotonin, norepinephrine and dopamine, have a circadian rhythm in their levels, release, and synthesis-related enzymes (Weiner et al., 1992;Shieh et al., 1997;Aston-Jones et al., 2001;Barassin et al., 2002;Khaldy et al., 2002;Castaneda et al., 2004;Weber et al., 2004;Malek et al., 2005). There are also circadian rhythms in the expression and activity of several of the receptors that bind these neurotransmitters, suggesting that these entire circuits are under circadian control (Kafka et al., 1983;Wesemann and Weiner, 1990;Witte and Lemmer, 1991;Coon et al., 1997;Akhisaroglu et al., 2005). It seems likely that disruptions in the normal rhythms in these circuits (either continuous or abrupt) could have major effects on mood and motivational states. How these circuits are controlled in a circadian fashion is still uncertain. Some of this modulation seems to occur through connections between the SCN and other brain regions. For example, an indirect projection from the SCN to the locus coeruleus appears to regulate the circadian rhythm in noradrenergic neuronal activity (Aston-Jones et al., 2001). Furthermore, circadian gene expression outside of the SCN, in these specific regions, may contribute to their rhythmic activity. Circadian activity rhythms in rodents can be entrained to daytime methamphetamine injections, even in SCN lesioned animals (Iijima et al., 2002). This treatment shifts the expression of the *period* genes in striatal regions typically associated with movement control, in a manner that matches the shift in activity rhythms (Iijima et al., 2002). This same shift in *period* gene expression does not occur in the SCN with methamphetamine treatment, thus there is a disconnect between the SCN, molecular rhythms in the striatum and locomotor activity rhythms. This suggests that the *period* gene expression and rhythms in striatal regions is important in producing rhythms in locomotor activity. Therefore, the circadian genes both

in the SCN and in these specific circuits may be involved in regulating this rhythmic activity in neurotransmission. Future studies are needed to determine exactly how these rhythms in dopamine, serotonin and other neurotransmitters are involved in mood regulation.

4. Treating mood disorders by altering the circadian cycle

4.1 Sleep deprivation therapy

Total sleep deprivation (TSD) is a rapid and effective short-term treatment for depression. It improves depressive symptoms in some 40–60% of patients (Wirz-Justice and Van den Hoofdakker, 1999;Giedke and Schwarzler, 2002). Partial sleep deprivation (through the second half of the night) can also be effective, though usually not to the same degree as TSD (Wirz-Justice et al., 2005). Sleep following treatment can lead to a relapse in symptoms, however, in some patients this is delayed for several weeks. Concurrent treatment with antidepressant medications or lithium may help prevent relapse (Wu and Bunney, 1990;Benedetti et al., 2001). Furthermore, follow up treatment with daily light therapy or a short phase advance in the sleep/wake cycle can also prevent relapse (Berger et al., 1997;Riemann et al., 1999;Wirz-Justice et al., 2005). Melatonin therapy, however, seems to be ineffective at preventing relapse following TSD in SAD patients (Danilenko and Putilov, 2005).

The biological basis of TSD as a treatment for depression is poorly understood. Several circadian phase setting and sleep-phase hypotheses have been put forth in an attempt to explain its therapeutic action (Wirz-Justice and Van den Hoofdakker, 1999). Interestingly, pindolol, a drug that blocks the serotonergic 5-HT_{1A} autoreceptor and is used to augment the antidepressant effects of serotonin reuptake inhibitors, was shown to potentiate the effects of TSD (Smeraldi et al., 1999). In contrast, pretreatment with the dopamine agonist, amineptine, prevents the antidepressant effects of TSD (Benedetti et al., 1996). TSD also seems to activate limbic dopaminergic pathways which can be measured in increased limbic blood flow, increased D2 dopamine receptor occupancy, and increased eye-blink rates after TSD treatment (Ebert et al., 1994a;Ebert et al., 1994b;Ebert et al., 1996). These results, and the significant similarities between the feelings induced by TSD and psychostimulant use, have implicated the limbic dopaminergic system in the therapeutic actions of TSD (Ebert and Berger, 1998). How TSD leads to an activation of this pathway, however, is currently unknown.

A few studies using rodent models have begun to look at the mechanism that underlies TSD's effects on depression. One night of TSD in rats decreases immobility in the forced swim test, similar to the actions of antidepressant drugs (Lopez-Rodriguez et al., 2004). Furthermore, like antidepressant treatment, TSD in rats stimulates hippocampal neurogenesis (Grassi Zucconi et al., 2006). It has also been shown in hamsters that TSD affects serotonin levels in the SCN and other brain regions, and results in a strong phase advance in activity rhythms (Asikainen et al., 1995;Grossman et al., 2000). These studies are just beginning, and are important in determining the mechanism underlying the therapeutic effects of TSD as an antidepressant.

4.2 Bright light therapy

Bright light therapy has been used for more than twenty years to treat SAD with comparable efficacy to antidepressant medications (Lam et al., 2006). Several studies also indicate that light therapy can be equally effective in treating non-seasonal depression, as well as many other mood disorders (Terman and Terman, 2005). It is thought that light therapy works by shifting the circadian clock, and indeed light therapy given in the morning will produce a phase advance in rhythms while light in the evening produces a phase delay (Wirz-Justice et al., 2005). The potential for light therapy as an effective treatment for a whole spectrum of mood disorders is appealing because it is safe, has few side effects, is relatively easy to use, and is noninvasive. The standard light treatment involves exposure to a ~10,000 lux light box, typically in the

morning after waking for 30–90 minutes (Terman and Terman, 2005). Over time, this will produce a phase shift in circadian body temperature rhythms of ~ 1 hour (Burgess et al., 2004). Similar to antidepressant treatment, it generally takes 2–4 weeks before the beneficial effects on mood are seen.

There are some indications that certain wavelengths of light are more effective than others in promoting a therapeutic response with the fewest side effects. This could be due to the ability of certain wavelengths of light to more effectively control circadian rhythms (Foster and Helfrich-Forster, 2001). Recent studies have found that light in the blue spectrum (446–477) outperforms other wavelengths in melatonin suppression, circadian phase shifting, and antidepressant effects (Brainard et al., 2001;Thapan et al., 2001;Lockley et al., 2003;Glickman et al., 2006). While there have been several studies that have investigated the mechanism by which light shifts the circadian clock and the specific photoreceptors involved in this effect (Foster and Helfrich-Forster, 2001;Foster et al., 2003), few studies have examined the effects of light-induced circadian phase shifting as an antidepressant in animal models.

4.3 Pharmacological treatments

In bipolar patients, the mood stabilizers lithium and valproate are commonly used for treatment. Interestingly, both of these drugs have been repeatedly shown to alter the circadian period, leading to a long period in *Drosophila*, non-human primates, rodents and humans (Johnsson et al., 1983;Welsh and Moore-Ede, 1990;Klemfuss, 1992;Hafen and Wollnik, 1994;Dokucu et al., 2005). This effect on circadian rhythms likely involves the inhibition of GSK3β which modifies multiple members of the molecular clock (Iwahana et al., 2004;Padiath et al., 2004;Gould and Manji, 2005;Iitaka et al., 2005;Yin et al., 2006). It is thought that this action of lithium on the circadian clock is important in its therapeutic efficacy. Lithium is able to slow the abnormally fast circadian rhythms found in many bipolar patients (Atkinson et al., 1975;Kripke et al., 1978). Furthermore, patients that have a shift in rhythms respond positively to lithium treatment in terms of mood stabilization, while those few bipolar patients that begin with an abnormally slow clock do not respond to lithium treatment. Furthermore, lithium treatment is able sustain and enhance the phase-shifting and mood-altering effects of TSD (Benedetti et al., 2001).

Similar to morning bright light therapy, the antidepressant, fluoxetine, also affects circadian output by producing a phase advance in the firing of SCN neurons in rat slice culture (Sprouse et al., 2006). Indeed, serotonin neurons from the midbrain raphe nuclei innervate the SCN, and local applications of 5-HT or 5-HT 1A and 7 receptor agonists to the SCN will also produce a phase advance in circadian activity (Dudley et al., 1999;Ehlen et al., 2001). Thus antidepressants in the selective serotonin reuptake inhibitor (SSRI) class may also exert some of their effects on depression through modulation of the circadian clock. Interestingly, SSRIs and mood stabilizers can have opposing therapeutic actions in bipolar patients (Thase, 2005). This could be linked to their opposing actions on rhythms since SSRIs cause a phase advance in rhythms while lithium can cause a phase delay (Campbell et al., 1989;Sprouse et al., 2006).

Recently, agomelatine, a potent agonist of the melatonin receptors and an antagonist at the serotonin 5-HT(2C) receptor, has proven to be highly effective in animal models of depression, and in several on-going clinical trials involving patients with MDD (den Boer et al., 2006;Hamon and Bourgoin, 2006;Zupancic and Guilleminault, 2006). Agomelatine also seems to produce fewer adverse side effects than some of the other antidepressant medications, and it alleviates many of the sleep problems associated with depression that are typically exacerbated by SSRI treatment, making it a potentially valuable new treatment for depression (Hamon and Bourgoin, 2006). As expected by its pharmacologic profile, agomelatine has been shown to resynchronize circadian rhythms in body temperature, cortisol, and other hormones

in animal models and in humans, which may underlie some of its therapeutic effects (Leproult et al., 2005). Interestingly, agomelatine is much more effective than melatonin in reversing depression-like behavioral responses in animal models, suggesting that the therapeutic actions of agomelatine are not exclusively due to its actions at the melatonin receptors (Delagrange and Boutin, 2006). However, the kinetics of agomelatine, and actions at the melatonin receptors, may differ greatly from those of melatonin, so this action may still underlie at least part of its efficacy as an antidepressant (Hamon and Bourgoin, 2006).

Though the latency to action is similar between agomelatine and the SSRIs, agomelatine seems to have no effect on central serotonin transmission or the density and function of 5-HT(1A) receptors (Hanoun et al., 2004;Millan et al., 2005). However, its actions at the 5-HT(2C) receptors enhances mesolimbic dopaminergic and noradrenergic transmission, an effect also seen with SSRIs (Millan et al., 2003;Serretti et al., 2004). Furthermore, chronic, but not acute, treatment with agomelatine also induces neurogenesis in the hippocampus similar to other antidepressants (Banasr et al., 2006). Interestingly, specific antagonists at the 5-HT(2C) receptor have potent anxiolytic-like activity in animal models, but they seem to have no effect in models of depression (Jenck et al., 1998). Therefore, the therapeutic actions of agomelatine in the treatment of depression are still uncertain, and may involve both the 5-HT(2C) and melatonin receptors.

5. Evidence linking specific circadian genes with mood disorders

5.1 Human genetic studies

Several human genetic studies have implicated specific genes that make up the molecular clock in the manifestation of mood disorders. For example, an amino acid substitution in NPAS2 (471 Leu/Ser) has been found to associate with the development of SAD (Johansson et al., 2003). Furthermore, in bipolar patients, a single nucleotide polymorphism (SNP) in the 3′ flanking region of the *CLOCK* gene (3111 T to C) associates with a higher recurrence rate of bipolar episodes (Benedetti et al., 2003). This SNP is also associated with greater insomnia and decreased need for sleep in bipolar patients, as well as greater insomnia in individuals undergoing antidepressant treatment (Serretti et al., 2003;Serretti et al., 2005). However, in patients with MDD, there appears to be no general association between the disease and this SNP (Desan et al., 2000). Since this SNP is in the 3′ flanking region, it could affect polyadenylation or RNA stability, however, these possibilities have not been tested.

In addition to the 3111 SNP in the *CLOCK* gene, two rare SNPs in the same region (3117 G to T and 3125 A to G) have been identified by Pirovano et al., in two subjects with major depression, and not in any of the healthy controls in their study (Pirovano et al., 2005). Interestingly, both of these individuals had the same pattern of sleep which consisted of alternating phases of good sleep and insomnia over the course of a few days, which may be related to this change in the *CLOCK* gene.

In recent studies, other members of the molecular clock have been implicated in BPD. Haplotypes in *BMAL1* and *Per3* were found to significantly associate with BPD in one study (Nievergelt et al., 2006). Furthermore, a SNP in *BMAL1* and a SNP in the *Timeless* gene have also been identified that associate with BPD (Mansour et al., 2006). It should be noted that additional studies have found associations between members of the molecular clock and other psychiatric disorders such as schizophrenia and alcoholism, suggesting that these genes are important in a range of psychiatric conditions (Spanagel et al., 2005;Mansour et al., 2006). However, in general, most of these studies only find modest associations, and other studies that have examined SNPs throughout the sequence of some of the central members of the circadian clock have found no associations with these genes and any psychiatric disorders (Shiino et al., 2003;Nievergelt et al., 2005;Mansour et al., 2006;Nievergelt et al., 2006).

Therefore the functional importance of these variations is still uncertain, and only certain members of the circadian clock may be involved.

One of the modulators of the circadian clock, GSK3β, is perhaps the most well characterized target of the mood stabilizer, lithium (Gould and Manji, 2005). Therefore it is somewhat surprising that most studies have not found general associations between variants in this gene and BPD, or the response to lithium. Two studies find that an identified SNP in the promoter of this gene (−50 T to C) does not appear to be related to the degree of prophylactic lithium response in bipolar patients (Michelon et al., 2006;Szczepankiewicz et al., 2006a). Furthermore, one genetic study failed to find any significant association between two SNPs (−1727 A to T, and −50 T to C) in *GSK3β* with BPD or schizophrenia in a Korean population (Lee et al., 2006). Similarly, other studies failed to show a general association between these SNPs and BPD, however, one of these SNPs (−50 T to C) is linked to a later age of onset of BPD and a greater response to total sleep deprivation (TSD) and long-term lithium treatment (Benedetti et al., 2004;Benedetti et al., 2005). Additionally, one study showed that this polymorphism may associate with the development of bipolar II disorder specifically in female patients (Szczepankiewicz et al., 2006b). Thus the effect of these polymorphisms, and perhaps others in *GSK3β*, may be very specific.

5.2 Gene expression studies

In addition to the human genetic studies, there have been a few gene expression studies implicating circadian genes in either the manifestation or treatment of mood disorders. One study found that the antidepressant, fluoxetine, altered the expression of *CLOCK*, *BMAL1* and *NPAS2* in the mouse hippocampus (Uz et al., 2005). The hippocampus is thought to be particularly relevant to mood disorders since stress and antidepressant treatments have opposing effects on neurogenesis in this region, and structural changes in the hippocampus have been observed in depressed patients (Campbell and Macqueen, 2004). The same changes in circadian gene expression did not occur in striatal regions, indicating that they may be hippocampal specific. In addition, these genes were all induced by chronic and not acute fluoxetine, suggesting that these changes may be therapeutically relevant since fluoxetine needs to be administered for days to weeks to see significant antidepressant effects in humans (Uz et al., 2005).

In addition to the fluoxetine study, a microarray study by Ogden *et al*., found that the mood stabilizer, valproate, decreased the expression of *CK1ε* and *Cry2* in the amygdala, a region of the brain known to be important in anxiety and emotional responses (Ogden et al., 2004). These changes were prevented by co-treatment with methamphetamine, which was given to induce manic-like symptoms, suggesting that they may be involved in the treatment of mania (Ogden et al., 2004). Additional microarray studies have found expression changes in circadian genes in striatal regions with psychostimulants such as cocaine, which suggest that expression of these genes in the striatum may be important in controlling the hedonic state (Yuferov et al., 2003;McClung et al., 2005;Uz et al., 2005).

5.3 Behavioral studies

A few studies using rodent models have examined the effects of an SCN lesion on measures of anxiety and depression to determine if this central circadian pacemaker is involved in modulating these responses. A study by Tataroglu et al found that bilateral SCN lesions in rats had an antidepressant-like effect in the forced swim test in that the animals showed less immobility time and more swimming (Tataroglu et al., 2004). Immobility in this task is regarded as “helpless” or “depressed” behavior, and it can be reduced with antidepressant treatment. These results would suggest that disruption of the SCN has a protective effect on depression-like behavior. However, a study by Tuma et al found that SCN lesions had no effect

on the depression and anxiety-like behaviors that are displayed after repeated bouts of social defeat (Tuma et al., 2005). The SCN does appear to play some role in this task, however, since the antidepressant, agomelatine, which is normally effective in reducing the depression and anxiety-like behavior following social defeat, was not effective in the SCN lesioned animals (Tuma et al., 2005). Thus the SCN might be needed to produce the therapeutic effects of agomelatine. It is not clear in this study whether the measurements performed are more indicative of anxiety or depression, and more specific paradigms will have to be employed to differentiate the two. It may seem in opposition to find that lesions of the SCN produce an antidepressant effect while SCN integrity is needed for antidepressant action. However, agomelatine is known to inhibit SCN neuronal firing, which would suggest that reducing SCN function has an antidepressant effect (Ying et al., 1996). The finding that the SCN lesion on its own does not have any effect on behavioral measures after social defeat suggests that other brain regions are clearly involved in these responses.

Behavioral studies aimed at investigating the role of individual circadian genes in mood regulation are just beginning. Interestingly, transgenic mice overexpressing the circadian modulator, *GSK3β*, are hyperactive, have reduced immobility in the forced swim test (indicative of lower depression-like behavior), and an increased startle response (Prickaerts et al., 2006). These behaviors are reminiscent of bipolar patients in the manic state. This is perhaps not surprising since lithium treatment is known to inhibit the actions of GSK3β (Jope and Roh, 2006). Besides its role in circadian rhythms, GSK3β is a widely expressed kinase that has many functions in the brain (Jope and Roh, 2006). Furthermore, it is unclear as to what brain region is involved in the manic-like behaviors since the transgene is expressed in several regions, or if this overexpression affects circadian rhythms or the regulation of circadian genes (Spittaels et al., 2002). One reason to suspect that the manic-like phenotype seen in these mice may involve the circadian clock is that our laboratory has found that mice harboring a mutation in the *CLOCK* gene also display a behavioral profile that is strikingly similar to human mania (Roybal et al., *in press*). These mice have a point mutation in the *CLOCK* gene caused by ENU mutagenesis that results in a dominant-negative protein (King et al., 1997). Their behavioral profile includes hyperactivity in response to novelty and over the light/dark cycle, reduced depression-like behavior in the forced swim test and learned helplessness tests, reduced anxiety or increased risk taking behavior in several measures, and an increase in the reward value of cocaine, sucrose and intracranial self-stimulation (McClung et al., 2005;Roybal et al, *in press*). Other laboratories have found that these mice sleep less and have increased exploratory activity, adding to their overall manic-like phenotype (Naylor et al., 2000;Easton et al., 2003). Importantly, when we treat these mice with the mood stabilizer, lithium, the majority of their behavioral responses return to wild-type levels (Roybal et al., *in press*). Since alterations in the midbrain dopaminergic system have been implicated in mania, we performed *in vivo* recordings from the dopaminergic neurons of the *CLOCK* mutant mice and we found an increase in dopamine cell firing and bursting in the ventral tegmental area (VTA) (McClung et al., 2005;Nestler, 2005;Nestler and Carlezon, 2006). CLOCK is expressed in the VTA, and it appears to regulate a number of genes that are important in dopaminergic transmission (McClung et al., 2005). When we expressed a functional CLOCK protein specifically in the VTA of the mutant mice using viral-mediated gene transfer, we are able to return several of their behavioral phenotypes to wild-type levels, including locomotor activity and levels of anxiety (Roybal et al., *in press*). These results suggest that CLOCK is important in the development of mania, and that at least some of the behavioral and mood related phenotypes seen in the mutant mice are a result of the loss of CLOCK in the dopamine-rich VTA. We have yet to determine how CLOCK function in other brain regions (including the SCN) is important in these behavioral measures. Since CLOCK is so widely expressed, it is likely that we will find important functions for CLOCK in several regions. The finding that antidepressant treatment increases CLOCK expression in the hippocampus is particularly interesting since the hippocampus has been widely implicated in depression (Campbell and Macqueen, 2004).

Additional behavioral studies with mice lacking other circadian genes are ongoing. They will undoubtedly prove useful in determining how these genes and the associated changes in rhythms regulate mood.

6. Summary and conclusions

The connection between mood disorders and circadian rhythms is becoming increasingly clear. With the cloning and identification of individual members of the molecular clock, studies examining the biology behind this association and the clock's influence on mood are now being conducted. These studies should provide valuable information in terms of our overall understanding of the development of mood disorders and the most appropriate ways to treat them. Treatments like TSD and light therapy are now commonly used by many physicians. Though these treatments are effective for many individuals, they still have limitations. Combinations of short term treatments such as TSD combined with longer-term pharmacological treatment may provide the quickest and most sustained relief of mood-related symptoms. An understanding of how these treatments alleviate symptoms, and how shifts in circadian rhythms result in changes in mood, will allow us to design specific, less invasive, and more effective treatments for these dehabilitating disorders.

Acknowledgements

I would like to thank Eric Nestler, John Enwright, Shibani Mukherjee, Joseph Peevey, and Addie Dickson for their helpful comments on this manuscript.

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Abbreviations

BMAL1
Brain and Muscle ARNT-like Protein 1

BPD
Bipolar disorder

CK1
Casein Kinase I

CLOCK
Circadian Locomotor Output Cycles Kaput Protein

GSK3β
Glycogen Synthase Kinase 3β

MDD
Major Depressive Disorder

NPAS2
Neuronal PAS domain Protein 2

SAD
Seasonal Affective Disorder

SCN
Suprachiasmatic Nucleus

SNP
Single Nucleotide Polymorphism

SSRI
Selective Serotonin Reuptake Inhibitor

TSD
Total Sleep Deprivation

VTA
Ventral Tegmental Area