

Role for the *Clock* Gene in Bipolar Disorder

C.A. McCLUNG

Department of Psychiatry and Center for Basic Neuroscience, University of Texas Southwestern Medical Center, Dallas, Texas 75390-9070

Nearly all patients with bipolar disorder have severely disrupted circadian rhythms. Treatment with mood stabilizers can restore these daily rhythms, and this is correlated with patient recovery. However, it is still uncertain whether clock abnormalities are the cause of bipolar disorder or if these rhythm disruptions are secondary to alterations in other circuits. Furthermore, the mechanism by which the circadian clock might influence mood is still unclear. With cloning and characterization of the circadian genes and recent advances in molecular biology, we are starting to understand this strong association between circadian rhythms and bipolar disorder. Recent human genetic and mouse behavioral studies indicate that the *Clock* gene is particularly relevant in the mood disruptions associated with this disorder. Furthermore, it appears that *Clock* expression outside of the central pacemaker of the suprachiasmatic nucleus (SCN) is involved in mood regulation. In this chapter, the evidence linking circadian rhythms, the *Clock* gene, and bipolar disorder is discussed, along with the possible biology that underlies this connection.

INTRODUCTION TO RHYTHMS AND MOOD

It has been known for some time that disruptions in biological rhythms are strongly associated with nearly all mood disorders. In fact, some of the most common symptoms of diseases such as major depressive disorder and bipolar disorder are abnormal sleep/wake, appetite, and social rhythms (Boivin 2000; Bunney and Bunney 2000; Lenox et al. 2002; Grandin et al. 2006; McClung 2007). Depressed individuals often experience the most severe symptoms in the early morning with gradual improvement throughout the day (Rusting and Larsen 1998). Furthermore, depression is more prevalent in areas of the world that receive little sunlight for extended periods of time (Booker et al. 1991). In fact, one of the most common mood disorders, affecting approximately 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).

Mood disorders may be caused by an abnormally shifted or arrhythmic clock. It is known that 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 are common in depressed and bipolar patients (Atkinson et al. 1975; Kripke et al. 1978; Souetre et al. 1989). Interestingly, these rhythms usually return to normal with antidepressant or mood stabilizer treatment and patient recovery. Furthermore, genetic sleep disorders such as familial advanced phase sleep syndrome (FASPS) or delayed sleep phase syndrome (DSPS) are both highly comorbid with depression and anxiety (Shirayama et al. 2003; Xu et al. 2005; Hamet and Tremblay 2006). Even individuals that are genetically predisposed toward “eveningness” (a preference for the evening) versus “morningness” (a preference for the morning) are more likely to develop mood disorders (Drennan et al. 1991; Chelminski et al. 1999).

Given the cyclic nature of bipolar disorder, many researchers have speculated that circadian abnormalities underlie its development (Kripke et al. 1978; Mitterauer 2000; Mansour et al. 2005). Bipolar patients have severely disrupted rhythms in nearly all measures, and this is often used as part of the disease diagnosis. In addition, it is very common for symptoms to be seasonal, in that patients are more likely to have depressive symptoms in the winter and manic symptoms during the summer (Mitterauer 2000). In many bipolar patients, manic or depressive episodes are stimulated by disruptions in their sleep/wake cycle (Frank et al. 2000). For these patients, shift work or jobs with erratic work schedules can be severely detrimental. These individuals may have a molecular clock that is unable to properly adapt to changes in the environment, and this underlies the precipitation of these episodes (Grandin et al. 2006). Often, dramatic mood stabilizing effects in bipolar patients can be obtained through strict regulation of the sleep/wake cycle (Wirz-Justice et al. 2005).

Manic or depressive episodes can also be brought on by periods of stress and this may be related to the effect of stress on the clock. The Social Zeitgeber Theory proposes that in vulnerable individuals, life stress affects sleep/wake and social rhythms, leading to circadian clock disruption and subsequent depressive or manic episodes (Grandin et al. 2006). Interpersonal and Social Rhythm Therapy has been used successfully to prevent the recurrence of these episodes in bipolar patients (Frank et al. 2000). Therefore, these disruptions in rhythms in bipolar patients could underlie their extreme mood fluctuations brought on by periods of stress.

TREATMENTS FOR MOOD DISORDERS INVOLVE THE CLOCK

Virtually all of the successful treatments for mood disorders alter circadian rhythms, and it appears that these rhythm changes are important for therapeutic efficacy.

Total sleep deprivation (TSD) is a rapid and effective short-term treatment for depression that is often used in hospitals. Similar to treatment with antidepressant drugs, it improves depressive symptoms in about 40–60% of patients (Wirz-Justice and Van den Hoofdakker 1999; Giedke and Schwarzler 2002). However, in bipolar patients, TSD can not only reverse the depression, but it can lead to a manic episode. It is thought that TSD acts by resetting the circadian clock, and several circadian phase-setting and sleep-phase hypotheses have been put forth to explain its therapeutic action (Wirz-Justice and Van den Hoofdakker 1999). Unfortunately, the effects of TSD are short, and patients often relapse after a few days. The effects can be extended by drug treatment or by a phase-advance in rhythms brought about by light therapy and regulation of the sleep/wake cycle.

Bright-light therapy on its own has been used to successfully treat seasonal depression for more than 20 years. Several studies also indicate that light therapy can be equally effective in treating nonseasonal depression, as well as other mood disorders (Terman and Terman 2005). Initially, SAD patients were treated with light therapy both in the morning and in the evening to mimic the longer days of spring and summer; however, it later was found that light therapy given exclusively in the morning (producing a phase-advance in rhythms) had a much greater therapeutic effect in most patients (Magnusson and Boivin 2003). Interestingly, a recent study by Lewy et al. (2006) found that most SAD patients are naturally phase-delayed; however, a small subgroup is phase-advanced. Specific phase-shifting treatments (either light or melatonin) given to these individuals at certain times of day lead to an optimal circadian period and alleviated their depressive symptoms. These data strongly suggest that specific circadian phase-shifting is crucial for therapeutic success in the treatment of depression.

In bipolar patients, the mood stabilizers lithium and valproate are commonly used for treatment. Both of these drugs have been repeatedly shown to alter the circadian period, leading to a long period in *Drosophila*, nonhuman primates, rodents, and humans (Johnsson et al. 1983; Welsh and Moore-Ede 1990; Klemfuss 1992; Hafen and Wollnik 1994; Dokucu et al. 2005). Lithium is also able to slow the abnormally fast circadian rhythms found in most bipolar patients (Atkinson et al. 1975; Kripke et al. 1978). Furthermore, patients that have an abnormally fast clock respond positively to lithium treatment, whereas the few bipolar patients that begin with an abnormally slow clock do not respond favorably to lithium treatment (Atkinson et al. 1975; Kripke et al. 1978). These actions of lithium on the free-running period appear to be suprachiasmatic nucleus (SCN)-dependent (LeSauter and Silver 1993).

Similar to morning bright-light therapy, the antidepressant, fluoxetine, can affect circadian output by producing a phase-advance in the firing of SCN neurons as shown in rat slice cultures (Sprouse et al. 2006). Other studies have shown that serotonin neurons from the midbrain raphe nuclei innervate the SCN, and local applications of 5-hydroxytryptamine (5-HT) or 5-HT1A and 5-HT7 receptor agonists to the SCN will also produce a phase-advance in circadian activity (Dudley et al. 1999; Ehlen et al.

2001). Thus, it is possible that 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 because SSRIs cause a phase-advance in rhythms, whereas lithium can cause a phase-delay (Campbell et al. 1989; Sprouse et al. 2006).

Recently, agomelatine, a potent agonist of the melatonin receptors, has proven to be highly effective in animal models of depression and in several ongoing clinical trials involving patients with major depression and bipolar depression (den Boer et al. 2006; Hamon and Bourgoin 2006; Zupancic and Guilleminault 2006). As expected by its pharmacologic profile, agomelatine resynchronizes the circadian rhythms in body temperature, cortisol, and other hormones in animal models and in humans (Leproult et al. 2005). Curiously, agomelatine is much more effective as an antidepressant than melatonin itself (Srinivasan et al. 2006). Agomelatine could have different binding or kinetic properties at the melatonin receptors, which makes the response different from that seen with melatonin. Furthermore, agomelatine seems to have no effect on central serotonin transmission or the density and function of 5-HT1A receptors as seen with SSRI administration (Hanoun et al. 2004; Millan et al. 2005). However, it does have 5-HT2C antagonistic properties, and it enhances mesolimbic dopaminergic and noradrenergic transmission (Millan et al. 2003; Serretti et al. 2004). Moreover, chronic, but not acute, treatment with agomelatine induces neurogenesis in the hippocampus similar to other antidepressants (Banar et al. 2006). Therefore, it is uncertain exactly how agomelatine alleviates depression, and if the circadian rhythm changes produced by this drug are involved.

EVIDENCE SUGGESTING A SPECIFIC ROLE FOR CLOCK AND BMAL1 IN BIPOLAR DISORDER

Several human genetic studies have implicated specific genes that make up the molecular clock in the manifestation of mood disorders. For example, genetic variants in *NPAS2*, *Per2*, and *BMAL1* have been found to associate with the development of SAD (Johansson et al. 2003; Partonen et al. 2007). Bipolar disorder has been most strongly linked to variations in *Clock* and *Bmal1*. 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 (Serretti et al. 2003, 2005). Other genetic studies have identified haplotypes and SNPs in *Bmal1* that significantly associate with bipolar disorder in general (Mansour et al. 2006; Nievergelt et al. 2006). These genetic studies suggest an association between the CLOCK/BMAL1 complex and certain aspects of bipolar disorder.

To determine more specifically how the *Clock* gene is involved in mood regulation we tested mice that have a

Table 1. Comparison of Behaviors in Humans and Mice

| Symptoms of mania | <i>Clock</i> mutant mice |
|------------------------------|----------------------------------|
| Disrupted circadian rhythms | disrupted circadian rhythms |
| Hyperactivity | hyperactivity |
| Decreased sleep | decreased sleep |
| Feelings of extreme euphoria | hyperhedonia/less helplessness |
| Increased risk-taking | reduced anxiety |
| Propensity toward drug abuse | increased preference for cocaine |

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point mutation in this gene which creates a dominant-negative protein (King et al. 1997). Interestingly, we found that these mice display a complete behavioral profile that is remarkably similar to that of human mania (Roybal et al. 2007). A comparison between human subjects and the *Clock* mutant mice is given in Table 1. These behaviors include general hyperactivity; a decrease in anxiety when measured in multiple tests; an increase in the reward value for sucrose, cocaine, and brain stimulation; and a decrease in measures of depression-like behavior (Roybal et al. 2007). Other groups have reported a decrease in sleep in these mice and an increase in exploratory behavior, adding to their manic-like profile (Naylor et al. 2000; Easton et al. 2003). Importantly, these mice display an increase in goal-directed activities with the potential for adverse consequences as shown by intracranial self-stimulation measures. This is a key feature in the diagnosis of the manic component of human bipolar disorder. Their increase in preference for cocaine also correlates with the high comorbidity for substance abuse in bipolar patients. Some of the largest rates of addiction occur in bipolar patients, with the greatest risk occurring in patients with frequent manic episodes (Regier et al. 1990; Kessler et al. 1996; Marenmani et al. 2006). The abuse of nearly all mood-altering drugs is significantly higher in bipolar patients than in the general population (Regier et al. 1990; Marenmani et al. 2006). However, the use of drugs such as alcohol and heroin seems to associate most strongly with the depression phase of the disorder, and patients in the manic state seem strongly drawn to psychostimulants such as amphetamines and cocaine (Estroff et al. 1985; Regier et al. 1990).

Lithium is still the most commonly prescribed mood stabilizer, and it is particularly effective in treating mania (Shastry 1997). To determine if the manic-like behavior of the *Clock* mutants can be rescued by lithium treatment, we gave LiCl in the drinking water at 600 mg/liter for 10 days as described previously (Dehpour et al. 2002). We found that this treatment produces a stable, serum Li⁺ concentration of 0.41 ± 0.06 mmole/liter which is at the low end of the therapeutic range for human patients (Gelenberg et al. 1989). Chronic lithium treatment restored the levels of behavioral despair of the *Clock* mutant mice to near wild-type levels. In addition, their responses in measures of anxiety also returned to normal levels after lithium treatment (Fig. 1).

Interestingly, behavior of the wild-type mice was not significantly affected by this concentration of LiCl in most measures. However, there was a significant decrease in the levels of anxiety in the elevated plus maze. Previous studies that looked at the effect of lithium on various behavioral measures in wild-type mice have reported mixed results. A recent study by Bersudsky et al. (2007) found that lithium treatments that produced high serum levels of 1.3–1.4 mmole/liter decreased the immobility time of wild-type mice in the forced swim test; however, levels of 0.8 mmole/liter or lower had no effect. Our mice have lithium serum levels that are much lower (~0.4 mmole/liter); thus, it is consistent that the wild-type mice may not have significant differences in behavioral measures of mood. Similar to the situation in wild-type mice, lithium treatment at therapeutic doses does not have a significant mood-altering effect on healthy human volunteers (Calil et al. 1990). Therefore, the *Clock* mutant mice provide us with an excellent opportunity to study the development of mania, as well as the molecular mechanisms that underlie the efficacy of lithium as a treatment in bipolar patients.

DOES CLOCK IN THE SCN INFLUENCE MOOD?

It is unclear as to what extent the manic-like phenotypes of the *Clock* mutant mice are due to the loss of *Clock* function in the central circadian pacemaker of the SCN or to the loss of *Clock* in other brain regions. A study by

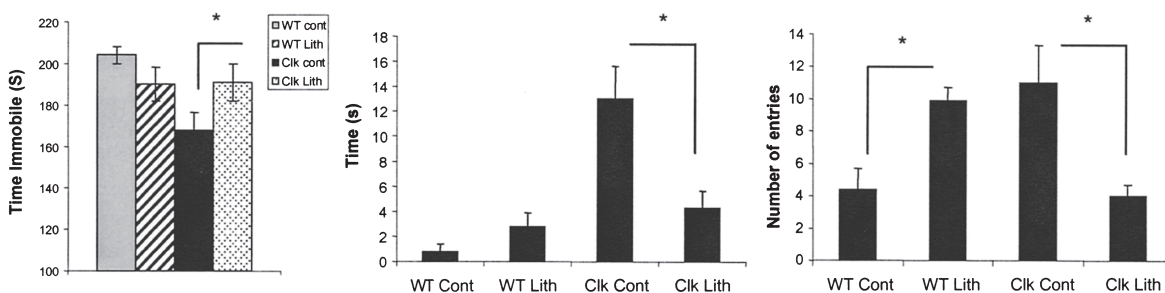


Figure 1. Effect of lithium treatment on the *Clock* mutants in behavioral measures (*left*) LiCl (600 mg/liter, 10 days) leads to an increase in the time immobile of the *Clock* mutants in the FST. LiCl treatment decreases the time spent by the *Clock* mutants in the center of an open field (*middle*) and in the open arms of the EPM (*right*) (In all tests, * $P < 0.05$, Student's *t*-test, $n = 8$.) (Reprinted, with permission, from Roybal et al. 2007 [© National Academy of Sciences].)

Tataroglu et al. (2004) found that bilateral SCN lesions in rats have an antidepressant-like effect in the forced swim test. Furthermore, SCN lesions prevent the anxiolytic effects of agomelatine following repeated bouts of social defeat (Tuma et al. 2005). Therefore, the SCN might be involved in the regulation of mood. However, these lesions had no effect on general activity or baseline measures of anxiety, suggesting that other brain regions are also involved in the full behavioral spectrum associated with mania. One intriguing possible connection between mania and central clock function comes from recent reports showing phosphorylation of multiple circadian genes by glycogen synthase kinase 3 β (GSK3 β). Lithium is known to inhibit the actions of GSK3 β , and there are indications that this action is important in mood stabilization (Gould and Manji 2005). Indeed, transgenic mice overexpressing *Gsk3 β* are hyperactive, have reduced immobility in the forced swim test, and an increased startle response, reminiscent of human mania (Prickaerts et al. 2006). The *Drosophila* ortholog of GSK3 β , SHAGGY, promotes the nuclear translocation of PER/TIM by phosphorylating TIM (Harms et al. 2003). In mammals, GSK3 β is expressed in the SCN, and there is a robust circadian rhythm in its phosphorylation and activity in this region (Iitaka et al. 2005). Furthermore, GSK3 β can phosphorylate PER2, CRY2, and Rev-er α , leading to the proper regulation of circadian rhythms (Iitaka et al. 2005; Kurabayashi et al. 2006; Yin et al. 2006). Lithium inhibits this activity and promotes a long circadian period (Padiath et al. 2004). Therefore, it is possible that some of the therapeutic effects of lithium on mood stabilization are derived from this inhibition of GSK3 β in the SCN. Intriguingly, the *Clock* mutant mice also have a long period in circadian activity rhythms when mice are kept in constant darkness (Vitataerna et al. 1994; King et al. 1997). It will be interesting to determine how lithium treatment affects the rhythms of these mice.

IMPORTANT RHYTHMS IN OTHER CIRCUITS

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; Akhilaroglu et al. 2005).

The hippocampus, and in particular, the neurogenesis that occurs in this region, is thought to be important in the development and treatment of mood disorders because chronic stress inhibits neurogenesis, whereas antidepressant treatment enhances it (Dranovsky and Hen 2006). Neurogenesis and cell proliferation are under circadian control, and recent studies have found that the circadian gene, *Per2*, is involved in this process (Kochman et al.

2006). Mice lacking *Per2* function display an increase in neurogenesis and proliferation, similar to antidepressant treatment (Borgs et al. 2006). In addition, two genes highly expressed in the hippocampus, brain-derived neurotrophic factor (*Bdnf*) and its receptor, tyrosine receptor kinase B (*TrkB*), have been strongly implicated in the regulation of mood and neurogenesis, and both have a robust circadian rhythm in their expression in this region (Liang et al. 1998; Berchtold et al. 1999; Schaaf et al. 2000; Dolci et al. 2003; Kuipers and Bramham 2006). It is possible that disruptions of the rhythms in the hippocampus or in any of these other systems could lead to mood destabilization.

REGULATION OF THESE RHYTHMS BY THE SCN

The modulation of circadian neurotransmission in other brain regions may occur through indirect projections from the SCN. For example, an indirect projection from the SCN to the locus coeruleus (LC) regulates the circadian rhythm in noradrenergic neuronal activity (Aston-Jones et al. 2001). A potential indirect pathway from the SCN to the ventral tegmental area (VTA) and dorsal raphe nucleus via the dorsomedial hypothalamic nucleus has also been described (Deurveilher and Semba 2005). There is also a dependence on the SCN for the circadian regulation of certain genes in the dopaminergic neurons of the VTA (Sleipness et al. 2007). The SCN could also influence rhythms in other brain regions through its control of circulating hormones and peptides. Melatonin receptors are widely expressed, and certain types of antidepressant treatments alter MT1 and MT2 levels in the hippocampus and striatum (Hirsch-Rodriguez et al. 2007). The stress hormone, corticosterone, also has a strong circulating rhythm controlled through an indirect SCN projection to the adrenal cortex, and alterations in its rhythm could influence long-term anxiety and mood (Engeland and Arnhold 2005). Furthermore, SCN's regulation of hormones and hypothalamic peptides involved in metabolism such as insulin, orexin, leptin, and ghrelin could also modulate neurotransmission in brain regions associated with mood regulation. Recent studies have found that leptin-mediated signaling in the mesolimbic dopaminergic pathway is involved in modulating neuronal activity, reward, and motivational behavior (Fulton et al. 2006; Hommel et al. 2006). There is also evidence to suggest that the orexin system regulates not only arousal states, but also dopaminergic activity, drug, and food reward (Harris and Aston-Jones 2006; Narita et al. 2006). Interestingly the *Clock* mutant mice have a metabolic phenotype leading to obesity (Turek et al. 2005). Obesity is very common in bipolar patients, and this is often worsened by lithium treatment (Newcomer 2006). In the *Clock* mutant mice, the levels and circadian rhythms of multiple hypothalamic peptides are severely attenuated (Turek et al. 2005). In addition, levels of serum leptin are significantly higher during the light phase and levels of corticosterone are lower throughout the light/dark cycle (Turek et al. 2005). It is possible that these altered hormone and peptide rhythms are involved in the manic-like state we see in these mice.

THE CIRCADIAN GENES IN OTHER BRAIN REGIONS

Circadian gene expression outside of the SCN, in key “mood-related” brain regions, may be important. These genes can form peripheral clocks that respond to SCN signals or function independently in response to certain stimuli. For example, 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 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 molecular rhythms in the SCN and striatum.

Interestingly, a microarray study by Ogden et al. (2004) found that the mood stabilizer, valproate, decreased the expression of the circadian genes *CK1δ* and *Cry2* in the amygdala, a region of the brain associated with emotional behavior and fear. These changes were prevented by cotreatment with methamphetamine, which was given to induce manic-like symptoms, suggesting that these changes may be involved in the treatment of mania (Ogden et al. 2004). Therefore, mood stabilizer treatment may involve a change in rhythms in the amygdala.

A recent study by Uz et al. (2005) found that treatment with the antidepressant fluoxetine altered the expression of *Clock* and *Bmal1*, along with *Npas2* in the mouse hippocampus. These same changes did not occur in striatal regions, indicating that they may be brain-region-specific. Furthermore, they were all induced by chronic and not acute fluoxetine, suggesting that these changes may be therapeutically relevant because fluoxetine must be administered for days to weeks to see significant antidepressant effects in humans (Uz et al. 2005). Therefore, this complex may be involved in rhythm and mood regulation through expression in the hippocampus. In addition, our recent studies suggest that *Clock* may function in the dopamine cells of the VTA to regulate the expression of other circadian genes and several genes involved in dopaminergic transmission including the rate-limiting enzyme in dopamine synthesis tyrosine hydroxylase (TH) (McClung et al. 2005; Roybal et al. 2007). Interestingly, TH and a number of other genes involved in dopaminergic

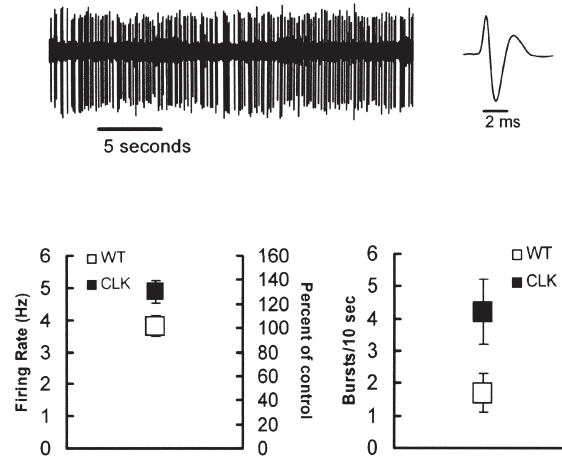


Figure 2. Dopamine cell-firing rates and bursting are increased in *Clock* mutant mice. (Top left) Representative recording of a mouse dopamine neuron. (Right) Example of an averaged dopamine triphasic waveform. (Bottom left) *Clock* mutant mice (*Clk*) ($n = 24$) exhibited higher basal dopamine firing rates compared with wild type (WT) ($n = 26$) mice ($P < 0.03$). Squares represent the mean \pm S.E.M. of each group. (Bottom right) *Clock* mutant mice exhibited more burst events per 10 seconds compared with wild type controls ($P < 0.01$). Each vertical bar represents the mean \pm S.E.M. of each group. The percentage of bursting activity, i.e., spikes emitted in bursts, was greater compared with wild-type mice (*Clk*, 23.5 ± 4.3 vs. 10.6 ± 3.6 in WT; $P < 0.03$). *Clock* mutant mice had larger burst sizes (number of spikes/burst) compared with controls (2.8 ± 0.1 vs. 2.0 ± 0.1 ; $P < 0.008$). (Reprinted, with permission, from McClung et al. 2005 [© National Academy of Sciences].)

transmission such as cholecystokinin, the dopamine transporter, and various dopamine receptors, all have a robust circadian rhythm in expression, suggesting that they might be regulated by circadian genes (Weber et al. 2004; Sleipness et al. 2007). We have found that the *Clock* mutant mice have an increase in dopaminergic activity in the VTA that correlates with their manic-like behavior (Fig. 2) (McClung et al. 2005). Furthermore, when we express a functional CLOCK protein specifically in the VTA using virus-mediated gene transfer, we are able to rescue at least a portion of their manic behavior (Fig. 3) (Roybal et al. 2007). The effects of CLOCK restoration in the VTA in other behaviors associated with

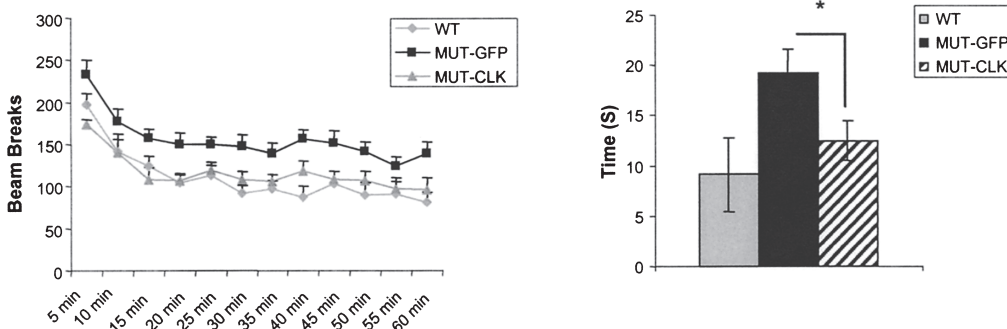


Figure 3. Effect of CLOCK viral expression in the VTA of *Clock* mutant mice. (Left) Locomotor hyperactivity in response to novelty and time spent in the center of an open field (right) is reduced following two weeks of functional CLOCK overexpression in the VTA of *Clock* mutant mice (For (left) total locomotor activity, levels are significantly different, $*P < 0.05$, Student's *t*-test, $n = 9-12$). (Reprinted, with permission, from Roybal et al. 2007 [© National Academy of Sciences].)

mania have yet to be tested. These studies suggest that proper CLOCK expression in the VTA is important in the regulation of dopaminergic activity and at least some of the behavior associated with mania. Future studies will determine to what extents other circadian genes and other brain regions are involved in these responses.

CONCLUSIONS

There is considerable evidence suggesting a connection between circadian rhythms and bipolar disorder. Studies are starting to unravel this complex association between disruptions in rhythms and mood regulation. Some of this regulation might be SCN-dependent, whereas other components are not. The Clock gene appears to have an important role in this disorder, however, it is still unclear how a disruption in CLOCK function leads to a manic-like state. Our data suggest that at least a subset of these behavioral abnormalities are due to a loss of CLOCK function in the dopamine cells of the VTA. Because CLOCK is a transcription factor, it is likely that its regulation of gene expression is centrally involved. CLOCK is widely expressed and regulates the expression of many different genes in many different tissues including regions of the brain implicated in mood-associated behavior (Miller et al. 2007). The large task ahead is to determine the target genes of CLOCK in specific brain regions that are the most relevant in mood regulation.

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