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Circadian Rhythms and Mood Regulation: Insights from Pre-Clinical Models

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Abstract

Affective disorders such as major depression, bipolar disorder, and seasonal affective disorder are associated with major disruptions in circadian rhythms. Indeed, altered sleep/wake cycles are a critical feature for diagnosis in the DSM IV and several of the therapies used to treat these disorders have profound effects on rhythm length and stabilization in human populations. Furthermore, multiple human genetic studies have identified polymorphisms in specific circadian genes that associate with these disorders. Thus, there appears to be a strong association between the circadian system and mood regulation, although the mechanisms that underlie this association are unclear. Recently, a number of studies in animal models have begun to shed light on the complex interactions between circadian genes and mood-related neurotransmitter systems, the effects of light manipulation on brain circuitry, the impact of chronic stress on rhythms, and the ways in which antidepressant and mood-stabilizing drugs alter the clock. This review will focus on the recent advances that have been gleaned from the use of pre-clinical models to further our understanding of how the circadian system regulates mood.

Introduction to circadian timing regulation

Nearly every organism on the planet has circadian rhythms of ~24 h in multiple biological processes which are controlled by both the light-dark cycle and an internal clock. The circadian system is composed of three main components: input pathways which relay environmental information to the clock, the central clock itself which can generate rhythms even in the absence of environmental input, and output pathways which synchronize clocks in individual cells and organs throughout the brain and the body. Through the work of many groups over the last ~35 years in a number of organisms including *Drosophila*, *Neurospora*, *Chlamydamonas*, hamsters, mice, rats, frogs, and others, many of the genes and circuits that regulate circadian rhythmicity have been identified (King and Takahashi, 2000; Ko and Takahashi, 2006; Reppert and Weaver, 2000; Rosbash, 1995).

In mammals, the central circadian oscillator is located in the suprachiasmatic nucleus (SCN) of the hypothalamus (Weaver, 1998). The SCN receives light input *via* a direct retinohypothalamic tract (RHT) from photosensitive retinal ganglion cells expressing the photopigment, melanopsin, and this input helps to entrain rhythms (Hankins et al. 2008). The SCN then sends signals via direct and indirect projections in the brain, and through coordinated timing of the release of multiple peptides and hormones that circulate

throughout the brain and body to synchronize “slave” oscillators in various tissues (Reppert and Weaver, 2002). Though nearly every cell in the body has its own molecular clock, the SCN serves as the master regulator to entrain rhythms and keep them synchronized. The mechanism by which it does this is primarily controlled by sodium-dependent action potentials regulated by at least two ionic currents: a Ca^{2+} current and a K^+ current which are necessary for the maintenance of proper membrane potential (Pennartz et al. 2002). Indeed, there is a substantial diurnal difference in L-type Ca^{2+} current in the rat SCN which contributes to the high-frequency firing in this region specifically during the light phase. Moreover, there is a reduction in tonically active K^+ current (and perhaps a Na^+ channel activation) in the light phase which helps to maintain membrane potential (Pennartz et al. 2002). The circadian regulation of these currents in the SCN is likely through transcriptional or translational control of channel subunits by the core molecular clock. Light is one of the most potent entrainers of circadian rhythms, but, other stimuli such as food, social cues, or drugs of abuse can entrain behavioral rhythms by bypassing the SCN and controlling oscillators in other brain regions (Webb et al. 2009). Though these extra oscillators have been studied for many years, their definitive location in the brain has yet to be determined.

This core molecular clock is composed of a series of transcriptional and translational feedback loops that cycle over ~24 h. The basic helix-loop-helix-PAS (Period-Arnt-Single-minded)–containing transcription factors, Circadian Locomotor Output Cycles Kaput (CLOCK) and Brain and Muscle Arnt-Like protein 1 (BMAL1; also called MOP3) heterodimerize and bind to E-box–containing sequences in a number of genes including the three *Period* (*Per*) genes (*Per1*, *Per2* and *Per3*) and the two *Cryptochrome* (*Cry*) genes (*Cry1* and *Cry2*). Over time, the PER and CRY proteins dimerize and are shuttled back into the nucleus where CRY proteins can directly inhibit the activity of CLOCK and BMAL1, thus forming a negative feedback loop (Ko and Takahashi, 2006; Reppert and Weaver, 2002). In addition to this feedback loop, the CLOCK and BMAL1 proteins regulate the expression of the nuclear hormone receptors, Rev-erbα and Rora which in turn can repress or activate *Bmal1* transcription, respectively, through actions at the Reb-Erv/ROR response element in the promoter (Preitner et al. 2002; Sato et al. 2004). Outside of the SCN, Neuronal PAS-Domain Protein 2 (NPAS2; also known as MOP4) can heterodimerize with BMAL1 and control *Per* and *Cry* gene expression (Reick et al. 2001). NPAS2 can also substitute for CLOCK to regulate rhythms in the SCN when the *Clock* gene has been disrupted (DeBruyne et al. 2007).

Chromatin modifications are key to transcriptional control of circadian rhythms. For example, the recruitment of CLOCK/BMAL1 heterodimers to certain target gene promoters is rhythmic (not constitutive) and is associated with acetylation of histone H3 at specific loci (Ripperger and Schibler, 2006). Furthermore, lysine trimethylation of histone H3 at Lys4, which is prominently associated with transcriptional activation, has a circadian rhythm at CLOCK controlled genes that is elicited by the histone methyltransferase protein Mixed Lineage Leukemia 1 (MLL1). MLL1 forms a complex with CLOCK/BMAL1 and recruits these proteins to chromatin to allow circadian transcription (Katada and Sassone-Corsi, 2010). Interestingly, the CLOCK protein itself has the unusual feature of intrinsic histone acetyl transferase (HAT) activity, and CLOCK-mediated histone H3 (lysine 14) acetylation at specific promoters has circadian rhythmicity (Doi et al. 2006; Nakahata et al. 2008). CLOCK can also associate with other HATs including CREB-binding protein (CBP), and it is still unclear what contribution the intrinsic HAT activity of CLOCK makes to histone acetylation vs these bound HATs that associate following cellular stimulation (Yujnovsky et al. 2006). In addition to histone acetylation, CLOCK can facilitate the acetylation of its binding partner BMAL1, which is essential for proper circadian transcription (Hirayama et al. 2007). Moreover, CLOCK and BMAL1 associate with the histone deacetylase (HDAC)

Sirtuin 1 (Sirt1), which negatively regulates transcription, providing a counterbalance to the HAT function of CLOCK (Nakahata et al. 2008; Asher et al. 2008).

There are several key proteins that regulate the timing of the molecular clock through phosphorylation, including the casein kinase 1 delta and epsilon proteins (CK1Δ and CK1ε) which can phosphorylate the PER, CRY and BMAL1 proteins (Virshup et al. 2007). The original circadian mutation found in mammals, the Syrian hamster *tau* mutation, was ultimately identified as a missense mutation that creates a dominant negative CK1ε protein which leads to a short (~20 h) period (Lowrey et al. 2000). Recent studies by Sprouse and colleagues have found that chronic administration of a pharmacological casein kinase 1 (delta/epsilon) inhibitor (PF-670462) causes cumulative phase delays in the activity onset of rats and monkeys in a fixed light/dark cycle (Sprouse et al. 2010; Sprouse et al. 2009). Interestingly, a selective CK1 epsilon inhibitor (PF-4800567) is able to block CK1 epsilon–mediated PER3 nuclear localization and PER2 degradation in fibroblasts, but has minimal effects on overall rhythms, which implicates CK1Δ as the predominant mediator of circadian timing (Walton et al. 2009).

Another kinase that helps to regulate rhythmicity is glycogen synthase kinase 3 beta (GSK3β). GSK3β phosphorylates the *Drosophila* PER protein and mammalian PER2 protein facilitating nuclear entry. Furthermore it phosphorylates the Rev-erbalpha protein which leads to increased protein stability, and the CRY2 and CLOCK proteins leading to proteasomal degradation (Iitaka et al. 2005; Ko et al. 2010; Kurabayashi et al. 2010; Spengler et al. 2009; Yin et al. 2006). Overexpression of GSK3beta in circadian pacemaker cells of *Drosophila* shortens the period and this is rescued partially by the mood-stabilizing drug lithium, which inhibits the activity of GSK3beta and has a well-characterized period-lengthening phenotype in nearly every organism tested (Dokucu et al. 2005; Gould and Manji, 2005; Iwahana et al. 2004). The period-lengthening effects of lithium are also correlated with changes in GSK3beta activity and expression in the SCN of mice, suggesting that the period-lengthening effects are mediated by altered GSK3beta activity (Iwahana et al. 2004). However, in a recent culture-based screen of pharmacologically active compounds, small molecule inhibitors of GSK-3 consistently led to a shortened period in molecular rhythms, while lithium led to a long period (Hirota et al. 2008). This period shortening was replicated by a shiRNA-mediated knockdown of GSK-3beta, suggesting that the period-lengthening effects of lithium may not be mediated by GSK-3beta inhibition (Hirota et al. 2008).

Clearly there are other protein kinases and specific phosphatases that help to orchestrate the timing of circadian rhythmicity. Indeed, BMAL1 can be phosphorylated by mitogen-activated protein kinases (MAPKs) and casein kinase 2α, both of which are important for clock function (Sanada et al. 2002; Tamaru et al. 2009). BMAL1 is also sumoylated by the small ubiquitin-like modifier 1 (SUMO-1) and the circadian pattern of sumoylation closely follows its activation (Cardone et al. 2005). In addition to chromatin remodeling and several post-translational modifications, recent studies have implicated a number of microRNAs (miRNA) and several RNA-binding protein complexes in the regulation of circadian polyadenylation, splicing, RNA stability and degradation (Garbarino-Pico and Green, 2007; Pegoraro and Tauber, 2008; Staiger and Koster, 2011). Thus the regulation of circadian timing is controlled by multiple processes from DNA to RNA to protein.

Effect of environmental changes in the light/dark cycle on mood-related behavior

In human populations, it is known that disruptions in circadian rhythms including the sleep/wake cycle through environmental means can produce mood-related problems in vulnerable

individuals. The impact of acute alterations in rhythms is evident to anyone who has experienced “jet lag” after a long flight across multiple time zones. A more chronic example is seasonal affective disorder (SAD) or “winter depression”, which is the most common of all mood disorders, affecting upwards of 10% of the population at temperate latitudes (Howland, 2009). Individuals with SAD are negatively affected by the shorter days and later sunrise of the winter months and develop a syndrome characterized by carbohydrate craving, lethargy, fatigue, and sadness. Similar to seasonal changes, shift work and particularly variations in work rotation schedules between day and night, can lead to profound mood-related changes in vulnerable individuals. Indeed, there is a high incidence of major depressive disorder observed during and after shift work experience with increased risk associated with duration of exposure (Cole et al. 1990; Scott et al. 1997). Recent work has found the relationship between severity of unipolar depression and circadian misalignment (Emens et al. 2009, Hasler et al. 2010).

Multiple groups have attempted to model the effects of seasonal changes, and general light/dark cycle disruption of mood regulation in rodent models. Unfortunately, most laboratory mouse strains may not be suitable for the study of SAD since they lack a functional melatonin system due to inbred mutations through domestication in genes involved in the melatonin synthesis pathway, and melatonin is thought to be keenly involved in the development of SAD in human populations (Kasahara et al. 2010; Pandi-Perumal et al. 2008; Srinivasan et al. 2006). Thus groups have turned to the use of other rodent models. Studies by Einat and colleagues have argued that diurnal rodents like the diurnal fat sand rat (*Psammomys Obesus*) and the unstriped Nile grass rat (*Arvicanthis niloticus*) are compelling models for studies of seasonal depression. In both species, 6 weeks in a very short photoperiod (5 h light/19 h dark) results in increased depression-like behavior in the forced swim test (FST) and saccharin preference test compared with animals kept on a traditional 12/12 light dark cycle (Ashkenazy et al. 2009; Ashkenazy-Frolinger et al. 2010; Einat et al. 2006). Bright light therapy in the morning has been used to treat seasonal depression in humans for more than 25 years, thus the efficacy of light therapy was tested on the sand rat. After three weeks in a short photoperiod, rats were treated 1 h daily with 3000 1x for three weeks, 1 h after “lights on”. Light therapy in the rats reduced anxiety-related and depression-related behavior in the elevated plus maze (EPM) and FST, but had no effect on saccharin preference, suggesting that the light therapy was able to reverse some, but not all of the induced phenotypes (Ashkenazy et al. 2009). The major limitation of these diurnal rats for future mechanistic study is the lack of genetic information and capabilities in these animals. However, evolving viral gene transfer technology can overcome some of these hurdles.

Siberian hamsters also show a depressive-like phenotype following short days in the FST, but do not show altered sucrose consumption, while Wistar rats in a short photoperiod have altered behavior in the FST and do show a reduction in sucrose consumption, suggesting that there are differences between species in their response to short days (Prendergast and Kay, 2008; Prendergast and Nelson, 2005; Pyter and Nelson, 2006). Interestingly, prolonged dark phase conditions (6 h light/18 h dark) administered from postnatal day 2 to 14 in Sprague-Dawley rats resulted in increased anxiety, decreased social interaction, and decreased object recognition memory later in life, suggesting that early life exposure to altered light/dark cycles can lead to lasting effects (Toki et al. 2007).

In an effort to model our modern world with nearly continuous light exposure, mice have been examined under constant light conditions. Constant light has interesting effects on circadian rhythms in mice. Unlike constant darkness where mice maintain a robust circadian rhythm in activity with a period that is slightly shorter than 24 h, in constant light they generally exhibit an initial long period and then become arrhythmic with overall reduced

locomotor activity (Ohta et al. 2005). Three weeks of constant light produced increased depression-like behavior in the FST and in sucrose preference in Swiss-Weber mice, however they also showed reduced anxiety in the open field (OF) and EPM (Fonken et al. 2009). Incidentally, chronic constant light also impairs spatial memory in rats and affects long-term depression (LTD) in the hippocampus (Ma et al. 2007).

Interestingly, rats kept in constant darkness for 6 weeks also have behavioral features that are similar to depression, and these may be the result of neuronal damage to monoamine systems (Gonzalez and Aston-Jones, 2008). Rats displayed profound apoptosis in a number of brain regions and a decrease in the number of cortical nucleus accumbens boutons following exposure to constant darkness (Gonzalez and Aston-Jones, 2008). They also had increased immobility in the FST. Chronic treatment with the antidepressant desipramine was able to reverse the effects of light deprivation on apoptosis in noradrenergic neurons and reverse depression-related behavior through a mechanism that is unclear (Gonzalez and Aston-Jones, 2008). Combined with previous results that demonstrate a decrease in the amplitude of SCN-dependent sleep-waking rhythms and loss of locus coeruleus (LC) terminals in the frontal cortex following a period of constant darkness, the authors propose that prolonged absence of light modifies the influence of the SCN over monoaminergic structures such as the LC and others that play a role in the regulation of mood (Gonzalez and Aston-Jones, 2006; Gonzalez and Aston-Jones, 2008).

Stress and the disruption of circadian rhythms

Exposure to stressful life events in human populations has long been associated with increased bouts of depression (Birley, 1972; Grandin et al, 2006). The social zeitgeber theory of depression put forth by Ehlers, Frank, and Kupfer in 1988 suggests that life events (usually stressful ones) disrupt the circadian cycle and in turn derail the internal circadian clock leading to depressive episodes in vulnerable individuals (Ehlers et al. 1988). A number of chronic stress models have been developed in animals that utilize some form of physical, prenatal, or social stress to induce a depression-like state in otherwise wild-type animals (Krishnan et al. 2008). Other models used are genetic in which rats or mice are bred for generations for their behavioral and hypothalamic-pituitary-adrenal (HPA) axis response to stressful stimuli. So the question becomes, is the development of a depression-like state in animals in response to stress associated with disruptions in circadian rhythms? The answer seems to be dependent on the species and type of stress, and circadian disruptions appear to be most prominent in social stress or prenatal stress models over other chronic stress models (Meerlo et al. 2002). One such model is the psycho-stress paradigm in the diurnal tree shrew (*Tupaia Belangeri*). Like many species, male tree shrews develop a social hierarchy when group housed. If a subordinate male is living with an alpha male that has defeated him, the subordinate develops several features reminiscent of human depression-related behavior, as well as profound changes in circadian rhythms with increased numbers of early morning awakenings and disrupted body temperature rhythms (Corbach et al. 2007; Fuchs, 2005). Treatment with antidepressant drugs like agomelatine or clomipramine, but not anxiolytic drugs, can reverse both the depression-related and circadian-related phenotypes.

Mice that have undergone a chronic social defeat paradigm, in which they are defeated daily for ten days and housed in an enclosure where they can constantly see and smell the aggressive mouse, also show disruptions in body temperature and locomotor rhythms (Krishnan et al. 2007). Interestingly, a subset of mice that undergo this chronic stress paradigm show a remarkable resilience where they do not develop a depressive-like phenotype following defeat. Only the susceptible, but not the resilient mice, show altered body temperature rhythms, suggesting that they are involved in the development of depression-related behavior (Krishnan et al. 2007). Similar disruptions in temperature, heart

rate and locomotor rhythms are seen with other social defeat stress paradigms in rats (Meerlo et al. 2002). The effects of social stress and defeat may not be due to disruptions in rhythms in the SCN since core circadian gene expression in this region is not altered, but rather these chronic stress paradigms are directly altering extra-SCN oscillators (Meerlo et al. 2002). It is unclear how long these changes in rhythms persist following defeat paradigms, and this likely varies depending upon the severity and extent of the stress.

Prenatal stress paradigms have also been used in rodents to model depression and these paradigms are also associated with long-lasting rhythm disruptions, presumably through epigenetic mechanisms in response to maternal HPA-axis activation. Prenatal exposure to repeated maternal restraint stress leads to increased anxiety and depression-like behavior in adulthood (Darnaudery and Maccari, 2008). Furthermore, these rats as adults have altered circadian rhythms in corticosterone secretion and serious sleep disturbances (Darnaudery and Maccari, 2008; Koehl et al. 1999; Koehl et al. 1997).

In addition, mice and rats selectively bred for their response to stress have differences in circadian rhythms. A recent stress reactivity mouse model has been developed that consists of three separate breeding lines, high responders (HR) intermediate responders (IR) and low responders (LR) based on their corticosterone increase in response to stress. The HR mice show altered circadian locomotor activity, sleep disturbances, early morning wakening, and lowered amplitude glucocorticoid rhythms which make the HR mice reminiscent of depressed human patients (Touma et al. 2009). Moreover, studies utilizing the Flinders sensitive line (FSL) rat, which displays anhedonia, behavioral despair, reduced appetite, sleep problems, and psychomotor function, found that measures of the power of the signal vs frequency of rhythms in heart rate, locomotor activity, and temperature were predictive of a depressed state, and these could be reversed with antidepressant treatment (Friedman et al. 2011; Overstreet et al. 2005). Thus there appears to be an association between circadian rhythm disruption and depression in a number of animal models, and further studies are needed to determine if any of these rhythm changes are directly responsible for the depression-related phenotypes.

Circadian genes and SCN disruption alters mood

The few studies that have examined the impact of SCN lesions on mood-related behavior have yielded mixed results. Two separate studies found that bilateral SCN lesions in rats lead to a reduction in depression-related behavior in the FST (Arushanian et al. 1994; Tataroglu et al. 2004). However, a study by Tuma et al found that lesions of the SCN had no effect on depression and anxiety-related behavior following social defeat stress, but SCN integrity was necessary for the effective antidepressant actions of agomelatine (Tuma et al. 2005). Thus, in certain paradigms, destruction of the SCN might lead to an antidepressant phenotype, and in others it is necessary for an antidepressant response. These results may not be at odds with each other since agomelatine is known to inhibit SCN neuronal firing, thus a reduction in SCN activity could be antidepressant (Ying et al. 1996). However, as mentioned previously, other regions outside of the SCN are obviously involved in the baseline response to social defeat.

In recent years a large number of human genetic studies have identified polymorphisms in individual circadian genes in humans which associate particularly with bipolar disorder, but also with seasonal affective disorder and major depression (Benedetti et al. 2003; Benedetti et al. 2008; Johansson et al. 2003; Kishi et al. 2009; Kripke et al. 2009; Lavebratt et al. 2010; Mansour et al. 2006; Mansour et al. 2009; Partonen et al. 2007; Sjoholm et al. 2010; Soria et al. 2010;). Mice with mutations in individual circadian genes have been tested in a variety of anxiety- and depression-related paradigms. The *Clock*Δ19 mutant mice were

created through ENU mutagenesis and contain a point mutation which results in the removal of exon 19 and a protein with a dominant-negative function (King et al. 1997a; King et al. 1997b; Vitaterna et al. 1994). In constant light conditions, these mice have either an extremely long circadian period or are arrhythmic (Vitaterna et al. 2006). When tested in a variety of behavioral measures, the *Clock*Δ19 homozygous mice are hyperactive in a novel environment, display lowered anxiety or greater "risk-taking" behavior on the EPM, OF and dark/light measures, display less depression-related behavior in both the FST and learned-helplessness measures, show an increase in sucrose preference, increased cocaine preference, and an increase in goal-directed behavior measured by intracranial self-stimulation (Easton et al. 2003; McClung et al. 2005; Roybal et al. 2007). In addition, these mice show a reduction in all phases of sleep (Naylor et al. 2000). Taken together, the behavioral profile of these mice looks remarkably like that of bipolar patients in the manic state as defined in the DSM IV. When these mice are given the mood-stabilizing drug lithium, the majority of their behavioral responses are normalized towards those of wild-type mice (Roybal et al. 2007). Interestingly, the *Clock*Δ19 mice show some similarities in phenotype to transgenic mice overexpressing GSK3β which are hyperactive and have reduced immobility in the FST, as well as *Per2* knock-out mice (*Per2*^{Brdm1}), which also have reduced immobility in the FST and an increase in alcohol preference (Hampp et al. 2008; Prickaerts et al. 2006; Spanagel et al. 2005). This might suggest that all circadian gene mutants have the same manic-like profile. However, the *Per1*^{Brdm1} and *Per2*^{Brdm1} gene knock-outs are not hyperactive in response to novelty like the *Clock*Δ19 mice, and *Per1* knock-out mice (*Per*1^{Brdm1}) display normal levels of alcohol intake and opposite responses to the *Clock*Δ19 mice in measures of conditioned cocaine preference (Abarca et al. 2002; Hampp et al. 2008; Zghoul et al. 2007). This suggests that individual members of the central circadian clock may have separate functions in regulating a range of mood-, anxiety-, and reward-related behaviors, perhaps through expression outside of the central circadian pacemaker of the SCN.

The *Clock*Δ19 mice have an increase in dopaminergic activity in the VTA when measured both *in vivo* and in coronal slices, suggesting intrinsic changes in the VTA and that the increased activity is not due to a loss of *Clock* in the SCN (McClung et al. 2005; Coque et al. *submitted*). Nearly all of the proteins involved in dopaminergic transmission have a diurnal rhythm in their expression, including tyrosine hydroxylase (TH), the dopamine transporter, the dopamine receptors and others (McClung, 2007). Moreover, dopamine levels in the nucleus accumbens have a strong rhythm, suggesting the entire circuit has circadian regulation (Hood et al. 2010). When *Clock* expression is knocked down specifically in the VTA of otherwise wild-type mice via RNA interference (RNAi), an increase in dopaminergic activity is seen (Mukherjee et al. 2010). *Clock*Δ19 mice have an increase in the expression of the rate-limiting enzyme in dopamine synthesis, TH, and this may be responsible at least in part for the increase in dopaminergic activity (McClung et al. 2005). Interestingly, the *Per2*^{Brdm1} mice also have an increase in dopamine levels in the ventral striatum which is associated with a decrease in activity of the enzyme monoamine oxidase A (MAOA), which normally breaks down dopamine (Hampp et al. 2008). Thus the *Clock*Δ19 mice and the *Per2*^{Brdm1} mice both have altered dopaminergic tone, though perhaps *via* separate mechanisms.

The role of dopamine in mood-related behavior is complex. Increases in dopamine are associated with both positive and negative stimuli. For example, all drugs of abuse increase dopamine signaling, however stress- and depression-related behavior produced following chronic social defeat is also associated with increased VTA dopaminergic activity (Nestler, 2005; Cao et al. 2010). Indeed, when *Clock* gene expression is reduced specifically in the VTA of wild-type mice, instead of producing an overall manic-like phenotype as seen in the *Clock*Δ19 mice, instead the mice show a "mixed-state" of hyperactivity, increased risk-

taking behavior, and increased depression-related behavior (Mukherjee et al. 2010). This is interesting given the variations in mood states that are found in bipolar disorder in human populations.

Recently, we reported that *Clock*Δ19 mice have defects in phase signaling within the nucleus accumbens (NAc) (Dzirasa et al. 2010). In wild-type mice, the phasic entrainment of low gamma (30-55 Hz) oscillations to delta (1-4 Hz) oscillations in the NAc is negatively correlated with the amount of exploration of the mice in a novel environment. The *Clock*Δ19 mice, which are very hyperactive in response to novelty, show a profound defect in this phase coupling (Dzirasa et al. 2010). Remarkably, lithium treatment is able to reverse these defects in coupling and exploratory behavior, suggesting that this entrainment of neurons is important in controlling exploratory drive (Dzirasa et al. 2010). This defect in coupling in the NAc of the *Clock*Δ19 mice is associated with abnormal dendritic morphology and a reduction in levels of the glutamate receptor subunit, GluR1 (Dzirasa et al. 2010). It is tempting to speculate that alterations in the balance between dopaminergic and glutamatergic signaling in the NAc is crucial for proper phase coupling and the development of manic-like behavior. Particularly since mice lacking the GluR1 gene have also been proposed as a model of schizoaffective disorder or bipolar mania, and they respond positively to lithium treatment (Fitzgerald et al. 2010). Since CLOCK and other core circadian genes are transcription factors, future studies will undoubtedly determine the relevant direct transcriptional target genes that are responsible for controlling neuronal activity and phase coupling in the VTA and NAc among other regions associated with mood regulation.

The metabolic link

Quite often mood disorders and their treatments are associated with an increased risk of metabolic disorder, eating disorders, and obesity (McIntyre, 2009). Metabolic disorders are also strongly associated with disruptions in the normal sleep/wake schedule (Bass and Takahashi, 2010), thus metabolic syndrome, circadian disruption, and depression are often co-morbid syndromes. Recently, it has become clear that several of the circulating peptides that control metabolic functions such as appetite are also involved in regulation of mood and reward. These include the peptides ghrelin, leptin, and orexin (hypocretin), among others, which have receptors located throughout the brain, including areas which are important in mood regulation. Most of these gut/brain peptides have a circadian rhythm in their expression and this rhythm is disrupted in the *Clock*Δ19 mice (Turek et al. 2005). The *Clock*Δ19 mice also become obese and develop a metabolic syndrome that is similar to diabetes (Turek et al. 2005). Interestingly, feeding mice a high-fat diet will lead to a disruption of circadian rhythms, so a disrupted clock can facilitate overeating and overindulging can disrupt the clock (Kohsaka et al. 2007). Indeed, many of the core clock components function as “redox sensors” which bind to nicotinamide adenine dinucleotide (NAD+) and are modulated by SIRT1, both of which are influenced greatly by the nutrient levels in the organism (Bass and Takahashi, 2010).

Studies by Zigman, Lutter, and colleagues have determined that circulating levels of the appetite-enhancing peptide ghrelin are elevated following chronic stress (Chuang and Zigman, 2010). Furthermore, mice lacking the ghrelin receptor show a greater depression-like response than control mice, suggesting that ghrelin is released as a way to combat the mood-altering effects of chronic stress (Lutter et al. 2008). This effect of ghrelin is dependent upon the presence of orexin, which is also necessary for the antidepressant effects of calorie restriction in mice (Lutter et al. 2008). The orexin (hypocretin) system is central to the regulation of arousal, and disruptions in orexin signaling lead to narcolepsy (Salin-Pascual, 2001). The effects of ghrelin on mood may ultimately be through its ability to

enhance the firing of VTA dopamine neurons (Abizaid et al. 2006). Intriguingly, orexin neuronal inputs to the VTA are essential for responses to reward-related stimuli, and there is a strong diurnal influence of orexin on VTA activity such that orexin-1 receptor antagonism reduces tonic dopaminergic activity only during the active phase, but not the normal sleep phase of animals (Aston-Jones et al. 2010; Moorman and Aston-Jones, 2010). Moreover, the peptide leptin, which acts to suppress feeding, leads to a reduction in VTA firing rates (Hommel et al. 2006). One might hypothesize that at least some of the mood alterations that are associated with a disruption in circadian rhythms could be due to abnormal rhythms in these circulating metabolic peptides.

Antidepressant and mood stabilizers alter circadian rhythms

Several therapies that are utilized for the treatment of mood disorders are known to modulate circadian rhythms. Some antidepressant treatments have a phase-advancing effect on circadian rhythms. For example, morning bright light therapy leads to a phase advance in several rhythms in human subjects with SAD and the proper phase alignment in SAD either through light or melatonin treatment is necessary for therapeutic effects (Lewy et al. 2006; Lewy et al. 2007; Terman and Jiuan Su, 2010). In addition, treatment with SSRI drugs such as fluoxetine produces a phase advance in the firing of SCN neurons in rat slice culture, and this is likely mediated by the 5-HT1A and 5-HT7 receptors in this region since treatment with agonists for these receptors in hamster SCN yields similar effects (Dudley et al. 1999; Ehlen et al. 2001; Sprouse et al. 2006). Agomelatine, which is a melatonin receptor agonist and antagonist at the 5-HT2c receptor, can also cause phase advance shifts in both mice and hamsters when administered at specific times of day (Van Reeth et al. 1997). Bipolar patients can develop a rapid and prolonged antidepressant response follow a combined therapy of total sleep deprivation, morning bright light therapy, and sleep phase advances as an adjunct to pharmacological treatment (Wu et al. 2009). Taken together, these results suggest that, in general, phase advances in rhythms are antidepressant and likely involve modulation of SCN activity through interactions with the serotonin or melatonin systems.

Interestingly, the mood-stabilizing drug lithium produces a strong phase delay in rhythms in a variety of organisms, including humans, and early reports have suggested that its therapeutic actions are dependent upon this circadian effect (Atkinson et al. 1975; Johnsson et al. 1983; Klemfuss, 1992; Kripke et al. 1978). Since the strongest effects of lithium are as an anti-manic agent, it is interesting that it has opposing effects on circadian period as seen with the antidepressant treatments. As mentioned previously, the mechanism by which lithium produces a phase delay in rhythms (either through inhibition of GSK-3beta or another target) is still controversial.

Rhythm stabilization can be effective in controlling mood-related episodes, particularly in bipolar patients. Interpersonal and social rhythm therapy has been developed to help control the sleep/wake, work, and social schedules of individuals with bipolar disorder and this helps to stabilize their mood (Frank et al. 2000). Recently, studies have demonstrated that some pharmacological agents can entrain disrupted rhythms. Perhaps the best example of this form of entrainment is with chronic methamphetamine treatment, which can stably entrain rhythms in mice even when the SCN has been lesioned, demonstrating that its site of action is outside of the central pacemaker (Iijima et al. 2002; Masubuchi et al. 2000). Methamphetamine, however, may not be the best choice for a mood and rhythm stabilization in humans since it is highly addictive. The novel antidepressant agomelatine can entrain rat circadian rhythms, but unlike methamphetamine this entrainment requires an intact SCN, suggesting that its mechanism of entrainment is through the central clock (Redman and Francis, 1998). Recently, Meng et al found that the CK1Δ inhibitor (PF-670462) was able to restore circadian rhythms in a Per2::Luciferase reporter gene in SCN slices from mice that

were arrhythmic due to a mutation in the *Vipr*2 gene (Meng et al. 2010). Moreover, treatment with PF-670462 restored 24-h locomotor activity cycles to both the *Vipr2*(-/-) mice and mice, which were arrhythmic due to housing in constant light (Meng et al. 2010). As mentioned previously, in wild-type animals PF-670462 leads to a phase delay in rhythms, thus it will be interesting to determine if this CK1Δ inhibitor is useful in the treatment of either mania or depression. What these studies certainly demonstrate is that pharmacological treatments can effectively alter or entrain rhythms in specific ways.

Conclusions: It's all about timing!

A flurry of studies over the last few years using animal models has pointed to the circadian system as a critical modifier of mood-related behavior. While the circadian system is internally controlled, it is influenced strongly by the environment. Thus, alterations in the light cycle, availability (or overindulgence) of nutrients, and exposure to stress will all impact rhythms. The major mood- and reward-related circuits of the brain have their own endogenous rhythms that are organized by the SCN, but can be desynchronized from the SCN under certain conditions. Individual circadian genes play key (and perhaps independent) roles in these mood-related circuits in not only regulating activity over a 24-h day, but also in the ultradian synchronization of neuronal firing within and between brain structures. Thus the synchronization between various circuits in the brain, peptides and hormones in the body, and the environment are all important in maintaining healthy mood. While a lot of work has been done, many questions regarding the exact role of rhythms in mood regulation remain unanswered. Future studies in animal models will undoubtedly determine how specific changes in rhythms within and between mood-related circuits in the brain alter mood-related behavior. Furthermore, they will identify the key molecular mechanisms by which individual circadian genes control the timing of neuronal activity. They will also discover the biochemical and timing-related consequences of human circadian gene polymorphisms that are linked to various mood disorders. Pharmacological treatments are currently being developed that can specifically phase advance or delay rhythms. Furthermore, it is clear that certain drugs can entrain rhythms in animals in which their endogenous rhythm is weak or disrupted. Along with existing chronobiological tools, these types of agents may be useful in the future for the treatment of a variety of mood disorders.

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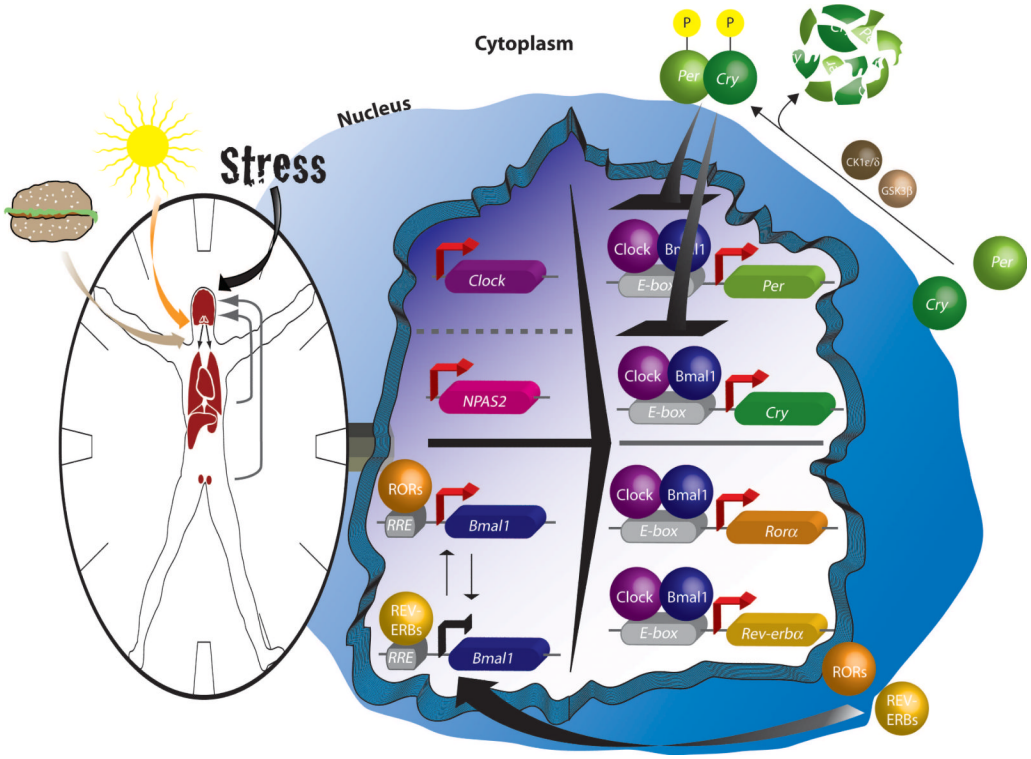

Figure 1. The circadian system is controlled by many factors

The SCN is the master pacemaker in the brain. It is responsive to light and orchestrates the timing of rhythms in other regions of the brain and throughout the body. In turn, various hormones and peptides produced in the periphery can influence rhythms in the brain. Other environmental influences like food and stress also impact rhythms in the brain and body. The cellular clock is a transcriptional translational feedback loop. CLOCK/BMAL1 dimers regulate the expression of *Per* and *Cry* genes. The PER and CRY proteins are modified by various kinases including CK1 and GSK3β and they ultimately feed back into the nucleus and inhibit their own transcription. NPAS2 functions similarly to CLOCK in certain brain regions. RevErbα inhibits while Rorα enhances *Bmal1* transcription as part of a secondary loop.