# How Might Circadian Rhythms Control Mood? Let Me Count the Ways.....

Colleen A. McClung

Mood disorders are serious diseases that affect a large portion of the population. There have been many hypotheses put forth over the years to explain the development of major depression, bipolar disorder, and other mood disorders. These hypotheses include disruptions in monoamine transmission, hypothalamus-pituitary-adrenal axis function, immune function, neurogenesis, mitochondrial dysfunction, and neuropeptide signaling (to name a few). Nearly all people suffering from mood disorders have significant disruptions in circadian rhythms and the sleep/wake cycle. In fact, altered sleep patterns are one of the major diagnostic criteria for these disorders. Moreover, environmental disruptions to circadian rhythms, including shift work, travel across time zones, and irregular social schedules, tend to precipitate or exacerbate mood-related episodes. Recent studies have found that molecular clocks are found throughout the brain and body where they participate in the regulation of most physiological processes, including those thought to be involved in mood regulation. This review will summarize recent data that implicate the circadian system as a vital regulator of a variety of systems that are thought to play a role in the development of mood disorders.

**Key Words:** Bipolar disorder, circadian rhythms, depression, immune system, metabolism, neurogenesis

Mood disorders are among the most prevalent and serious diseases. Furthermore, the rate of antidepressant use has almost tripled in the last 15 years and only one third of patients attain remission (1). The seemingly ever growing rates of mood disorder diagnosis might involve our modern, hectic lifestyle, which includes increasing exposure to artificial light (and computer screens) at night, shift work, travel across time zones, and reduced exposure to daytime sunlight. Throughout most of human evolution, there was no electricity, so people mostly stuck to a routine diurnal schedule. These environmental disruptions to circadian rhythms may be particularly deleterious for vulnerable individuals (i.e., those with a mutation in one or more circadian genes). Circadian rhythm abnormalities have been described in patients with mood disorders since the 1950s (2). These include rhythms in activity, sleep, blood pressure, hormone secretion, and monoamines (3). The Social Zeitgeber Theory of mood disorders, which was put forth in the late 1980s, postulates that stressful life events lead to changes in the sleep/wake schedule that then alter molecular and cellular rhythms in vulnerable individuals, leading to mood-related episodes (4). This theory is backed by several clinical studies that find direct correlations between the severity of rhythm disruptions and mood and restoration of rhythms with treatment (2,3). Indeed, essentially all current treatments for mood disorders shift or stabilize circadian rhythms (2,3). However, the mechanisms by which circadian rhythm disruptions might lead to changes in mood has been unclear.

Multiple hypotheses have been put forth over the years to try to explain the development of depression and other mood disorders. The circadian system is best known for its role in controlling the timing of sleep, and certainly chronic sleep deprivation can exacerbate mood-related problems and may play a direct role in the development of mood disorders (5,6). However, recent studies have determined that the circadian system is also intricately involved in the molecular and cellular control of a wide range of processes that are hypothesized to underlie mood disorders. Thus, both genetic and environmental disruption of circadian rhythms could lead to mood-related problems via any (or all) of these potential paths.

## The Circadian System and Mood

The proteins that make up the core molecular clock are shown in Figure 1 (7). The master circadian oscillator is located in the suprachiasmatic nucleus (SCN) of the hypothalamus, where it receives light input via a direct retinohypothalamic tract. The SCN then sends signals via direct and indirect projections throughout the brain. It also coordinates the timing of the release of multiple peptides and hormones, including melatonin, which promotes sleep onset (8). Interestingly, the SCN seems to regulate the timing of rhythms in the periphery via alterations in body temperature, which serve as a universal cue to entrain multiple organ systems to the light/dark cycle (9).

To date, at least 50 human genetic studies have identified polymorphisms in several of the circadian genes that associate with various psychiatric diseases using candidate gene approaches and genome-wide association studies. These results have recently been reviewed (10,11). This argues that circadian rhythm abnormalities might be the cause of mood disruption rather than the effect of mood disruption, though likely one exacerbates the other. Moreover, a number of animal studies have implicated individual circadian genes in the regulation of mood, anxiety, and reward (12). Mice with an induced mutation in the *Clock* gene, which creates a protein with dominate-negative function (*Clock*Δ19) (13), have a behavioral profile that strongly resembles that of bipolar patients, specifically in the manic state (14). When these mice are given the mood-stabilizing drug lithium, the majority of their behavioral responses are normalized toward those of wild-type mice (14). Other circadian gene mutations lead to similar behavioral phenotypes. These include transgenic mice overexpressing glycogen synthase kinase 3β (15) and mice with a mutation in FBXL3, a protein that targets CRY for degradation (16). Sirtuin 1 (SIRT1) is a histone deacetylase that antagonizes the transcriptional activating properties of circadian locomotor output cycles kaput (CLOCK) and brain and

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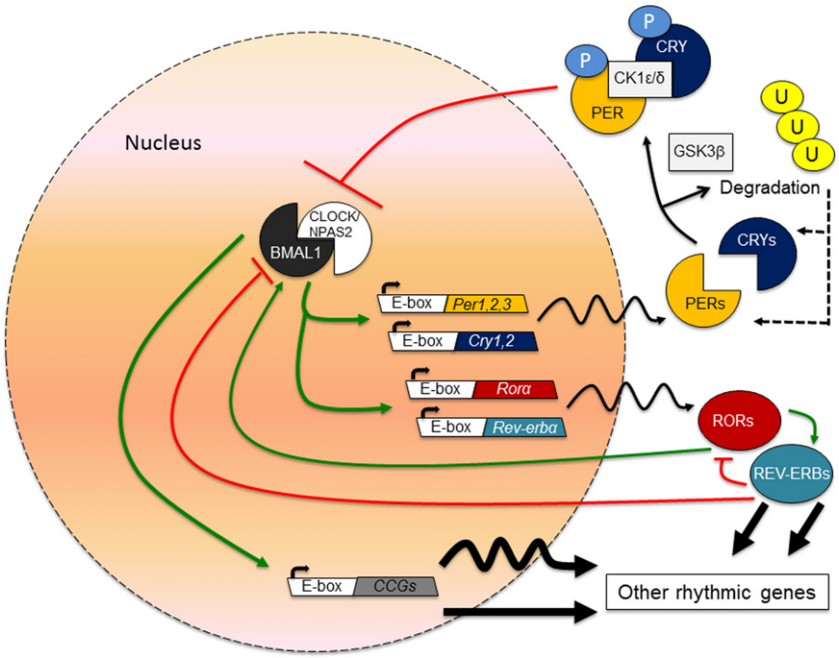


**Figure 1.** This core molecular clock is composed of a series of transcriptional and translational feedback loops. The basic helix-loop-helix-period-Arnt-single-minded (PAS)-containing transcription factors, circadian locomotor output cycles kaput (CLOCK) and brain and muscle Arnt-like protein 1 (BMAL1; also called MOP3 and ARNTL), heterodimerize and bind to Enhancer Box (E-box) containing sequences in a number of genes, including the three *Per* genes (*Per1*, *Per2,* and *Per3*) and the two *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, forming a negative feedback loop, which cycles every 24 hours. In addition to this feedback loop, the CLOCK and BMAL1 proteins regulate the expression of the nuclear hormone receptors, Rev-erbα and Rorα, which, in turn, can repress or activate *Bmal1* transcription, respectively, through actions at the REV-ERB/ROR response element in the promoter. Outside of the suprachiasmatic nucleus, neuronal PAS-domain protein 2 (NPAS2; also known as MOP4) can heterodimerize with BMAL1 and control *Per* and *Cry* gene expression. There are several key proteins that regulate the timing of the molecular clock through phosphorylation, sumoylation, and other mechanisms. Casein kinase 1 delta and epsilon proteins (CK1δ and CK1ε) phosphorylate the PER, CRY, and BMAL1 proteins, altering their stability and nuclear entry. Glycogen synthase kinase 3 beta (GSK3β) also phosphorylates the PER2 protein facilitating nuclear entry, the Rev-erbα protein increasing protein stability, and the CRY2 and CLOCK proteins leading to proteasomal degradation. CCG, Clock controlled gene; P, phosphorylation; ROR, RAR-related orphan receptor; U, ubiquitination.

muscle Arnt-like protein 1 (BMAL1) (17). Sirtuin 1 knockout mice also have a decrease in anxiety-related behavior at baseline and lowered depression-related behavior following chronic social defeat (18). Overexpression of SIRT1 leads to the opposite effect (18). Sirtuin 1 knockout should lead to increased CLOCK activity; yet, the mutant mouse has a similar manic-like phenotype, suggesting that perhaps any circadian gene mutation will lead to the same behavioral profile. However, while *Per2* knockout mice ($Per2^{Brdm1}$) also have reduced immobility in the forced swim test (19), mice with mutations in both *mPer1* and *mPer2* ($mPer1;mPer2^{ldc}$ double mutant) have a normal locomotor response to novelty and an increase in anxiety-related behavior that is the opposite of what is observed in the *Clock*Δ19 and other mutant mice (20). Thus, these genes have some specificity in their function and the same phenotype is not produced with the mutation of any circadian factor. Of course, some of these proteins are involved in other processes besides circadian rhythm regulation, and it is possible that the mood and anxiety-related behavioral phenotypes are due to changes in other systems.

## How Do Rhythm Disruptions Lead to Mood Disruptions?

### Monoamine Signaling

Antidepressant, antipsychotic, and mood-stabilizing drugs all alter monoaminergic (i.e., serotonin, dopamine, and norepinephrine) function. For example, the major class of antidepressant drugs used today are selective serotonin reuptake inhibitors. Multiple human imaging studies have also found alterations in these systems in subjects with mood disorders (21). Animal studies have now taken advantage of optogenetics or other means of controlling neuronal activity to confirm the importance of the monoaminergic circuitry in mood, reward, and anxiety-related behavior. Some results are controversial in that stimulation of dopamine neurons in the ventral tegmental area (VTA) can lead to both a prodepressive and antidepressive response in certain chronic stress models, so the exact function of these monoamines is still unclear (22,23).

Administration of the antidepressant agomelatine (a melatonin receptor agonist and weak serotonin 2C receptor antagonist) leads to direct (2-day) and indirect (14-day) increases in monoaminergic neuronal activity, which can be blocked with the melatonergic antagonist S22153 (24). These results point to a modulatory role for melatonin in monoaminergic activity, linking the circadian and monoamine systems. Numerous studies have found that serotonin, norepinephrine, and dopamine all have a circadian rhythm in their levels, release, synthesis-related enzymes, and receptors (3). Since these systems are keenly involved in arousal, motivation, and reward, it seems like it would be advantageous for these circuits to have a diurnal rhythm so that the motivation to find a mate or look for food are not in temporal conflict with the drive for sleep. Some of the rhythms in these circuits arise from projections of the SCN (Figure 2). All of these neuronal populations also express

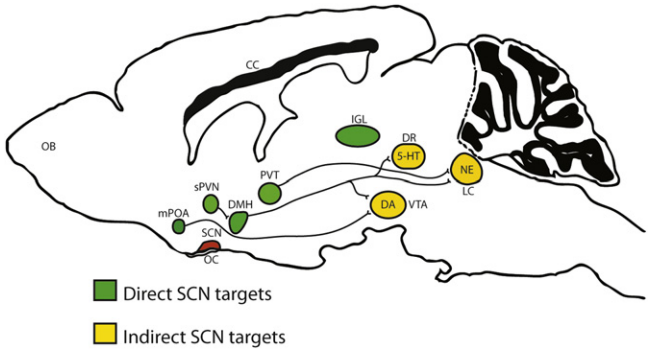


**Figure 2.** The circadian system regulates multiple monoaminergic brain regions that control mood, anxiety, and motivated behaviors through local expression of *Clock* genes, as well as indirect connections originating from the master pacemaker in the suprachiasmatic nucleus (SCN). The SCN projects monosynaptically to multiple hypothalamic nuclei (in green), which subsequently communicate with regions (in yellow) that synthesize dopamine (DA), serotonin (5-HT), and norepinephrine (NE). As a result, serotonin, norepinephrine, and dopamine all have a circadian rhythm in their levels, release, and synthesis-related enzymes. CC, corpus callosum; DMH, dorsomedial hypothalamus; DR, dorsal raphe; IGL, intergeniculate leaflet; LC, locus coeruleus; mPOA, medial preoptic area; OB, olfactory bulb; OC, optic chiasm; PVT, paraventricular nucleus of the thalamus; sPVN, subparaventricular nucleus of the hypothalamus; VTA, ventral tegmental area.

circadian genes that directly regulate expression of genes involved in monoamine synthesis and release. One example is *Maoa*, a gene important in monoaminergic metabolism, which is a direct transcriptional target of neuronal PAS-domain protein 2, BMAL1, and PER2 in the striatum (25).

*Per2*$^{Brdm1}$ mice have increased dopamine levels and altered neuronal activity in the striatum, which may explain some of their abnormal behavioral phenotypes in measures of mood, reward, and anxiety (19). In response to chronic stress, *mPer1* and *mPer2* messenger RNA levels are altered in the nucleus accumbens (NAc) (20). Furthermore, selective knockdown of both *mPer1* and *mPer2* via RNA interference in the NAc is sufficient to produce an increase in anxiety-like behavior, suggesting prominent roles for the *Per* genes in this region (20). *Clock*Δ19 mutants have increased dopamine synthesis and increased dopaminergic activity (26). Moreover, they have an increase in tyrosine hydroxylase (TH) expression in the VTA (27). Chronic lithium treatment restores normal levels of VTA dopaminergic activity to the *Clock*Δ19 mice (26), suggesting that this activity may underlie their manic-like behavior. The regulation of TH expression and dopamine levels by CLOCK appears to be evolutionarily conserved, as fruit flies (*Drosophila melanogaster*), which carry a mutation in the *Clock* gene (*Clk*$^{Jrk}$), have increased TH levels and increased dopamine synthesis (28). Many, but not all, of the manic-like phenotypes of the *Clock*Δ19 mice are rescued by expression of a functional CLOCK protein specifically in the VTA (14). Interestingly, knockdown of *Clock* expression only in the VTA of otherwise wild-type mice leads to a mixed state where mice are less anxious and hyperactive but have greater levels of depression-related behavior (29). This is particularly interesting, given the fact that bipolar patients cycle through periods of depression, mania, and mixed states. Thus, circadian genes appear to have a prominent and direct role in the VTA and likely other monoaminergic regions in the regulation of anxiety and mood-related behavior. Undoubtedly, this function is key in understanding the mechanisms that connect disrupted circadian rhythms to mood disorders and should be the focus of future study. However, other systems involving the periphery and additional brain regions may also factor into these diseases.

## Immune Function

Alterations in the immune system are thought to underlie a number of health problems, including rheumatoid arthritis, inflammatory bowel disease, and asthma. Many of these disorders are associated with increased depression (30). Thus, a neuroinflammatory hypothesis has recently been proposed to explain the development of depression in general and particularly in people with immune-associated conditions. In humans and animal models, proinflammatory cytokines can themselves induce a syndrome resembling depression with feelings of anhedonia, psychomotor slowing, and fatigue (31,32). Proinflammatory cytokines in the brain lead to reduced neurogenesis, decreased synaptic plasticity, and less long-term potentiation in the rodent hippocampus, which is similar to effects often seen with chronic stress (33). Moreover, the reduction in neurogenesis and abnormal behaviors produced in response to stress in rodents can be blocked with an inhibitor of nuclear factor-κB (NF-κB) (34). Proinflammatory cytokines can also impact monoamine signaling, leading to reductions in serotonin and dopamine release, as well as altered hypothalamus-pituitary-adrenal (HPA) axis function in animal models (linking several systems that are discussed in this review) (33).

Circadian rhythm disruption in people and in animal models leads to an increase in proinflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), macrophage inflammatory protein 2, and leukemia inhibitory factor (35–37). In turn, TNF-α, interferon-gamma, and interleukin-6 alter the sleep/wake cycle and circadian gene expression via NF-κB signaling pathways (38). Several studies have found that a lipopolysaccharide-induced immune challenge leads to a depressive-like phenotype in rodents and it also alters circadian gene expression and SCN activity (39,40). Interestingly, a central infusion of interleukin-1 beta causes a significant phase delay in locomotor rhythms, a state often associated with an increased risk for depression (36). Constant darkness (for 4 weeks) in rodents leads to both increased depression-like behavior and elevated levels of plasma interleukin-6 and hippocampal interleukin 1 receptor, type 1 (41). In addition, mice with a deletion of *Il6* (a target gene of NF-κB) do not develop depression-like behavior in constant darkness, suggesting a prominent role for NF-kB signaling and cytokine induction in the development of depression-like behavior following diurnal rhythm disruption (41). Recently, it was discovered that the CLOCK protein interacts directly with NF-κB to activate transcription at NF-κB responsive promoters (42). Furthermore, activation of NF-κB in response to immunostimuli is reduced in cells that lack the CLOCK protein (42). Interestingly, retinoic acid receptor-related orphan receptor α inhibits NF-κB function by inducing IκB-α, a protein that antagonizes NF-κB signaling (43). Thus, there appears to be complex bi-directional crosstalk between the circadian and immune systems.

Thus, a scenario could be proposed in which genetic or environmental disruptions of circadian rhythms lead to a proinflammatory response in the brain that alters monoamine signaling, SCN function, and hippocampal neuroplasticity, ultimately leading to a depression-like state. However, a recent review of clinical data by Raison and Miller (30) concluded that "the question of whether depression is an inflammatory disorder is a resounding 'no'." Rather, certain groups of depressed individuals have elevated inflammatory biomarkers that might indicate

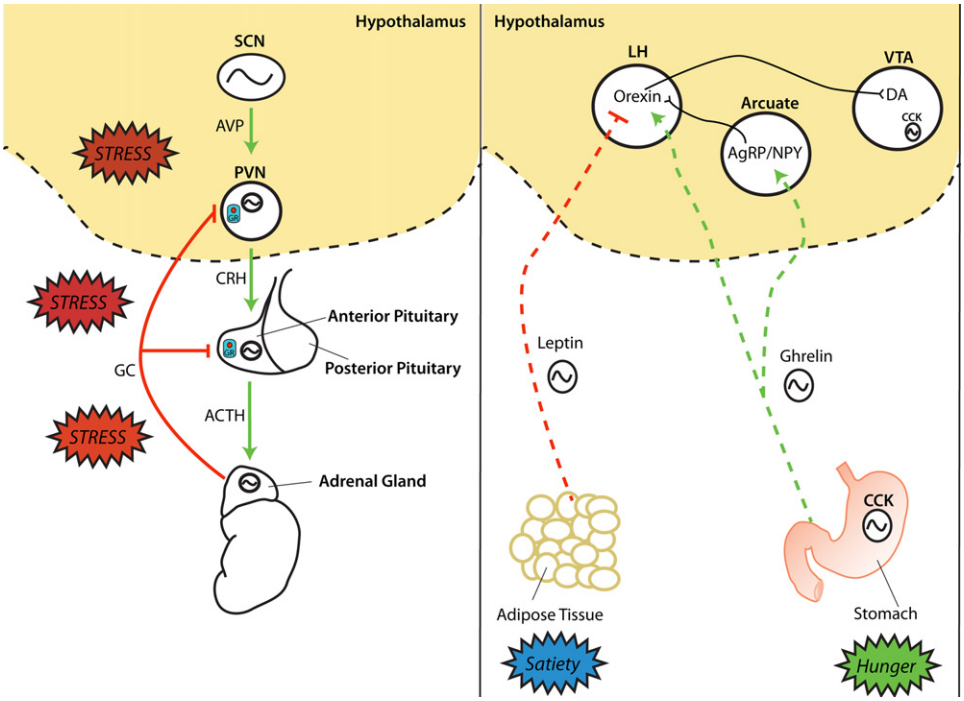


**Figure 3.** The circadian system regulates many hormones and peptides in the brain and periphery that impact mood and reward. (Left panel) The circadian control of the hypothalamus-pituitary-adrenal axis originates in the suprachiasmatic nucleus (SCN), which projects to the paraventricular nucleus (PVN) with arginine vasopressin (AVP) synthesizing neurons causing the release of corticotropin-releasing hormone (CRH). Subsequently, CRH stimulates the synthesis and release of adrenocorticotropin hormone (ACTH) from the anterior pituitary, which travels through the blood stream and stimulates the release of glucocorticoids (GC) from the adrenal gland. Glucocorticoids negatively feed back to multiple sites via interaction with the intracellular glucocorticoid receptor to maintain basal stress hormone levels within a homeostatic range. Rhythmic *Clock* gene expression coordinates incoming hormonal signals to rhythms in local receptor expression at the level of the PVN, pituitary gland, and adrenal gland. (Right panel) The hormone leptin is expressed in adipose tissue and is a satiety signal conveying a positive energy balance to the brain. Leptin levels also fluctuate on a daily basis, as *Clock* genes are expressed in adipose tissue, and lead to circadian rhythms in hunger and satiety. Leptin is sleep inducing and may alter mood by inhibiting orexin neurons in the lateral hypothalamus (LH). An opposing metabolic signal, ghrelin, is released by the stomach to convey a negative energy balance to the brain by stimulating orexigenic agouti-related peptide (AgRP)/neuropeptide Y (NPY) secreting neurons in the arcuate nucleus of the hypothalamus. Additionally, ghrelin directly stimulates orexinergic neurons in the LH, which induces arousal and feeding behavior. These orexigenic neurons also project directly to dopaminergic neurons in the ventral tegmental area (VTA). Finally, cholecystokinin (CCK) is a circadian regulated peptide that is synthesized in the gut and contributes to feeding behavior, as well as the VTA, which contributes to motivated behavior and reward sensitivity. DA, dopamine.

either a discrete depressive subtype or that even very low levels of inflammation could cause depressive-like symptoms in certain individuals through interactions with other compromised systems (30). Moreover, records from the STAR*D trial (a large multicenter study of antidepressant efficacy) found that the remission rate fell from 54% to 40% in patients taking selective serotonin reuptake inhibitors when they were also taking an anti-inflammatory drug, an effect that was also replicated in animal models of depression (44–46). However, a small trial ($n = 20$) found that the addition of a cyclooxygenase-2 inhibitor (celecoxib, a drug that inhibits the production of proinflammatory cytokines) to an antidepressant (reboxetine a norepinephrine-transport inhibitor) produced a more robust antidepressive effect (47). Thus, the role of a proinflammatory response in the development of depression is still unclear and is very likely a contributing factor in certain individuals rather than a central cause of depression. Indeed, depression scores did improve significantly in patients with psoriasis and comorbid depression following treatment with etanercept (a TNF-$\alpha$ inhibitor) in a phase III clinical trial (48), and anecdotal evidence supports an antidepressant effect of minocycline (a tetracycline-like antibiotic) in patients with somatoform spectrum disorders and other infections (49).

## HPA Axis Regulation

Glucocorticoids are multifunctional adrenal steroid hormones that are associated with metabolism and arousal. They are also intimately involved in the response to stress via activation of the HPA axis (Figure 3). Glucocorticoids have a strong circadian rhythm in expression and peak in expression just before the onset of awakening (8). CRY proteins also interact with the glucocorticoid receptor (GR) in a ligand-dependent fashion leading to rhythmic repression in GR activity (50). Furthermore, CLOCK directly acetylates GR, leading to decreased sensitivity to glucocorticoids in the morning and increased sensitivity at night when acetylation is reversed (51).

Interestingly, the degree of glucocorticoid dysregulation can be quite different depending on the type of mood disorder (i.e., major depressive disorder vs. bipolar disorder vs. posttraumatic stress disorder), as well as the amount of early life trauma the individual has experienced (52). Moreover, hypercortisolemia is only observed in a subset of patients with depression (53). Thus, the exact role of glucocorticoids in the development of mood disorders is uncertain; however, there is evidence to suggest that antidepressant treatment helps to stabilize HPA axis function via the serotonergic system (54). Therefore, it seems that restoration of the circadian rhythm of HPA axis function in individuals with

mood disorders should be beneficial to mood stabilization (some evidence of this will be discussed later). Moreover, the direct regulation of GR expression and activity by circadian genes might be extremely important in mediating the response to chronic stress.

**Metabolic Peptides**

Metabolic disorders are very highly comorbid with mood disorders (55). Circadian rhythms in the liver, stomach, adipose tissue, and gut are robust, leading to distinct 24-hour cycles in metabolic functions (56). Peptides involved in metabolism and feeding, including ghrelin, orexin (also known as hypocretin), leptin, and cholecystokinin (CCK), all display a significant circadian rhythm in expression (57) (Figure 3). In human blood samples, leptin is increased during the night, orexin A levels are increased during the day, and ghrelin and CCK levels are increased before meals and during the night (58,59). Leptin and ghrelin both signal through orexin neurons in the brain, which enhance wakefulness when stimulated by ghrelin and promote sleep when inhibited by leptin (60). In fact, narcolepsy, a condition where individuals experience sudden sleep bouts, is caused by a dysfunctional orexin system, linking regulation of feeding and sleep to a small population of hypothalamic neurons (61). CCK is more widely expressed throughout the brain and gut, including high levels of expression in gamma-aminobutyric acidergic (GABAergic) interneurons of the prefrontal cortex, dopaminergic neurons of the VTA, and the shell of the SCN (62–64). These peptides and others involved in feeding behaviors are arrhythmic in the *Clock*Δ19 mice, demonstrating that their expression is regulated by the core molecular clock (57). *Clock*Δ19 mice also gain weight rapidly on a high-fat diet and display many features of obesity and metabolic syndrome (57).

Both ghrelin and leptin from the periphery modulate reward-related circuits in the brain (65–67). Moreover, ghrelin (Ghr −/−) knockout mice are more anxious after acute restraint stress and this is likely due to a problem with the normal glucocorticoid feedback in response to stress (68). Ghrelin receptor-null mice also show a greater response to chronic social defeat stress in tests of social interaction compared with wild-type mice (69). Interestingly, chronic social defeat stress produces long-lasting disruptions in body temperature rhythms and in the diurnal rhythms of plasma ghrelin and leptin (70,71). Thus, proper daily rhythms in ghrelin and leptin signaling may be important in mood regulation.

Many studies have found a prominent role for CCK in the regulation of anxiety-related and mood-related behavior. Increased CCK or CCK receptor agonists are generally associated with increased anxiety (72). In turn, CCK receptor antagonists have antidepressant-like properties in acute rodent measures of behavioral despair (73). Moreover, chronic blockade of CCK receptors prevents HPA axis hyperactivity, reduction of hippocampal volume, and cell proliferation and decreases sucrose intake normally evoked by repeated social defeat stress (74). Cholecystokinin is co-released with dopamine in the NAc and acts to silence dopamine neurons in the VTA (63). Cholecystokinin has a strong circadian rhythm in expression in the VTA and it is a direct transcriptional target of CLOCK in this region (75,76). *Clock*Δ19 mice have very low levels of *Cck* in the VTA and increased dopaminergic activity (27). Recently, we found that treatment with lithium restores /Cck/ expression to wild-type levels in the *Clock*Δ19 mice through changes in chromatin structure at the *Cck* promoter (76). Moreover, CCK knockdown in the VTA is sufficient to recapitulate many of the manic-like behaviors of the *Clock*Δ19 mice. Interestingly, CCK knockdown in the basolateral amygdala also has anxiolytic and antidepressant effects in mice, suggesting that it is involved in modulating activity within multiple limbic regions (77).

The relationships between obesity, stress, and inadequate sleep (which are all common in today's society) have been examined in several studies and it is thought that these factors represent a vicious cycle of interacting epidemics (78). Undoubtedly, depression can be added to this cycle, at least for a subset of individuals. There is certainly a need for more studies that examine the metabolic and mood-related effects that come with therapeutic treatments to improve sleep and circadian rhythms. Moreover, the relationship between disrupted rhythms in metabolic factors and the consequences of these disruptions on brain function have yet to be fully explored.

**Redox/Mitochondria/Apoptosis**

A mitochondrial dysfunction hypothesis of psychiatric disorders (bipolar disorder in particular) has been proposed based on the findings that 1) abnormalities in mitochondrial morphology, localization, and mitochondrial DNA sequences are found in postmortem brain samples from bipolar subjects; 2) patients with bipolar disorder often show somatic symptoms that resemble those seen with mitochondrial diseases; 3) in turn, patients with mitochondrial diseases often have comorbid mood disorders; and 4) bipolar patients display altered energy metabolism in the brain and reduced mitochondrial respiratory chain activity, which resembles that seen in patients with mitochondrial disorders (79). Bipolar disorder is also associated with increased neuronal death and axon-dendritic degeneration (80). In turn, antiapoptotic and neuroprotective proteins like BCL-2 are robustly induced by mood-stabilizing drugs (79). Interestingly, mice with forebrain specific mitochondrial DNA mutations have behaviors that resemble human mania including altered circadian rhythms (81). The mitochondria supply most of the cell's adenosine triphosphate (ATP) and are involved in controlling the redox state of the cell. Nicotinamide cofactors nicotinamide adenine dinucleotide monophosphate hydride/nicotinamide adenine dinucleotide phosphate and nicotinamide adenine dinucleotide hydride/nicotinamide adenine dinucleotide have recently been identified as essential partners of CLOCK, neuronal PAS-domain protein 2, and SIRT1, providing a direct link between the redox state of the cell and circadian rhythms (17,82,83). Moreover, CLOCK/BMAL1 directly regulates the expression of nicotinamide phosphoribosyltransferase (*Nampt*) in a circadian fashion, which then determines the availability of nicotinamide adenine dinucleotide in the cell over 24 hours (17).

Another measure of cellular metabolism is the ratio of adenosine monophosphate (AMP) and ATP. An important sensor of the AMP/ATP ratio is adenosine monophosphate-dependent protein kinase, which is activated upon binding to AMP (84). Adenosine monophosphate-dependent protein kinase is activated in neurons in response to metabolic or ischemic stressors and elicits compensatory responses (85). Adenosine monophosphate-dependent protein kinase phosphorylates casein kinase 1ε, which enhances phosphorylation of PER2, again directly coupling cellular metabolism and the response to stress to the circadian system (86). Moreover, the mitochondrial biogenesis stimulator, peroxisome proliferator-activated receptor gamma co-activator 1-α, directly regulates expression of BMAL1 and Rev-erbα and is necessary for circadian pacemaker function (87). The ultimate consequences of metabolic dysfunction in neurons are oxidative stress, hypoxia, and apoptosis; so given the intimate connection between the circadian system and redox

sensing, it seems reasonable to suspect that circadian rhythm disruption might lead to poor cellular health. In fact, the apoptotic genes, *Wnt10*, β-catenin, Dishevelled2, and transcription factor 3 promoters are all bound by BMAL1, and Wnt pathway signaling is attenuated when BMAL1 levels are reduced (88). The Wnt pathway has been implicated in bipolar disorder through human genetic association studies, and major depression through studies of animal models (89). It is also interesting to note that many of the genes involved in apoptosis are also involved in neuroplasticity (89). Thus, the response to antidepressant or mood-stabilizing medications may involve these same pathways that are directly regulated by the circadian system. Indeed, as depression and other mood disorders do not seem to be generally associated with severe neurodegeneration, the influence of cellular stress-related pathways are likely much more subtle and perhaps alter plasticity and dendritic complexity rather than direct cell death (90).

### Neurogenesis

The neurogenic hypothesis of depression stems from animal studies showing that chronic stress and depression-inducing behavioral models reduce hippocampal neurogenesis while antidepressants enhance neurogenesis (91). While studies have been mixed regarding the role of neurogenesis in the development of depression, most point toward a significant role for neurogenesis in the therapeutic effects of antidepressants (91). Neurogenesis varies greatly over the circadian cycle (92,93). Moreover, there is a functional link between the expression of *Per*2 and the regulation of cell proliferation and cell death in the dentate gyrus (DG) (94). Chronic disruption in circadian rhythms via weekly phase shifts inhibits hippocampal neurogenesis, and the degree of reduction in neurogenesis depends on the direction and duration of the shifts (95,96). Rhythmic changes in corticosterone can help regulate the rhythmic expression of *Per1* in the DG (92). Moreover, rhythms in corticosterone are necessary for the proliferation of progenitor cells in the DG in response to fluoxetine (97). Flattening of the diurnal corticosterone rhythm in rats also prevents the stimulating action of L-NAME (a nitric oxide synthase inhibitor) on progenitor cell proliferation in the DG, as well as brain-derived neurotrophic factor and neurotrophic tyrosine kinase receptor 2 (TrkB) expression (98). Brain-derived neurotrophic factor and its receptor, TrkB, have been shown in multiple studies to be important in the actions of antidepressant medications and both have a strong circadian rhythm in expression in the hippocampus (99,100). Brain-derived neurotrophic factor loses its effects on cell proliferation rates in the absence of a daily rhythm in corticosterone (98). These results demonstrate that the diurnal rhythm of corticosterone regulates the stimulating action of antidepressants on neurogenesis and brain-derived neurotrophic factor signaling in the DG. It will be interesting in future studies to determine the impact of circadian gene mutations on neurogenesis and TrkB signaling following antidepressant treatment.

## Conclusions

Though a great deal of work remains, our understanding of the circadian clock and how it is potentially involved in mood regulation has grown considerably over the last several years. We now know that circadian genes are not only found in the SCN but rather they are expressed widely throughout the brain and body, including expression in mood-related centers of the brain. The circadian genes are keenly involved in the regulation of immune function, monoamine transmission, neurogenesis, and metabolism (Figure 4). It is possible that circadian rhythm disruption alters mood through multiple systems. Indeed, all of these systems interact at some level. The role of sleep disruption in the pathophysiology of mood disorders is also important and should not be ignored. The circadian system is now being targeted for drug development in the hopes of treating a number of diseases including cancer, obesity, sleep disorders, and diabetes. It is likely that these types of medications could also be beneficial for the treatment of mood disorders.

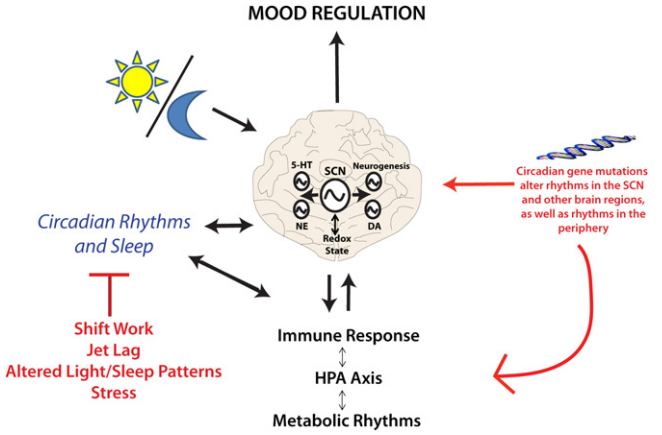


**Figure 4.** The circadian clock influences multiple systems and pathways that are thought to underlie mood disorders. In most cases, there are reciprocal interactions that, in turn, regulate circadian rhythms. Circadian gene mutations might make an individual more vulnerable to mood changes and these are exacerbated by environmental deviations in the daily schedule. DA, dopamine; HPA, hypothalamus-pituitary-adrenal; 5-HT, serotonin; NE, norepinephrine; SCN, suprachiasmatic nucleus.

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