



Mood-related central and peripheral clocks

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Abstract

Mood disorders, including major depression, bipolar disorder, and seasonal affective disorder, are debilitating disorders that affect a significant portion of the global population. Individuals suffering from mood disorders often show significant disturbances in circadian rhythms and sleep. Moreover, environmental disruptions to circadian rhythms can precipitate or exacerbate mood symptoms in vulnerable individuals. Circadian clocks exist throughout the central nervous system and periphery, where they regulate a wide variety of physiological processes implicated in mood regulation. These processes include monoaminergic and glutamatergic transmission, hypothalamic-pituitary-adrenal axis function, metabolism, and immune function. While there seems to be a clear link between circadian rhythm disruption and mood regulation, the mechanisms that underlie this association remain unclear. This review will touch on the interactions between the circadian system and each of these processes and discuss their potential role in the development of mood disorders. While clinical studies are presented, much of the review will focus on studies in animal models, which are attempting to elucidate the molecular and cellular mechanisms in which circadian genes regulate mood.

Keywords

bipolar disorder; circadian; depression; inflammation; metabolism; microbiome; stress

1 | INTRODUCTION

Mood disorders, such as major depression, bipolar disorder, and seasonal affective disorder, are highly prevalent and debilitating disorders. Circadian rhythm and sleep disturbances are one of the major diagnostic criteria for these disorders. Individuals with mood disorders display altered rhythms in activity, sleep/wake, blood pressure, and hormone secretion (McClung, 2007). Furthermore, many drugs used for the treatment of mood disorders shift or stabilize circadian rhythms, which may be important for their therapeutic efficacy (McClung, 2011). According to the “social zeitgeber theory” of mood disorders, stressful life events disrupt social routines that may lead to altered biological rhythms and increased

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CONFLICT OF INTEREST

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vulnerability for the development of mood disorders (Ehlers, Frank, & Kupfer, 1988). In support of this theory, circadian rhythm disturbances, such as jet lag or shift work, have been shown to precipitate or exacerbate mood symptoms (Asaoka et al., 2013; Inder, Crowe, & Porter, 2016; Kalmbach, Pillai, Cheng, Arnedt, & Drake, 2015). Several human genetic studies have implicated circadian genes in mood disorders including genome-wide association studies (GWAS), which take into account the entire clock gene network (Etain, Milhiet, Bellivier, & Leboyer, 2011; McCarthy & Welsh, 2012). Reduced amplitude in circadian gene expression is found in fibroblast cultures taken from subjects with bipolar disorder compared to controls (Yang, Van Dongen, Wang, Berrettini, & Bucan, 2009). Moreover, a study in human postmortem brain found that subjects with major depressive disorder (MDD) have much weaker 24-hr rhythms in gene expression compared to healthy controls in a number of mood-associated brain regions, including the dorsolateral prefrontal cortex, hippocampus, nucleus accumbens, and amygdala (Li et al., 2013). These changes suggest shifts in peak timing and disruptions in phase relationships in clock-regulated genes across multiple regions of the brain. Thus, it has been hypothesized that abnormalities in the circadian system may play a role in the development and maintenance of mood disorders.

The master circadian clock resides in the suprachiasmatic nucleus (SCN) of the hypothalamus and coordinates rhythms throughout the brain and the periphery. The SCN is composed of self-sustaining oscillators that are entrained to the external environment through both photic and non-photoc cues, also known as zeitgebers. Circadian rhythms in individual cells throughout the SCN and the rest of the body are generated by a molecular clock composed of multiple transcriptional-translational feedback loops. Within the core molecular clock, the transcription factor Circadian Locomotor Output Cycles Kaput (CLOCK) or the homologous protein Neuronal PAS Domain Protein 2 (NPAS2) heterodimerize with the transcription factor Brain and Muscle Arnt-like Protein 1 (BMAL1) and bind to enhancer box (E-box) sequences to activate the transcription of *Period* (*Per1*, *Per2*, and *Per3*) and *Cryptochrome* (*Cry1* and *Cry2*) genes. PER and CRY are translated in the cytoplasm, where they dimerize and shuttle back into the nucleus to inhibit their own transcription, forming a negative feedback loop that cycles every 24 hr. CLOCK/BMAL1 also regulate the expression of the nuclear hormone receptors, *Rev-erba* and *Rora*, which repress or activate *Bmal1* transcription, respectively, to form an auxiliary feedback loop that stabilizes the core loop.

Circadian rhythms in the brain are incredibly important for maximizing energy efficiency and neuronal health. The brain requires a large amount of energy to function on a daily basis. In fact, the brain uses approximately 20% of the energy of the entire body and it needs to do so in an efficient manner (Du et al., 2008). During wake, neurons are actively firing in response to activity and environmental stimuli, creating the buildup of reactive oxygen species (ROS) and other by-products (Albrecht & Ripperger, 2018; Musiek & Holtzman, 2016). During sleep, antioxidants remove excess ROS and misfolded and aggregated proteins are cleared via a glymphatic system (Musiek et al., 2013; Xie et al., 2013). Disruptions to the timing and duration of sleep and wake will disrupt these processes. In fact, a recent study found that even one night of sleep deprivation can result in accumulation of amyloid- β (one of the proteins that accumulates in the brain in Alzheimer's disease) in human brain (Shokri-Kojori et al., 2018). Moreover, the antiphasic circadian activity patterns

between astrocyte support cells (which are involved in antioxidant responses and provide an energy supply to neurons) and neurons, is key to optimal neuronal function. In the rodent SCN for example, glial cells become active during circadian nighttime, suppressing the activity of neurons, and neurons are active during the circadian day (Brancaccio, Patton, Chesham, Maywood, & Hastings, 2017). Thus, optimal brain function depends upon consistent sleep/wake timing and synchronization across various cell types in the brain.

A number of hypotheses have been proposed to explain the underlying mechanisms by which circadian rhythms may influence mood (McClung, 2011, 2013). Mood disorders are highly heterogeneous and are thought to develop due to a combination of various factors. Mood episodes and symptoms can be frequent (daily or weekly symptoms or monthly episodes) or can be separated by many years. Some people have a seasonal pattern of episodes, while others do not. In addition, depression can involve too little sleep or too much sleep, too much eating, or starvation. Bipolar disorder includes not only depressive episodes, but episodes of mania and periods of euthymia or “stabilized mood” in between. Thus, a wide range of physiological processes have been implicated in mood regulation, including monoamine signaling, glutamatergic transmission, hypothalamic-pituitary-adrenal (HPA) axis function, metabolic peptide signaling, microbiome, neuroinflammation, and mitochondrial function. The circadian system has been shown to interact with each of these systems. Here, we highlight these interactions and discuss their potential role in mood disorders.

2 | MONOAMINE SIGNALING

Alterations in monoamine (i.e., serotonin, dopamine, and norepinephrine) neurotransmitter systems have been observed in mood disorders, such as MDD (Meyer, 2008). Furthermore, antidepressants, antipsychotics, and mood-stabilizing drugs used in the treatment of these disorders all affect monoaminergic signaling. Serotonin, dopamine, and norepinephrine show circadian rhythms in expression and release (McClung, 2007). Furthermore, the receptors and enzymes involved in the synthesis of these monoamines show rhythmic expression (McClung, 2007). On a circuit level, these rhythms arise, in part, due to indirect projections from the SCN to brain regions responsible for the synthesis of these neurotransmitters, including the dorsal raphe (serotonin), ventral tegmental area (VTA; dopamine), and locus coeruleus (norepinephrine; Parekh & McClung, 2015).

Studies from our laboratory using the *Clock*¹⁹ mouse have revealed an important role for the dopamine system in the circadian regulation of mood and reward. *Clock*¹⁹ mice contain a single base mutation in the *Clock* gene, which leads to a loss of exon 19 and a protein with dominant-negative function (King et al., 1997). The phenotype of the *Clock*¹⁹ mice consists of circadian and metabolic abnormalities, as well as a manic-like phenotype (Kristensen, Nierenberg, & Ostergaard, 2018; Logan & McClung, 2016). While no animal model will ever fully recapitulate the complex phenotypes that characterize bipolar disorder, and in particular the phenomenon of mood cycling, *Clock*¹⁹ mice display primarily manic-like behavior during the day and euthymia-like behavior at night, which at least suggests some sort of spontaneous cycling behavior in these animals (McClung et al., 2005; Roybal et al., 2007; Sidor et al., 2015). This manic-like phenotype consists of enhanced

hyperactivity and reward-related behaviors, as well as a reduction in anxiety- and depressive-like behaviors, and the majority of these behaviors can be reversed with lithium, a first-line treatment for bipolar disorder (Arey et al., 2014; McClung et al., 2005; Roybal et al., 2007; Sidor et al., 2015). Many studies have established that the VTA is a primary site of action for the manic-like phenotype of the *Clock*^{A19} mouse (Coque et al., 2011; McClung et al., 2005; Sidor et al., 2015). The manic-like phenotype coincides with daytime increases in VTA dopamine neuron activity, tyrosine hydroxylase (TH) expression, and dopamine synthesis in the VTA (Logan et al., 2018; Sidor et al., 2015). Notably, the manic-like phenotype can be reversed by daytime-specific administration of a TH inhibitor. Moreover, chronic stimulation of VTA dopamine neurons through optogenetics recapitulates the manic-like phenotype (Sidor et al., 2015). Interestingly, site-specific knockdown of *Clock* in the VTA results in a mixed manic/depressive state, with hyperactivity and decreased anxiety-like behavior, but also an increase in depressive-like behavior (Mukherjee et al., 2010).

Other studies have investigated the molecular mechanisms underlying the manic-like phenotype of the *Clock*^{A19} mouse and have found that CLOCK negatively regulates *TH* expression by binding to E-box sequences at promoter regions of the gene (Figure 1; Sidor et al., 2015). The expression of *TH* is also regulated by cAMP response element-binding protein (CREB)-mediated binding to CRE sites in the *TH* promoter (Lazaroff, Patankar, Yoon, & Chikaraishi, 1995; Piech-Dumas & Tank, 1999). A recent study from our laboratory demonstrated that CLOCK activity is sensitive to cellular redox state and represses CREB-induced *TH* transcription through diurnal interactions with the histone and protein deacetylase, Sirtuin 1 (SIRT1), at the *TH* promoter (Logan et al., 2018). This repression of CREB-induced *TH* transcription is eliminated in *Clock*^{A19} mice, resulting in increased *TH* expression during the day, during which the mice exhibit manic-like behavior. Interestingly, cocaine exposure abolishes SIRT1 rhythms in the VTA and pharmacological activation of SIRT1 reduces both dopamine signaling and cocaine-conditioned place preference in *Clock*^{A19} mice, suggesting a role for this mechanism in reward and addiction (Logan et al., 2018). Other clock genes, such as REV-ERB α , also play an important role in mood regulation. A study by Chung et al. (2014) showed that *Rev-erba* knockout mice display a hyperdopaminergic state that is accompanied by manic-like behavior. Similar effects were induced through pharmacological inhibition of REV-ERB α in the ventral midbrain. Furthermore, they demonstrated that *TH* expression is directly repressed by REV-ERB α , providing a mechanism through which this effect may occur (Chung et al., 2014). Taken together, these data strongly implicate VTA dopaminergic activity in the circadian regulation of mood and reward.

In addition to the dopamine system, several studies have implicated a role for serotonin in the circadian regulation of mood and reward. The circadian and serotonergic systems are reciprocally connected and likely interact to influence mood regulation (Ciarleglio, Resuehr, & McMahon, 2011). Studies have shown serotonin manipulation can influence circadian rhythms in both the SCN and locomotor activity (Vadnie & McClung, 2017). For example, SSRIs have been shown to phase advance SCN neural activity, as well as locomotor activity (Cuesta, Clesse, Pevet, & Challet, 2009; Cuesta, Mendoza, Clesse, Pevet, & Challet, 2008; Prosser, Lee, & Wehner, 2006; Sprouse, Braselton, & Reynolds, 2006), which could play a role in improving rhythm disturbances observed in mood disorders. Interestingly, the

influence of circadian and monoaminergic systems on mood has also been demonstrated through manipulations of the melatonin system. Melatonin is a hormone produced by the pineal gland that plays an important role in sleep regulation. The antidepressant effects of the drug, agomelatine, are mediated through its interactions with both melatonin receptors and serotonin 5-HT_{2C} receptors (Guardiola-Lemaitre et al., 2014). Agomelatine is a melatonin receptor agonist and 5-HT_{2c} antagonist and has been shown to modulate monoaminergic neuronal activity (Chenu, El Mansari, & Blier, 2013). Furthermore, melatonin MT1 receptor knockout mice show increased depressive-like behavior, which is reversed by chronic treatment with the tricyclic antidepressant desipramine (Comai, Ochoa-Sanchez, Dominguez-Lopez, Bambico, & Gobbi, 2015). Another study demonstrated the anxiolytic effects of agomelatine after social defeat require an intact SCN (Tuma, Strubbe, Mocaer, & Koolhaas, 2005). Furthermore, serotonergic signaling in the amygdala can modulate the anti-depressant actions of melatonin (Micale, Arezzi, Rampello, & Drago, 2006). These studies highlight a role for the interaction of circadian and monoamine systems in regulating mood.

Lastly, norepinephrine may also be involved in the circadian regulation of mood. A study by Ben-Hamo et al. (2016) found that rats exposed to a short light-dark cycle (22 hr) showed desynchronized oscillations in the SCN and a depressive phenotype during the active phase (Ben-Hamo et al., 2016). These changes are paralleled by increased norepinephrine and dopamine levels and serotonin turnover in the prefrontal cortex (PFC; Ben-Hamo et al., 2016). These changes may be stress-induced, as norepinephrine and dopamine release are enhanced in the PFC in response to stress (Di Chiara, Loddo, & Tanda, 1999; Finlay, Zigmond, & Abercrombie, 1995). Interestingly, deletion of *Bmal1* in the cerebral cortex induces depressive-like behavior in the tail suspension test and a reduction in cortical norepinephrine levels, suggesting cortical clock regulation of mood may involve norepinephrine function (Bering, Carstensen, Wortwein, Weikop, & Rath, 2018). Lastly, studies have shown that constant darkness can induce a depressive-like state and apoptosis of monoaminergic neurons, particularly noradrenergic neurons in the locus coeruleus, and these effects are reversed with the norepinephrine reuptake inhibitor, desipramine (Gonzalez & Aston-Jones, 2008).

Together, these studies reveal a role for monoamine-related neuronal activity in the circadian regulation of mood. A more thorough understanding of the mechanisms underlying this relationship may lead to novel therapeutic targets for the treatment of mood disorders, as well as the circadian rhythm alterations associated with these disorders.

3 | GLUTAMATERGIC TRANSMISSION

The discovery that ketamine, a glutamate NMDA receptor channel blocker, can produce rapid antidepressant effects has generated a great deal of interest in the role of glutamatergic transmission in mood regulation (Duman, 2018). As opposed to most antidepressant medications which require weeks to months before there are therapeutic effects, a single, subanesthetic dose of ketamine can produce an antidepressant response within hours that can last for up to a week (Zarate et al., 2006). The exact mechanisms by which ketamine produces these effects are still unclear; however, it seems likely that at least initially

ketamine increases glutamatergic transmission in the mPFC, hippocampus, and other regions of the brain. This increase in glutamatergic transmission is potentially mediated through blockage of NMDA receptors on GABA interneurons that normally inhibit this transmission (Duman, 2018). Another recent study found that ketamine blocks NMDA receptors in the lateral habenula, leading to a reduction in burst firing normally driven by NMDA receptor activity (Yang et al., 2018). Since the lateral habenula is involved in inhibiting monoaminergic reward circuitry, this reduction in burst firing results in activation of dopamine and serotonin neurons, potentially leading to the rapid (but perhaps not sustained) antidepressant response. Interestingly, studies over the last 30 years have found that one night of sleep deprivation (SD) can also produce similar rapid antidepressant effects in about 50% of subjects (Borbely & Wirz-Justice, 1982; Wu & Bunney, 1990), leading people to question whether these rapid antidepressant effects of ketamine and SD share common mechanisms of action, and if they involve the modulation of the molecular clock. In cell culture (NG108–15 neuronal cells), ketamine can inhibit CLOCK:BMAL1-mediated transcriptional activation and this is attenuated by treatment with a GSK3 β antagonist (Bellet, Vawter, Bunney, Bunney, & Sassone-Corsi, 2011). This suggests that ketamine alters CLOCK:BMAL1 function perhaps via activation of GSK3 β , a key modulator of the molecular clock. Another study from the same group treated mice with either ketamine or SD and subjected the mice to the forced swim test, a measure of antidepressant efficacy. They then took tissue samples from the anterior cingulate cortex and compared the transcriptional response between treatments. They found 64 genes which were commonly altered by both treatments (representing 5% of genes changed by ketamine and 11% of genes changed by SD, $p < 0.001$), including a number of downregulated circadian genes, such as *Per2*, *Npas4*, *Rorb*, *Dbp*, and *Ciart*. The authors speculate that both ketamine and SD alter common molecular clock components, resulting in changes in neuronal plasticity and an antidepressant effect (Orozco-Solis et al., 2017). The longer lasting antidepressant effects of ketamine (up to 2 weeks) involve activation of mTOR signaling pathways, brain-derived neurotrophic factor (BDNF) release, and changes in dendritic spines (Autry et al., 2011; Li et al., 2010). These changes may occur primarily during sleep following ketamine treatment. A study of 30 subjects with treatment-resistant depression found a positive correlation between the baseline delta sleep ratio (SWA(NREM1)/SWA(NREM2)) the night before ketamine treatment and the response to ketamine the following day, suggesting that a low baseline delta sleep ratio, indicative of deficient production of slow wave sleep, may be a predictor of ketamine response (Duncan, Selter, Brutsche, Sarasso, & Zarate, 2013). Moreover, following ketamine treatment, there was an increase in slow wave activity in the first non-REM sleep episode, along with increased plasma BDNF (Duncan, Sarasso, et al., 2013). Furthermore, the response included an increase in high amplitude waves during early sleep, along with an increase in slow wave slope, suggesting increased synaptic strength. Changes in BDNF were proportional to changes in EEG measures and these changes were only found in subjects who experienced an antidepressant response to ketamine. These data suggest that ketamine is modulating synaptic connections during the first sleep episode following treatment, and that this first sleep episode may be crucial to the sustained antidepressant response.

Changes in sleep/wake activity rhythms can also be predictive of a response to ketamine. In a study of 51 subjects with treatment-resistant depression, activity rhythms were measured using actigraphy (Duncan, Slonena, et al., 2017). The study found that those who would go on to respond to ketamine had lower central value (mesor) and earlier acrophase measures at baseline. They also showed advanced timing on day 1 after ketamine and importantly, increased rhythm amplitude on day 3. In contrast, ketamine non-responders had a lower mesor and blunted amplitude in response to ketamine on day 1. These findings are exciting in that they demonstrate an association between the clinical response to ketamine and sleep/wake rhythms along with a potential modulation of the internal circadian system. They show not only that treatment response can be predicted by certain diurnal patterns of activity, but also that ketamine may produce lasting effects in these individuals, at least in part, through amplification of diurnal rhythms. It is also worth noting that depression can be the result of many different factors, disrupted circadian rhythms being only one of them, and thus other types of treatments may be more advantageous for those individuals without these particular circadian phenotypes, while ketamine may be therapeutic only for a particular population with these specific circadian phenotypes. Interestingly, both lithium and valproic acid (mood-stabilizing medications) also increase molecular rhythm amplitude in fibroblast cultures and this effect may underlie their ability to stabilize rhythms and prevent the precipitation of mood episodes (Johansson, Brask, Owe-Larsson, Hetta, & Lundkvist, 2011; Li, Lu, Beesley, Loudon, & Meng, 2012). While we know that glutamatergic activity in the SCN is involved in setting the central clock, future studies are needed to determine if and how ketamine impacts the central clock in the SCN, as well as molecular clocks in other brain regions. With this knowledge, we may be able to use additional chronotherapies, like bright light therapy, to extend and sustain therapeutic effects of ketamine or SD (Duncan, Ballard, & Zarate, 2017).

4 | HPA AXIS

The neuroendocrine component of the stress response is mediated by the HPA axis. In response to stress, corticotropin-releasing factor (CRF) is released from neurons in the paraventricular nucleus of the hypothalamus (PVN) into the hypophyseal portal system, where it travels to the anterior pituitary and stimulates the release of adrenocorticotropic hormone (ACTH) into the circulation. ACTH stimulates the release of glucocorticoids (corticosterone or cortisol) from the adrenal gland, which then mediates the stress response. Glucocorticoids inhibit the HPA axis through negative feedback at the PVN and anterior pituitary. HPA axis and glucocorticoid dysregulation has been implicated in mood disorders, such as depression (Pariante & Lightman, 2008). Hypercortisolism is often observed in patients with depression (Hinkelmann et al., 2012; Linkowski et al., 1987; Rubin, Poland, Lesser, Winston, & Blodgett, 1987). However, atypical depression, a subtype of major depression characterized by symptoms such as lethargy, fatigue, hyperphagia, and weight gain, is associated with lower levels of cortisol (Gold & Chrousos, 2002). Furthermore, in depressed patients with increased cortisol levels, antidepressant treatment has been shown to return cortisol to control levels (Hinkelmann et al., 2012; Linkowski et al., 1987).

The HPA axis is under circadian control by the SCN (Moore & Eichler, 1972). Glucocorticoids show robust circadian rhythms in expression, with peak levels occurring at

the beginning of the active phase. This temporal rhythmicity is controlled by diurnal variations in CRF and ACTH activity, as well as a peripheral clock in the adrenal glands (Ishida et al., 2005; Nader, Chrousos, & Kino, 2010; Oster et al., 2006; Son, Chung, & Kim, 2011). In addition, molecular clock proteins interact with the glucocorticoid receptor (GR) to produce diurnal variations in its expression and sensitivity. For example, CRY proteins interact with the GR to rhythmically repress its transcriptional activity (Lamia et al., 2011). The CLOCK/BMAL1 complex also modulates the circadian sensitivity of GR through CLOCK-mediated acetylation (Charmandari et al., 2011; Kino & Chrousos, 2011; Nader, Chrousos, & Kino, 2009). The function of GR is also modulated through interactions with other clock proteins, such as REV-ERBa (Okabe et al., 2016) and CHRONO, a novel circadian protein that negatively regulates the molecular clock and interacts with GR to decrease its transcription activity (Anafi et al., 2014; Goriki et al., 2014). Notably, the interaction between the circadian system and the HPA axis is reciprocal, as glucocorticoids provide feedback on the clock by binding to glucocorticoid response elements and altering the transcription of circadian clock genes, such as *Per1* and *Per2*, allowing for synchronization of peripheral clocks and extra- SCN brain clocks (Koch, Leinweber, Drengberg, Blaum, & Oster, 2017; Oster et al., 2017; Spencer, Chun, Hartssock, & Woodruff, 2018).

A number of studies suggest the circadian system interacts with the stress system to influence mood regulation (Landgraf, McCarthy, & Welsh, 2014). Circadian clock regulation of HPA axis function has been demonstrated through studies utilizing genetic mouse models containing mutations in circadian clock genes. For example, *Bmal1* mutant mice show reduced glucocorticoid levels, adrenal sensitivity to ACTH, and a downregulation in gene expression related to cholesterol synthesis in adrenal cells (Leliavski, Shostak, Husse, & Oster, 2014). These mice also show an attenuation in stress-induced glucocorticoid levels and reduced depressive-like behavior in the forced swim test (Leliavski et al., 2014). Mutations in *Clock*, *Cry*, and *Per* are also associated with alterations in glucocorticoid levels and rhythmicity (Becker-Krail & McClung, 2016; Koch et al., 2017). The relationship between the circadian and stress system is bidirectional, with stress also affecting function of the molecular clock. For example, stress increases *Per1* expression in the brain and peripheral tissues (Al-Safadi, Branchaud, Rutherford, & Amir, 2015; Al-Safadi et al., 2014; Takahashi et al., 2001, 2013; Yamamoto et al., 2005). In addition, *Per2* rhythms are stimulated by glucocorticoids and these rhythms are altered in the bed nucleus of the stria terminalis and the amygdala following inactivation of the GR (Segall, Milet, Tronche, & Amir, 2009; So, Bernal, Pillsbury, Yamamoto, & Feldman, 2009). A study from our laboratory explored the effects of unpredictable chronic mild stress, a rodent model of depression, on *Per2* rhythms in the mouse brain using *Per2* luciferase reporter (*Per2::luc*) mice (Logan et al., 2015). Chronic stress decreased rhythm amplitude in the SCN and increased rhythm amplitude in the nucleus accumbens (NAc), with these changes directly correlating to depressive-like behavior (Logan et al., 2015). These changes in amplitude may be due to differences in GR expression, as the NAc expresses high levels of GR and the SCN is largely absent of GR expression (Balsalobre et al., 2000; Barik et al., 2010; Der-Avakian et al., 2006). A study by Landgraf et al. (2016) investigated the role of the circadian clock in the SCN in regulating mood. The authors found that site-specific knockdown of *Bmal1* in

the SCN of *Per2::luc* mice significantly suppressed *Per2* rhythms and induced depressive- and anxiety-like behavior, demonstrating a causal role for SCN rhythms in mood regulation. The authors speculate that disruption of the central clock may affect mood through downstream systems that are more directly involved in mood regulation. In support of this, they find that disrupting rhythms in the SCN altered HPA axis function, as the mice displayed altered corticosterone rhythms and an attenuated stress-induced corticosterone response (Landgraf et al., 2016). Of note, the mood-related findings from this study contrast with the study described above by Leliavski et al. (2014), in which *Bmall* mutant mice showed a reduction in depressive-like behavior. However, these discrepancies may be explained, in part, by the method of *Bmall* knockdown. Landgraf et al. (2016) site-specifically knocked down *Bmall* in the SCN, whereas Leliavski et al. (2014) used mutant mice that lack *Bmall* in both the brain and periphery.

A variety of studies have utilized inappropriate light exposure and extreme photoperiod changes to investigate the interaction of stress and circadian systems in mood regulation. For example, inappropriate light exposure (i.e., light at night) is associated with increased corticosterone levels in rodents (Koch et al., 2017). In addition, short photoperiods induce anxiety- and depressive-like behavior in diurnal rodents, which are reduced after bright light treatment (Ashkenazy, Einat, & Kronfeld-Schor, 2009a,b; Einat, Kronfeld-Schor, & Eilam, 2006). A study by Dulcis, Jamshidi, Leutgeb, and Spitzer (2013) found that long-day (i.e., short-active) photoperiods elevate corticosterone levels and enhance anxiety- and depressive-like behaviors in nocturnal rats, while short-day (i.e., long-active) photoperiods produce the opposite effect. Interestingly, photoperiod changes caused individual interneurons in the PVN to switch between dopamine and somatostatin expression, with increased switching from somatostatin to dopamine for short-day periods and dopamine to somatostatin for long-day periods. Moreover, ablation of dopamine neurons in the PVN produced anxiety- and depressive-like behavior, which was rescued through short-day photoperiod induction of new dopaminergic neurons (Dulcis et al., 2013). The authors also revealed that somatostatin (SST2/4) and dopamine (D2) receptors colocalize with CRF in the hypothalamus and observed an increase in CRF and corticosterone levels in the cerebrospinal fluid and plasma, respectively, following long-day photoperiod. This may represent a potential mechanism by which long-day photoperiod induces depressive- and anxiety-like behavior in mice (Dulcis et al., 2013). While the PVN receives direct input from the SCN, the mechanisms by which the central clock may regulate neurotransmitter switching remain to be determined.

A study by Young et al. (2018) utilized similar short-day and long-day photoperiod changes in mice to model season-induced switching between mood states. The authors found that a short-day (i.e., long-active) period induced a manic state, while a long-day (i.e., short-active) period induced a depressive state, consistent with season-induced switching between mood states observed in patients with bipolar disorder (Wang & Chen, 2013; Young & Dulcis, 2015). Interestingly, similar to the Dulcis et al. (2013) study, switches in mood states were correlated with neurotransmitter switching from dopamine to somatostatin in the PVN. Mice with a reduction in dopamine transporter (DAT) expression showed exacerbated manic and depressive-like states in response to their respective photoperiods, revealing an important role for dopamine function in season-induced switching between mood states (Young et al., 2018). Together, these studies suggest that the interaction of circadian and stress systems is

important for regulation of mood. However, it is worth noting that studies from the Hattar laboratory have identified specific projections from the intrinsically photosensitive retinal ganglion cells (ipRGCs) and the perihabenular nucleus that may potentially mediate the depression-inducing effects of aberrant light cycles independent from the central clock in the SCN (Fernandez et al., 2018; LeGates et al., 2012). Thus, future studies will be necessary to determine the exact role of these interactions in the development of mood disorders.

5 | METABOLIC PEPTIDES

Mood disorders and metabolic disorders show a high rate of comorbidity (Amare, Schubert, Klingler-Hoffmann, CohenWoods, & Baune, 2017; Mansur, Brietzke, & McIntyre, 2015; Milaneschi, Simmons, van Rossum, & Penninx, 2018). For example, depression is highly comorbid with obesity, and the relationship between the two is bidirectional (Milaneschi et al., 2018). This association is particularly strong among obese individuals with an adverse metabolic profile, including dyslipidemia or insulin resistance (Jokela, Hamer, Singh-Manoux, Batty, & Kivimaki, 2014). Recent evidence indicates environmental and genetic disruptions of circadian rhythms may play a role in the link between metabolic and mood disorders (Barandas, Landgraf, McCarthy, & Welsh, 2015). Peripheral tissues, including the liver, pancreas, and gut, express local self-sustaining clocks that regulate metabolic function. Moreover, peptides and hormones that regulate metabolism and feeding, such as leptin, ghrelin, orexin, and cholecystokinin (CCK), display circadian rhythms in expression (Feillet, 2010; Schade et al., 1993; Turek et al., 2005).

Food intake is largely regulated by the hormones leptin and ghrelin, which are released from the adipose tissue and gut, respectively. These hormones act within the arcuate nucleus of the hypothalamus to regulate food intake and energy homeostasis. Ghrelin is released from the gut in response to hunger and stimulates food intake, while leptin is released from adipose tissue and reduces feeding (Sobrino Crespo, Perianes Cachero, Puebla Jimenez, Barrios, & Arilla Ferreiro, 2014). Both leptin and ghrelin show circadian rhythms in expression, and their levels in the plasma are sensitive to food availability (Feillet, 2010). In addition to their role in obesity (Cui, Lopez, & Rahmouni, 2017), ghrelin and leptin have been implicated in the regulation of mood and reward (Lu, 2007; Milaneschi et al., 2018; Morris, Voon, & Leggio, 2018; Spencer, Emmerzaal, Kozicz, & Andrews, 2015). A number of rodent studies have revealed an antidepressant effect of leptin, with the hippocampus being a primary site of action (Garza, Guo, Zhang, & Lu, 2012; Lu, Kim, Frazer, & Zhang, 2006; Yamada et al., 2011). Furthermore, global and site-specific (i.e., hippocampus and cortex) knockout of the leptin receptor induces depressive-like behavior (Guo, Huang, Garza, Chua, & Lu, 2013; Guo et al., 2012; Liu et al., 2017; Sharma, Elased, Garrett, & Lucot, 2010). In humans, high levels of leptin are associated with atypical depression, with the association being more robust for increased adiposity, appetite, and weight (Milaneschi, Lamers, Bot, Drent, & Penninx, 2017). These data implicate a role for leptin dysregulation in the comorbidity between obesity and depression. However, the exact role of ghrelin in mood regulation is a little less clear, as some studies show that ghrelin produces anxiety-like behavior, while others show anxiolytic and antidepressant effects (Morris et al., 2018; Spencer et al., 2015; Wittekind & Kluge, 2015). Ghrelin and leptin may modulate mood through their interaction with the HPA axis (Barandas et al., 2015; Morris et al., 2018;

Roubos, Dahmen, Kozicz, & Xu, 2012; Spencer et al., 2015). Furthermore, chronic restraint stress disrupts diurnal rhythms in leptin expression (de Oliveira et al., 2014). Given their important role in mood and metabolism, circadian disruptions in leptin and ghrelin expression may have an impact on mood regulation and its relationship to obesity.

Ghrelin and leptin also interact with orexin neurons in the lateral hypothalamus, which promote arousal and feeding when activated by ghrelin and induce sleep when inhibited by leptin (Adamantidis & de Lecea, 2008). Orexin is a peptide that stimulates food intake and is known for its role in regulating arousal, energy, as well as mood and reward. Orexin also plays a role in the stress response and the interactions between these systems are bidirectional (Blasiak, Gundlach, Hess, & Lewandowski, 2017; Grafe & Bhatnagar, 2018; James, Campbell, & Dayas, 2017). Interestingly, orexin modulation of the stress response is mediated by leptin through leptin-sensitive neurons in the lateral hypothalamus, suggesting an interaction between these two systems in the stress response (Bonnavion, Jackson, Carter, & de Lecea, 2015). Depression is linked to both hyperactivity and hypoactivity of the orexin system (Nollet & Leman, 2013). In addition, individuals with depression display altered rhythms in activity, sleep/wake, body temperature, and hormone secretion (Germain & Kupfer, 2008; McClung, 2007; Souetre et al., 1989). Interestingly, depressed subjects also exhibit a reduction in diurnal rhythms of orexin expression (Salomon et al., 2003). Circadian rhythms of orexin expression are regulated by the SCN (Blasiak et al., 2017). Furthermore, *Clock* mutant mice show a decrease in orexin expression, as well as a loss of rhythmicity (Turek et al., 2005). These mice also lose circadian rhythmicity in other peptides, such as ghrelin and cocaine- and amphetamine-regulated transcript (Turek et al., 2005). Moreover, microarray analysis of VTA tissue from *Clock*^{-/-} mice identified altered transcription of a number of genes involved in dopaminergic transmission (McClung et al., 2005). One of the genes significantly downregulated was *Cck*, a peptide that shows robust circadian rhythms in expression in the brain and plays a role in feeding and regulation of mood and anxiety-related behavior (Arey et al., 2014; McClung et al., 2005; Schade et al., 1993; Weber, Lauterburg, Tobler, & Burgunder, 2004). CCK is a direct transcriptional target of CLOCK in the VTA and *Cck* levels are decreased in this region in *Clock*^{-/-} mice (Arey et al., 2014; McClung et al., 2005). Furthermore, site-specific knockdown of *Cck* in the VTA of wild-type mice produces a manic-like phenotype similar to the *Clock*^{-/-} mice. Chronic lithium treatment increases *Cck* levels in *Clock*^{-/-} mice, which is necessary for the therapeutic actions of the drug in this mouse model (Arey et al., 2014). These data suggest a critical role for CCK in the manic-like phenotype of the *Clock*^{-/-} mice. Interestingly, *Clock* mutant mice become obese on a high-fat diet and develop a metabolic syndrome (Turek et al., 2005). Moreover, mutations in other clock genes, such as PER and CRY, also produce both metabolic and mood phenotypes, further demonstrating the important role of the core circadian clock in regulating both metabolism and mood (Barandas et al., 2015). Future studies are necessary for a more comprehensive understanding of the molecular mechanisms that underlie this relationship.

6 | MICROBIOME

A high comorbidity exists between gastrointestinal disorders and stress-related psychiatric disorders. For example, over 50% of patients with irritable bowel syndrome have depression

or anxiety (Kelly et al., 2015; Kennedy, Cryan, Dinan, & Clarke, 2014). This comorbidity highlights a potentially important role of the gut-brain axis in mood regulation. The microbiome is a key component of the gut-brain axis, which comprises the microbiota-gut-brain axis, a bidirectional pathway that influences metabolism, behavior, and mood (Cussotto, Sandhu, Dinan, & Cryan, 2018; Dinan & Cryan, 2017; Kelly et al., 2015; Rogers et al., 2016). The mammalian microbiome consists of trillions of bacteria that reside in the intestine of the host. Recent evidence suggests the gut microbiome may play a role in mood regulation and stress-related psychiatric disorders, such as depression. For example, germ-free mice show alterations in the stress response and exhibit alterations in monoaminergic signaling in limbic brain regions (Cussotto et al., 2018; Rogers et al., 2016). Interestingly, prebiotics and probiotics, which stimulate the growth of healthy bacteria in the gut, can produce anxiolytic effects and normalization of the HPA axis in response to stress (Cussotto et al., 2018). Alterations in gut microbiome composition and diversity have been observed in patients with MDD (Jiang et al., 2015; Kelly et al., 2016; Lin et al., 2017; Zheng et al., 2016). Notably, a study by Zheng et al. (2016) showed that fecal transplantation of samples from patients with MDD into germ-free mice resulted in depressive-like behavior in the recipient mouse compared to those that received transplants from healthy controls. Mice that received transplants from depressed patients also displayed alterations in microbial gene expression and fecal and serum metabolites related to carbohydrate and amino acid metabolism, suggesting that alterations in host metabolism may be a potential mechanism by which the microbiome influences mood (Zheng et al., 2016). A similar fecal transplant study was performed by Kelly et al. (2016), but instead of using germ-free mice, rats treated with a cocktail of antibiotics were utilized. These microbiota-deficient rats that received a fecal transplantation from patients with MDD showed depressive- and anxiety-like behaviors, as well as alterations in tryptophan metabolism, which could influence serotonin production (Kelly et al., 2016). Taken together, these data suggest a potential role for the microbiome in the development of depressive-like behavior.

Several recent studies have demonstrated a significant interaction between circadian rhythms and the gut microbiome. A study by Thaïss et al. (2014) showed the intestinal microbiota in rodents and humans displays diurnal rhythms in abundance and metabolic function that are highly regulated by feeding rhythms. Furthermore, diurnal oscillations in microbial localization and metabolite production regulate circadian activity in host metabolism, including systemic metabolite oscillations and transcriptional oscillations in peripheral tissues (Thaïss et al., 2016). Microbiota rhythmicity is also sensitive to circadian disruptions in the host. For example, mice exposed to a jet lag paradigm exhibit a disruption in microbiota rhythmicity and metabolic alterations, such as glucose intolerance and obesity (Thaïss et al., 2014). Fecal transplantation of microbiota from jet-lagged mice and humans into germ-free mice recapitulated these metabolic deficits, demonstrating a role for the gut microbiota in the metabolic disturbances observed after circadian disruption (Thaïss et al., 2014). Microbiome alterations in response to host circadian disruption may be influenced by diet, as mice undergoing weekly light-dark reversals showed alterations in the gut microbiome composition that were dependent on being fed a high-fat or high-sugar diet (Voigt et al., 2014). Furthermore, a high-fat diet disrupts diurnal oscillations in microbiota composition and metabolite production, which may alter hepatic circadian rhythms in the

host (Leone et al., 2015). Similarly, diet-induced obesity disrupts diurnal variations in microbial composition, which is partially restored by time-restricted feeding (Zarrinpar, Chaix, Yooseph, & Panda, 2014). Together, these studies demonstrate an important role for diet in the relationship between circadian rhythms and the microbiome. The role of the host central clock in regulating microbial rhythms has also been demonstrated in genetic mouse models with mutations in circadian clock genes (Voigt, Forsyth, Green, Engen, & Keshavarzian, 2016). For example, microbiota rhythmicity is disrupted in mice with mutations in *Per1/2* (Thaiss et al., 2014) and *Bmal1* (Liang, Bushman, & FitzGerald, 2015). Studies using the *Clock*^{-/-} mice have found a reduction in microbial diversity compared to wild-type mice (Voigt, Summa, et al., 2016) and intestinal barrier dysfunction (i.e., increased hyperpermeability) that is worsened by alcohol intake (Summa et al., 2013). Alterations in intestinal barrier integrity can lead to gut leakiness and increase systemic inflammation, which may increase the risk for psychiatric diseases (Bauer & Teixeira, 2018).

There are a variety of proposed mechanisms by which the microbiome may influence brain function, including the vagus nerve, enteric nervous system, microbiota metabolite production, the neuroendocrine system, immune signaling, and inflammation (Cussotto et al., 2018). Increased levels of lipopolysaccharide from gram-negative enterobacteria have been observed in the serum of patients with MDD (Maes, Kubera, & Leunis, 2008). This translocation may result in systemic inflammation, which has been observed in patients with mood disorders (Bauer & Teixeira, 2018). Metabolites produced by the microbiome also influence metabolism, behavior, and perhaps mood. Short-chain fatty acids, such as butyrate, acetate, and propionate, are common metabolic byproducts released by gut microbiota and have been shown to alter host immune responses, metabolism, and neurotransmitter synthesis (Cussotto et al., 2018; Rogers et al., 2016). Gut bacteria also produce a wide variety of neurotransmitters, including GABA, dopamine, norepinephrine, serotonin, and acetylcholine (Cussotto et al., 2018). However, it is currently unknown what effect these microbial-derived neurotransmitters might have (if any) on brain function, as many of these neurotransmitters are not able to cross the blood-brain barrier. Nevertheless, microbial-derived neurotransmitter precursors could play a role in mood regulation. For example, tryptophan is produced by gut microbiota and may influence mood through altering serotonin production. Interestingly, germfree mice have increased plasma tryptophan and hippocampal 5-HT levels (Clarke et al., 2013). Lastly, a recent study found that the ketogenic diet, a known treatment for intractable epilepsy in children, alters the intestinal microbiota and these changes are necessary and sufficient for seizure protection in mice (Olson et al., 2018). Ketogenic diet- and microbiota-dependent seizure protection was correlated with reductions in peripheral gamma-glutamyl amino acids and increases in hippocampal GABA/glutamate ratios, suggesting that the gut microbiome may modulate seizure susceptibility in response to diet through alterations in host metabolism (Olson et al., 2018). Together, the studies described above suggest a role for the microbiome in both metabolism and mood regulation and highlight a need for future studies to investigate how the circadian system may be important for this connection.

7 | NEUROINFLAMMATION

In recent years, there has been a great deal of interest in the potential role of inflammation and the production of pro-inflammatory cytokines in the pathophysiology of depression. Major depression is common in patients suffering from chronic inflammatory conditions (Menard, Pfau, Hodes, & Russo, 2017). Subsets of MDD patients also have higher levels of both pro-inflammatory cytokines and circulating leukocytes. Chronic stress can increase pro-inflammatory cytokines, and nuclear factor kappa-light-chain-enhancer of activated B cells (NF κ B) signaling in the periphery and CNS, as well as microglial activation in the brain (Frank, Baratta, Sprunger, Watkins, & Maier, 2007; Pace et al., 2006). Furthermore, when cytokines produced from macrophages are given to healthy subjects, they induce depressive-like symptoms (Smith, 1991). Cytokines, like interleukin-1 β , can alter monoamine levels by increasing metabolism of norepinephrine and 5-HT, and increase the production of CRF in the hypothalamus, activating the HPA stress axis (Takahashi, Flanigan, McEwen, & Russo, 2018). These mechanisms may contribute to the regulation of mood in people with increased cytokine production. Moreover, anti-inflammatory treatments can be beneficial in certain people with increased levels of inflammatory cytokines and depression-related symptoms (Kopschina Feltes et al., 2017).

Even modest circadian rhythm and sleep disruption can result in elevated levels of pro-inflammatory cytokines in humans and exaggerated responses to a lipopolysaccharide (LPS) challenge in mice (Castanon-Cervantes et al., 2010; Fonken, Weil, & Nelson, 2013; Vgontzas et al., 2004). In turn, LPS can induce phase delays in free-running hamsters and alter the response to light in the SCN of mice (Marpegan, Bekinschtein, Costas, & Golombek, 2005; Palomba & Bentivoglio, 2008). LPS treatment can also transiently alter expression of clock genes, like *Per1* and *Per2*, in the hypothalamus and liver (Okada et al., 2008; Takahashi et al., 2001). Inflammatory cytokines can decrease the frequency of excitatory and inhibitory currents in the SCN and ablate the circadian rhythm of spontaneous activity in the SCN, reducing frequency to nadir levels across the 24-hr cycle (Lundkvist, Hill, & Kristensson, 2002). This is similar to what is reported with aging, suggesting that the effects of age on SCN function could be mediated by increased levels of inflammatory cytokines in the brain (Nygard, Hill, Wikstrom, & Kristensson, 2005; Watanabe, Shibata, & Watanabe, 1995). Circadian genes are expressed rhythmically in peripheral immune cells, including macrophages and natural killer (NK) cells (Arjona & Sarkar, 2005, 2006; Hayashi, Shimba, & Tezuka, 2007; Kusanagi et al., 2004). Mice with a mutation in *Per2* lose the well-defined circadian pattern of resistance to an LPS challenge that is normally seen in mice, and they are more resistant to LPS-induced mortality (Liu et al., 2006). These mice are deficient in the production of IFN- γ and IL-10 by NK cells, which suggests that PER2 is involved in the production of certain cytokines following an immune challenge (Liu et al., 2006).

Nuclear factor kappa-light-chain-enhancer of activated B cells signaling plays a central role in the cellular response to stress, inflammation, and immunity. Importantly, CLOCK is found in protein complexes with the transcription factor, p65, a member of the NF κ B family (Spengler et al., 2012). In the absence of BMAL1, CLOCK can upregulate NF κ B-mediated transcription and the immune response is reduced in cells derived from *Clock-deficient* mice (Spengler et al., 2012). Moreover, hCLOCK is induced by insults like hypoxia and activates

inflammatory responses through its interactions with the NF κ B pathway (Tang et al., 2017). Thus, there is a bidirectional relationship between immune stimulation and the clock such that inflammation can alter circadian rhythms, and the circadian clock helps to regulate immune responses. Future studies are needed to determine how these immune factors impact mood and to what extent genetic or environmental changes to circadian rhythms influence inflammatory responses.

8 | MITOCHONDRIAL FUNCTION

Mitochondria are the primary energy-producing organelles in cells. Neurons in the brain require high levels of energy to function. In fact, the brain, with its high aerobic activity, requires approximately 20 times more energy than the rest of the body by weight and a cortical neuron consumes 4.7 billion ATP molecules per second in a resting human brain (Kety, 1950; Zhu et al., 2012). In addition, a by-product of energy production by mitochondria is the creation of reactive oxygen species (ROS), which can have toxic effects if not properly cleared by antioxidants. This makes the brain highly vulnerable to changes in mitochondrial function or antioxidant production. Indeed, several studies have linked mitochondrial dysfunction to psychiatric disorders including bipolar disorder, schizophrenia, and major depression (Allen, Romay-Tallon, Brymer, Caruncho, & Kalynchuk, 2018; Clay, Sillivan, & Konradi, 2011; Manji et al., 2012; Marazziti et al., 2011). In turn, patients with mitochondrial diseases often display symptoms which are characteristic of psychiatric disorders.

Mitochondrial morphology including fusion and fission, as well as the formation of new mitochondria, is dependent on a functional molecular clock (de Goede, Wefers, Brombacher, Schrauwen, & Kalsbeek, 2018). For example, both *Bmal1* KO and *Clock* *19* mutant mice have reduced muscle mitochondrial volume and respiratory function and altered levels of *pgc1a* and *pgc1b*, key genes involved in mitochondrial biogenesis (Andrews et al., 2010). While mitochondrial mass and content do not seem to change over the light/dark cycle, mitochondrial respiration and fusion and fission processes do display diurnal rhythms (de Goede et al., 2018). Some of these diurnal differences are due to changes in activity and food consumption at different times of day, but the molecular clock also seems to play a role. Indeed, the molecular clock regulates a large number of genes that are involved in mitochondrial function and the antioxidant response (Panda et al., 2002). One important link between circadian regulation of transcription in the nucleus and the mitochondrial redox system involves the NAD⁺-dependent deacetylase, SIRT1 (Figure 2). SIRT1 becomes active in the presence of NAD⁺, thus it is responsive to the NAD⁺/NADH ratio indicative of the cellular redox state. Activated SIRT1 can bind to CLOCK and deacetylate BMAL1 and PER2, altering circadian transcription (Asher et al., 2008; Nakahata et al., 2008). In turn, CLOCK and BMAL1 regulate the production of NAMPT, part of the NAD⁺ salvage pathway, resulting in a feedback loop of SIRT1- CLOCK-BMAL1 interaction (Nakahata, Sahar, Astarita, Kaluzova, & Sassone-Corsi, 2009; Ramsey et al., 2009). SIRT3 is also an important, NAD⁺-dependent, regulator of mitochondrial function and a recent study found diurnal rhythms in acetylation of SIRT3 protein targets in mouse liver (Mauvoisin et al., 2017). In addition to redox regulation, the molecular clock is involved in the antioxidant response. Studies in the mouse lung find that the nuclear factor erythroid-derived 2-like 2

(NRF2)/glutathione-mediated antioxidant pathway is under direct control of the molecular clock (Pekovic-Vaughan et al., 2014). *NRF2* is controlled by *CLOCK* directly through E-box binding, resulting in rhythmic expression of *NRF2*, as well as its transcriptional target genes which are involved in glutathione redox homeostasis. *Clock*^{-/-} mice have reduced levels of both NRF2 and glutathione and associated oxidative damage (Pekovic-Vaughan et al., 2014). It is likely that *CLOCK* is also regulating these pathways in the brain, though this has yet to be determined experimentally.

Another prominent way in which circadian rhythms might contribute to the antioxidant response is through production of melatonin (Figure 2). Many studies have found that melatonin acts as a potent antioxidant. In fact, this appears to be its original function, as it was discovered to be involved in the antioxidant response in bacteria, which evolved several billion years ago (Manchester, Poeggeler, Alvares, Ogden, & Reiter, 1995; Tan et al., 2010). More recent studies have discovered that melatonin is present at high concentrations in mitochondria due to both internal transport by PEPT1/2 and direct synthesis within the mitochondria (Reiter et al., 2018; Suofu et al., 2017). Moreover, melatonin type 1 receptors (MT1), the associated G protein, and β -arrestins are all expressed on and within neuronal mitochondria (Suofu et al., 2017). Melatonin synthesized in the mitochondria is released by the organelle where it then binds and activates MT1 receptor-associated signal transduction cascades, which inhibit stress-mediated cytochrome c release and caspase activation, protecting the cell from programmed cell death (Suofu et al., 2017). While melatonin produced by the pineal gland is strongly controlled by diurnal SCN activity and light exposure, it is unclear whether melatonin production or signaling within the mitochondria is also under circadian control. Suofu et al. (2017) examined levels of the rate limiting enzyme in melatonin synthesis, (AANAT), in brain non-synaptosomal mitochondria at 2:00 a.m. and 2:00 p.m. and found that in contrast to pineal tissue, there was no fluctuation in mitochondrial AANAT at these two timepoints. Thus, it is possible that only melatonin, which is transported into mitochondria, displays such diurnal variations and would be altered by disrupted environmental rhythms. Future studies are needed to determine the exact role of melatonin signaling within mitochondria and how disruptions to this system may contribute to psychiatric disorders.

9 | CONCLUSIONS

Our knowledge of the circadian clock and its potential role in mood regulation has expanded over the recent years. The circadian clock interacts reciprocally with multiple systems and processes in the central nervous system and periphery, including monoaminergic and glutamatergic transmission, HPA axis function, metabolism, and immune function (Figure 3). Given the diversity of processes regulated by the circadian clock, it is likely that circadian rhythm disruption may alter mood through multiple systems. However, despite the progress that has been made over the years, some questions remain regarding the exact mechanisms by which circadian rhythms influence mood. Future studies using animal models will be necessary to clarify the causative roles that circadian rhythms play in mood regulation in each of the systems described above. Additional genetic studies will also further elucidate the roles that individual circadian clock genes in central and peripheral tissues play in mood regulation. Ultimately, a better understanding of the molecular

mechanisms underlying the interactions between circadian rhythms and mood may lead to the development of novel therapeutic targets for the treatment of mood disorders and the circadian rhythm disturbances associated with these conditions.

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Abbreviations:

| | |
|---------------|--|
| 5-HT | 5-hydroxytryptamine |
| AANAT | aralkylamine N-acetyltransferase |
| ACTH | adrenocorticotrophic hormone |
| ATP | adenosine triphosphate |
| BDNF | brain-derived neurotrophic factor |
| BMAL1 | Brain and Muscle Arnt-like Protein 1 |
| CCK | cholecystokinin |
| CHRONO | chIP-derived repressor of network oscillator |
| CLOCK | Circadian Locomotor Output Cycles Kaput |
| CNS | central nervous system |
| CREB | cAMP response element-binding protein |
| CRF | corticotropin-releasing factor |
| CRY | cryptochrome |
| DA | dopamine |
| DAT | dopamine transporter |
| E-box | enhancer box |
| EEG | electroencephalography |
| GABA | γ -aminobutyric acid |
| GLUT | glutamate |
| GR | glucocorticoid receptor |

| | |
|-------------------------------|--|
| GSK | glycogen synthase kinase |
| GWAS | genome-wide association studies |
| HPA | hypothalamic-pituitary-adrenal |
| IFN | interferon |
| IL | interleukin |
| ipRGC | intrinsically photosensitive retinal ganglion cells |
| LPS | lipopolysaccharide |
| MAOA | monoamine oxidase A |
| MDD | major depressive disorder |
| MT1 | melatonin type 1 receptor |
| MT | melatonin |
| NAc | nucleus accumbens |
| NAD | nicotinamide adenine dinucleotide |
| NAMPT | nicotinamide phosphoribosyltransferase |
| NE | norepinephrine |
| NFκB | nuclear factor kappa-light-chain-enhancer of activated B cells |
| NK | natural killer |
| NMDA | N-methyl-D-aspartate |
| NPAS2 | Neuronal PAS Domain Protein 2 |
| NREM | non-rapid eye movement |
| NRF2 | nuclear factor erythroid-derived 2-like 2 |
| PER | period |
| PFC | prefrontal cortex |
| PVN | paraventricular nucleus of the hypothalamus |
| ROS | reactive oxygen species |
| SCN | suprachiasmatic nucleus |
| SD | sleep deprivation |
| SIRT | Sirtuin |
| SST | somatostatin |

| | |
|-------------|---|
| SWA | slow-wave activity |
| TH | tyrosine hydroxylase |
| TTFL | transcriptional-translational feedback loop |
| VTA | ventral tegmental area |

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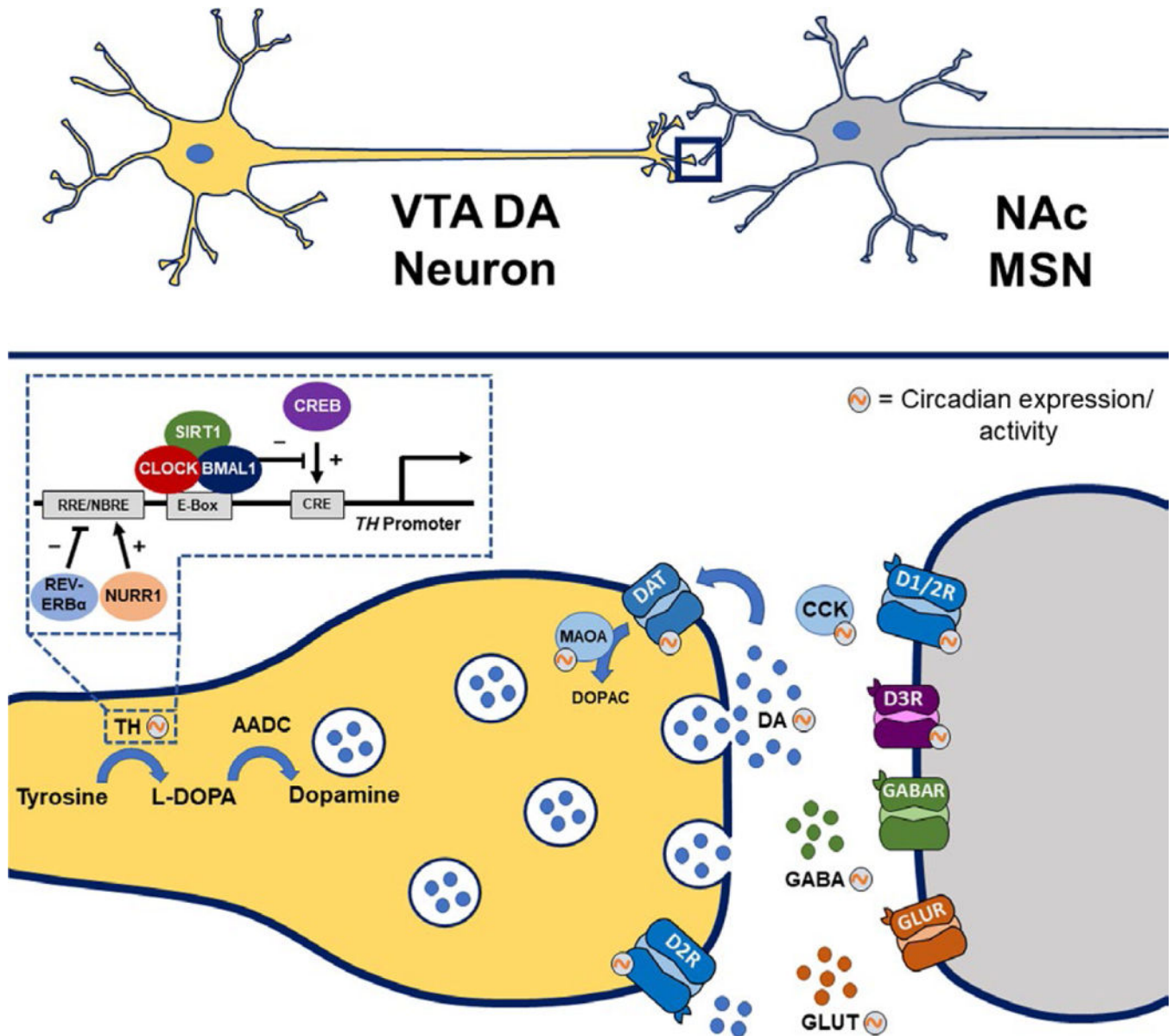
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**FIGURE 1.**

Clock genes regulate components of dopaminergic transmission within the ventral tegmental area (VTA)-nucleus accumbens (NAc) circuitry. Components of the dopamine synapse involved in the synthesis, uptake, and degradation of dopamine show circadian rhythms in expression or activity. These rhythmic components include tyrosine hydroxylase (TH), monoamine oxidase A (MAOA), dopamine transporter (DAT), and dopamine receptors type 1 (D1R), type 2 (D2R), and type 3 (D3R). *Tyrosine hydroxylase* transcription is activated by cAMP response element-binding protein (CREB)-mediated binding to CRE sites in the TH promoter. The CLOCK/BMAL1 complex interacts with the histone and protein deacetylase, Sirtuin 1 (SIRT1), to repress CREB-induced *TH* transcription in a diurnal-dependent manner. There are also circadian rhythms in various neurotransmitters and neuropeptides,

including dopamine (DA), glutamate (GLUT), γ -aminobutyric acid (GABA), and cholecystokinin (CCK)

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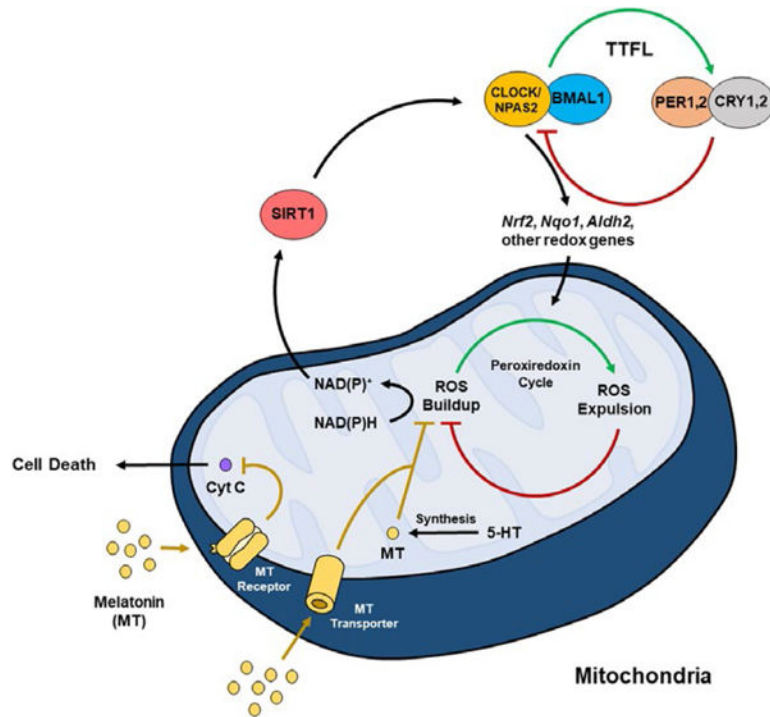


FIGURE 2.

Interactions between the circadian clock and peroxiredoxin cycle. The transcription factors CLOCK, NPAS2, and BMAL1 make up the positive arm of the transcriptional-translational feedback loop (TTFL) and control the expression of period (PER) and cryptochrome (CRY). PER and CRY make up the negative arm of the TTFL and inhibit the activity of CLOCK/BMAL1, forming a negative feedback loop. CLOCK(NPAS2)/BMAL1 controls the expression of various output genes (including *Nrf2*, *Nqo1*, and *Aldh2*), which influences ROS accumulation in the peroxiredoxin cycle. Sirtuin 1 (SIRT1), an NAD⁺-dependent histone and protein deacetylase, regulates the activity of the CLOCK/BMAL1 complex. Interestingly, melatonin (MT) acts as an antioxidant to inhibit ROS. Melatonin enters the mitochondria through MT transporters and is also synthesized within the mitochondria. Melatonin can also bind to MT receptors on the mitochondria to inhibit cytochrome c release, which may be protective against cell death

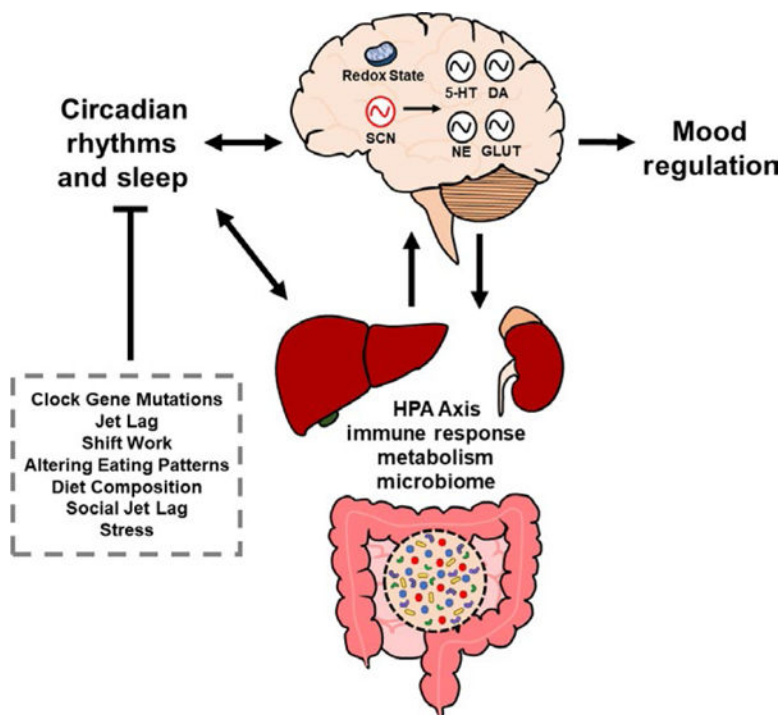


FIGURE 3.

The circadian system interacts reciprocally with a variety of physiological processes and systems that are involved in mood regulation. These processes include monoamine and glutamatergic signaling, HPA axis function, immune response, metabolism, and microbiome. Both environmental and genetic disruptions to circadian rhythms may produce alterations in these systems that ultimately affect mood. SCN, suprachiasmatic nucleus; 5-HT, serotonin; DA, dopamine; NE, norepinephrine; GLUT, glutamate