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Circadian regulation of depression: A role for serotonin☆

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ABSTRACT

Synchronizing circadian (24 h) rhythms in physiology and behavior with the environmental light-dark cycle is critical for maintaining optimal health. Dysregulation of the circadian system increases susceptibility to numerous pathological conditions including major depressive disorder. Stress is a common etiological factor in the development of depression and the circadian system is highly interconnected to stress-sensitive neurotransmitter systems such as the serotonin (5-hydroxytryptamine, 5-HT) system. Thus, here we propose that stress-induced perturbation of the 5-HT system disrupts circadian processes and increases susceptibility to depression. In this review, we first provide an overview of the basic components of the circadian system. Next, we discuss evidence that circadian dysfunction is associated with changes in mood in humans and rodent models. Finally, we provide evidence that 5-HT is a critical factor linking dysregulation of the circadian system and mood. Determining how these two systems interact may provide novel therapeutic targets for depression.

1. Introduction

The circadian and stress systems are complementary regulatory networks that are important for homeostasis. Life on Earth has evolved under a highly consistent light: dark (LD) cycle and as a result, most organisms have adopted an internal time keeping mechanism, which enables them to anticipate predictable events within the environment. The output of this system is daily (~24 h) rhythms in physiology and behavior that are synchronized with the light-dark cycle to optimize survival. In addition, organisms have adapted another system which allows them to either confront or escape unexpected homeostatic challenges, termed "stressors." The stress system is primarily comprised of the sympathetic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis (Helfrich-Forster, 2017). The stress response initiates complex changes that are highly adaptive under most circumstances, permitting organisms to recuperate from ongoing distress and even buffer against future adverse events (Packard et al., 2016). These two systems are critical for anticipating both predictable (circadian) and unpredictable (stress) environmental events.

The circadian and stress systems are highly interconnected. Under basal conditions, the stress system is under circadian control (Spencer and Deak, 2017), and is primed during the organism's active phase to optimize interactions with the environment (Spencer et al., 2018). For example, components of the stress system are increased during an organism's active phase to maintain vigilance and these stress signals decrease towards the end of the active phase to allow the organism to sleep/rest, and thereby restore depleted resources. Reciprocally, the stress system can feed back onto the circadian system and provide timing information to the rest of the body (Spencer et al., 2018).

Understanding the relationship between these two systems is of clinical importance because perturbation of either system is strongly implicated in the development of mood disorders [reviewed in (Bedrosian and Nelson, 2013; Helfrich-Forster, 2017)]. Major depressive disorder (MDD) is a debilitating psychiatric disorder affecting approximately 6% of the adult population worldwide (Otte et al., 2016). The World Health Organization (WHO) predicts that MDD will become the single greatest contributor to the global burden of disease by the year 2030 (WHO, 2017). MDD is associated with diminished quality of life (Hofmann et al., 2017) and increased risk for mortality (Gilman et al., 2017). MDD is characterized by recurrent episodes of anhedonia and depressed mood, as well as a subset of heterogeneous symptoms involving physiological, behavioral, and cognitive impairments (American Psychiatric Association, 2013). Stress is the greatest known risk factor in the etiology of MDD (Kendler et al., 1999); however, not all individuals who encounter seemingly similar traumatic life events go to develop MDD. Thus, other environmental factors and genetic risk are likely involved in regulating stress resistance and/or resilience.

Many of the symptoms of depression are related to dysregulation of

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the circadian system. For example, alterations in daily rhythms such as the sleep-wake cycle, body temperature, neurotransmitter and hormone levels, among others, are prevalent among depressed individuals (Bunney et al., 2015). Additionally, several human genetic studies have linked circadian genes to mood disorders including MDD (Buoli et al., 2018). Thus, considerable epidemiological evidence implicates circadian abnormalities in the pathophysiology and maintenance of depression. However, the link between the circadian system and depression is not fully understood.

In this review, we will present evidence that disruption of the circadian system can increase vulnerability to MDD. While significant circadian alterations are present in other mood disorders such as bipolar disorder and seasonal affective disorder [for review see (Logan and McClung, 2016) and (Wirz-Justice, 2018) respectively], here we will focus on non-seasonal unipolar depression (i.e. MDD) because impaired monoamine neurotransmission (i.e. serotonin, dopamine, and norepinephrine) is strongly linked to the pathophysiology and current treatment strategy for this disorder. In particular, the serotonin (5-hydroxytryptaime, 5-HT) system is reciprocally connected with the circadian system and regulates circadian function.

In order to understand how perturbations of the circadian system can have profound consequences for mood and mental health, we first provide an overview of the basic components of the circadian system (Section 2). Next, we discuss evidence showing that circadian dysfunction is prevalent among depressed individuals (Section 3). We also review preclinical studies, which show that various stressors can disrupt the circadian system and induce affective behavioral changes analogous to human depression (Section 4). Further, we summarize evidence that 5-HT is an important intermediate between stress-induced disruption of the circadian system and depression (Section 5). Finally, we conclude with discussion on alternative treatment approaches for MDD that target the circadian system (Section 6).

2. The circadian system

2.1. Circadian rhythms

The daily rotation of the Earth about its axis relative to a stationary light source, the Sun, provides a predictable cycle of alternating light and dark. In response, most organisms ranging from cyanobacteria to humans evolved an internal timekeeping mechanism. The output of this system is approximately 24 h oscillations in nearly all physiological processes and behaviors. The circadian system is highly adaptive: there is selection pressure against animals with non-24 h circadian clocks (Spoelstra et al., 2016). The circadian system allows organisms to anticipate day and night and thereby respond to stimuli in a proactive, rather than reflexive manner in order to anticipate food availability, mating opportunities, and time of peak predation (Vaze and Sharma, 2013). Thus, proper synchronization with the environmental LD cycle is essential for survival (Spoelstra et al., 2016). Disruption of the circadian system is associated with adverse health outcomes including cardiovascular disease, metabolic syndrome, obesity, cancer, as well as mood disorders [reviewed in (Bedrosian et al., 2016)].

In mammals, the circadian system has traditionally been described as consisting of three main components: (1) afferent synchronizing pathways which receive and transmit photic information to a central oscillator; (2) a central oscillator (or "master clock") responsible for generating circadian rhythms; and (3) efferent pathways which synchronize rhythms throughout the body (Hastings et al., 2018). It is now clear, however, that the circadian system is more complex than this simplified model. For example, while the SCN is somewhat buffered against behavioral feedback, it does receive afferent non-photic input. For example, Section 5.2 of this review discusses afferent serotonin input to the SCN. Moreover, efferent pathways synchronize rhythms throughout the body, but these peripheral oscillators also generate self-sustaining oscillations in the absence of SCN input (Tahara and Shibata, 2018).

Overall, there are criteria a biological rhythm must meet to be classified as circadian. First, the rhythm must have a period of approximately 24 h, which persists even in the absence of external time cues [e.g., persists in continuous darkness, DD; (Aschoff, 1965)]. Second, the rhythm must exhibit temperature compensation, meaning that, unlike most biochemical reactions, its periodicity is buffered against large fluctuations in ambient temperature (Reyes et al., 2008). Third, the rhythm resets (i.e. phase shifts) in response to external time cues within a specific range, a process referred to as entrainment (Aschoff, 1960).

2.2. The master clock

The bilateral suprachiasmatic nuclei (SCN) of the anterior hypothalamus comprise the primary oscillator for the circadian system. The SCN autonomously generates an intrinsic rhythm that is sustained even in the absence of photic information (Herzog et al., 2017). The SCN is also responsible for regulating rhythms in extra-SCN clocks present throughout the body. Lesion of the SCN abolish the expression of most circadian rhythms (Eastman et al., 1984; Moore and Eichler, 1972; Stephan and Zucker, 1972). The SCN is comprised of a relatively small number of neurons (approximately 8000–20,000 neurons in rodents and 50,000 in humans) (Lydic et al., 1980; Van den Pol, 1980; Lydic et al., 1982), the majority of which express the neurotransmitter gamma-aminobutyric acid [GABA; (Moore and Speh, 1993; Abrahamson and Moore, 2001)] and co-localize one or more neuropeptides. The two primary subdivisions of the SCN are the ventrolateral "core" region which is characterized by vasoactive intestinal polypeptide (VIP) immunoreactivity (Samson et al., 1979), and the dorsomedial "shell" region, which requires arginine vasopressin (AVP) signaling (Vandesande et al., 1975; Edwards et al., 2016). However, the neuropeptide distribution of the SCN is heterogeneous across species (Morin, 2013).

2.3. Molecular machinery of the master clock

Daily oscillations of core "clock" genes and proteins in the SCN are necessary to generate circadian rhythms. The master clock is driven by interlocked transcriptional-translational feedback loops, each of which is composed of a positive arm that behaves as the system activator and a negative arm that acts as the repressor. In the primary feedback loop, in mammals, brain and muscle arnt-like protein 1 (BMAL1), and circadian locomotor output cycles kaput (CLOCK) dimerize and bind to E-box cis-regulatory enhancer sequences (CACGTG) in the promoter region of target clock genes thus driving expression of period (*Per1*, *Per2*, and *Per3*) and cryptochrome (*Cry1* and *Cry2*) genes (van der Horst et al., 1999; Zheng et al., 2001). These proteins accumulate in the cytoplasm and upon reaching sufficient levels, translocate back into the nucleus to associate with the CLOCK-BMAL1 complex and thereby repress their own transcription (Kume et al., 1999). This entire process takes approximately 24 h to complete (Fig. 1). The timing of this feedback loop is fine-tuned by posttranslational modifications; clock proteins are subject to phosphorylation, ubiquitination, small ubiquitin-related modification, acetylation, as well as others (Gallego and Virshup, 2007; Duguay and Cermakian, 2009). For example, Per and Cry proteins can be phosphorylated by casein kinase δ1 and ε (CK1δ/ε), which tags them for degradation via ubiquitination or for translocation into the nucleus, respectively (Lee et al., 2001; Reppert and Weaver, 2002). Indeed, disruptions in CK1δ/ε function in SCN GABAergic neurons can lengthen the period of the SCN clock (van der Vinne et al., 2018). Overall, the molecular machinery of the master clock is highly complex, involving accessory transcriptional-translational feedback loops and regulatory proteins that influence the speed, precision, and function of the master clock [reviewed in (Partch et al., 2014)].

It is estimated that at least 10% of the mammalian transcriptome is

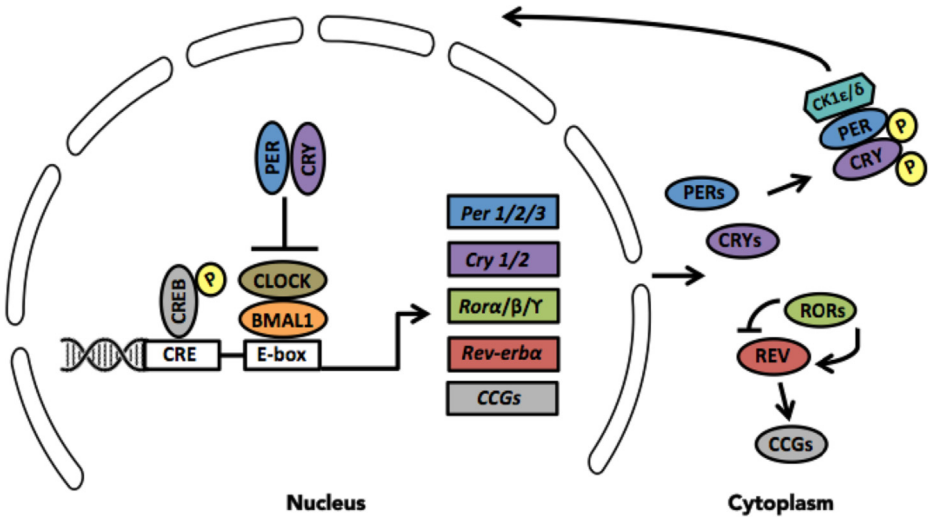

Fig. 1. Molecular machinery of the circadian clock. In mammals, the circadian clock is driven by a primary transcriptional-translational feedback loop, which is composed of a positive arm that acts as the system activator and a negative arm that acts as the system repressor. Brain muscle arnt like protein 1 (BMAL1) and circadian locomotor output cycles kaput (CLOCK) proteins form heterodimers, which bind to the E-box enhancer unit of three period (PER1/2/3) and two cryptochrome (CRY1/2) genes thereby driving their transcription. Over the course of the subjective day, PER and CRY proteins accumulate in the cytoplasm and upon reaching sufficient levels, dimerize and associate with CK1ε/δ, thereby phosphorylating them and allowing translocation back into the nucleus to inhibit BMAL1/CLOCK-mediated transcription. In a similar fashion, BMAL1/CLOCK activates some nuclear orphan receptor genes (e.g. *Rorα/Rorβ/*Rorϒ or Reverbα), which repress or activate *Bmal1* transcription, respectively to form an auxiliary feedback loop that stabilizes the primary loop. BMAL1/CLOCK can also activate a multitude of clock-controlled genes (CCGs).

under circadian control (Panda et al., 2002; Reddy et al., 2006) and possibly as high as 40% of transcripts cycle in some organ systems in the body (Zhang et al., 2014). Furthermore, a recent transcriptomic analysis in primate tissue revealed that 82% of genes coding for druggable targets show cyclic changes in transcription in at least one tissue (Mure et al., 2018). These rhythmic transcripts are almost entirely distinct across tissue types indicating that the role of extra-SCN clocks is unique, and might reflect tissue-specific functions. Oscillatory genes regulate diverse functions such as metabolism, transcription, translation, protein turnover, cell cycle, cell death, vesicle trafficking, transport, and signal transduction (Li and Zhang, 2015) emphasizing the importance of the circadian system in homeostasis.

2.4. Photic entrainment of the master clock

In the absence of time cues (i.e. constant dim light or darkness), the circadian system is 'free-running'. The period of the free-running circadian system is close to, but not exactly 24 h, and so, the master clock must reset every cycle in order to maintain synchronicity with the environment (Patton and Hastings, 2018). Light serves as the most potent entrainment factor (or zeitgeber, German for "time-giver") to the master clock. Light enters the inner retina and activates intrinsically photosensitive retinal ganglion cells (ipRGCs) that contain the photopigment melanopsin, which is primarily sensitive to blue wavelength light in the range of 470–480 nm (Gooley et al., 2001; Berson et al., 2002; Hattar et al., 2002; Bailes and Lucas, 2013). The SCN receives non-image forming information from rods, cones, and ipRGCs; however, all photic information is transmitted through ipRGCs (Freedman et al., 1999; Panda et al., 2002; Guler et al., 2008). Excitation of ipRGCs is relayed to the ventrolateral portion of the SCN via the retinohypothalamic tract through direct and indirect projections (Moore, 1973; Levine et al., 1991). The electrical signal is then converted to a chemical signal. Glutamate (Castel et al., 1993) and/or pituitary adenylate cyclase-activating polypeptide (Hannibal et al., 2000) are released directly onto SCN neurons to initiate calcium-dependent second messenger signaling (O'Neill and Reddy, 2012). This results in binding of phosphorylated cyclic adenosine monophosphase (cAMP) response element binding protein to cAMP-response elements on the promoter region of the Per1 gene, thereby inducing Per1 expression [Fig. 2; (Albrecht et al., 1997)]. In SCN neurons, Per1 expression is high during the middle of the subjective day and declines to reach its nadir in the subjective night, in anti-phase with Bmal1 expression. During the

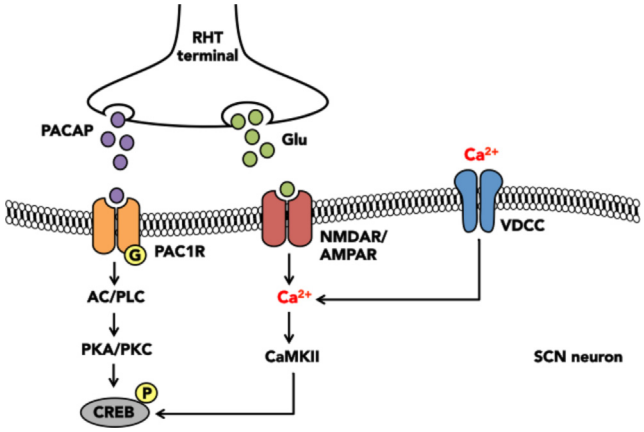

Fig. 2. Photic entrainment of the master clock. Photic information received by the retina is relayed to the suprachiasmatic nucleus (SCN) via the retinohypothalamic tract (RHT). RHT axon terminals release excitatory molecules such as pituitary adenylate cyclase-activating peptide (PACAP) and/or glutamate (glu) onto ventrolateral SCN neurons. PACAP then binds to the G-coupled PAC type 1 receptor (PAC1R) and glutamate binds to N-methyl-d-aspartate receptor (NMDAR) on the post-synaptic cell. Activation of these receptors initiate distinct signaling second messenger signaling cascades, which ultimately result in phosphorylation of the transcription factor cyclic-AMP response element binding protein (CREB) in the promotor region of the Per gene.

subjective day, Per1 expression is maximal so light has little to no effect on the master clock. However, during the subjective night, Per1 expression is minimal, and photic information can produce phase shifts of the master clock (Miyake et al., 2000; Schwartz et al., 2011). Thus, photic sensitivity of the master clock is circadian gated, meaning that the response to light varies across the LD cycle and responses to light can vary. Other factors such as light intensity and duration can influence the phase shifting capacity of a light pulse (Sharma et al., 1999; Comas et al., 2008; Dewan et al., 2011).

2.5. Extra-SCN clocks

In mammals, circadian clocks exist in virtually every cell type within the body (Mure et al., 2018). Moreover, these extra-SCN clocks appear to possess the same molecular machinery as does the master clock (Yagita et al., 2001). Cells isolated from the liver, lung, skeletal

muscle, etc. continue to oscillate *in vitro*, but dampen after a few cycles, whereas cells isolated from the SCN can oscillate presumably indefinitely (Yamazaki et al., 2000). Because most cells are not retinorecipient, they are not directly entrained by photic signals. Rather, extra-SCN clocks can be entrained by photic information that is indirectly conveyed via SCN-mediated relay pathways. For example, the master clock relays timing information to extra-SCN clocks via neuronal projections and through the coordinated release of various neuropeptides and hormones [see below; (Buijs and Kalsbeek, 2001; Dibner et al., 2010)]. Extra-SCN clocks can also respond to non-photic zeitgebers that provide salient tissue specific information. For example, extra-SCN clocks can respond directly and robustly to cyclic non-photic stimuli such as feeding behavior, social interaction, exercise, and stress independently of the SCN [for review see (Tahara and Shibata, 2018)].

SCN efferent projections are relatively sparse and most notably project to hypothalamic regions involved in hormone synthesis and secretion, including the paraventricular nucleus (PVN), the subparaventricular zone, and the dorsomedial hypothalamic nucleus (Morin, 2013), Rhythms generated by extra-SCN clocks in the periphery lag behind that of the SCN and vary in a tissue-specific manner (Yamazaki et al., 2000; Abe et al., 2002; Chun et al., 2015), supporting the idea that the master clock synchronizes these rhythms.

2.6. Glucocorticoid-dependent entrainment of extra-SCN clocks

Entrainment of some extra-SCN clocks depends on glucocorticoids (CORT; primarily cortisol in humans, corticosterone in rodents) (Balsalobre et al., 2000). CORT is the primary (systemic) effector hormone of the HPA axis and is critically involved in the stress response (Spencer-Segal and Akil, 2018). During stress, corticotropin-releasing factor (CRF) is released from neurons in the paraventricular nucleus (PVN) of the hypothalamus into the hypophyseal portal system where it stimulates release of adrenocorticotropic hormone (ACTH) into the circulation. ACTH then initiates release of glucocorticoids from the adrenal gland. Glucocorticoids can feedback and inhibit the HPA axis at the level of the PVN and anterior pituitary. Under basal conditions, CORT exhibits a diurnal pattern of secretion with peak levels coinciding with the onset of active phase in vertebrate species (Spencer and Deak, 2017). The SCN is necessary for generation of CORT rhythmicity (Moore and Eichler, 1972). As mentioned earlier, the SCN projects to the PVN, and so the master clock can regulate CORT at this level or independently of the HPA axis, via splanchnic nerve innervation of the adrenal glands (Buijs and Kalsbeek, 2001), the site of CORT synthesis.

As a steroid hormone, CORT can readily pass through phospholipid membranes to bind its receptor and influence transcription of circadian-related genes. Intracellularly, CORT binds to cytosolic glucocorticoid receptors (GRs), allowing translocation of the CORT-GR complex into the nucleus where it can act as a transcription factor at glucocorticoid response elements (GREs). Core clock genes Per1 and Per2 contain GREs in their promoter regions (Yamamoto et al., 2004; Reddy et al., 2007; So et al., 2009; Cheon et al., 2013). Administration of CORT or GR agonists to tissue explants *ex vivo* acutely increases gene expression of some core clock genes (Balsalobre et al., 2000; Reddy et al., 2007; So et al., 2009). Furthermore, removal of endogenous CORT via adrenalectomy produces arrhythmic or phase-shifted clock gene expression in some extra-SCN clocks (Amir et al., 2004; Woodruff et al., 2016), an effect that can be restored with in-phase CORT replacement (Woodruff et al., 2016). GRs are ubiquitously expressed in most tissues (De Kloet et al., 1998), with the SCN as a notable exception (Rosenfeld et al., 1988). This suggests that the SCN is largely insensitive to glucocorticoids but that CORT may serve as an entrainment factor for some extra-SCN clocks.

3. The circadian system and mood

3.1. Circadian variation in mood and depressive symptomatology

Mood exhibits daily fluctuations in healthy individuals. Mood is typically dissociated into two separate dimensions, positive and negative affect. A recent study evaluating over 800 million Twitter messages revealed a sharp morning peak in words associated with positive affect and a late evening peak in words associated with sadness and anger (Dzogang et al., 2017). This study supports previous results indicating that positive and negative affect fluctuate independently across the 24 h cycle (Golder and Macy, 2011; Peeters et al., 2006). Interestingly, diurnal variation in negative affect appears to be more stable whereas rhythms in positive affect vary across the week and season (Golder and Macy, 2011).

Diurnal variation in mood is altered in a subset of depressed individuals. Not surprisingly, depressed individuals report overall lower levels of positive affect (i.e. anhedonia), with peak values occurring later in the day compared to healthy controls (Peeters et al., 2006). However, negative affect exhibits a robust circadian rhythm with more moment-to-moment variability. Furthermore, in depressed individuals, peak negative affect occurs in the late morning and steadily declines throughout the day (Peeters et al., 2006). Diurnal variation of symptom severity was also reported in roughly 22% of depressed patients enrolled in the Sequenced Treatment Alternatives to Relieve Depression (STAR-D) study (Morris et al., 2007). Of these, 32% experienced worsening of symptoms in the morning, 20% in the afternoon, and 49% in the evening (Morris et al., 2007). Overall, there is inter-study variability in timing of peak negative and positive affect. For example, the STAR-D study reported a higher percentage of individuals with worsening of symptoms in the evening which contrasts with the earlier study by Peeters et al. It is possible that methodological differences, such as tools for assessing mood and the study populations, may account for some of this variability. It should also be noted that none of the aforementioned studies utilized an experimental design that permits unmasking of endogenous circadian rhythms (e.g. constant routine or forced desynchrony protocols), and so the timing of these rhythms are likely impacted by several exogenous factors.

Diurnal variation in mood can be influenced by an individual's chronotype, which describes an individual's biological predisposition for morning, afternoon, or evening activities (Roenneberg et al., 2007). Chronotype is considered to be a relatively stable trait that varies across developmental periods. Interestingly, depressed individuals with a late chronotype (i.e. evening preference) are more likely to experience worsening of symptoms in the morning (Antypa et al., 2017), more frequent and severe depressive episodes (Hasler et al., 2010; Hidalgo et al., 2009 Kim et al., 2010; Kitamura et al., 2010; Au and Reece, 2017), reduced responsiveness to antidepressants (McGlashan et al., 2018), as well as greater suicidality (Bahk et al., 2014). These findings indicate that a subset of depressed individuals exhibit an altered circadian rhythm of mood. Furthermore, non-depressed individuals with an early chronotype score higher on self-report measures of psychological resilience than do late chronotypes (Jeon et al., 2017), suggesting that circadian factors may contribute to susceptibility to mood disorders.

3.2. Circadian rhythms are disrupted in depression

In addition to rhythms in mood, various other circadian rhythms are disrupted in depression. For example, changes in the sleep-activity cycle are common in depression. One main diagnostic criterion for MDD is insomnia or hypersomnia (American Psychiatric Association, 2013), and up to 90% of depressed individuals experience other sleep-wake cycle disturbances including poor sleep quality, increased rapid-eye movement (REM; or paradoxical) sleep, and early morning awakening (Murphy and Peterson, 2015). Sleep disturbances are associated

with an increased risk of suicide (Bernert et al., 2015), highlighting the importance of treating sleep in depressed patients. Furthermore, a large scale (91,105 participants) study measuring activity levels by a wrist-worn accelerometer, reported that reductions in the amplitude of activity rhythms are associated with increased risk of MDD and bipolar disorder, greater mood instability, higher neuroticism, more subjective loneliness, lower happiness, and lower health satisfaction (Lyall et al, 2018).

Another common circadian rhythm abnormality involves the HPA axis. In healthy individuals, maximal CORT secretion occurs in the morning prior to waking, and progressively declines across the day (Spencer and Deak, 2017). Depressed individuals, however, often exhibit a 2–3 h phase advance of the morning CORT peak and elevated levels across the day (Koenigsberg et al., 2004 Linkowski et al., 1994). Elevated CORT concentrations can also present as a flattened amplitude of the diurnal cortisol rhythm in depressed individuals and impaired suppression of cortisol following dexamethasone administration (Jarcho et al., 2013). Importantly, flattened cortisol rhythms or elevated CORT concentrations can persist in individuals in remission from MDD (Doane et al., 2013) and may leave individuals susceptible to subsequent episodes of depression.

Many other physiological circadian rhythms are altered in MDD including melatonin, norepinephrine, thyroid stimulating hormone, blood pressure, and pulse [reviewed in (McClung, 2007)]. Furthermore, the degree of circadian misalignment is positively correlated with symptom severity (Emens et al., 2009). Global changes in gene expression rhythms may underlie the disruptions in circadian rhythms in physiology and behavior in patients with MDD. Rhythms in human gene expression were determined in six major cortical and limbic brain regions based on time-of-death from patients with or without a history of MDD. Several hundred transcripts in each region showed 24-h cyclic patterns in controls (including a number of canonical clock genes). Cyclic patterns were, however, much weaker in the brains of patients with MDD (Li et al., 2013).

The observation that so many diverse rhythms are altered in MDD suggests that such disturbances may not be unique to one rhythm but may instead have a central origin (i.e. dysfunction of the master clock itself) and/or an alteration in a key extra-SCN entrainment factor (e.g. glucocorticoids or time of food intake). It remains unclear whether these disturbances induce MDD or are simply symptomatic of MDD. However, in rodents, alterations in circadian entrainment can precede the onset of depression-like behavior suggesting that circadian alterations may be causal and/or predictive of the onset of depression (Spulber et al., 2015).

3.3. Circadian disruption impacts mood

Given the common occurrence of rhythm disturbance in MDD, it is not surprising that environmental perturbations can produce alterations in mood. This section will highlight evidence from humans and animal models linking circadian disruption to changes in negative affect.

3.3.1. Epidemiological evidence

3.3.1.1. Jet lag. Air travel across multiple time zones can produce a transient period of circadian misalignment (termed “jet lag”) in which internal time is not synchronized with the new environmental LD cycle (Sack, 2010). Similarly, “social” jet lag occurs when an individual shifts schedules to align the timing of their sleep-wake cycle with social obligations (most commonly by using an alarm clock on workdays) (Foster et al., 2013). Jet lag is characterized by a constellation of symptoms including: fatigue, irritability, gastrointestinal issues, reduced mental and physical acuity, and poor mood (Arendt, 2018). The circadian clock likely resets more rapidly following travel in the Westward direction (i.e. phase delay) compared to travel in the Eastward direction (i.e. phase advance) because the phase response curve to light is asymmetrical such that the delay zone is larger than the advance zone (Hilaire et al., 2012; Minors et al, 1991). Furthermore, the endogenous period of the human circadian clock is slightly longer than 24 h (Czeisler, 1999) and this may also contribute to speed of re-entrainment, albeit to a lesser degree. A number of other factors can also influence the severity of jet lag symptoms, including: the number of time zones crossed, ability to sleep during travel, availability and intensity of local circadian time cues, as well as coping ability (Sack, 2010). There is some evidence that long-haul flights can precipitate depressive episodes in individuals with a history of mental illness (Jauhar and Weller, 1982; Katz et al., 2002; Young, 1995). This finding suggests that the circadian misalignment induced by a rapid phase shift can trigger a depressive episode in individuals predisposed to alterations in mood. Furthermore, chronic jet lag, as experienced by flight attendants and crew, produces temporal lobe atrophy and cognitive deficits (Cho, 2001). Interestingly, the degree of cognitive impairment is positively correlated with salivary CORT concentrations (Cho, 2001). Altered CORT patterns have also been observed following acute jet lag (Doane et al., 2010). Interestingly, glucocorticoids modulate the resetting kinetics after abrupt shifts in the LD cycle in rodents (Kiessling et al., 2010; Mohawk et al., 2005), suggesting that changes in CORT may serve as a compensatory mechanism during jet lag recovery.

3.3.1.2. Shift work. Approximately one fifth of the U.S. labor force engages in evening or rotating shift work (McMenamin, 2007). The symptoms of shift work are similar to jet lag, but the overall impact on health is more severe because shift workers are typically unable to synchronize with their new LD cycle due to frequent work schedule changes and shifted sleep-wake patterns on non-work days (Rajaratnam and Arendt, 2001). Shift workers report poor mood and exhibit an increased risk for development of MDD (Angerer et al., 2017; Asaoka et al., 2013; Dumont and Beaulieu, 2007; Scott et al., 1997). Furthermore, duration of shift work history is positively correlated with severity of depressive symptoms (Lee et al., 2017). Even student nurses who work a single evening shift, experience alterations in mood (Healy et al., 1993). There are multiple factors associated with shift work that could produce affective changes including: exposure to light at night, mistimed meals, and sleep loss.

3.3.2. Evidence from animal models

The epidemiological evidence presented above indicates that the circadian system and mood are linked. In parallel, mounting preclinical research indicates that environmental perturbations of the circadian system can lead to depressed mood. For instance, exposing animals to aberrant lighting environments misaligns internal biological processes from the external environment, and can lead to affective behavioral changes.

An extreme example of this involves experiments that use continuous exposure to light (constant light). Unlike constant darkness or constant dim light, which reveal the free running circadian cycle in rodents, exposure to constant light can desynchronize mammalian clock neurons resulting in arrhythmicity (Ohta et al., 2005; Fonken et al., 2010; Tapia-Osorio et al., 2013). Constant light increases depressive-like behaviors in adult mice and rats (Fonken et al., 2009; Tapia-Osorio et al., 2013) and has a lasting impact on mood related behaviors when mice are exposed during early life (Coleman et al., 2016).

Less extreme disruptions of the environmental light cycle can also have important implications for mood related behaviors. Rodents exposed to dim light during the dark phase (12:12 light:dim cycle) maintain circadian rhythms in activity (Fonken et al., 2010; Fonken et al., 2012; Bedrosian et al., 2013a) but show blunted rhythms in clock gene expression in the SCN and periphery (Bedrosian et al., 2013a; Fonken et al., 2013). Additionally, exposure to dim light during the dark phase increases depressive-like behaviors in several rodent models (Bedrosian et al., 2011; Fonken et al., 2012; Bedrosian et al., 2013b; Fonken and Nelson, 2013) although the effects of dim light at night may

be strain specific (Martynhak et al., 2017; Cleary-Gaffney and Coogan, 2018). Interestingly, decreasing the level of daytime illumination that rodents are exposed to can also affect components of the HPA axis and lead to changes in mood related behaviors (Ikeno et al., 2016).

Studies using non-24 h light cycles also support a role for circadian disruption impacting mood and cognitive behaviors. Mice housed in a shortened light cycle (10:10 light:dark) exhibit metabolic changes, impaired cognition, and decreased neuronal complexity compared to mice housed on a 24 h LD cycle (Karatsoreos et al., 2011). Furthermore, exposure to a T7 light cycle (3.5 h light:3.5 h dark) increases depressive-like behaviors in mice, which are reversible with administration of the antidepressant drugs fluoxetine or desipramine (LeGates et al., 2012).

Other models of circadian disruption involve repeated phase shifts of the LD cycle to mimic chronic jet lag or shift work schedules. For example, rats subjected to 4 weekly 6 h phase advances of the LD cycle exhibit impaired escape learning (i.e. learned helplessness), and this deficit is not prevented by behavioral control, a robust stress-protective factor (Daut et al., 2019). Taken together, these studies highlight the importance of light rhythms and intensity, and challenges to the circadian system in regulating behavior. Disrupting the alignment between endogenous biological rhythms and the external lighting environment can have profound consequences for mood.

3.4. Clock genes in depression

3.4.1. Epidemiological evidence

Genetic factors undoubtedly play a role in the onset of MDD as the heritability estimate ranges from 31 to 42% (Flint & Kendler, 2014). Human genetic studies have identified several variants or single nucleotide polymorphisms (SNPS) in clock genes and their modifiers that are linked to mood disorders. SNPs in the *Cry1*, *Npas2* (Soria et al., 2010), and *Cry2* (Kovanen et al., 2017) genes are strongly associated with MDD. Additionally, individuals with a history of depression exhibit higher expression of *Clock*, *Per1*, and *Bmal1* mRNA levels compared to healthy controls as measured in peripheral blood leukocytes in the morning (Gouin et al., 2010). Furthermore, a SNP in the 3′-flanking region of *Clock* is correlated with sleep profiles, sleep-wake cycle, and depressive episode relapse (Benedetti et al., 2003; Benedetti et al., 2007). Interestingly, some clock gene variants (*Clock*, *Per3*, and *Npas2)* are sex-dependently associated with MDD (Shi et al., 2016). This finding has clinical relevance because MDD prevalence is 2–3 times greater in females than males (Albert, 2015), and there is pre-clinical evidence that aspects of the circadian system are sexually dimorphic (Bailey & Silver, 2014; Chun et al., 2015; Mahoney et al., 2009). Furthermore, several clock genes exhibit weaker cyclic expression patterns in mood-related brain regions in postmortem tissue of depressed individuals compared to non-depressed controls (Li et al., 2013); rhythms were also phase shifted and desynchronized from external time in depressed individuals (Li et al., 2013). Additionally, SNPs in *Clock* predict response to SSRIs (Kishi et al., 2009). Thus, it appears that variation in clock genes and their promoters may predispose individuals to develop MDD (Desan et al., 2000).

3.4.2. Evidence from animal models

Direct manipulation of the molecular circadian clock in mice provides further support for a role of the circadian system in mood disorders. Roybal et al. (2007) were the first to report that a global mutation in the *Clock* gene produces manic-like behaviors in mice including hyperactivity, decreased sleep, reduced anxiety, and increased reward valence (Roybal et al., 2007). Subsequent work revealed that global mutations in other clock genes including *Per3* (Zhang et al., 2016a; Martynhak et al., 2017), *Cry1* (Schnell et al., 2015), and *Arntl* (BMAL1-coding gene) (Leliavski et al., 2014), alter anxiety and depressive-like responses. Importantly, clock genes act as transcription factors for a number of gene products throughout the lifespan so it is unclear from these types of global clock mutant manipulations if changes in behavior are caused by ongoing disruptions to the circadian system. More targeted mutations of clock genes, however, support a role for disruption of the circadian clock in mood. For example, challenging the circadian system with an SCN-specific knockdown of BMAL1 disrupts circadian rhythms in the SCN and increases depressive-like behavior. BMAL1-knockdown mice showed increases in learned helplessness in the forced swim and tail suspension tests as well as a reduction in sucrose preference (Landgraf et al., 2016). BMAL1-knockdown was also associated with an altered diurnal CORT rhythm and suppressed CORT release in response to stress (Landgraf et al., 2016). Furthermore, knockdown of both Per1 and Per2 in the nucleus accumbens with RNA interference increases anxiety-like responses in mice (Spencer et al., 2013).

3.5. Circadian based treatments of depression

The potential circadian basis for mood disorders is further supported by evidence that circadian strategies can alleviate depressive symptomatology.

3.5.1. Sleep deprivation therapy

One night of total sleep deprivation produces a rapid improvement in mood that persists for up to 36 h in 40–60% of depressed patients (Giedke & Schwarzler, 2002; Wirz-Justice & Van den Hoofdakker, 1999). Partial sleep deprivation (restricted to the second half of the night) is also effective, although not to the same degree (Wirz-Justice et al., 2005). In healthy control subjects, sleep deprivation increases fatigue and irritability with little to no effect on mood (Wirz-Justice, 2008). Importantly, the clinical utility of this treatment is limited because patients typically relapse following sleep recovery. The antidepressant effect of sleep deprivation may be mediated by non-circadian mechanisms. For example, acute sleep deprivation increases plasma cortisol levels, especially during the trough of the CORT rhythm, whereas chronic sleep deprivation reduces overall CORT (Wright et al., 2015). Therefore, sleep deprivation may act as an acute stressor by increasing arousal hormones until sleep homeostasis is restored (McEwen, 2006). This may explain the transient nature of sleep deprivation's antidepressant effect.

3.5.2. Bright light therapy

Bright light therapy was originally developed to treat seasonal affective disorder (SAD), a mood disorder associated with reduced light exposure during short photoperiod months. More recently, bright light therapy has shown clinical promise in treating non-seasonal depression. Standard bright light therapy involves exposing patients to a light box (10,000 lx) for 30–90 min, typically in the morning shortly after waking (Terman and Terman, 2005). A meta-analysis by Golden et al. (2005) revealed that the effect size produced by bright light therapy is similar to those reported in clinical trials for pharmacological antidepressants. Repeated daily bright light therapy produces a 1 h phase advance in body temperature rhythms in depressed patients (Burgess et al., 2004). Blue light may be more effective than other wavelengths of light in phase shifting circadian rhythms and producing antidepressant effects (Glickman et al., 2006) because human melanopsin-containing ipRGCs are most strongly stimulated by blue light (~480 nm) and minimally influenced by red light (> 600 nm) (Brainard et al., 2001). Furthermore, bright light therapy co-administered with antidepressants is significantly more effective than either treatment alone (Benedetti et al., 2003a, 2003b; Lam et al., 2016). This suggests that circadian based therapies and 5-HTergic drugs have synergistic effects on mood disorders.

3.5.3. Agomelatine

Agomelatine is a potent melatonin receptor (MT_1 and MT_2) agonist and 5-HT_{2C} receptor antagonist that has antidepressant properties in both humans and animal models of depression (Kennedy and Emsley,

2006; Loo et al., 2002; Papp et al., 2003) with comparable efficacy to other antidepressant drugs (Lemoine et al., 2007 Loo et al., 2002). Agomelatine does improve aspects of sleep, but it is especially effective in treating circadian rhythm disruption in depression. In particular, agomelatine accelerates resynchronization of circadian rhythms following abrupt shifts of the LD cycle in both humans and rodents (Weibel et al., 2000). Interestingly, melatonin administration during the day produces dysphoria and worsens depressive symptoms indicating that melatonin itself does not have antidepressant properties (Carman et al., 1976). This suggests that the antidepressant effects of agomelatine may be due, in part, to action at the 5-HT_{2C} receptor (see below for further details).

4. Stress and the circadian system

As noted above, the circadian and stress systems are complementary regulatory networks that prepare organisms for both predictable (circadian) and unpredictable (stressors) daily challenges; these systems work to restore homeostasis in response to a continuously changing external environment. Importantly, the stress and circadian systems are also highly interrelated. For example, circulating glucocorticoid concentrations exhibit robust regulation by the circadian system and are a primary output of the stress response (via activation of the HPA axis) [reviewed in (Oster et al., 2017)]. Here we will review research on crosstalk between the circadian system and stress.

4.1. Stress disrupts the circadian system

The "social zeitgeber theory of depression" proposes that stressors disrupt the circadian system and precipitate depressive episodes in vulnerable individuals (Grandin et al., 2006). The occurrence of significant life events (e.g. retirement, bereavement, birth of a child, shift work) can impact daily habits which normally serve as auxiliary entrainment factors for the circadian system, and thereby disrupt circadian rhythms including mood (Luan et al., 2011). Bipolar subjects report fewer daily activities than healthy controls and the degree of social rhythm irregularity is predictive of depressive and manic episodes (Shen et al., 2008). Thus, disruption of the circadian system may not only be an epiphenomenon but may actually play a causal role in the development of mood disorders.

In rodents, exposure to an acute traumatic stressor or chronic mild stress elicits a variety of behavioral changes analogous to human depression including reductions in locomotion, exploration, social interaction, sexual motivation, as well as food and water consumption [reviewed in (Maier et al., 2006; Willner, 2005)]. Furthermore, many acute and chronic stress paradigms induce circadian abnormalities. For example, chronic variable stress induces brain region-specific alterations in circadian clock gene rhythms that directly correlate with mood related behaviors (Logan et al., 2015). Furthermore, mice subjected to a chronic social defeat protocol exhibit marked changes in body temperature and locomotor activity rhythms (Krishnan et al., 2007). Interestingly, a subset of resilient mice that do not develop a depression-like phenotype following stress also do not exhibit the same circadian changes as the susceptible mice (Krishnan et al., 2007). In contrast, perceived behavioral control over a stressor produces stress resilience/resistance in rats, but does not protect against stress-induced changes in diurnal rhythms. Both controllable and uncontrollable stressors altered locomotor activity and core body temperature diurnal rhythms to the same extent in rats (Thompson et al., 2013)

Stress-induced changes in circadian rhythms are concomitant with disruptions of clock genes. Animal studies utilizing acute stress paradigms consistently report a rapid (30–60 min) stress-induced increase of *Per1* mRNA in extra-SCN clocks in the brain and periphery, but not the master clock itself (Takahashi et al., 2001). As stated above, the SCN lacks GRs (Balsalobre et al., 2000), and so stress-induced glucocorticoids can impact extra-SCN clocks but leave the master clock relatively unperturbed. Stress can, however, increase *Per1* expression in a CORT-independent manner (Al-Safadi et al., 2015; Bohacek et al., 2015; Chun et al., 2018). This suggests that a different stress-induced signal is likely responsible for driving *Per1* expression in extra-SCN clocks. Furthermore, the *Per1* gene also contains a functional cAMP response element (CRE) (Tischkau et al., 2003). Thus, *Per1* may act as an immediate early gene during stress (Spencer et al., 2018).

Studies using *predictable* chronic mild stress paradigms show that chronic stress can serve as an entrainment factor for extra-SCN clocks. For example, rats exposed to several days of restraint or social defeat stress exhibit phase shifted *Per2* rhythms in extra-SCN clocks (Tahara et al., 2015). Furthermore, the time of day during which stress occurred determined the direction of the shift (Tahara et al., 2015). Thus, the entraining ability of stress may be an adaptive feature of the circadian system to anticipate and buffer against recurring challenges. In contrast, studies using *unpredictable* chronic stressors have a more disruptive effect and can even alter clock genes in the SCN (Jiang et al., 2011; Logan et al., 2015).

4.2. Circadian variation in stress susceptibility

In addition to stress altering the circadian system, there is evidence that the circadian system regulates the stress response and stress-induced comorbidities. For example, the time of day during which a stressor is encountered can potently modulate its outcome (Fonken et al., 2016; Johnson et al., 2003). For example, prior stress can increase vulnerability to inflammatory challenges (Fonken et al., 2018). However, the timing of the stressor is critical for regulating the subsequent response to immune challenge: rats exposed to inescapable tail shock stress during the middle of their inactive (light) phase exhibited an exaggerated immune response, whereas rodents exposed to stress during their active (dark) phase, did not (Fonken et al., 2016). Furthermore, rats exposed to stressors during their inactive phase develop an anxiety- and depressive-like phenotype, whereas rodents stressed during the beginning of the active phase, do not (Aslani et al., 2014; Cohen et al., 2015; Fonken et al., 2016; Retana-Márquez et al., 2003; Rybkin et al., 1997). Taken together, these findings suggest that organisms may be more resistant/resilient to stressors during their active phase. This may be an adaptive mechanism whereby an organism upregulates processes that permit stressor recovery and adaptation during the time of day that it is more likely to encounter a homeostatic threat.

5. Interactions between the circadian system, the serotonin system, and stress

The evidence presented in this review thus far supports a role for the circadian system in regulating mood and vulnerability to depression. However, the mechanism(s) by which the circadian system targets these complex behavioral processes remains unclear. Here we propose that the 5-HT system may serve as the common link between the circadian system, stress, and mood.

One potential mechanism by which stressors might directly impact the circadian system is by way of the 5-HT system. There is bi-directional communication between 5-HT and the circadian system. 5-HT plays a role in producing non-photic phase shifts (Mistlberger et al., 2000) and also opposes the action of light in the SCN (Rea & Pickard, 2000). Conversely, the 5-HT system is under circadian control. The synthesis of 5-HT is driven by the daily rhythmic secretion of glucocorticoids (Malek et al., 2005; Malek et al., 2007), resulting in rhythmic 5-HT release within the SCN (Cagampang and Inouye, 1994) and other limbic projection regions. During exposure to certain types of stressors, 5-HT neurons are under afferent control of stress-responsive brain regions (Chaouloff, 2000). In turn, 5-HT neurons project to regions involved in the regulation of mood (Lowry et al., 2008) as well as the ventrolateral SCN. Thus, altered 5-HT signaling may play a role in circadian dysfunction in MDD. Congruent with this hypothesis,

commonly prescribed antidepressants, which increase synaptic 5-HT levels, alter circadian rhythms and clock gene expression (see below).

5.1. The serotonin system

In addition to its role in the circadian system, 5-HT is implicated in a diverse array of physiological processes and behaviors including: the sleep-wake cycle, cardiovascular functions, respiration, thermoregulation, appetite, aggression, sexual behavior, pain, and learning [Reviewed in (Lesch and Waider, 2012)}. The 5-HT system is considered the most architecturally complex and extensive neurotransmitter system in the mammalian central nervous system (Hainer et al., 2015). 5-HT projections are highly collateralized (Waselus et al., 2011): it is estimated that each 5-HT neuron targets at least 500,000 other neurons in the brain (Jacobs and Azmitia, 1992), implicating 5-HT as a modulatory neurotransmitter.

Not all types of stressors produce identical neural activation patterns. "The midbrain raphe nuclei (comprised of the dorsal and median raphe nuclei, DRN and MRN, respectively) are responsive to various types of physical (e.g. forced swim), psychological (e.g. inescapable tailshock, social defeat, immobilization), and metabolic (e.g. hypoglycemia) stressors [reviewed in (Hale et al., 2012)]. The midbrain raphe nuclei are well positioned to modulate fear and anxiety as they innervate many points in the limbic circuit (Graeff et al., 1996). For example, distinct DRN targets include the prefrontal cortex, lateral septum, and amygdala, whereas MRN targets include the medial septum, cingulate, and dorsal hippocampus (Azmitia and Segal, 1978). Moreover, the midbrain raphe nuclei are under afferent control of stress-responsive nuclei. The DRN is the largest 5-HTergic nucleus, containing approximately 50% of all 5-HT synthesizing neurons in the brain (approximately 15,000 neurons in the rat) (Vertes and Crane, 1997). 5-HT signaling is regulated by 17 receptors, the majority of which are G-coupled receptors (Yohn et al., 2017). Dysfunction of the 5-HT system has been implicated in the etiology of MDD since the 1950s (Loomer et al., 1957)."

5.2. Serotonergic regulation of the master clock

A major afferent projection to the SCN originates from the midbrain raphe complex; in hamsters, primarily from the median raphe nucleus [MRN; (Meyer-Bernstein and Morin, 1996; Leander et al., 1998; Yamakawa and Antle, 2010)] and in rats, from both the MRN and DRN [Fig. 3; (Kawano et al., 1996; Moga and Moore, 1997;). In fact, this is

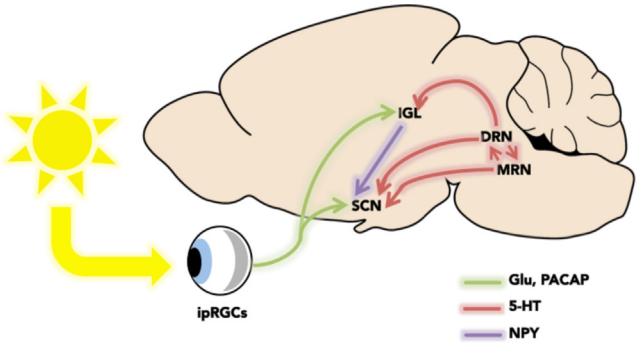

Fig. 3. Neural circuitry of the circadian system. Photic information enters the retina and stimulates melanopsin-containing intrinsically photosensitive retinal ganglion cells (ipRGCs). Photic information is directly relayed to the suprachiasmatic nucleus (SCN) and intergeniculate leaflet (IGL) via the retinohypothalamic tract (RHT), a glutamatergic and/or pituitary adenylate cyclase-activating peptide (PACAP) pathway. The SCN also receives non-photic information from an NPY-ergic pathway from the as well as from a 5-HTergic pathway from the dorsal raphe and median raphe nuclei (DRN and MRN, respectively).

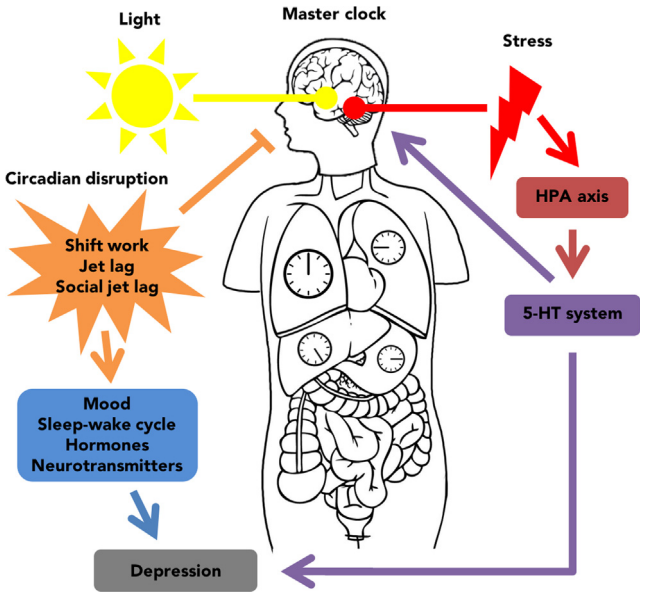

Fig. 4. Schematic summarizing the relationship between the circadian system and stress systems in the regulation of mood. The master clock of the circadian system is entrained by light and synchronizes extra-SCN and peripheral clocks using neural and humoral signals. Circadian disruption can dysregulate the master clock resulting in altered circadian rhythms and increased vulnerability to depression. Stress is a risk factor for depression and can impact the 5-HT system. The 5-HT system and the master clock are reciprocally connected and so circadian disruption may exacerbate depressive symptoms through 5-HT innervation of mood-related brain regions.

one of the densest 5-HT-ergic plexuses in the brain (Beaudet and Descarries, 1979; Bolser and Beaudet, 1985), so it follows that 5-HT is likely critical for circadian function. For example, developmental loss of Pet-1, a transcription factor that determines 5-HT neuron phenotype, disrupts locomotor activity rhythms and lengthens the period and amplitude of SCN neuronal activity *ex vivo* (Ciarleglio et al., 2011).

The circadian role of 5-HT differs across the LD cycle. During the subjective day, 5-HT produces non-photic phase shifts (Mistlberger et al., 2000). For example, application of selective 5-HT receptor agonists during the middle of the light phase shifts SCN activity by approximately 3 h (Lovenberg et al., 1993; Sprouse et al., 2004). While during the subjective night, 5-HT opposes the action of light. 5-HT acts both pre-synaptically on 5-HT terminals and post-synaptically on SCN VIP neurons to inhibit the effect of light on the SCN (Ciarleglio et al., 2011). Furthermore, manipulation of brain 5-HT levels significantly alters endocrine and behavioral circadian rhythms (Smale et al., 1990; Morin and Blanchard, 1991; Whitney et al., 2016).

5.3. Circadian regulation of serotonin

5-HT varies across the LD cycle. 5-HT is highest during the active phase in both nocturnal and diurnal rodents (Challet, 2007). This rhythm persists in constant conditions indicating that this rhythm is endogenously generated. Furthermore, 5-HT transporter mRNA expression and *in vivo* 5-HT reuptake activity exhibits significant time-dependent changes with higher levels during the dark phase and lower levels during the light phase in midbrain raphe nuclei (Ushijima et al., 2005; Ushijima et al., 2012). Additionally, the 5-HT metabolite, 5-hydroxyindoleacetic acid (5-HTIAA), also exhibits diurnal variation in the hamster SCN with greater release occurring during the dark phase (Glass et al., 1992). Taken together, these findings indicate that 5-HT signaling is greater during the active phase.

The circadian regulation of 5-HT requires input from the sympathetic nervous system. For example, adrenergic blockade or ablation of

the superior cervical ganglion abolishes the 5-HT circadian rhythm (Snyder et al., 1965; Snyder et al., 1967; Sun et al., 2002). The TPH2 gene, which encodes tryptophan hydroxylase, the rate-limiting enzyme in the synthesis of 5-HT from its precursor L-tryptophan (Walther et al., 2003), exhibits circadian variation within the midbrain raphe nuclei with peak expression occurring 2 h prior to the light-dark transition in rats (Malek et al., 2005; Malek et al., 2007). Furthermore, this rhythm appears to be mediated by the daily glucocorticoid surge as removal of endogenous glucocorticoids via adrenalectomy suppresses *tph2* (Malek et al., 2007) and 5-HT (De Kloet et al., 1982; Singh et al., 1990; Azmitia et al., 1993), whereas replacement with exogenous CORT restores the *tph2* rhythm (Malek et al., 2007). These findings suggest that glucocorticoids have a stimulatory effect on *tph2* expression. Indeed, DRN 5-HT neurons are highly enriched with GRs (Harfstrand et al., 1986). GRs display low affinity for glucocorticoids under basal conditions and so only conditions during which glucocorticoids are secreted to a high degree (e.g. peak of the daily glucocorticoid rhythm, stress) are associated with GR-mediated effects. In support, a variety of acute and chronic stressors (Clark et al., 2005; Donner et al., 2012a; Donner et al., 2018) as well as chronic non-invasive CORT administration (Donner et al., 2012b) abolish the DRN *tph2* rhythm. However, it is important to note that the DRN is under afferent control from several brain regions that are also responsive to glucocorticoids and so systemic manipulation of glucocorticoids could impact 5-HT synthesis independently of DRN GRs. Interestingly, Vincent and colleagues (2018) demonstrated that viral-mediated knockdown of DRN GRs in mice increases *tph2* at the circadian nadir, indicating an inhibitory effect of glucocorticoids on 5-HT synthesis. These contradictory findings might be explained by the method of glucocorticoid manipulation (i.e. systemic depletion vs. localized inhibition) and/or species-specific differences. Taken together, these data show that stress-induced changes in glucocorticoids could impact the 5-HT system and thereby interfere with normal circadian function.

5.4. The serotonin system is retino-recipient

In addition to the SCN, several mood-related brain regions receive direct retinal input including the amygdala, bed nucleus of the stria terminalis, lateral habenula, as well as the DRN (Hattar et al., 2006). This suggests that light can regulate mood independently of the master clock. The pattern of DRN innervation is similar across all species studied thus far; retinal fibers emerge from the optic tract at the level of the pretectum/anterior superior colliculus and descend into the PAG and terminate in the dorsomedial and lateral subdivisions of the DRN (Fite et al., 1999; Fite and Janusonis, 2001). The majority of these RGCs are described as having alpha-like morphological features and Y type visual response properties (Luan et al., 2011). These can be further subdivided into 'ON' or 'OFF' type cells. ON-type DRN projecting RGCs (80%) increase firing in response to light increments and preferentially synapse onto GABA neurons. OFF-type DRN projecting RGCs (20%) increase firing in response to light decrements and preferentially synapse onto 5-HT neurons (Luan et al., 2011; Zhang et al., 2016b). These cells may play a role in visual altering responses although their precise function remains unknown (Peichl, 2005).

The fact that the DRN is retino-recipient suggests that the 5-HT system is light sensitive. In gerbils, low frequency light stimulation in the middle of the dark phase significantly increases DRN activity (Fite et al., 2005). In addition, in cats, exposure to intermittent light pulses increases the discharge rate above active waking levels in a subpopulation of putative 5-HT neurons located in the midbrain raphe complex (Mosko & Jacobs, 1974). In addition, in rats, 10% of DRN-projecting RGCs are melanopsin-immunopositive and representative of the M1 subtype (Li et al., 2015). Thus, the DRN appears to be involved in photic as well as non-photic circadian functions. In gerbils, selective silencing of DRN-projecting RGCs induces a depression-like phenotype and reduces DRN 5-HT levels (Ren et al., 2013). This suggests that DRN-projecting RGCS may play a role in the regulation of mood. Interestingly, in humans, exposure to blue wavelength light significantly increases activity in the brainstem (Vandewalle et al., 2007; Vandewalle et al., 2009); however, the effect of light-induced stimulation of the DRN on mood remains to be tested.

5.5. Serotonergic drugs impact the circadian system

The three main classes of pharmacological antidepressants that target the serotonin system are: (1) monoamine oxidase inhibitors (MAOIs) that prevent metabolism of monoamines; (2) tricyclic drugs that block the reuptake of monoamines; and (3) selective serotonin reuptake inhibitors (SSRIs) that specifically block the reuptake of 5-HT. Currently, SSRIs are the first line treatment for MDD (Cascade & Kalali, 2007; Kubitz et al., 2013), and prevalence of use continues to rise in the U.S. (Pratt et al., 2017). Originally, SSRIs were thought to exert their antidepressant effects by globally increasing synaptic levels of central 5-HT, but other mechanisms (e.g. hippocampal neurogenesis) may also be involved (Santarelli et al., 2003). SSRIs can also impact the circadian system, and in general, are associated with phase-advancing circadian rhythms. For example, *in vitro* application of the SSRI, fluoxetine (preloaded with the 5-HT precursor L-tryptophan), significantly phase advances the firing rate of SCN neurons (Ehlen et al., 2001; Sprouse et al., 2006). In addition, intra-SCN administration of 5-HT or specific 5-HT receptor agonists produces phase shifts in locomotor activity rhythms (Dudley et al., 1999; Ehlen et al., 2001). The phase-shifting effects of 5-HTergic drugs are strongest during the middle of the light phase (Horikawa and Shibata, 2004; Prosser, 2003). The 5-HT transporter is highly expressed in the SCN (Amir et al., 1998; Legutko and Gannon, 2001; Sur et al., 1996); therefore, SSRIs likely increase extracellular 5-HT in the SCN and thereby inhibit light-induced phase shifts. Additionally, fibroblasts from Per1 reporter mice treated with SSRIs dose-dependently shortens the period and accelerates the damping rate of Per1 (Nomura et al., 2008). Moreover, acute administration of the SSRI citalopram increases sensitivity of the circadian system in humans (McGlashan et al., 2018). This may explain why bright light therapy is more effective when administered with SSRIs. Importantly, not all antidepressants produce these effects, as non-5-HTergic antidepressants (e.g. imipramine) have no impact on circadian rhythms (Refinetti and Menaker, 1993). Thus, it appears that SSRIs may, in part, exert their therapeutic effects by modulating circadian clockwork through 5-HTergic pathways.

6. Conclusion

Proper synchronization with the environmental LD cycle is necessary for optimal health. Environmental disruption of circadian rhythms can impact mood and increase susceptibility to mood disorders. For example, shift workers exhibit high rates of MDD and risk increases as a function of shift work duration (Lee et al., 2017). Exposure to unnatural or mistimed light is pervasive in modern society: nearly 80% of the global population encounters light pollution at night (Falchi et al., 2016). In the present review we summarized several lines of research showing that circadian changes are associated with an increased susceptibility to mood disorders. First, the circadian system controls rhythmicity in numerous physiological processes and behaviors, including both the positive and negative components of mood. Depressed individuals exhibit alterations in the amplitude and/or phase timing of a diverse array of circadian rhythms including mood. Interestingly, these disturbed rhythms often return to normal following relapse from a depressive episode. Second, variations and SNPs in core clock genes predispose individuals to MDD. Third, some circadian-based strategies for treating depression (e.g. bright light therapy, sleep deprivation, agomelatine) can alter circadian rhythms and improve mood, and are as efficacious as SSRIs. Fourth, stress is the dominant predisposing factor for MDD and there is bi-directional regulation between stress and the

circadian system. Finally, animal studies using clock gene mutant rodents and models of circadian disruption support a causative relationship between circadian dysfunction and affective behavioral changes.

The exact mechanisms by which disruptions to the circadian system change mood are unclear. Here we provided evidence that modulation of the serotonin system is one of the possible pathways through which the circadian system regulates vulnerability to depression (Fig. 4). The SCN has relatively few direct neural projections, but is reciprocally connected to the 5-HT system via the midbrain raphe nuclei. The midbrain raphe nuclei innervate several brain regions involved in affective regulation. Not surprisingly, 5-HT is important for normal circadian function, and drugs that alter components of 5-HT signaling (e.g. SSRIs) can modulate components of the clock. Therefore, 5-HTergic drugs may contribute to the restoration of circadian function in depressed individuals. Future clinical studies should explore whether novel optimized combinations of circadian and pharmacologic-based treatments help to improve mood. One advantage of circadian based strategies is that they can be tailored to treat individual symptoms. For example, the timing of bright light therapy can be shifted to treat either an advanced or delayed component of circadian rhythms. Ultimately, the etiology and progression of MDD is determined by a complex interaction among genetic, environmental, and neurobiological factors. The 5-HT system may serve as an important intermediate in the circadian regulation of vulnerability to MDD.

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