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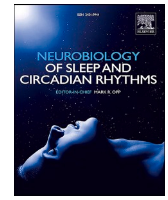

Mood phenotypes in rodent models with circadian disturbances

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ABSTRACT

Many physiological functions with approximately 24-h rhythmicity (circadian rhythms) are generated by an internal time-measuring system of the circadian clock. While sleep/wake cycles, feeding patterns, and body temperature are the most widely known physiological functions under the regulation of the circadian clock, physiological regulation by the circadian clock extends to higher brain functions. Accumulating evidence suggests strong associations between the circadian clock and mood disorders such as depression, but the underlying mechanisms of the functional relationship between them are obscure. This review overviews rodent models with disrupted circadian rhythms on depression-related responses. The animal models with circadian disturbances (by clock gene mutations and artifactual interventions) will help understand the causal link between the circadian clock and depression.

1. Introduction

Depression is a mood disorder that causes loss of motivation and suicidal thoughts. Clinically, major depressive disorder (MDD) is characterized by alterations in mood, typically increased sadness or irritability that is accompanied by at least one of the following psychophysiological symptoms, such as disturbances in sleep, appetite, sexual desire, inability to experience pleasure, slowing of speech or actions, crying, and suicidal thought (Belmaker and Agam, 2008). The disorder is a pathology of the central nervous system that results from genetic, endocrine, metabolic, neurological, and environmental factors and affects vast numbers of people worldwide (~300 million people, according to World health organization WHO; https://www.who.int/news-room/fact-sheets/detail/depression). MDD ranks first in terms of disability globally, and these numbers are continuously increasing (Han and Nestler, 2017; Mendoza, 2019). Moreover, unfortunately, lines of evidence indicate that the recent COVID-19 pandemic, which began at the end of 2019, has had profound effects on the general population on distress, anxiety, insomnia, and also depression (Iadecola et al., 2020; Sher, 2020). Further understanding of pathologies in mood disorders may allow us to provide adequate therapy and improve many individuals' quality of life. However, despite the epidemic scope of the disease, an understanding of their molecular circuitry remains at an early stage, underlying systems-level behavioral mechanisms are poorly understood, and current therapies are relatively limited (Duman and Aghajanian, 2012; Steel et al., 2014).

Previous studies of the functional relationship between circadian rhythms and depressive behaviors can provide essential clues for the issues. Circadian rhythms with an approximately 24-h periodicity of behavioral and biochemical processes are governed by an internal time-measuring system of the circadian clock. In mammals, a master pacemaker of the clock in the hypothalamic suprachiasmatic nucleus (SCN) receives input from retinal photoreceptors. Accordingly, it synchronizes peripheral clocks distributed throughout the body, driving various physiological functions (Balsalobre et al., 1998, 2000). A considerable number of studies have been made on the relationship between the clock and depression, as reviewed in Vadnie & McClung's review (Vadnie and McClung, 2017). For example, many patients with depression often show disrupted sleep and reduced latency to REM sleep. They show phase-delayed circadian rhythms. Consistent with this, many cross-sectional studies in the clinical field showed that individuals with morning chronotype have a lower risk of developing depression.

Abbreviations: SCN, suprachiasmatic nucleus; MDD, major depressive disorder; DSPS, delayed sleep phase syndrome; FASPS, familial advanced sleep phase syndrome; ipRGCs, intrinsically photosensitive retinal ganglion cells; VTA, ventral tegmental area; NAc, nucleus accumbens; EMS, ethyl methane sulfonate; MAOA, monoamine oxidase A; LHb, lateral habenula; D1R-MSN, dopamine 1 receptor-expressing medium spiny neurons; CMS, chronic mild stress; DG, dentate gyrus; PHb, perihabenular nucleus; LAN, light-at-night; vLGN/IGL, ventral lateral geniculate nucleus and intergeniculate leaflet.

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Besides, a treatment involving exposure to an artificial bright light source in the early morning (light therapy, also known as phototherapy) can be used to treat depression. Conversely, delayed sleep phase syndrome (DSPS) or westbound flight can increase vulnerability to depression. However, substantial justification linking the circadian clock and major depressive disorder (MDD) in humans is relatively limited due to experimental limitations. To fill the gap, this review primarily focuses on the mood phenotypes of animal models with circadian disturbances (by clock gene mutations and artifactual interventions). These models will help to understand the underlying mechanism of mood regulation.

2. Molecular mechanism of the circadian clock

Many aspects of physiologies and behaviors, such as sleep-wake cycles, feeding patterns, hormone secretion, and body temperature, exhibit daily rhythms even under constant conditions. The circadian rhythms are governed by the circadian clock, an internal time-measuring system (Asher and Schibler, 2011; Hastings et al., 2003; Reppert and Weaver, 2002). In mammals, a master pacemaker resides in the hypothalamic SCN, while self-sustained molecular clocks are distributed across the peripheral tissues and even in cultured fibroblasts (Balsalobre et al., 1998, 2000).

In the molecular oscillation of individual cells, CLOCK and BMAL1 proteins form heterodimers as basic helix-loop-helix-PAS transcriptional factors and bind to a specific DNA cis-element, E-box (5′-CACGTG-3′), to activate transcription of a set of clock-controlled genes. The set of genes includes negative arms of the feedback loop, such as *Period*1-3 (*Per*1-3), *Cryptochrome*1 (*Cry1*), and *Cry*2. Translated PER and CRY proteins translocate into the nuclei and directly inhibit the transcriptional activity of CLOCK-BMAL1, forming a negative feedback loop (core-loop). When freed from repression by PER and CRY proteins, CLOCK-BMAL1 rebinds to the E-box and starts a new day (Fig. 1) (Bass and Takahashi, 2010; Dunlap, 1999). In addition to PER and CRY proteins, some additional factors have been identified as the negative regulator of E-box-dependent transactivation, *e.g.*, DEC1 and DEC2 (Honma et al., 2002; Nakashima et al., 2008). Through genome-wide profiling of BMAL1 binding on the E-boxes, *Gm129* (also known as *Circa*) was identified as a robustly oscillating transcript (Hatanaka et al., 2010) and renamed *Chrono* (ChIP-derived Repressor of Network Oscillator) (Goriki et al., 2014). CHRONO operates as a repressor of the core loop in mammalian clockwork through the recruitment of histone-modifying enzyme HDAC (Anafi et al., 2014; Annayev et al., 2014; Goriki et al., 2014). In an additional sub-loop coupled with the core-loop, CLOCK--BMAL1 activates the expression of nuclear receptors, REV-ERB and ROR. REV-ERB represses, and ROR activates *Bmal1* transcription, respectively, via the RORE elements in the *Bmal1* promoter, thereby reinforcing circadian oscillation and generating various phase angles of gene-expression rhythms (Fig. 1) (Akashi and Takumi, 2005; Bass and Takahashi, 2010; Ueda et al., 2005).

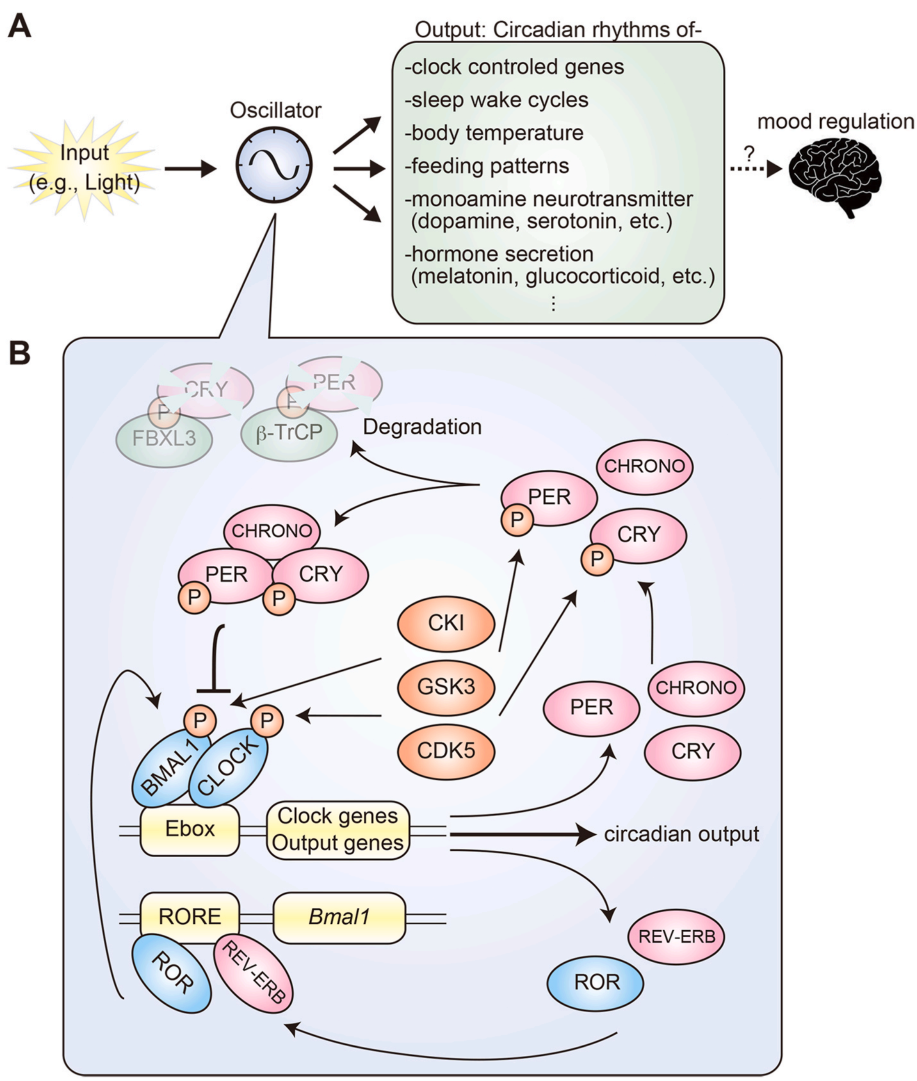

Fig. 1. Molecular mechanism of the circadian clock. (**A**) The circadian clock system is composed of input, the core oscillator, and output. Environmental time cues (*zeitgeber*), such as light, input to the core oscillator of the circadian clock and entrain it. The circadian time information from the core oscillator is output as a variety of physiological phenotypes. Disturbances in the circadian input and oscillator lead to abnormalities in the circadian outputs, which could include mood regulation. (**B**) The mammalian molecular clock (core oscillator) consists of multiple autoregulatory transcriptional/translational feedback loops. The positive arms and negative arms of the feedback loops are shown as blue and magenta, respectively. P: phosphorylation.

In the oscillatory system, the clock proteins are finely regulated by multiple post-translational modifications such as phosphorylation and ubiquitination, and the posttranslational modifications enable clock genes and clock-controlled output genes to express in a circadian manner (Fig. 1) (Gallego and Virshup, 2007; Hirano et al., 2016; Lee et al., 2001). For example, casein kinase I (CKI) phosphorylates PER proteins, and the subsequent proteasome system through an E3 ubiquitin ligase β-TrCP degrades them (Akashi et al., 2002; Camacho et al., 2001; Eide et al., 2005; Keesler et al., 2000; Miyazaki et al., 2004). In cultured cells, the inhibition of CKI activity stabilizes PER and lengthens the circadian period of cellular rhythms (Akashi et al., 2002; Camacho et al., 2001; Eide et al., 2005; Isojima et al., 2009; Keesler et al., 2000). An *in vivo* role of PER2 phosphorylation was strengthened by the identification of a human mutation at a phosphorylation site within the CKI binding domain of PER2 protein and CKI kinase gene itself, which causes familial advanced sleep phase syndrome (FASPS) (Jones et al., 1999; Toh et al., 2001; Xu et al., 2005). FASPS is characterized by shortened circadian period, early sleep times, and early-morning awakening. It is also known that glycogen synthase 3 (GSK3) phosphorylation signal regulates the molecular and physiological functions of clock proteins, including PER (Iitaka et al., 2005; Sakakida et al., 2005), CRY(Harada et al., 2005; Kurabayashi et al., 2010), CLOCK (Spengler et al., 2009), BMAL1 (Sahar et al., 2010), and REV-ERV (Yin et al., 2006, 2010). It should be added that cyclin-dependent-like kinase 5 (CDK5) is critically involved in regulating the circadian clock. CDK5 has been reported to phosphorylate CLOCK at the Thr-451 and Thr-461 residues (Kwak et al., 2013). The CDK5-dependent phosphorylation alters CLOCK stability and subcellular distribution, resulting in transcriptional activation of CLOCK. Moreover, CDK5 is also reported as a responsible kinase for PER2 at Ser-394 residue (Brenna et al., 2019). The phosphorylation facilitates PER2 interaction with CRY1 and nuclear entry of the PER2-CRY1 complex. The ubiquitination-mediated proteasome pathway is also essential for the regular oscillation of the circadian clock. Two mouse mutations, after-hours (*Afh*) and overtime (*Ovtm*), have a point mutation in FBXL3 (an F-box-type E3 ligase) (Godinho et al., 2007; Siepka et al., 2007). In these mutant mice, the degradation of CRY is strongly inhibited, resulting in markedly prolonged free-running periods (Busino et al., 2007; Godinho et al., 2007; Siepka et al., 2007)

The circadian oscillatory system is composed of the transcriptional/translational feedback loop, and the post-translational modifications confer robustness on the circadian clock even under constant conditions. On the other hand, the circadian period and phase respond flexibly to a wide variety of environmental time cues to synchronize, or entrainment, with the external daily cycles. In circadian entrainment, for almost all organisms, the universal time cue (*zeitgeber*) is the daily cycles of light and darkness (photo-entrainment) (Hirota and Fukada, 2004; Johnson et al., 2003; Reppert and Weaver, 2002). In the photo-entrainment, the photic signal is captured by a non-visual opsin, OPN4 (also known as melanopsin), in intrinsically photosensitive retinal ganglion cells (ipRGCs), which constitute some fraction of the retinal ganglion cells (Berson et al., 2002; Gooley et al., 2001; Hattar et al., 2002; LeGates et al., 2014). In response to light, the OPN4-containing ipRGCs release glutamate and stimulate their receptors expressed in the SCN neurons. In the activated SCN neurons, Ca^{2+} influx is induced, and a series of kinase signaling is activated (Hirota and Fukada, 2004). The photo-entrainment in the central SCN clock is accomplished relatively within a short time, whereas the entrainment in the peripheral clocks takes longer. Under the disturbance of the photic environment by jet lag or shift-work, temporary misalignments between the central and peripheral clocks (internal desynchronization) cause chronic fatigue and various types of diseases (Gentry et al., 2021). Thus, disturbances in the circadian input and oscillation systems lead to abnormalities in the circadian outputs, which could include mood regulation (Fig. 1).

3. Genetic and pharmacological manipulation of clock genes (Table 1)

3.1. Clock genes

Clock is the first mammalian clock gene to be cloned from the generation of mutant mice by forward genetics (Vitaterna et al., 1994). The *Clock* mutant mice show a longer circadian period (~27 h), and they become arrhythmic within ~1 week under constant dark conditions (Antoch et al., 1997; King et al., 1997; Vitaterna et al., 1994). In the mutant mice, an adenine (A) to thymine (T) substitution in the splice donor site occurs, resulting in the deletion of 51 amino acids corresponding to exon 19 ($Clock^{\Delta 19}$) (King et al., 1997). The encoded CLOCK mutant protein has a dominant-negative effect and cannot activate transcription (Gekakis et al., 1998). It should be noted that the $Clock^{\Delta 19}$ is an overexpression variant; hence, the observations related to that mutant may not necessarily be related to CLOCK itself but due to indirect effects of overexpression of a stable CLOCK protein variant that will change the equilibria in many unrelated processes in an indirect manner. An overall behavioral profile of the *Clock* mutant mice is similar to human mania, *i.e.*, hyperactivity, decreased sleep, lowered depression-like behavior, lower anxiety, and an increase in the reward value for cocaine, sucrose, and medial forebrain bundle stimulation (Roybal et al., 2007). Knockdown of *Clock* in the ventral tegmental area (VTA), the origin of the dopaminergic cell bodies, is resulted in a manic-like state of less anxiety and hyperactivity but also depressive behavior (Mukherjee et al., 2010). The *Clock* mutant mice show hyperactivity in the novel environment and exhibit profound deficits in low-gamma and nucleus accumbens single-neuron phase coupling (Dzirasa et al., 2010). NAc neurons in the *Clock* mutant mice show complex changes in dendritic morphology and reduced *GluR1* expression compared to those observed in control WT. Treatment with lithium, a mood stabilizer widely used in treating depression in bipolar disorders, ameliorates several of these neurophysiological deficits and suppresses exploratory drive in the mutants. CLOCK directly targets *Cholecystokinin* (*Cck*) gene, and expression levels of *Cck* are reduced in the VTA of the *Clock* mutant mice (Arey et al., 2014). The reduced *Cck* expression in the *Clock* mutant mice is restored to near WT by chronic treatment with lithium. Importantly, knockdown of the *Cck* gene in the VTA of WT mice produces a manic-like phenotype, showing a pivotal role for *Cck* under the control of *Clock* on mood regulation. Whole-cell patch-clamp electrophysiology revealed that the *Clock* mutant mice show reduced functional synaptic response in NAc neurons (Parekh et al., 2018). Consistent with this, NAc surface protein levels and the rhythm of GRIA1 are decreased in the *Clock* mutant mice diurnally. On the other hand, overexpression of functional *Gria1* in the NAc of mutant mice normalizes increased exploratory drive and reward sensitivity behavior in the *Clock* mutant mice. NPAS2, a paralog of CLOCK, forms heterodimers with BMAL1 to transcriptionally activate repressor genes such as *Per* and *Cry* members. NPAS2 is highly expressed in reward- and stress-related brain regions such as the striatum. *Npas2* KO mice exhibit less anxiety-like behavior than WT control in elevated plus maze, light/dark box, and open field tests (Ozburn et al., 2017). Acute or chronic stress increases the expression levels of the *Npas2* gene in the striatum. Knockdown of *Npas2* in the ventral striatum results in a similar reduction of anxiety-like behaviors as seen in the *Npas2* KO mouse.

Bmal1 (also known as *Mop3* or *Arntl*) is the only non-redundant gene in the core clock genes, and it is indispensable for circadian oscillations of clock-controlled gene expressions (Bunger et al., 2000; Reppert and Weaver, 2002). While the circadian rhythms of single gene deletion in most clock genes are compensated by their homologs, *Bmal1* single-gene deletion completely abolishes circadian rhythms. SCN-specific *Bmal1* knockdown through RNA interference results in a depressive-like phenotype, *i.e.*, helplessness, behavioral despair, and anxiety-like behavior (Landgraf et al., 2016). The mice also show more significant weight gain and an abnormal circadian pattern of corticosterone, and an

Table 1
Genetic and pharmacological manipulation of clock genes.

Genotype	Circadian period	Phenotype	Refs
Clock mutant (*Clock*$^{\Delta 19}$)	Long	hyperactivity, decreased sleep, decreased depression-like behavior, decreased anxiety, increased reward value for cocaine and sucrose	Roybal et al 2007
Clock KD in VTA	Unknown	hyperactivity, increased manic-like state of less anxiety increased depression-likebehavior	Mukherjee et al 2010
Bmal1 KD in SCN	Unknown	increased depression-like behavior, despair, increased anxiety-like behavior	Landgraf et al 2016
glia-specific *Bmal1* KO	Unknown	no effect on mood related behaviors	Martini et al 2021
Per2 KO (*Per2*^{brdm1})	Short	depression-resistant-like behavior reduced expression and activity of MAOA increased dopamine levels in the ventral striatum	Hampp et al 2008
Per1/2 double KO (*Per1*^{ltc}/*Per2*^{ltc})	Arrhythmic	increased anxiety-like behavior	Spencer et al 2013
Per1/2 double KD in Nac	Unknown	increased depression-like behavior	
glia-specific *Per2* KO	Normal	alters despair and anxiety	Martini et al 2021
neurn-specific *Per2* KO	Normal	alters despair but not anxiety	
glia-specific *Per2* KO in Nac	Normal	alters despair but not anxiety	
Per1 KO	Short	increased depression-like behavior	Olejniczak et al 2021
LHb-specific *Per1* KO	Unknown	no efect on mood related behaviors, abolish beneficial light effects at late evening on despair	
Cry1 KO	Short	increased anxiety-like behavior unaffected depression-related behaviors	De Bundel et al 2013
Cry2 KO	Long		
Cry1/2 double KO	Arrhythmic		
Cry1/2 double KO	Arrhythmic	increased anhedonia unaffected despair behavior	Saavlli et al 2015
Cry1/2 double KO	Arrhythmic	limited ability to habituate to new environments, no differences in anxiety or depression-related behaviors	Huhne et al 2020
Cry2 KO	Long	decreased despair-like behavior increased anhedonia unbaffected anxiety-like behavior	Sokolowska et al 2021
Cry1/2 double KD in D1R-MSN	Unknown	decreased susceptibility to stress-induced helplessness increased NAc neuronal activation at night	Porcu et al 2020
Rev-erb α KO	Short	increased mania-like behavior	Chung et al 2014
Rev-erb α KD in Nac	Unknown	increased sociability, reduced anxiety-like behavior, unaffected depressive-like behavior (female mice) no significant behavioral effects (male mice)	Zhao et al 2018
Chorno KO	Long	increased glucocorticoid levels in response to stress	Goriki et al 2014
heterozygote GSK3β knock-out	Short?	attenuated hyperlocomotion after amphetamine administration	Beaulieu et al 2004
GSK3β [S9A] overexpression	Long?	increased mania-like behavior, *i.e.*, hyperactivity, decreased habituation, disturbed eating pattern	Prickaerts et al 2006
Fbxl3$^{Afh/Afh}$	Long	decreased anxiety-like behavior, decreased depression-like behavior	Keers et al 2012
CKI inhibition in *ClockΔ19* mutant	Unknown	reversal of the anxiety-related behavior, and partial reversal of the depression-related phenotypes of the Clock mutant mouse	Arey and McClung 2012

attenuated increase of corticosterone in response to stress (Bae et al., 2001). Notably, glial cells specific deletion of *Bmal1* does not affect mood-related behaviors (*i.e.*, the forced swim test and O-maze test) (Martini et al., 2021).

Period is the first gene responsible for a circadian rhythm mutant isolated in an EMS mutagenesis screen in Drosophila (Konopka and Benzer, 1971; Zehring et al., 1984). As mammalian orthologues, *Per1*, *Per2*, and *Per3* genes have been cloned (Albrecht et al., 1997; Sun et al., 1997; Takumi et al., 1998a, 1998b; Tei et al., 1997). Mice with a single deficiency of *Per1* or *Per2* show short-period behavioral rhythms, and *Per1/2* double-KO mice show arrhythmic behaviors in constant conditions (Bae et al., 2001; Zheng et al., 1999, 2001). On the other hand, the *Per3* gene KO causes only minor effects on the period length of behavioral rhythms (Bae et al., 2001; Shearman et al., 2000), showing a more significant contribution of *Per1* and *Per2* to the formation of circadian rhythms. Acute physical stress elevates mouse *Per1* expression via a glucocorticoid-responsive element (Yamamoto et al., 2005). The *Per1* knock-out animals (Zheng et al., 2001) show a depression-like phenotype in the forced swim test (Olejniczak et al., 2021). Loss of functional mouse PER2 ($Per2^{brdm1}$ strain), lacking 87 residues at the carboxyl portion of the PAS dimerization domain (Zheng et al., 1999), leads to reduced expression and activity of monoamine oxidase A (MAOA), resulting in elevated dopamine levels in the ventral striatum (Hampp et al., 2008). Due to the elevated dopamine levels, the $mPer2^{brdm1}$ mice show a depression-resistant-like phenotype. Mice lacking both *Per1* and *Per2*; $Per1^{ltc}/Per2^{ltc}$ strain (Bae et al., 2001), have a robust increase in anxiety and depression-like behavior (Spencer et al., 2013). NAc region-specific double-knockdown of both *Per1* and *Per2* leads to a similar phenotype in the mutant animals. Recently, by using *Per2* floxed mice (Chavan et al., 2016), glial- and neural-specific *Per2* KO mice were generated (Martini et al., 2021). Deletion of *Per2* in glial cells alone or neuronal cells alone is sufficient to alter mood-related behaviors. The glial *Per2* deletion alters despair (forced swim test) and anxiety (O-maze), whereas neuronal deletion of *Per2* only alters despair (forced swim test) but not anxiety (O-maze). The change in mood-related behavior is probably not a result of a defective molecular clock because deletion of *Bmal1* in glial cells does not affect either despair or anxiety-related behavior, as described above. Notably, exclusive deletion of *Per2* in the glia of the NAc reduced despair but did not influence anxiety. Olejniczak et al., generated *Per1* floxed mice (Olejniczak et al., 2021). In the lateral habenula (LHb), a brain region known to modulate mood-related behaviors, specific deletion of *Per1* does not affect the forced swim test, but beneficial light effects at late evening on despair are abolished in the animals. Hence light-inducible *Per1* in the LHb should be necessary for beneficial light effects on despair. *Per1* in other brain areas, probably involving the NAc, is important for the despair-related phenotype.

CRY1 and CRY2 function as potent repressors of E-box-mediated transcription. Single-KO of *Cry1* or *Cry2* shorten or lengthen the circadian free-running period in mice behavioral rhythms, respectively, and double-KO of *Cry1* and *Cry2* leads them to arrhythmic (Thresher et al., 1998; van der Horst et al., 1999; Vitaterna et al., 1999). While the physiological importance of CRYs in normal emotional behavior has been accepted, previous studies have disagreed on anxiety-like and depression-like behaviors of *Cry* genes KO mice (Sokolowska et al., 2021). De Bundel et al. showed that each *Cry1* or *Cry2* single-KO and *Cry1/2* double-KO mice displayed increased anxiety-like behavior and unaffected depression-related behaviors (De Bundel et al., 2013). Savalli et al. demonstrated increased anhedonia and unaffected despair behavior in *Cry1/2* double-KO compared to WT mice (Savalli et al., 2015). Recently, Huhne et al. observed that *Cry1/2* double-KO mice have limited ability to habituate to new environments but no differences in anxiety or depression-related behaviors (Huhne et al., 2020). Sokolowska et al. reported that *Cry2* deficient mice showed reduced despair-like behavior and increased anhedonia, but the mice did not show anxiety-like behavior (Sokolowska et al., 2021). Some of these contradictions may be due to genetic differences between the strains of each study. Moreover, since maternal care influences the pup's behavior, the breeding method (by breeding heterozygous mice or breeding single KOs with each other) is also essential. Notably, higher levels of CRY in the NAc region may block D1 dopamine receptor activation during the nocturnal, active phase of mice, thereby compromising the normal daily activation of NAc neurons and leading to helpless behavior. Dopamine 1 receptor-expressing medium spiny neurons (D1R-MSN) specific *Cry1* and *Cry2* knockdown in the NAc region reduces susceptibility to stress-induced helplessness and increases NAc neuronal activation at night (Porcu et al., 2020).

The nuclear receptor REV-ERB constitutes the circadian sub-loop and stabilizes the core loop by repressing the RORE elements in the *Bmal1* gene promoter (Preitner et al., 2002). REV-ERBα deficient mice show shorter activity rhythms in constant conditions. On the other hand, the nuclear receptor ROR is an activator of RORE elements in the circadian sub-loop (Akashi and Takumi, 2005; Sato et al., 2004). A loss-of-function mutant of ROR*α* (*staggerer* mouse strain) shows somewhat unstable but almost normal behavior rhythm, suggesting the more significant contribution of REV-ERB to the formation of circadian clockwork. Genetic ablation or pharmacological inhibition of REV-ERB*α* in the ventral midbrain induced mania-like behavior in association with a central hyperdopaminergic state (Chung et al., 2014). The other research group reported that region-specific knockdown of *Rev-erbα* in the NAc enhances sociability and reduces anxiety but does not affect depressive-like traits in female mice (Zhao and Gammie, 2018). In male mice, *Rev-erbα* knockdown has no significant behavioral effects.

A novel clock protein CHRONO (also known as CIRCA) forms a complex with other clock components and operates as a repressor of the core mammalian clockwork (Anafi et al., 2014; Annayev et al., 2014; Goriki et al., 2014), has been identified. *In vivo* loss-of-function studies of *Chrono,* including Avp neuron-specific (SCN-targeted) KO mice, exhibited slightly longer circadian periods in their activity rhythms (Goriki et al., 2014). Notably, CHRONO is involved in glucocorticoid receptor-mediated metabolic pathways triggered by behavioral stress. Since abnormal glucocorticoid levels are associated with the development of mood disorders (Landgraf et al., 2014), CHRONO could have a crucial role in mood regulations.

3.2. Clock-related enzymes

GSK3β is a protein kinase that regulates the molecular functions of a variety of clock proteins, including CLOCK, BMAL1, PER, CRY, and REV-ERB, through phosphorylation (Harada et al., 2005; Iitaka et al., 2005; Kurabayashi et al., 2010; Sahar et al., 2010; Sakakida et al., 2005; Spengler et al., 2009; Yin et al., 2006, 2010). In mammals, it has been reported that RNAi-induced knockdown of GSK3β shortens the circadian period of cellular rhythms and mice behavior rhythms (Hirota et al., 2008). In conflict with this fact, lithium, a well-characterized mood stabilizer, lengthens mammalian circadian periods despite inhibiting the GSK3β activity (Iwahana et al., 2004; Li et al., 2012). As suggested by Hirota et al. and Li et al., the exact mode of action of lithium is still uncertain, and lithium also suppresses other signal pathways. Therefore, the long-period phenotype might be mediated by multiple functions of the lithium treatment. Although homozygote GSK3β-KO mice die during embryogenesis, heterozygote mice develop normally without any overt phenotypes (Hoeflich et al., 2000). The heterozygote GSK3β KO mice show attenuated hyperlocomotion after amphetamine administration, an activator of the dopaminergic system (Beaulieu et al., 2004). In agreement with the results, transgenic mice overexpressing a constitutively active form of GSK3β; GSK3β [S9A] strain (Spittaels et al., 2000, 2002), show locomotor hyperactivity, decreased habituation, and a disturbed eating pattern as seen in the manic phase of bipolar disorder (Prickaerts et al., 2006).

FBXL3 is a member of the F-box protein family, a component of the SKP1-CUL1-F-box-protein (SCF) E3 ubiquitin ligase complex. FBXL3 directly interacts with CRY proteins, promoting their degradation by the ubiquitin/proteasome system (Busino et al., 2007; Godinho et al., 2007; Siepka et al., 2007). FBXL3 also interacts with REV-ERBα/histone deacetylase 3 (HDAC3) complex and decreases the repression of *Bmal1* transcription (Shi et al., 2013). Loss-of-function mutations or a deficiency of FBXL3 result in extremely long-period phenotypes in mice, indicating that FBXL3 plays a vital role in circadian period determination (Busino et al., 2007; Godinho et al., 2007; Hirano et al., 2013; Siepka et al., 2007). A loss-of-function mutant of FBXL3; $Fbxl3^{Afh/Afh}$ mouse strain (Godinho et al., 2007), exhibits a behavioral profile analogous to aspects of human mania, *i.e.*, reduced anxiety- and depression-like behavior (Keers et al., 2012).

CKI is a critical protein kinase involved in the normal oscillation of the molecular clock (Jones et al., 1999; Toh et al., 2001; Xu et al., 2005). Chronic administration of a CKI ε/δ inhibitor (CK01) leads to a reversal of the anxiety-related behavior and partial reversal of the depression-related phenotypes of the *Clock* mutant mouse (Arey and McClung, 2012).

As mentioned before, it has appeared that CDK5 is critically involved in regulating the mammalian circadian clock (Brenna et al., 2019; Kwak et al., 2013). Indeed, the knockdown of CDK5 in the SCN shortened the free-running period in mice (Brenna et al., 2019). In the dorsal striatum, the main recipient of dopaminergic innervation, specific knockdown of the *Cdk5* gene causes deficits in locomotor activity and disturbances in activity/rest behavior in mice (Zhou et al., 2022). CDK5 modulates the brain reward system (Benavides et al., 2007; Bibb et al., 2001) and is consequently linked to psychiatric diseases, including depression (Zhu et al., 2012). Zhu et al. found that chronic mild stress (CMS) in rats increases CDK5 activity in the hippocampus, accompanied by translocation of neuronal-specific activator p35 from the cytosol to the membrane in the dentate gyrus (DG) subregion. Inhibition of CDK5 in DG but not in the cornu ammonis 1 (CA1) or CA3 hippocampal subregions attenuates the development of depressive-like symptoms. The development of depressive-like behavior is associated with increased CDK5 activity in the hippocampus, and the CDK5/p35 complex plays a vital role in regulating depressive-like behavior.

4. Disruptions of the circadian clock by artificial perturbations (Table 2)

4.1. SCN lesion

In mammals, a master pacemaker controlling the circadian rhythms resides in the hypothalamic suprachiasmatic nucleus (SCN), located directly above the optic chiasm. The behavioral and physiological rhythms are lost when the brain region is destroyed. In a previous study, to assess the role of the SCN in regulating depression-related behavior, rats' SCN was bilaterally destructed. The SCN-lesioned rats demonstrate reduced immobility in forced swim tests (Arushanyan and Popov, 1995). About a decade later, similar results were also reported by another research group (Tataroglu et al., 2004). These results suggest that bilateral destruction of the SCN has an antidepressant effect protecting the animals against the stress of swimming and induction of behavioral despair. However, as we have mentioned before, the opposite results were obtained in genetic disruption of circadian rhythms in the SCN by SCN-specific *Bmal1* knockdown (Landgraf et al., 2016). A possible reason for the discrepancy could be the presence or absence of projections from the SCN to other brain regions involved in depression and/or anxiety.

4.2. Aberrant light

Since the light-dark cycle is a pivotal time cue (*zeitgeber*) for the mammalian circadian clock, previous studies assessed the effects of altered light environment on mood-related behaviors (LeGates et al., 2014). Light exposure at night perturbs molecular circadian rhythms (Fonken et al., 2013). In hamsters, the photic stimuli at the nighttime induce depression-like behaviors with anatomical changes and inflammatory responses in the hippocampus (Bedrosian et al., 2011, 2013). Similar effects of photic stimuli at night are also observed in both nocturnal mice (Fonken and Nelson, 2013) and diurnal Nile grass rats (Fonken et al., 2012).

In today's modern society, so many people adapt to a nocturnal lifestyle and disrupt the harmonies of circadian rhythms. To mimic the prolonged light exposure experienced as a result of artificial lighting, previous studies have examined the effect of constant light exposure (LL). In nocturnal animals, the higher the light intensity in LL, the longer the circadian period (known as Aschoff's rule) (Aschoff, 1960; Imamura et al., 2018; Yoshitane et al., 2012). High light intensity in LL eventually induces the disruption of circadian arrhythmicity (Ohta et al., 2005). Under the LL conditions, mice show increased depressive-like behavior, such as desperate behavior and anhedonia, and decreased anxiety-like responses (Fonken et al., 2009). Interestingly, providing a light escape tube reverses the effects of LL. Similar effects of LL conditions are also observed in rats (Tapia-Osorio et al., 2013).

As an experimental model, aberrant photoperiods have been used to mimic seasonal light changes. In mice, a winter-like short photoperiod markedly increases the length of the activity band, an interval between the activity onset and the end of activity (Inagaki et al., 2007). As an animal model of seasonal affective disorder, the short photoperiod was

Table 2
Disruptions of the circadian clock by artificial perturbations.

Manipulation	Animal	Circadian rhythm	Phenotype	Refs
SCN lesion	rat	arrhythmic	decreased depression-like behavior	Arushanyan and Popov (1995)
				Tataroglu et al (2004)
Light exposure at night	hamster	phase-shift	increased depression-like behavior	Bedrosian et al (2011)
				Bedrosian et al (2013)
	mouse			Fronken et al (2013)
	Nile grass rat			Fronken et al (2012)
Constant light exposure	mouse	long period or arrhythmic	increased depressive-like behavior	Fronken et al (2009)
	rat		decreased anxiety-like behavior	Tapia-Osorio et al (2013)
Short photoperiod	hamster	change the length of activity phase	increased depressive-like behavior increased anxiety-like behavior	Pyter and Nelson (2006)
T7 cycle	mouse	not affected	increased depression-like behavior	LeGates et al (2012)
				Fernandez et al (2018)
Light-at-night	mouse	not affected	increased depression-like behavior	An et al (2020)

exposed to nocturnal hamsters, resulting in increased depressive-like behavior and anxiety-like responses (Pyter and Nelson, 2006).

Ultradian light cycles consisting of 3.5-h light and 3.5-h dark (T7), similar to shift work, impair mood-related behaviors in mice. Notably, the T7 cycle does not cause circadian arrhythmicity in core body temperature, general activity rhythms, and the molecular basis of the circadian clock (LeGates et al., 2012). Despite normal circadian and sleep structures, mice under the T7 cycles show increased depression-like behaviors. In mice lacking ipRGCs, the T7 cycles do not alter mood-related behaviors, showing that light can influence mood functions directly through ipRGCs. ipRGCs project to numerous brain regions, including not only SCN but also nuclei involved in depression and/or anxiety (LeGates et al., 2014). Indeed, mood regulation by light requires an SCN-independent pathway linking ipRGCs to a brain region, the perihabenular nucleus (PHb) (Fernandez et al., 2018). The PHb is integrated into a distinctive circuitry with mood-regulating centers and is both necessary and sufficient for driving the effects of light on affective behavior. An et al. also showed mood regulation mechanism by light through an SCN-independent pathway linking ipRGCs to PHb (An et al., 2020). Light-at-night (LAN) induces depressive-like behaviors without disturbing the circadian rhythm in mice. The light effect is mediated by a neural pathway; ipRGC → dorsal PHb → NAc. Notably, the dorsal PHb is gated by the circadian rhythm, which is more excitable at night than during the day, mediating LAN-induced depressive-like behaviors. On the other hand, the contribution of LHb to mood regulation has also been shown (Huang et al., 2019). Retinal ipRGCs innervate GABA neurons in the thalamic ventral lateral geniculate nucleus and intergeniculate leaflet (vLGN/IGL), which in turn inhibit CaMKIIa neurons in the LHb. A dedicated retina-vLGN/IGL-LHb circuit regulates depressive-like behaviors and provides a potential mechanistic explanation for light treatment of depression. Recently, Olejniczak et al. showed LHb specific *Per1* deletion does not affect mood-related behavior but suppresses the beneficial effects of light on the mood, as mentioned above (Olejniczak et al., 2021). Light affects mood-related behavior in mice, at least in part via induction of *Per1* in the LHb with consequences on mood-related behavior.

5. Conclusion

To date, therapies for mood disorders, especially depression, are still limited, and the development of more adequate treatments for them is eagerly awaited. A better understanding of the functional relationship between circadian rhythms and mood disorders can provide important clues for the aim. While the reviewed studies provide essential insights into mood abnormalities arising from clock dysfunction, the diversity of the phenotypes observed in multiple animal models remains unexplained. For example, the behavioral phenotypes observed in each clock mutant mouse cannot necessarily be explained by their circadian period. Each clock-disrupted mouse (*e.g.*, $Clock^{\Delta 19}$, *Per1/2* double-KO, *Cry1/2* double-KO, and SCN-lesioned) shows different phenotypes from each other. As we have mentioned, some of these diversities may be due to the differences in strains and breeding methods in each study. In addition, it was reported that mood-related behaviors are expressed in a time-of-day-dependent manner in mice (Nakano et al., 2016). It is possible that the timing (time of day) of the tests may have contributed to the diversity of behavioral phenotypes. On the other hand, it is notable that aberrant light schedules directly affect mood through ipRGCs and PHb or LHb, independently of circadian arrhythmicity or sleep disturbances (An et al., 2020; Fernandez et al., 2018; Huang et al., 2019; LeGates et al., 2014; Olejniczak et al., 2021). Light can regulate mood through two pathways; an indirect pathway modulating sleep and circadian rhythms and a direct pathway that does not mediate the SCN clock. It is possible that other clock entrainment factors (time cues or *zeitgeber*) also regulate mood in this way via multiple pathways.

Declaration of competing interest

The authors declare no competing interests.

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