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 (Jadecola 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 methanesulfonate; 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 Period1-3 (Per1-3), Cryptochrome1 (Cry1), and Cry2. 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.](image)
In the oscillatory system, the clock proteins are finely regulated by multiple post-translational modifications such as phosphorylation and ubiquitination, and the post-translational 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 1 (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; Isijima et al., 2005; 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 glucagon synthetase (GSK3) phosphorylation signal regulates the molecular and physiological functions of clock proteins, including PER (Itakka 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-ERB (Yin et al., 2006, 2010). It should be added that cyclin-dependent 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 (Aff) and overtime (Ovtm), have a point mutation in FBXL3 (an F-box-type E3 ligase) (Antoch et al., 1997; King et al., 1997; Vitaterna et al., 1994). In the mutant protein has a dominant-negative effect and cannot activate transcription (Gekakis et al., 1998). It should be noted that the Clock mutation 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 (Dizirasa 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 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 andCRY. NPAS2 is highly expressed in reward- and stress-related brain 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.

### 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 (ClockΔ19) (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 ClockΔ19 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 (Dizirasa 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 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. 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 dispensable 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., helpless, 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<sup>−/−</sup>)     | 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-like behavior | 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<sup>crelo</sup>)           | Short            | depression-resistant-like behavior reduced expression and activity of MAOA increased dopamine levels in the ventral striatum | Hanapp et al 2008     |
| Per1/2 double KO (Per1<sup>1/2</sup>/Per2<sup>1/2</sup>) | Arrhythmic       | increased anxiety-like behavior increased depression-like behavior          | Spencer et al 2013    |
| Per1/2 double KD in Nac                   | Unknown          | alters despair and anxiety                                                | Martini et al 2021    |
| glia-specific Per2 KO                     | Normal           | alters despair but not anxiety                                             |                       |
| neuron-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 no effect on mood related behaviors, abolish beneficial light effects at late evening on despair | Olejniczak et al 2021 |
| LHB-specific Per1 KO                      | Unknown          | increased anxiety-like behavior                                            | De Bandel et al 2013  |
| Cry1 KO                                   | Short            | increased anxiety-like behavior                                            |                       |
| Cry2 KO                                   | Long             | unaffected depression-related behaviors                                     | Saavli et al 2015     |
| Cry1/2 double KO                          | Arrhythmic       | increased anhedonia unaffected despair behavior                            |                       |
| Cry1/2 double KO                          | Arrhythmic       | limited ability to habituate to new environments, no differences in anxiety or depression-related behaviors | Huhe et al 2020       |
| Cry1/2 double KO                          | Arrhythmic       | decreased despair-like behavior increased anhedonia unaffected anxiety-like behavior | Sokolowska et al 2021 |
| Cry2 KO                                   | Long             | decreased despair-like behavior increased anhedonia unaffected anxiety-like behavior |                       |
| 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                                              | Chang 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 |
| Fbox19<sup>401/403</sup>                 | Long             | decreased anxiety-like behavior decreased depression-like behavior         | Keers et al 2012      |
| CKI inhibition in Clock419 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., 1999a, 1999b; 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; Shearnman 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 (Oleijnikczak et al., 2021). Loss of functional mouse *Per2* (*Per2<sup>brdm1</sup>* 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 m*Per2<sup>brdm1</sup>* mice show a depression-resistant-like phenotype. Mice lacking both *Per1* and *Per2*; *Per1<sup>brdm1</sup>*/<sup>brdm1</sup>* 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. Oleijnikczak et al., generated *Per1* floxed mice (Oleijnikczak 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 (Trescher 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-related behaviors (De Bundel et al., 2015). Savalli et al. demonstrated increased anhedonia and unaffected despair behavior in *Cry1*/2 double-KO compared to WT mice (Savalli et al., 2015). Recently, Huhe 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 (Huhe 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 KO 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 (D1-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 RORα (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-ERBs 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-erba* 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-erba* 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; Itaka 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<sup>−/−</sup> 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<sup>−/−</sup> 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

#### 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 knockout (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.

| 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)    |
|                            | mouse         |                            |                                                 | Bedrosian et al (2013)    |
|                            | Nile grass rat|                            |                                                 | Fronken et al (2013)      |
| Constant light exposure    | mouse         | long period or arrhythmic  | increased depression-like behavior              | Fronken et al (2009)      |
|                            | rat           |                            | decreased anxiety-like behavior                 | Tapia-Osorio et al (2013) |
| Short photoperiod          | hamster       | change the length of       | increased depressive-like behavior              | Pyter and Nelson (2006)   |
|                            | mouse         | activity phase             | increased anxiety-like behavior                 |                            |
| T7 cycle                   | mouse         | not affected               | increased depression-like behavior              | LeGates et al (2012)      |
| Light-at-night             | mouse         | not affected               | increased depression-like behavior              | Fernandez et al (2018)    |

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 decreased activity and increased 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...
exposed to nocturnal hamsters, resulting in increased depressive-like behavior and anxiety-like responses (Pryer 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 depression-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., ClockΔ19, 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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