Cell and Tissue Research (2019) 377:81–94
https://doi.org/10.1007/s00441-019-03033-7

REVIEW

Circadian neurogenetics of mood disorders

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Received: 5 September 2018 / Accepted: 9 April 2019 / Published online: 10 May 2019

Abstract

Mood state alterations are often accompanied by disruptions of daily rhythms of physiology. Circadian rhythms of physiology are controlled by a central clock harbored in the suprachiasmatic nucleus (SCN), which is functionally dependent on the rhythmic expression of several clock genes. The molecular clockwork has been identified in other extra-SCN brain regions, some of which are implicated in the regulation of motivational and emotional states, although their specific circadian role is not fully known. In mood disorders, alterations of the molecular clock have been reported. Thus, functional expression of circadian genes in the brain is compromised in mood diseases. In the present review, we describe the current evidence that implicates the clock gene alterations as an important factor in the development of mood-related disorders. Furthermore, we describe the possible role of other brain clocks, beyond the SCN, in the circadian control of mood. The comprehension of the circadian neural and genetic mechanisms underlying mood alterations might guide towards the identification of optimal drug and non-drug therapies for the cure of depression and other mood disorders.

Keywords Circadian · Clock genes · Depression · Mood · Suprachiasmatic nucleus · Habenula

Introduction

Regulation of daily physiology is a common characteristic in living organisms (Pittendrigh 1993). In the wild, rhythmic biological functions are necessary to adapt organisms to daily changes in the environment such as day-night cycles, food source availability and the presence of predators. In humans, daily rhythms in physiology (biological rhythms entrained to a 24-h period) are determinant to optimize metabolic, behavioral and cognitive processes to the 24-h day-night cycle (Roenneberg et al. 2003). Thus, when these rhythms are disrupted, survival is compromised in nature (DeCoursey 2014) and human diseases might result (Takahashi et al. 2008; Foster et al. 2013). Therefore, behavior, metabolism and molecular endogenous rhythms (self-sustained biological rhythms that persist under constant conditions) are under the control of a circadian system (circa = close to; *diem-* = day) in the body, composed of organs and tissues expressing an endogenous timekeeping activity around the 24-h clock (Dibner et al. 2010). The whole system is set in time by a central clock: the hypothalamic suprachiasmatic nucleus (SCN) (Patton and Hastings 2018).

The clock in the hypothalamic SCN

In the anterior hypothalamus, above the optic chiasm, resides the brain pacemaker in mammals, the SCN, a heterogeneous structure that serves as the principal circadian clock pacing behavioral and physiological rhythms (Patton and Hastings 2018). The SCN coordinates local brain clocks and peripheral oscillators (e.g., liver, heart) through neural and hormonal pathways in order to maintain synchrony in the entire body and avoid anomalous physiology (Buijs et al. 2006; Herzog et al. 2017). Hence, if the SCN circadian activity is disrupted, all the other brain and peripheral clocks become desynchronized, even if some of them are self-sustained circadian oscillators (Guilding and Piggins 2007). To be in time with the external world, the SCN is synchronized principally to the solar time from the day-night cycle (Golombek and Rosenstein 2010).

Light is able to reach the SCN via a monosynaptic pathway, the retinohypothalamic tract (RHT) (Moore et al. 1995). In the

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retina, light is perceived by specific intrinsically photosensitive retinal ganglion cells (ipRGCs) containing the photopigment melanopsin (Hattar et al. 2006; Schmidt et al. 2011b). Then, at night, ipRGCs transmit the light information to the SCN by the release of glutamate (Hannibal 2002; Shirakawa and Moore 1994; Moore 1995). Glutamate binds specific receptors on SCN cells from the core region (also called the retinorecipient region), leading to an intracellular increase of calcium (Ca^{+}), the activation of the MAPK signaling pathway, the phosphorylation of the cAMP-response element-binding protein (CREB) and finally the induction of *Per* genes (Fig. 1) (Yan et al. 1999). Whereas the exposure to light during late night is able to advance the phase of the SCN activity, light exposure at early night is able to delay the phase activity of the clock (Fig. 1) (Albrecht et al. 1997; Zheng et al. 2001; Meijer 1990).

Within the SCN, neurons are distributed anatomically and functionally in two main parts: a ventromedial (core) and a dorsolateral (shell) region (Fig. 1). In these, vasoactive intestinal polypeptide (VIP) and arginine vasopressin (AVP) are, respectively, the principal neuropeptides (Hastings et al. 2018). Moreover, all SCN neurons contain the inhibitory neurotransmitter γ-aminobutyric acid (GABA) (Herzog et al. 2017; Ono et al. 2018). VIP neurons receive "light" inputs from the retina and project to the dorsal SCN in AVP cells (Fig. 1). Furthermore, VIP serves as a coupling signal (via VPAC2 receptors) to keep a synchronization of the cellular activity across the whole nucleus (Jones et al. 2018; Mazuski et al. 2018). AVP neurons are the SCN clock-output cells to communicate to other brain structures and body organs to time behavioral and physiological rhythms (Fig. 1) (Kalsbeek et al. 2010).

The molecular code of the SCN timekeeping

The identification of genes controlling circadian rhythms in *drosophila* was awarded with the Nobel Prize in 2017 (Callaway and Ledford 2017). These genes were also characterized in mammals and are responsible for rendering the oscillations of each cell in the SCN and body with a period close to 24 h. Basically, the clock mechanism is formed by a positive loop with two transcription factors: the proteins CLOCK (circadian locomotor output cycles kaput) and BMAL1 (brain and muscle ARNT-like 1 protein). These form a protein dimer complex (CLOCK/BMAL1) with the capacity to bind to the E-box regulatory sequence in the promoters of *period* (*Per1–3*) and *cryptochrome* (*Cry1–2*) genes to induce their transcription. Then, *Per* and *Cry* mRNAs are translocated to the cytoplasm and translated into PER and CRY proteins, respectively, which are involved in the negative feedback loop of the clockwork. When they accumulate enough within the cytoplasm, they translocate into the nucleus and inhibit their own transcription. Once the PER and CRY proteins are degraded in the nucleus, the CLOCK/BMAL1 complex reinitiates another 24-h cycle (Fig. 1).

In the cytoplasm and nucleus, degradation of PER and CRY proteins is dependent on ubiquitination mechanisms (Takahashi 2015). PER and CRY protein complex stability and degradation are regulated by other molecular components of the clock such as the casein kinases, CKIδ and CKIε, which phosphorylate PER proteins and the E3 ubiquitin ligase (FBXL3–21) and the glycogen synthase kinase 3 beta (GSK3β) acting on CRY proteins (Meng et al. 2008; Siepka et al. 2007; Godinho et al. 2007; Kurabayashi et al. 2010). These regulations will determine the intrinsic period of the clock (Fig. 1). As a complementary loop, the CLOCK/BMAL1 protein complex activates the nuclear receptor reversed-viral erythroblastosis α (REV-ERBα), which binds retinoic orphan receptor-binding elements (ROREs) in the promoter of *Bmal1* gene (Preitner et al. 2002) (Fig. 1). Thus, REV-ERBα, as a transcription repressor, inhibits *Bmal1* transcription inducing the rhythmic expression of this gene with a peak at night, in contrast to the peaks of rhythms of *Per* gene expression (Preitner et al. 2002; Takahashi 2015).

Clock gene alterations in mood states: from mice mutations to human polymorphisms

The clock gene

Besides the role of clock genes in the molecular construction of circadian rhythms, they have been implicated in the regulation of diverse non-circadian functions and pathological conditions, including psychiatric disorders (Rosenwasser 2010). Locomotor activity rhythms are altered when an important component of the clockwork is missing. In parallel, some of these mutations lead to alterations in mood-like behavior (Table 1).

Mice carrying a $Clock^{\Delta 19}$ mutation, one of the principal components of the positive feedback loop of the clockwork, exhibit a mania-like phenotype; these animals show hyperlocomotion, sleep reduction, anxiety-like behavior and an increase in behavioral responses to reward (Roybal et al. 2007). Moreover, this behavioral mania-like phenotype is reduced when animals are treated with lithium, a widely prescribed mood stabilizer. At the neurobiological level, $Clock^{\Delta 19}$ mutant mice present a hyperdopaminergic state, implicating the midbrain CLOCK protein in the regulation of mania-like behaviors (Roybal et al. 2007; McClung et al. 2005). Interestingly, the specific knockdown of *Clock*, in neurons of the dopaminergic (DA) ventral tegmental area (VTA) in the midbrain, leads to a bipolar disorder-like phenotype in mice. This suggests a selective role of CLOCK in the

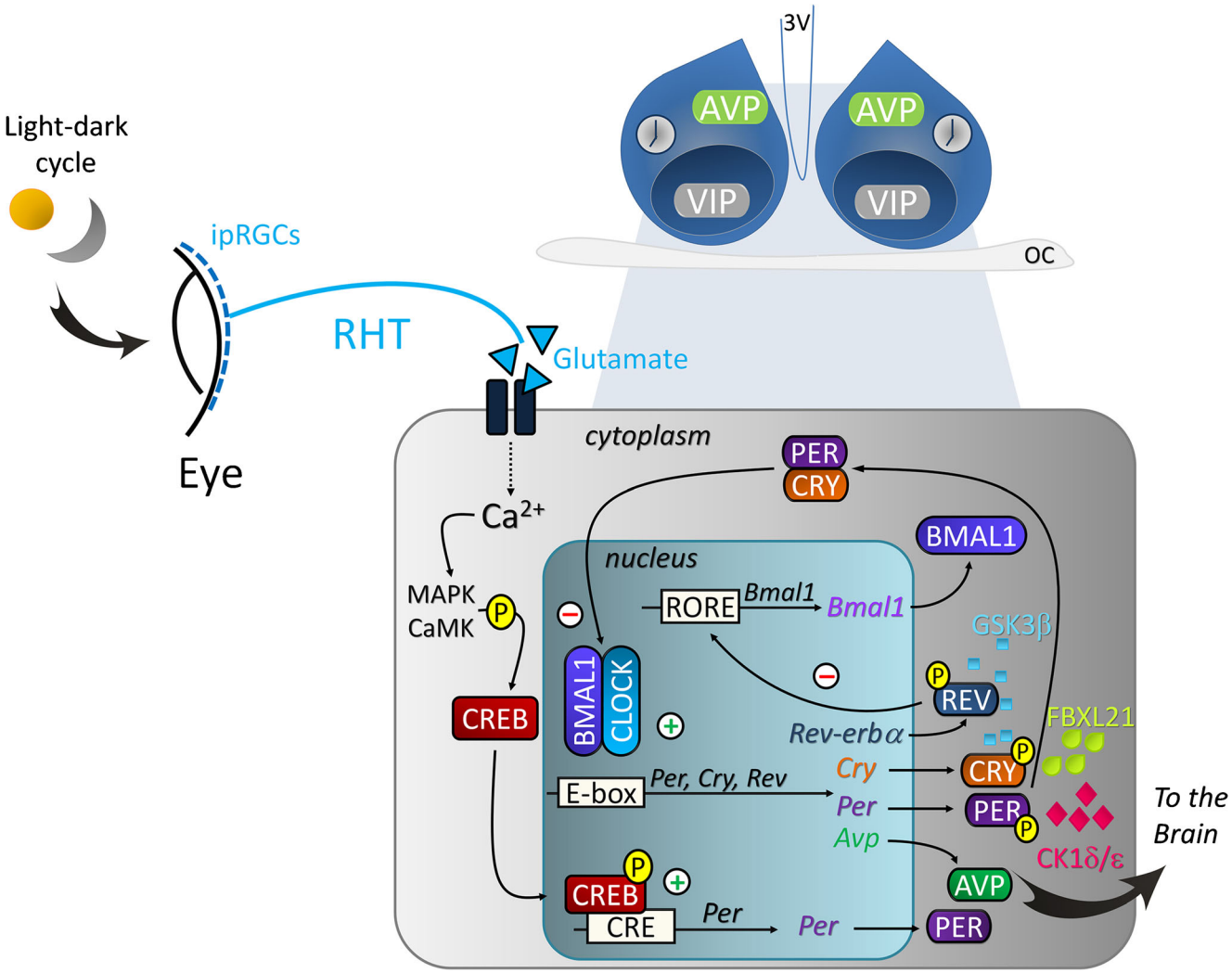

Fig. 1 The suprachiasmatic clock and the molecular code. Schematic representation of the bilateral suprachiasmatic nuclei in the hypothalamus and the anatomical subdivisions in the dorsal AVP-expressing and the ventromedial VIP-expressing regions. The SCN is principally entrained to the light-dark cycle through the RHT that connects the ipRGCs from the ganglion cell layer in the retina with the SCN. Glutamate receptors in the SCN are activated by light signals that lead to an increase of the intracellular calcium concentration and a phosphorylation (P) of CREB (pCREB) by the activation of CaMK and MAPK kinase pathways. pCREB binds the CRE sequence in the promoter of *Per* genes into the nucleus to promote gene expression. Inside each SCN cell, there is a molecular pacemaker based in positive and negative feedback loops of clock gene expression. The proteins of the positive feedback loop, CLOCK and BMAL1, activate the transcription of genes *Per*, *Cry*, and *Rev-Erbα* via the E-box enhancers in the promoter region. The PER and CRY protein dimer complexes formed in the cytoplasm (part of the negative feedback loop) translocate into the nucleus to repress the CLOCK/BMAL1 transcriptional activity. PER and CRY protein stability and degradation in the cytoplasm are modulated by other genes such as GSK3β, FBXL21 and CK1δ/ε. The stability of PER-CRY proteins will determine the intrinsic period of the clock. A third loop is composed of the nuclear receptor REV-ERBα, which represses the transcription of *Bmal1* through binding to ROR elements (ROREs). The molecular clock in the SCN also transcribes the so-called clock-controlled genes such as vasopressin (*Avp*) to communicate the circadian message to the rest of brain. AVP, vasopressin; CaMK, Ca^{2+}/calmodulin-dependent kinase; CK1δε, casein kinase I delta, epsilon; CRE, cAMP-response element; CREB, cAMP response element-binding protein; E-box, enhancer box; FBXL, F-box and leucine-rich repeat protein; GSK3β, glycogen synthase kinase-3 beta; ipRGCs, intrinsically photosensitive retinal ganglion cells; MAPK, mitogen-activated protein kinase; OC, optic chiasm; P, phosphoryl group; RHT, retinohyopthalamic tract; RORE, retinoic acid receptor-related orphan receptor response element; VIP, vasoactive intestinal polypeptide; 3V, third ventricle

DAergic-VTA for the regulation of mood behavior (Mukherjee et al. 2010) (Table 1).

Moreover, *Clock*$^{\Delta 19}$ mutant mice show alterations in the excitatory synaptic response at the level of accumbal spiny neurons with an increase of the hyperpolarized state in these cells and a mania-like phenotype (Parekh et al. 2018).

Diverse studies have been interested in the functional link between clock gene human polymorphisms and mood disorders, finding an important close relationship between clock-related gene polymorphisms with bipolar disorder (BD), a mood disorder characterized by recurrent episodes of mania, depression, or mixed states (Kennaway 2010).

Table 1 Summary of the effects of clock gene mutations on circadian rhythms and mood-related behavior

Clock gene mutation	Circadian phenotype	Mood phenotype	Reference
Clock$^{\Delta 19}$	Arrhythmic in DD	Mania-like behavior	Roybal et al. (2007)
Clock$^{\Delta 19}$ VTA specific	Shortened period	Mania-depressive-like behavior	Mukherjee et al. (2010)
Bmal1 SCN specific	Lengthened period	Depressive-like behavior	Landgraf et al. (2016)
Cry1	Shortened period	Mania-depressive-like behavior	Schnell et al. (2015)
Cry1-Cry2	Arrhythmic in DD	Mania-like behavior	De Bundel et al. (2013)
Per2^{Brdm1}	Arrhythmic in DD	Depression-resistant behavior	Hampp et al. (2008)
Per1-Per2 NAcc specific	ND	Mania-like behavior	Spencer et al. (2013)
Rev-Erbα	Shortened period	Mania-like behavior	Chung et al. (2014)

DD constant darkness, *NAcc* nucleus accumbens, *ND* not determined, *SCN* suprachiasmatic nucleus, *VTA* ventral tegmental area

Polymorphisms in the *CLOCK* gene have been associated with sleep physiology and circadian preferences or chronotypes, referred to as the preference of an individual for sleep timing (earlier or later) (Roenneberg et al. 2003). *CLOCK* gene single nucleotide polymorphism rs1801260 C3111T located in the 3′ flanking region has showed an association of C allele with subjective eveningness (night-type subjects) (Katzenberg et al. 1998). Thus, some studies have proposed the hypothesis that an eveningness preference might be associated with the development of mood disorders (Elmore et al. 1993; Hakkarainen et al. 2003; Johansson et al. 2003; Merikanto et al. 2013).

Patients with BD and insomnia, showing the rs1801260C allele polymorphism of the gene *CLOCK*, experience higher activity at night and reduced amount of sleep than patients with the T allele (Benedetti et al. 2007). Moreover, *CLOCK* rs1801260 gene polymorphism is correlated with suicide attempted under high stress conditions (Benedetti et al. 2015). Interestingly, recently, it was reported that *CLOCK* rs1801260 gene polymorphism in BD patients is correlated with modification of the brain white matter, which might lead to alterations in brain connectivity and functional exchange of information between diverse structures (Bollettini et al. 2017). Myelination and proliferation of oligodendrocyte precursor cells occur during sleep. Because people carrying a *CLOCK* polymorphism present sleep alterations (insomnia), authors proposed that *CLOCK* might modulate the structure and organization of brain white matter via the circadian and homeostatic regulation of sleep (Bollettini et al. 2017). Hence, modifications of the gene *CLOCK* in humans influence circadian (i.e., circadian rhythms, sleep) and non-circadian behaviors (i.e., mood, feelings, suicide attempts) in depressive disorders by anatomical and functional modifications in the brain.

Bmal1 or ARNLT

The second component of the positive feedback loop, *Bmal1*, has also been involved in the regulation of mood states. Selective SCN knockdown of the *Bmal1* clock gene induced a depressive-like phenotype in mice and altered molecular (PER oscillations in the SCN) and behavioral rhythms (locomotor activity) (Landgraf et al. 2016) (Table 1). On the other hand, global mutations of *Bmal1* induce hyperlocomotion (Kondratova et al. 2010); thus, *Bmal1* has a central role in the regulation of mood. Notwithstanding, the SCN may not be the only clock implicated and other circadian clock(s) in the limbic and reward brain areas might also be involved (Mendoza 2017).

Single nucleotide polymorphisms (SNPs) of *ARNTL* (*Bmal1*) are associated with BD. In a recent study, volunteers carrying the T/T genotype of *ARNTL* rs7107287 SNP showed depressive symptoms with a cyclothymic temperament, stress and negative responses to seasonal changes (Jankowski and Dmitrzak-Weglarz 2017). Interestingly, in another report, the *ARNTL* rs2278749 SNP was correlated with body weight gain and food intake, changes associated to seasonal affective disorder (SAD) (Kim et al. 2015), a mood state that is related to or caused by seasonal changes, often occurring during winter time, when the days are short and sunlight is reduced (Wirz-Justice 2018). Moreover, the combination of sequence variations of *PER2*, *ARNTL* and the neuronal PAS domain 2 (*NPAS2)* genes may present a genetic origin for the susceptibility to SAD (Partonen et al. 2007). Thus, despite that the *ARNTL* rs2278749 polymorphism was not directly associated to SAD, it presents some negative phenotypes (e.g., food intake and body weight increase) in response to seasonality and a vulnerability to SAD when this is combined with a polymorphism of other clock genes.

Per genes 1 to 3

Similar to the $Clock^{\Delta 19}$ mutants, $Per2^{Brdm1}$ mutant mice show an increase of dopamine (DA) release in the striatum (Hampp et al. 2008). The hyperdopaminergic state in $Per2^{Brdm1}$ KO mice is explained by alterations in the daily rhythms of the enzyme for DA degradation, the monoaminoxidase-a (Mao-a). In *Per2* mutant mice, there are no diurnal variations of *Mao-a* and the expression of this enzyme is low in KO animals compared with WT control mice, in both the dorsal and ventral regions of the striatum. Thus, PER2 seems to provide a positive signal for DA degradation. Hyperdopaminergic $Per2^{Brdm1}$ KO mice show a depression-resistant-like behavior, showing less immobility in both the forced-swim test (FST) and the tail suspension test (TST) and when these animals are treated with the tyrosine hydroxylase blocker alpha-methyl-p-tyrosine (AMPT), normal behavior is rescued. Thus, the "antidepressive" like behavior in KO mice is in part due to the higher levels of DA (Hampp et al. 2008) (Table 1).

The double *Per1-Per2* global mutant mice and animals with a specific knockdown of both *Per(1–2)* genes in the nucleus accumbens (NAcc) exhibit anxiety-like behavior (Hampp et al. 2008; Spencer et al. 2013). Furthermore, the expression of both *Per1–2* genes is reduced in the NAcc of mice showing anxiety-like behavior due to the exposure to a chronic social defeat stress paradigm (Spencer et al. 2013). Therefore, *Per1–2* genes in the NAcc appear to be key clock components in the regulation of mood sates.

The clock gene *Per3*, although not necessary to maintain robust circadian rhythms, modulates the period of locomotor activity rhythms and other non-circadian functions such as sleep homeostasis, cognition and light sensitivity (Shearman et al. 2000; Archer et al. 2018). *Per3* KO mice display depression-like behavior (i.e., increase of immobility in the TST and FST) when exposed to short photoperiods (Zhang et al. 2016). Moreover, when these mutants are treated with imipramine (a tricyclic antidepressant), the normal phenotype is rescued (Zhang et al. 2016). Interestingly, in the same study, authors reported that transgenic mice with a variant in the *PER3* gene, similar to that found in humans (hPER3-P415A/H417R) with the familial advanced sleep phase disorder and mood alterations, show abnormal behavioral rhythms and depression-like behavior. Thus, this study highlighted two important points: the relevance of *PER3* in the regulation of sleep-wake rhythms and mood and the closely related phenotype of a transgenic mouse model with the *PER3* variation in humans that exhibit sleep and mood perturbations (Zhang et al. 2016).

Two polymorphisms of human *PER3* gene in exons 15 (hPer3ex15) and 18 (hPer3ex18), respectively, were associated with the delayed sleep phase syndrome (DSPS) (Ebisawa et al. 2001) and mood disorders, including depression-like symptoms and temperament changes (Artioli et al. 2007). People with hPer3ex18 polymorphisms and DSPS show an incapacity to sleep and wake-up at regular times with sleep onset after midnight and wake-up times mainly at early afternoon (Chang et al. 2009). People with hPer3ex18 polymorphisms present significant daily changes in mood (depressive episodes) that are increased at the evening (Artioli et al. 2007). Moreover, people with the hPer3ex15 polymorphism have a significantly enhanced response to selective serotonin reuptake inhibitors (SSRIs), one of the drug classes mostly used to treat depression (Artioli et al. 2007). Furthermore, *PER3* gene variants have also been correlated with the postpartum mood disorder and sleep alterations in women (Dallaspezia et al. 2011).

PER3 polymorphisms have been associated with an extreme diurnal preference (assessed with the Horne-Östberg questionnaire that determines morningness-eveningness in human circadian rhythms) (Horne and Ostberg 1976). Importantly, the preference between morning and evening (also termed "morningness" and "eveningness," respectively) is determined by length polymorphisms in *PER3* (Archer et al. 2003). Whereas a *PER3* longer allele polymorphism is associated with morningness, the shorter allele polymorphism is associated with eveningness and the delayed sleep phase syndrome (Archer et al. 2003; Liberman et al. 2018; Jones et al. 2007). Using a mathematical model approach, in a recent study, it was reported that clock gene polymorphisms, associated to mood disorders, induce changes in the period of clock gene expression. These changes observed in the model were correlated with circadian phenotypes and mood in a group of volunteers with genotypic associations between *PER3* variants and diurnal preference. Subjects with a G/G genotype of *PER3* SNP (rs228697) showed an association with eveningness as well as high anxiety and the *PER3* length polymorphism (rs57875989) was correlated with depression (Liberman et al. 2018). All these studies show a link between clock genes, SNP, mood disorders and diurnal preference.

The nuclear receptor Rev-Erbα

Another important component of the clockwork is the nuclear receptor and transcriptional repressor *Rev-Erbα* (Preitner et al. 2002). *Rev-Erbα* mutant mice, in addition to circadian alterations, show higher activity and less immobility, in the TST and FST, than control wild-type animals (Chung et al. 2014; Jager et al. 2014) and an even aggressive behavior (Chung et al. 2014). Interestingly, similar to $Clock^{\Delta 19}$ and $Per2^{Brdm1}$ KO mice, *Rev-Erbα* KO animals also show an increase in DA release and content in the striatum and hippocampus (Chung et al. 2014; Jager et al. 2014). In the mouse VTA, whereas tyrosine hydroxylase (*Th*), the rate-limiting enzyme of catecholamine synthesis, mRNA rhythmic expression peaks at the late night-early morning, *Rev-Erbα* circadian rhythms peak at the midday-early night, opposite to *Th* peak of expression (Chung et al. 2014). *Rev-Erbα* is a repressor of *Bmal1* in the

clockwork competing with the retinoid-related orphan receptor *Rorβ*, for *Bmal1* transcription (Preitner et al. 2002). In a similar manner, in VTA-DA neurons, *Rev-Erbα* competes with the nuclear receptor-related 1 protein (NURR1; an activator of *Th* transcription) for DAergic neuronal function and the circadian expression of *Th* (Chung et al. 2014).

Polymorphism on the nuclear receptor subfamily 1, group D, member 1 (NR1D1) (also known as *Rev-Erbα*) (rs2314339) gene is associated with BD (Kripke et al. 2009). Moreover, Caucasian BD patients with a variant in the promoter of NR1D1 (rs2071427) gene show a positive response to lithium, a drug with an important positive effect in BP disorder and a principal action on the *Rev-Erbα* stability (McCarthy et al. 2011). *Rev-Erbα* mutant mice are hyperactive and importantly, this arousal condition is followed by states of low activity (unpublished observations). Therefore, despite animal and human studies in the *Rev-Erbα* clock gene variant share closely related phenotypes, further studies on the effects of genetic polymorphisms in this gene in mood are necessary to advance the comprehension of this clock gene in mood pathologies.

Cry genes

Mutations of other clock genes such as the single *Cry1* knockout result in both depressive and mania-like behaviors in mice, similar to symptoms observed in BD patients. Furthermore, *Cry1* gene expression is significantly upregulated in the striatum by lithium in animals with a depressive-like phenotype, giving an important implication of the *Cry1* clock gene in BD-like behaviors (Schnell et al. 2015). On the other hand, double *Cry1–2* mutant mice show anxiety-like behavior and higher sensitivity to psychostimulants (De Bundel et al. 2013) (Table 1).

In a Chinese population, patients with major depressive disorder (MDD) have a higher frequency of the C allele of the *CRY1* rs2287161 SNP (Hua et al. 2014). Whereas MDD and BD have been correlated with the *CRY1* (rs2287161) polymorphism, *CRY2* (rs10838524) has been correlated with SAD (Lavebratt et al. 2010). Moreover, in the same study, authors observed that CRY2 expression is rhythmic in blood mononuclear cells of healthy volunteers and that BP patients show lower CRY2 expression and no responses to sleep deprivation as treatment. Thus, this and other studies imply a significant role of *CRY2* in both BP and SAD (Lavebratt et al. 2010; Sjoholm et al. 2010).

The molecular mechanism by which CRY affects the circadian clock and then mood is not totally clear but it might be dependent on the negative feedback loop in which CRY inhibits the CLOCK/BMAL1 dimer activity and then the transcription of *Per* genes not only in the SCN but also in other brain clocks regulating mood and motivation.

Timeless: a circadian and mood regulator in fly and human, respectively

In *Drosophila melagnoster*, circadian rhythms of locomotor activity are robust with a crepuscular pattern in the night-day (dawn) and day-night (dusk) transitions of the light-dark cycle (LD) (Klarsfeld et al. 2003). Similar to mammals, these rhythms are controlled by CLOCK neurons and genes (Rouyer 2015). In *Drosophila melagnoster*, the positive feedback loop of the transcription factors CLOCK and CYCLE activates the genes *period* (*Per*) and *timeless* (*Tim*), which encode PER and TIM proteins, respectively. Consequently, PER and TIM proteins form the negative feedback loop to inhibit the dimer activity of CLOCK/CYCLE (Peschel and Helfrich-Forster 2011). The TIM protein is also present in mammals although its role in the molecular clockwork is not totally clear. However, several studies indicate non-circadian functions of TIM in mammalian cells (Mazzoccoli et al. 2016).

A SNP in *TIM* has been associated with BD. People carrying the A allele of SNP rs774045 on the *TIM* gene are more susceptible to developing BD and the *TIM* SNPs rs2291739 and rs10876890 are correlated with cyclothymic temperament and suicidal attempts (Etain et al. 2014; Pawlak et al. 2015, 2017). Moreover, SAD has been associated with gene variations of TIM in a sex-dependent manner. Whereas females show mood and sleep alterations and energy reduction associated with SAD, males with *TIM* polymorphisms present more fatigue and an early awakening phenotype (Utge et al. 2010). Despite these important associations of *TIM* variants and mood alterations, the molecular and neural mechanisms implicated remain undetermined.

Polymorphisms of clock components might affect protein post-translational modifications such as phosphorylation, an important process in the regulation of clock protein stability.

GSK3β phosphorylates and regulates the stability of clock proteins (Besing et al. 2015). In addition to the circadian role, GSK3β has been implicated in the pathophysiology of depression (Costemale-Lacoste et al. 2018). Within the clock mechanism, GSK3β interacts with PER, CRY and REV-ERBα proteins (Yin et al. 2006; Besing et al. 2015). Moreover, the antidepressant effects of lithium in circadian rhythms occur through the inhibitory action on GSK3β that phosphorylates and stabilizes REV-ERBα (Yin et al. 2006). Interestingly, associations between genetic variations in GSK3β (GSK3β rs334558) and MDD have been found in human populations with insomnia (Costemale-Lacoste et al. 2018).

Lithium has important effects on circadian rhythms of physiology and behavior (Malhi et al. 2017). In mammals (including humans), lithium lengthens the circadian rhythms of locomotor activity (LeSauter and Silver 1993; Hafen and Wollnik 1994; Iwahana et al. 2004; Johnsson et al. 1983) and the rhythms of electrical activity of SCN cells (Abe et al.

2000). Lithium is able to inhibit the activity of GSK3β (Stambolic et al. 1996), leading to an inhibition of the phosphorylation and stability of REV-ERBα (Iitaka et al. 2005; Yin et al. 2006). Thus, whereas GSK3β activation advances the phase of rhythms of clock gene expression, lithium inhibits GSK3β resulting in a delay and lengthening of the period of gene expression and circadian behavior. Therefore, the therapeutic effects of lithium in mood might be due to the modulation of clock gene phosphorylation by the inhibition of GSK3β. Lithium is often used to treat BD, although the use for the treatment of MDD is less common since it does not have therapeutic actions in all patients. For this, other molecules that target and inhibit GSK3β would provide beneficial effects on depressive disorders. For instance, the GSK3β inhibitor L803-mts reduces depressive-like behavior and potentiates the antidepressive effects of ketamine in mice (Kaidanovich-Beilin et al. 2004). These results provide important therapeutic perspectives to treat depression via GSK3β inhibition. However, it is still necessary to find brain circadian targets affected in mood disorders.

Brain clocks in mood beyond the SCN: the particular case of the epithalamic habenula

The identification of clock genes and, more importantly, the oscillatory properties of these in organs and tissues allowed the identification of other circadian clocks apart from the SCN (Herzog 2007; Albrecht 2012). In mammals, clock genes are expressed in the central nervous system and this expression is rhythmic and autonomous in few nuclei. Among them, the retina, the olfactory bulb and the lateral habenula are self-sustained oscillators (Jaeger et al. 2015; Ruan et al. 2008; Granados-Fuentes et al. 2004; Guilding et al. 2010; Salaberry et al. 2018). The habenula (Hb) is a little tiny structure that, together with the pineal gland, forms the epithalamus. The Hb is subdivided into two nuclei according to their anatomical and physiological properties: the medial (MHb) and lateral (LHb) habenula (Fig. 2). Despite that circadian gene expression has been reported to be rhythmic in both subdivisions, it is in the LHb in which the clock is more robust when isolated ex vivo (Sakhi et al. 2014b; Sakhi et al. 2014a; Guilding et al. 2010; Zhao and Rusak 2005).

Electrically, LHb cells show diverse patterns of firing rate activity (tonic, irregular), although as a whole, action potentials of LHb neurons are rhythmic in vivo and in vitro (Zhao and Rusak 2005; Sakhi et al. 2014b). The firing rate of LHb cells is higher at day than night in vivo and in vitro and these cells keep circadian firing at the projected day, indicating their self-capacity and independence from the LD cycle (Zhao and Rusak 2005).

The first study showing the circadian activity of clock gene expression in the LHb was reported using the PER2::luciferase transgenic mouse (Fig. 2). In the medial portion of the LHb, PER2 bioluminescence activity was showed to be rhythmic and self-sustained, even after treatment with tetrodotoxin, a sodium channel blocker, suggesting the presence of circadian properties in each recorded cell of the LHb (Guilding et al. 2010). Moreover, recently, it was reported that the clock in the LHb is present in both the rostral and the caudal regions, independent of the SCN but is affected by clock gene mutations (Salaberry et al. 2018). Therefore, the LHb behaves as an autonomous clock, functionally dependent on the molecular clockwork.

Similar to the main circadian clock in the SCN, an important percentage of LHb cells are light responsive at night (Zhao and Rusak 2005). Interestingly, a recent study using the functional magnetic resonance imaging (fMRI) approach indicated that the human Hb is light responsive in a circadian manner. Indeed, light induces a decrease of activation in the human Hb significantly greater in the morning than in the afternoon (Kaiser et al. 2019).

ipRGC cells project to the brain for the control and regulation of non-visual functions including the light entrainment of the SCN circadian clock (Li and Schmidt 2018; Hattar et al. 2006) (Figs. 1 and 2). Different subtypes of ipRGCs project to brain centers (Schmidt et al. 2011a). Further from the SCN, ipRGCs project to the LHb at the perihabenular region (PHb), the intergeniculate leaflet (IGL) and the lateral geniculate nucleus (LGN) (Hattar et al. 2006; Li and Schmidt 2018; Fernandez et al. 2018). Thus, the external LD cycle might entrain the SCN clock and modulate the cellular circadian activity of the LHb and those neurochemical changes and behaviors are regulated by these epithalamic nuclei (LeGates et al. 2014). Therefore, the LHb is in a good anatomical and functional condition to link circadian rhythms and motivational systems for the regulation of behavior (Mendoza 2017).

The LHb has a relevant role in the control of monoamine systems in the midbrain and brainstem (Metzger et al. 2017; Mizumori and Baker 2017). Anatomically, LHb neurons send a functional glutamatergic projection, via the *fasciculus retroflexus* (*fr*), to the GABAergic rostromedial tegmental nucleus (RMTg) and then to the VTA for the regulation of DA release. Similarly, serotonin (5-HT), from the raphe nuclei, is also regulated by the LHb through the GABAergic projections from the RMTg, although some glutamatergic projections from the LHb target also 5-HT and GABA neurons in the dorsal raphe (Jhou et al. 2009; Brinschwitz et al. 2010; Sego et al. 2014; Metzger et al. 2017; Mizumori and Baker 2017). Importantly, both DA and 5-HT release is rhythmic and regulated by the SCN, albeit it might be also modulated in a circadian manner by the clock in the LHb (Mendoza 2017; Dudley et al. 1998; Hood et al. 2010) **(**Fig. 2**)**.

Besides the little knowledge of the clock role of the LHb, it is well established that there is a strong implication of this structure in diverse functions related to reward and motivation and in certain pathological states like addiction and depression

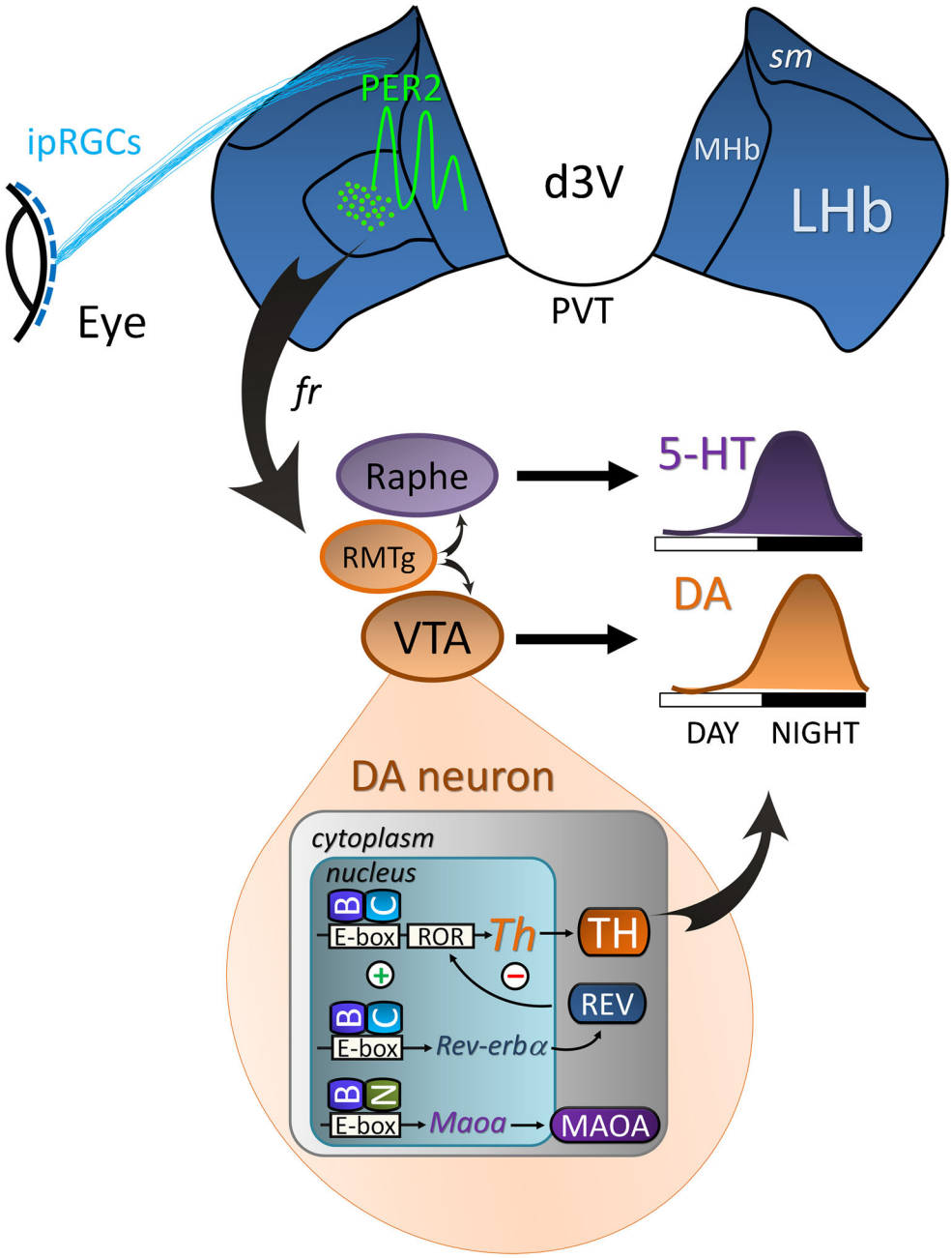

Fig. 2 The epithalamic habenula as a circadian clock. The mammalian habenula is principally subdivided into the medial (MHb) and the lateral (LHb) parts. The LHb contains a circadian clock that expresses a rhythmically spontaneous firing rate and PER protein expression. ipRGCs in the retina project fibers to the boundary region in the LHb (the perihabenular region), suggesting that light might modulate the activity of the LHb clock. The LHb serves as a negative modulator of the monoamine system in the mid and hindbrain. LHb glutamatergic neurons project to the GABAergic RMTg, via the *fr*, which innervates the VTA and raphe nuclei for the regulation of DA and 5-HT, respectively. Importantly, DA and 5-HT release is rhythmic. In VTA-DA cells, the circadian clock regulates rhythms of TH, the precursor enzyme for DA synthesis and MAO-A, the principal enzyme for DA oxidation. Thus, the LHb clock might, together with the SCN, regulate the daily rhythms of monoamines. B, BMAL1; C, CLOCK; d3V, dorsal third ventricle; DA, dopamine; E-box, enhancer box; *fr*, *fasciculus retroflexus*; ipRGCs, intrinsically photosensitive retinal ganglion cells; LHb, lateral habenula; MAOA, monoaminoxidase a; MHb, medial habenula; N, NPAS2; PVT, paraventricular thalamus; RMTg, rostromedial tegmental nucleus; RORE, retinoic acid receptor-related orphan receptor response element; *sm*, *stria medularis*; TH, tyrosin hydroxylase; VTA, ventral tegmental area; 5-HT, serotonin

(Mizumori and Baker 2017; Namboodiri et al. 2016). Significant evidence supports the implication of a hyperactivation of the LHb (an increased electrical activity and cerebral blood flow at the Hb level) in depression in both humans and animal models; moreover, a rescue to a normal rate of electrical activity ameliorates depressive-like symptoms (Lecca et al. 2016; Proulx et al. 2014; Cui et al. 2014; Lecca et al. 2014; Aizawa et al. 2013; Li et al. 2013b). Furthermore, in high-

resolution imaging studies, it was reported that the Hb volume is significantly greater in depressed patients than in healthy control subjects, which is positively correlated with anhedonic symptoms (Liu et al. 2017).

The LHb is activated by non-rewarded stimuli. Thus, negative emotional cues might induce abnormal activity in the LHb, which may lead to depression (Hikosaka et al. 2008; Matsumoto and Hikosaka 2007). In depression, the neurotransmission of DA and 5-HT is unbalanced (reducing extracellular monoamine levels) (Russo and Nestler 2013; Chaudhury et al. 2013). Thus, since the LHb negatively regulates these neurochemical pathways, it would be very possible to imply LHb in the regulation of mood states via the control of monoaminergic nuclei. Hence, because in normal conditions DA and 5-HT release is rhythmic and controlled by the LHb, an altered circadian activity in the LHb might lead to the disruption of daily rhythms of DA and 5-HT in depression. This hypothesis places the LHb clock as an important target for the treatment of depression (Mendoza 2017). Interestingly, light, at day time, inhibits the activity of the Hb (Kaiser et al. 2019); light is used as a treatment for depression and circadian disturbances (phototherapy) (Wirz-Justice et al. 2004). Taken together, light therapy might ameliorate mood and circadian perturbations by direct actions in the clock properties and activity of the human habenula.

The anterior cingulate cortex (ACC) is another brain structure that shows circadian rhythmic expression of clock genes and has been importantly implicated as a central hub in mood regulation (Barthas et al. 2015). A transcriptome-wide analysis in postmortem human brains showed that clock gene rhythmic expression is affected in the ACC of MDD subjects in comparison with control brains (Li et al. 2013a). Furthermore, in a recent study, it was reported that in mice treated with ketamine (a rapid-acting antidepressant), circadian genes are downregulated in the ACC. Moreover, similar effects are observed by sleep deprivation in mice, which is also used as a treatment of depression (Orozco-Solis et al. 2017). Thus, ACC as a putative circadian oscillator emerges as a new and important target for pharmacological and non-pharmacological treatments for mood disorders.

Importantly, using a non-invasive method such as deep transcranial magnetic stimulation, it might be possible to target cortical circadian clocks (e.g., the ACC) in a time-dependent manner (chronotherapy) for an improved treatment of depression (Mutz et al. 2018).

Conclusion

Circadian disruptions (e.g., polymorphisms, environmental perturbations) might lead to mood changes and depression-like behavior. Polymorphism studies linking the circadian clock and mood disorders give important information for understanding the mechanisms implicated in the development of MDD, BD, or SAD and the possibility to propose new treatments. However, all these studies still have some limitations (sample size, populations, etc.), which sometimes give contradictory results and require further verification.

More essential studies are needed that investigate the effects of genetic variants in mood disorders in order to understand the circadian molecular mechanisms underlying these pathological conditions. In addition to the SCN, brain structures involved in the control of monoamine balance and the regulation of behavior show circadian properties that are affected in mood diseases. Thus, the brain's circadian system regulating mood and rhythmic behavior is an attractive target for the current and new treatments in MDD, BD and SAD. In light of this knowledge, novel treatments (pharmacological and non-pharmacological), acting at the level of the brain circadian system (e.g., clock genes, monoamine rhythms), are promising therapeutic opportunities to cure mood disorders. Nevertheless, there is still new knowledge to decipher about how the interaction between genetic (chronotypes) and environmental factors (circadian misalignment) participate in the development of mood-related behaviors. Moreover, it is necessary to identify other molecular and brain circadian targets (LHb, ACC) and circuits to improve treatments, as well as mental health and human well-being.

Acknowledgments We thank Dr. Ipek Yalcin for the invitation to contribute to the special issue and Dr. Tando Maduna and Dr. Cristina Sandu for comments on the manuscript.

Funding information Funding sources are provided by the Agence National de la Recherche (ANR-14-CE13-0002-01 ADDiCLOCK JCJC), the Centre National de la Recherche Scientifique and the Institut Danone France-Fondation pour la Recherche Médicale Consortium.

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