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Rhythm and Mood: Relationships Between the Circadian Clock and Mood-Related Behavior

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Mood disorders are multifactorial and heterogeneous diseases caused by the interplay of several genetic and environmental factors. In humans, mood disorders are often accompanied by abnormalities in the organization of the circadian system, which normally synchronizes activities and functions of cells and tissues. Studies on animal models suggest that the basic circadian clock mechanism, which runs in essentially all cells, is implicated in the modulation of biological phenomena regulating affective behaviors. In particular, recent findings highlight the importance of the circadian clock mechanisms in neurological pathways involved in mood, such as monoaminergic neurotransmission, hypothalamus-pituitary-adrenal axis regulation, suprachiasmatic nucleus and olfactory bulb activities, and neurogenesis. Defects at the level of both, the circadian clock mechanism and system, may contribute to the etiology of mood disorders. Modification of the circadian system using chronotherapy appears to be an effective treatment for mood disorders. Additionally, understanding the role of circadian clock mechanisms, which affect the regulation of different mood pathways, will open up the possibility for targeted pharmacological treatments.

Keywords: mood disorders, circadian clock, animal models, chronotherapy

Today, mood disorders pose both a significant health risk to the individuals afflicted and a financial burden to society. In 2012, the World Health Organization (WHO) reported that 350 million people suffer from mood disorders worldwide (http://www.who.int/mental_health/en/). Mood disorders form a heterogeneous group of mental illnesses, including "depressive disorders" (DD) and "bipolar and related disorders" (BD) (American Psychiatric Association, 2013). Common depressive symptoms are sadness, loss of interest or pleasure (anhedonia), disturbed sleep (insomnia or sleepiness) and appetite (excessive or low), feelings of guilt, low self-confidence, irritable mood, and suicidal ideation. Patients affected by BD experience so-called "mixed features," which refer to episodes of depression, alternating with manic or hypomanic symptoms. Manic features include hyperactivity, extreme happiness, decreased need for sleep, inflated self-esteem, and increased recklessness behavior.

Mood disorders show a complex etiology, in which genetic, environmental and social variables play a role in their incidence (Lau & Eley, 2010; Wittchen et al., 2011). The importance of the genetic component in mood disorders has been demonstrated in different surveys. Recently, case-control analyses of single-nucleotide polymorphisms (SNPs) and genome-wide association (GWA) studies identified several allelic variants in different genes, which may be related to an increased susceptibility to depression (Lau & Eley, 2010; Wittchen et al., 2011). Currently, a widely accepted view to explain both occurrence and hereditability of mood disorders is based on the "sensitivity threshold" model, in which many genes with minor effects contribute to the "disease predisposition" character (Lau & Eley, 2010; Mitjans & Arias, 2012). In addition, recent studies emphasize the importance of gene-environment interactions. From this perspective, a genetically predisposed sensitivity to physical and/or social factors might explain the higher probability of some individuals (with a vulnerable genotype) to develop the pathology when exposed to modified/unfamiliar environmental conditions (Lau & Eley, 2010; Mitjans & Arias, 2012).

During our life, we are constantly exposed to periodic environmental changes such as daily and seasonal variations in light intensity, humidity, and temperature, determined by the Earth's rotation and revolution. These geophysical phenomena likely acted as selective pressures for living organisms to evolve endogenous 24-h clocks (circadian), which allow them to anticipate periodic environmental variations and to optimize the daily timing of their physiological and behavioral processes (Albrecht, 2012). Recently, the circadian oscillator has been succinctly described as a system located "at the interface between the environmental response pathways and internal programs" (Millar, 2004). Because the genetic basis of the circadian clock appears to have evolved early along the course of evolution, it is not surprising to find multiple lines of evidence supporting circadian disruption (genetic or environmental) in the etiology of mood disorders.

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In this review, we will present recent findings supporting the relationship between the circadian clock and mood regulation. After a description of the circadian clock at the organismal and cellular levels, we will point to the possible association between an environmentally induced misalignment of the circadian system and human health problems, comprising affective disorders. Subsequently, we will review a number of studies performed both in humans and animal models supporting the role of the circadian clock in mood regulation. Finally, we will illustrate how the manipulation of the clock, via the use of different therapies, shows beneficial effects in the treatment of mood disorders.

The Organization of the Circadian System

Clock System at the Level of the Organism

In mammals, the central circadian clock resides in the suprachiasmatic nucleus (SCN) of the hypothalamus and governs the rhythm and phase of subsidiary clocks located in virtually all tissues of the body (see Figure 1) (Reppert & Weaver, 2002). The master clock is synchronized by light, which represents the primary environmental cue. This cue is perceived by a specialized type of non-image-forming photoreceptors which are located in a dispersed manner in the retina. These cells are named intrinsically photosensitive retinal ganglion cells (ipRGCs) and contain the photopigment melanopsin. The ipRGCs send information to the SCN via the retinohypotalamic tract (RHT; Figure 1) (for a review see Ecker et al., 2010; Golombek & Rosenstein, 2010). The SCN in turn coordinates the temporal release of several peptides and hormones, which synchronize the secondary oscillators located in peripheral organs (Reppert & Weaver, 2002). Ultimately, the clock-controlled phenotypes, such as body temperature, glucose homeostasis, fat metabolism and sleep/wake cycle are synchronized in phase with the natural 24-h light–dark (LD) cycle. Besides light, other stimuli, such as food, social cues, and physical activity are able to synchronize (entrain) the clock, but with a weaker efficiency compared to light (see Figure 1) (Salgado-Delgado, Tapia Osorio, Saderi, & Escobar, 2011; Webb, Baltazar, Lehman, & Coolen, 2009).

Clock Mechanism at the Level of the Cell

At the molecular level, the circadian clock relies on a series of interlocked autoregulatory transcriptional/translational feedback loops and on a sequence of cycling posttranslational modifications of the clock proteins (see Figure 2) (Albrecht, 2012). In mammals, the basic-helix-loop-helix (bHLH)-PAS (Period-Arnt-Single minded) transcriptional factors CLOCK (or NPAS2 in the forebrain) (Gekakis et al., 1998; Reick, Garcia, Dudley, & McKnight, 2001) and BMAL (isoforms 1 and 2) (Hogenesch, Gu, Jain, & Bradfield, 1998; S. Shi et al., 2010) act as a heterodimer, binding E-box elements (CACGTG) which are located in the promoter of several genes, including three *Period* (*Per1*, *Per2*, and *Per3*) (Albrecht, Sun, Eichele, & Lee, 1997; Sun et al., 1997; Tei et al., 1997; Zylka, Shearman, Weaver, & Reppert, 1998) and two *Cryptochrome* (*Cry1* and *Cry2*) genes (van der Horst et al., 1999). CRYs form complexes with PER proteins, which are then transported into the nucleus and repress their own transcription inhibiting CLOCK-BMAL1 activities, thus forming a negative feedback loop (Kume et al., 1999). The inhibitory activity of PER-CRY complexes appears to be mediated by their capability to recruit a PSF-Sin3-HDAC complex, which inhibits transcription through Histones 3 and 4 deacetylation (Duong, Robles, Knutti, & Weitz, 2011). In addition, CLOCK-BMAL1 heterodimers indirectly regulate *Bmal1* rhythmic expression by promoting the transcription of the *Rev-erb* and *Ror* nuclear orphan receptor genes. Once translated, REV-ERBs and RORs compete for the same elements in the *Bmal1* promoter, activating or repressing its transcription (reviewed in Albrecht, 2012).

Posttranslational modifications of clock proteins are mediated by an elaborate series of interactions with kinases and phosphatases. These impart temporal control over the mammalian clock

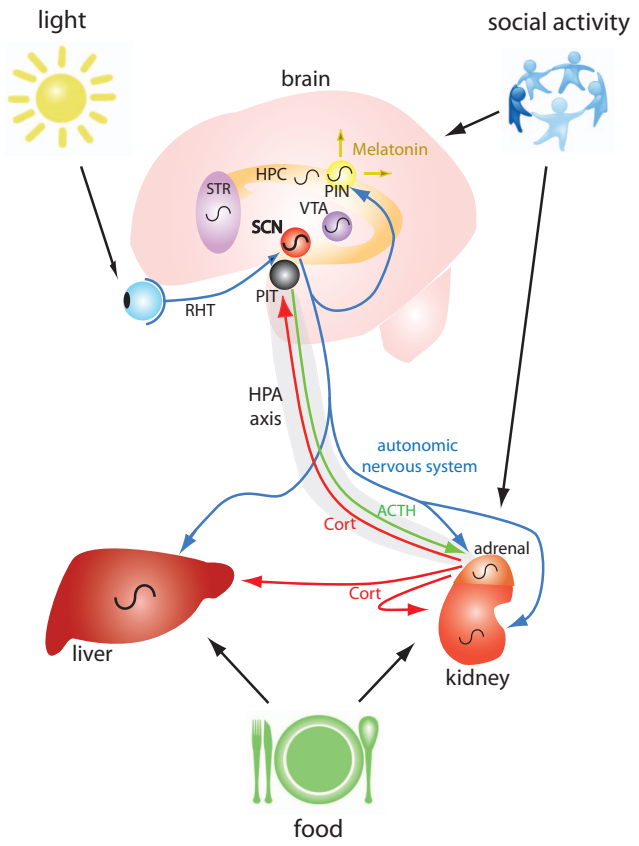

Figure 1. Mammalian clock system at the level of the organism. The master clock localized in the SCN coordinates the circadian rhythms of secondary oscillators located in the brain (VTA, HPC, PIN, STR) and in the periphery (e.g., liver, kidney, adrenal gland), by humoral (green) and neuronal (blue) signals. The pineal gland rhythmically produces the hormone melatonin, which regulates the sleep/wake cycle (yellow). The SCN modulates the HPA axis (gray). The release of ACTH (green) by the pituitary (PIT) controls the rhythmic production of cortisol (Cort) by the adrenal gland (adrenal), forming the HPA axis. Cortisol acts as a synchronizer for peripheral organs and a stabilizer of SCN rhythmicity. Light is the main entrainment cue. The light stimulus reaches the SCN via the retinohypothalamic tract (RHT). Social activity and food are able to entrain the clock acting on peripheral organs or the brain. VTA: ventral tegmental area, HPC: Hippocampus, PIN: pineal gland, STR: Striatum, PIT: pituitary gland, RHT: retinohypothalamic tract, HPA: hypothalamo–pituitary–adrenal, ACTH: Adrenocorticotropic hormone.

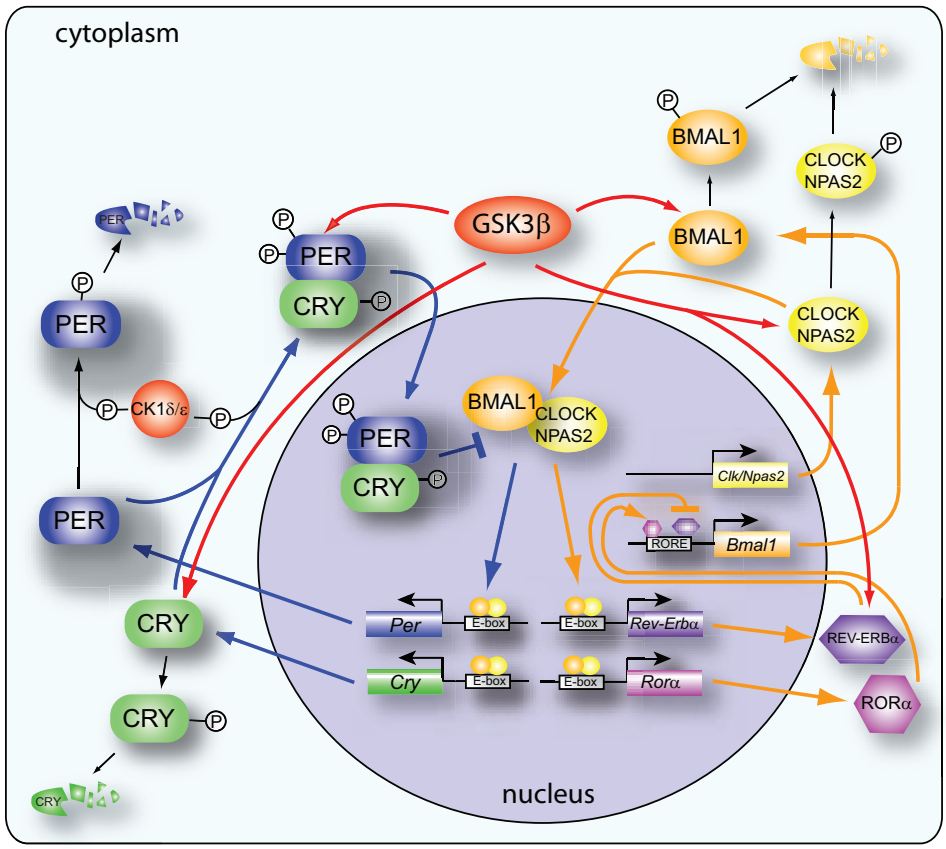

Figure 2. Mammalian circadian clock mechanism at the level of the cell. In the negative feedback loop (blue), BMAL1 together with CLOCK (or NPAS2 in the brain) binds E-boxes in the promoter of *Per* and *Cry* clock genes. CRY and PER proteins form heterodimers, which enter into the nucleus and inhibit CLOCK-BMAL1 activities. An additional loop controls *Bmal1* expression (orange): CLOCK-BMAL1 complexes promote the transcription of *Rev-erb* and *Ror* nuclear orphan receptor genes. REV-ERBs and RORs compete for the same element (RORE) in the *Bmal1* promoter, modulating *Bmal1* transcription. Phosphorylation mediated by CKs (δ/ε) and GSK3β regulates clock protein activities modulating protein–protein interactions, nuclear entry and degradation (see text for details). CLOCK: Circadian Locomotor Output Cycles Kaput; BMAL1: Brain and Muscle ARNT-Like 1; NPAS2: Neuronal PAS domain-containing protein 2; CRY: Cryptochrome; PER: Period; REV-ERB: nuclear receptor subfamily 1, Group D; ROR: Rar-related orphan receptor; CKδ: Casein Kinase delta; CKε: Casein Kinase epsilon; GSK3β: Glycogen Synthase Kinase 3-beta.

feedback loops, modulating protein–protein interactions, nuclear entry and export, and degradation (Jolma, Laerum, Lillo, & Ruoff, 2010). Phosphorylation mediated by Casein Kinases (CKs) exerts a dominant role in circadian timing (Toh et al., 2001; Xu et al., 2005). Both CK1ε and CK1δ interact with PER and CRY proteins and phosphorylate PER proteins, leading to their nuclear translocation and proteasome-mediated degradation (Virshup, Eide, Forger, Gallego, & Harnish, 2007). Another kinase involved in the fine-tuning of the circadian rhythmicity is the Glycogen Synthase Kinase 3β (GSK3β) which phosphorylates PER2 promoting its nuclear translocation (Iitaka, Miyazaki, Akaike, & Ishida, 2005; Ko et al., 2010). In addition, GSK3β phosphorylates REV-ERBα protein, increasing its stability and CRY2, CLOCK and BMAL1 factors, promoting their degradation (Kurabayashi, Hirota, Sakai, Sanada, & Fukada, 2010; Sahar, Zocchi, Kinoshita, Borrelli, & Sassone-Corsi, 2010; Spengler, Kuropatwinski, Schumer, & Antoch, 2009; Yin, Wang, Klein, & Lazar, 2006). Finally, there is growing evidence that several microRNAs are involved in the circadian control of diverse posttranscriptional processes, such as RNA stability, translation and degradation, regulating various aspects of the circadian clock system (Mehta & Cheng, 2013). These data indicate that the circadian timing is controlled at several levels, from DNA to RNA to protein.

Misalignment of the Circadian Clock System in Modern Lifestyle: Jet Lag, "Social" Jet Lag and Shift Work

Since the second industrial revolution (end of 19th century), electricity and subsequent technological advances have progressively uncoupled human's habits from the natural LD cycle, allowing social and work activities at any time of the 24-h day, in particular at night. These lifestyle modifications are currently considered to contribute to a misalignment between the circadian

clock and the environment, which can have deleterious effects in vulnerable individuals. Studies performed in humans who experienced irregular light exposure, such as recurrent jet lag and shift work support this view (Katz, Durst, Zislin, Barel, & Knobler, 2001; Knutsson, 2003; Stevens, 2005).

Jet lag has been described as a travel-induced mismatch between the timing of the endogenous circadian clock and the external environment (Arendt, 2009). Such a mismatch is found in individuals traveling long distances across numerous time zones (Katz et al., 2001). The time zone modification produces a rapid shift in time cues to which the internal circadian clock must realign. It has been estimated that the circadian clock readapts slowly to the new schedule, with a mean rate of 1 day per each hour of time zone crossed (Arendt, 2009; Waterhouse, Reilly, Atkinson, & Edwards, 2007). The common jet lag symptoms are poor sleep, daytime fatigue, and poor performance (Waterhouse et al., 2007). The daytime jet lag complaints seem to be ascribed in part to sleep deprivation and in part to the parallel nighttime physiology of circadian outputs (e.g., core body temperature, alertness, and metabolism are at their minimum, while melatonin, the circadian hormone promoting sleep onset, reaches its secretion peak) (Arendt, 2009). Even if jet lag symptoms are transient (until the realignment of the internal clock), different studies suggest that chronic jet lag experienced by aircrew members might have long term effects on health, such as cognitive deficits, increased risk of heart diseases and cancer (Cho, 2001; Dumser, Borsch, & Wonhas, 2013; Kojo, Pukkala, & Auvinen, 2005).

Another type of chronic jet lag is the *"social" jet lag*, a term coined to indicate the systematic variations in sleep timing between work and free days, which occur regularly every week in people during their work life (or in adolescents during their school career) (Roenneberg, Allebrandt, Merrow, & Vetter, 2012; Wittmann, Dinich, Merrow, & Roenneberg, 2006). In a large-scale epidemiological study, Roenneberg and colleagues demonstrated that the misalignment between the circadian and social clocks could be considered one of the possible risk factors for overweight and obesity (Roenneberg et al., 2012).

A third significant cause of desynchronization between internal clock and environment is *shift work*. In industrialized countries, shift work represents a relevant proportion of the total workforce [~15% of the working population in United States., 23% in Japan, and 20% in the European Union; (Barger et al., 2012; Eurofound, 2012)]. The sleep–wake cycle of shift workers is frequently out of phase with respect to the circadian rhythm (Eastman, Liu, & Fogg, 1995; Gumenyuk, Roth, & Drake, 2012; Richardson & Malin, 1996) and ~10–30% of shift workers develop a Circadian Rhythm Sleep Disorder known as Shift Work Disorder (SWD), characterized by excessive sleepiness during working hours and/or a transient insomnia concomitant to the shift-work schedule (American Academy of Sleep Medicine, 2005; Drake, Roehrs, Richardson, Walsh, & Roth, 2004). Shift work has been associated with decreased productivity, increased work accident episodes [comprising recent catastrophes as Three Mile Island (1979), Bhopal (1984), Chernobyl (1986), the Rhine chemical spill (1986), and Exxon Valdez (1989)] (Williamson et al., 2011), lower quality of life and health problems, such as cardiovascular diseases, diabetes, gastrointestinal problems and cancer (Culpepper, 2010; Gumenyuk et al., 2012; Knutsson, 2003; Stevens, 2005).

Jet lag, "social" jet lag, and shift work might represent environmental risk factors for mood disorders. Jet lag has been suggested as a possible cause in the exacerbation of existing mood disorders (Katz et al., 2001; Katz, Knobler, Laibel, Strauss, & Durst, 2002), while Levandoski and colleagues suggested that "social" jet lag might represent a risk factor for developing depression, particularly in individuals aged from 31 to 40 (Levandovski et al., 2011). Moreover, a recent study evaluating the impact of working time arrangement on mood indicates that depressed mood is significantly higher among shift workers than in day workers (Driesen, Jansen, Kant, Mohren, & van Amelsvoort, 2010). This association resulted more pronounced in males, with percentages of individuals showing both depression and depressive symptoms ranging from 9.8 to 13.6% among shift-workers versus ~6.5% in day workers (Driesen et al., 2010).

Circadian Clock in Mood Disorders

Evidence in Humans

In humans, many indications suggest a relationship between mood disorders and circadian rhythms (Kronfeld-Schor & Einat, 2012). In particular, patients affected by different types of mood disorders show daily variations in their symptoms, with a general improvement of their mood conditions during the evening (Wirz-Justice, 2008), although some individuals may show an opposite trend (Joyce et al., 2005). In addition, depressed patients display an altered sleep/wake cycle, generally suffering from insomnia in the night and sleepiness during the day (Salgado-Delgado et al., 2011; Srinivasan et al., 2009). Frequently, DD and BD individuals show abnormalities in different circadian parameters such as body temperature cycle, blood pressure, melatonin and cortisol secretion (Bunney & Bunney, 2000; Emens, Lewy, Kinzie, Arntz, & Rough, 2009; McClung, 2007; Srinivasan et al., 2009; Srinivasan et al., 2006). Recently a transcriptome-wide analysis showed that in different brain regions the 24-h cyclic expression profile of several circadian genes exhibits lower amplitudes in patients affected by major depressive disorder (J. Z. Li et al., 2013). Moreover, in depressed patients, social activities (e.g., eating and exercising) seem to be less effective as time-givers (Zeitgebers) in the entrainment of the cortisol circadian rhythm (Stetler, Dickerson, & Miller, 2004).

A particular type of depressive disorder is the "seasonal affective disorder" (SAD) (Faedda et al., 1993). People affected by SAD exhibit depressive symptoms mainly during winter and a spontaneous remission during summer, recurrently over years. Besides depressive mood state, SAD patients frequently show hypersomnia, carbohydrate craving and weight gain during the depressive phase, symptoms reminiscent of "hibernation" (Bunney & Bunney, 2000; Lewy et al., 2009).

Several lines of data suggest a relationship between SAD and photoperiod. SAD incidence ranges from 2% to 5% of the general population in temperate zones, but may show higher values in northern regions (as Canada or Scandinavia), which are characterized by extremely short photoperiods during winter (Albrecht, 2010; Bunney & Bunney, 2000; Salgado-Delgado et al., 2011). In addition, it has been noticed that SAD patients traveling from north to south during winter (therefore from shorter to longer photoperiods) report a transient improvement of their mood conditions

(Kronfeld-Schor & Einat, 2012). As patients affected by nonseasonal mood disorders, SAD individuals might show irregularities in different circadian parameters (Bunney & Bunney, 2000). In particular, recent studies associated SAD to a delayed circadian rhythm (Lewy, Lefler, Emens, & Bauer, 2006).

There exist a few syndromes in which circadian rhythm disturbances primarily alter sleep architecture and do not directly affect emotional behavior. For example, familial advanced sleep phase syndrome (FASPS) and delayed sleep phase syndrome (DSPS) are two inherited disorders, which are characterized by shortened or lengthened circadian rhythms due to mutations in the phosphorylation site of PER2 or in casein kinases (Jones et al., 1999; Okawa & Uchiyama, 2007; Toh et al., 2001; Xu et al., 2005). However, only a fraction of patients reported altered mood status and hence, these disorders may not be classified as mood disorders (Shirayama et al., 2003; Xu et al., 2005).

Human population genetic studies associated mood disorders and specific SNPs at the level of different circadian clock genes. These have been recently reviewed by Etain, Milhiet, Bellivier, and Leboyer (2011) and Partonen (2012). Although most of these variants are located in noncoding regions, it is interesting to note that SAD has been associated with polymorphisms at the level of the clock genes *Per2*, *Bmal1*, *Npas2* and *Cry2* and in the *Melanopsin* gene, while associations between both DD or BD disorders and SNPs have been found for clock genes such as *Clock*, *Npas2*, *Bmal* (*1* and *2*), *Per* (*1*, *2* and *3*) and *Cry1* (a more comprehensive list is reported in Table 1).

Finally, it has been observed that treatments modulating the circadian clock (e.g., bright light therapy, sleep deprivation, or lithium treatment) exhibit positive effects on the relief of depressive symptoms, as discussed later in this review. Taken together these data support the hypothesis that at least some affective disorders may be due to a disruption and/or a misalignment of the circadian system (Srinivasan et al., 2006). Further strong indications arise from studies performed using animal models.

Insights From Animal Models

Modeling depression in nonhumans is extremely challenging. The impracticality of measuring mood, guilt or suicidal ideation, the subjective interpretation of depressive-like behavior, and the lack of biomarkers for depression increase the difficulties in finding suitable models to study mood disorders in animals. Appropriate modeling of depressive behaviors is essential, however, to understand and explain neuropsychiatric disorders.

Mice and rats, which show a complex variety of affective-like behaviors, in combination with widely established genetic and molecular tools to study neuronal mechanisms, have been demonstrated to be adequate models to investigate mood disorders. The first challenge is to induce a state of depression or mania, since nonprimates suffering from a basic state of depression hardly exist. Current paradigms to induce a state of depression in rodents include chronic mild stress (Willner, 1997, 2005), social defeat (Golden, Covington, Berton, & Russo, 2011), chronic corticosterone administration (David et al., 2009; Murray, Smith, & Hutson, 2008), olfactory bulbectomy (Song & Leonard, 2005), and genetic manipulations. The second challenge is to measure alterations in mood-related behaviors. Assessment of motivation and despair are principal characteristics used to screen for affective behaviors. The forced swim test (FST), the tail suspension test (TST) and the learned-helplessness (LH) test are widely used methods. The assessment of anhedonia, another core symptom of depression, is used as additional indicator of depression and can be measured by sucrose preference or intracranial self-stimulation (ICSS) (Crawley, 2000; Pollak, Rey, & Monje, 2010). Antidepressant treatments have been shown to restore preference for rewarding stimuli as well as to increase escape-like behaviors in the FST and TST (Crawley, 2000).

The use of these paradigms allows for the characterization of multiple biological mechanisms associated with the etiology of mood disorders. In the following paragraphs we will discuss recent

Table 1
Studies Showing Evidence of Association Between Circadian Clock Genes and Mood Disorders in Humans

Gene	BD	DD	SAD
Clock	Shi et al., 2008; Kripke et al., 2009; Lee et al., 2010; Soria et al., 2010	Soria et al., 2010	
Npas2	Kripke et al., 2009; Mansour et al., 2009; Soria et al., 2010	Soria et al., 2010	Johansson et al., 2003; Partonen et al., 2007
Bmal1	Nievergelt et al., 2006; Mansour et al., 2006, 2009; Soria et al., 2010; McCarthy et al., 2012	Soria et al., 2010; Utge et al., 2010	Partonen et al., 2007
Bmal2	Soria et al., 2010	Soria et al., 2010	
Per1	Kripke et al., 2009		
Per2	Kripke et al., 2009	Soria et al., 2010	Partonen et al., 2007
Per3	Mansour et al., 2006; Nievergelt et al., 2006; Soria et al., 2010	Soria et al., 2010	
Cry1	Soria et al., 2010	Soria et al., 2010	
Cry2	Mansour et al., 2009		Lavebratt et al., 2010
Rev-erbα	Kishi et al., 2008; Kripke et al., 2009; Severino et al., 2009	Soria et al., 2010	
Rora	Soria et al., 2010	Utge et al., 2010	
Rorb	Mansour et al., 2009; McGrath et al., 2009; McCarthy et al., 2012		
Ck1δ	Kripke et al., 2009		
Ck1ϵ	Shi et al., 2008; Mansour et al., 2009; Soria et al., 2010	Utge et al., 2010	
Gsk3β	Szczepankiewicz et al., 2006		
Melanopsin			Roecklein et al., 2009

Note. Modified from Etain et al., 2011.

findings which provide strong evidence for interactions between clock and mood, focusing on neurological pathways, such as monoamine transmission, hypothalamus-pituitary-adrenal (HPA) axis regulation, SCN and olfactory bulb activities, and neurogenesis (Figure 1; Table 2).

The Monoaminergic Hypothesis of Depression, Insights From Clock Mutant Mice

A variety of studies performed in mice indicate the importance of the monoaminergic circuitry in mood regulation, even if the precise role of the different monoamines (e.g., dopamine, serotonin) still remains unclear (Chaudhury et al., 2013; McClung, 2013). Interestingly, it has been demonstrated that brain structures of the dopaminergic reward system, such as the ventral tegmental area (VTA), prefrontal cortex, nucleus accumbens (NAc) and amygdala, express clock genes in a 24-h pattern but not necessarily in the same phase (see Figure 1) (Albrecht, 2013; Guilding & Piggins, 2007; Lamont, Robinson, Stewart, & Amir, 2005). Insights into the impact of the circadian clock on the reward pathway rise from the two well-studied clock gene mutant mice *Per2*^{Brdm1} and *Clock*Δ19, which both show mania-like behaviors.

Compared to wild-type animals, *Per2*^{Brdm1} mutants display lower immobility time in the FST, altered neuronal activity and higher dopamine levels in the striatum (Hampp et al., 2008). Additionally, they show increased preference toward drugs of abuse, such as ethanol (Barger et al., 2012; Spanagel et al., 2005) and cocaine (Abarca, Albrecht, & Spanagel, 2002), which indicates a dysregulation of the reward circuit. A possible molecular target, which might explain the mania-like phenotype in *Per2*^{Brdm1} mice, is the *monoamine oxidase A* (*MaoA*) gene, which codes MAOA, the rate-limiting enzyme in the amine neurotransmitter catabolism (Hampp et al., 2008). In the VTA and striatum (see Figure 1), both *MaoA* mRNA levels and MAOA activity show a circadian variation. In the VTA, BMAL1 binds the *MaoA* promoter in a daytime dependent manner, while in both VTA and striatum PER2 appears to act as a positive factor in the regulation of *MaoA* expression. In *Per2*^{Brdm1} mice, PER2 absence leads to an aberrant and dampened *MaoA* transcription profile during the 24-h day and a parallel increase of dopamine in the mesolimbic system, suggesting a direct link between the circadian clock and mood regulation (Hampp et al., 2008).

The *Clock*Δ19 mutants also show symptomatic behaviors of mania, that is, aberrant reward-seeking behavior. They exhibit greater sensitization to the rewarding stimulus of cocaine as well as increased sucrose preference and ICSS (McClung et al., 2005; Roybal et al., 2007). Moreover, compared to wild-type mice they show less depression-related behavior, reduced anxiety, increased specific exploration and a higher sensitivity to altered photoperiod (Roybal et al., 2007; van Enkhuizen, Geyer, Kooistra, & Young, 2013), reflecting additional hallmarks of mania in humans suffering from BD disorders.

Dysregulation of dopamine signaling appears to be associated to the *Clock*Δ19 manic phenotype. The absence of a functional CLOCK protein leads to increased dopamine release and turnover in the striatum, augmentation in type 1 and 2 dopamine receptors (DR) and a significant shift in the ratio of DR1:DR2 in favor of DR2 receptor signaling (Spencer et al., 2012). It is interesting that the VTA specific knockdown (KD) of *Clock* leads to increased dopaminergic activity and altered regulation of multiple genes controlling dopamine metabolism (Mukherjee et al., 2010). Besides physiological measures, hyperactivity and anxiety-like behaviors are also recapitulated in the *Clock* KD mice; and depression-like symptoms have been observed in this model (Mukherjee et al., 2010). It is interesting to note that the VTA *Clock* KD alters the free running amplitude and period of locomotor activity (Mukherjee et al., 2010).

The mania-like phenotypes of *Per2*^{Brdm1} and *Clock*Δ19 mutant mice may be only partially due to elevated dopamine levels, while modifications in the glutamatergic signaling may also contribute to the altered mood state. Glutamate levels are abnormally elevated in *Per2*^{Brdm1} mice, possibly caused by a lack of glutamate clearance from the synaptic cleft (Spanagel et al., 2005). This likely leads to an abnormal neural phase signaling, a putative mechanism through which the brain ties the activity of neurons across distributed brain areas to generate thoughts, percepts, and behaviors (Lisman & Buzsaki, 2008). This appears to be similar for *Clock*Δ19 mutants, since they lack inhibitory control and show an abnormal neural oscillatory phase signaling, which is partially explained by changes in dendritic morphology and reduced glutamate receptor subunit (GluR1) expression (Dzirasa et al., 2010). Neurochemical alterations in glutamatergic signaling, such as increased glutamate and decreased serotonin in the hippocampus have also been shown in mice lacking a subunit of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor 1, GluA1 (Chourbaji et al., 2008). The GluA1 KO mice exhibit abnormal affective behaviors relevant for schizoaffective disorders and mania (Fitzgerald et al., 2010), but repeated stressful events lead to a depression-like phenotype (Chourbaji et al., 2008). A misbalance of dopaminergic and glutamatergic signaling may underlie the etiology of mood disorders, in particular manic behaviors, and clock components appear to play pivotal roles in these pathways.

Table 2
Studies Showing Evidence of Association Between Circadian Genes and Mood Regulation in Animal Models

Gene	Monoaminergic and glutamatergic signaling	HPA-axis	Neurogenesis
Clock	McClung et al., 2005; Roybal et al., 2007; Mukherjee et al., 2010; Dzirasa et al., 2011; Spencer et al., 2012		
Per2	Abarca et al., 2002; Spanagel et al., 2005; Hampp et al., 2008		Lamont et al., 2005; Borgs et al., 2009
Per1		Yamamoto et al., 2005; Gillhooley et al., 2011	Gillhooley et al., 2011
Cry1		Lamia et al., 2011	
Cry2		Lamia et al., 2011	

The Importance of the HPA-Axis in Mood Disorders and Links to Clock Genes

Mood disorders have been related to a dysregulation of the hypothalamus-pituitary-adrenal (HPA) axis (see Figure 1). The final product of this neuroendocrine system is cortisol, a glucocorticoid hormone with several functions, including regulation of circadian phenomena, learning and memory and response to stress (Watson & Mackin, 2009). Secretion of cortisol in humans (or predominantly corticosterone in rodents) is tightly regulated by the circadian clock. The SCN controls the daily release of adrenal glucocorticoids immediately before the onset of awakening (Kalsbeek et al., 2012) and both hypercortisolemia and/or a dampening in the cortisol circadian production have been frequently observed in DD and BD patients (Pariante & Lightman, 2008; Watson & Mackin, 2009). It is interesting that glucocorticoids can drive rhythmic expression of clock genes in vitro (Balsalobre, 2000) and in vivo in various tissues (Torra et al., 2000; Yamamoto et al., 2005). One of the possible targets is *Per1*, most studied and very promising in terms of circadian synchronization by glucocorticoids. The *Per1* promoter region contains glucocorticoid response elements (GREs), which likely mediate the enhancing effect of glucocorticoids on *Per1* expression. In mouse peripheral tissues, acute physical stress and glucocorticoids were shown to specifically increase *Per1* mRNA levels but not the transcription of other clock genes (Yamamoto et al., 2005). In addition, glucocorticoids affect *Per1* expression in the brain. Flattening of plasma corticosterone rhythms in rats led to a dampening of *Per1* transcriptional rhythms in the SCN and abolished *Per1* expression in the dentate gyrus (DG) of the hippocampus (HPC; Figure 1) (Gilhooley, Pinnock, & Herbert, 2011).

Moreover, the clock elements CRY1 and CRY2 bind the Glucocorticoid Receptor (GR) in a ligand-dependent fashion, leading to its rhythmic activity. Mice lacking *Cry1* or/and *Cry2* show alterations of HPA axis signaling and display constitutively increased serum levels of corticosterone, as observed in depressed human subjects (Lamia et al., 2011).

An interesting model is the glucocorticoid receptor-impaired (GR-i) mouse (Pepin, Pothier, & Barden, 1992). Compared to wild-type, GR-i mice show aberrant *Glucocorticoid receptor* (GR) mRNA levels and abnormal GR-specific binding sites in the brain, especially in the hippocampus, under both normal and mild stress conditions (Froger et al., 2004). In addition, GR-i mice exhibit hyperactivity of the HPA axis and altered mood-related and anxiety behavioral responses (Barden et al., 2005; Païzanis et al., 2010). Impaired GR function is widely believed to contribute to depression and is considered a possible target for antidepressant therapies. It is interesting to note that expression of clock genes, such as *Per1*, *Per3*, *NPAS2* and *Rev-erb* are altered in GR-i mice (Massart, Mongeau, & Lanfumey, 2012), which again underlines a strong interaction between the circadian clock and the HPA axis in mood regulation.

Role of the Master Clock SCN and the Semiautonomous Oscillator Olfactory Bulb in the Etiology of Depression

The SCN, as master pacemaker, is crucial for circadian timing (see Figure 1). But is it also involved in mood regulation? Only few studies address this question. A lesion study demonstrated a SCN dependent diurnal expression of dopamine transporter and thyrosine hydroxylase in rodents (Sleipness, Sorg, & Jansen, 2007). In addition, bilateral destruction of the SCN led to reduced depressive-like behaviors in rats (Tataroğlu, Aksoy, Yilmaz, & Canbeyli, 2004). On the contrary, a different study found that SCN lesions did not affect depressive and anxiety-related behavior following social defeat, although the anxiolytic/antidepressant action of the novel drug agomelatine requires the integrity of the SCN (Tuma, Strubbe, Mocaer, & Koolhaas, 2005). Taken together these data suggest that the SCN has some impact on mood regulation. It remains to be clarified if this is due to a direct regulation of mood components or simply because the SCN orchestrates the circadian system.

Many symptoms with high relevance for mood disorders are observed after olfactory bulbectomy in rats (Song & Leonard, 2005) and mice (Zueger et al., 2005). The behavioral changes include increased exploratory behavior, reduced anxiety, increased open field activity, impaired stress adaptation and increased immobility in the FST (Morales-Medina, Dumont, Bonaventure, & Quirion, 2012; Song & Leonard, 2005). Antidepressant treatment of olfactory bulbectomized animals largely corrects aberrant neurotransmitter levels, neuroendocrinological changes and behavioral symptoms (Machado et al., 2012; O'Connor & Leonard, 1988; Pandey, Rajkumar, Mahesh, & Radha, 2008). It appears that the projections of the olfactory bulb to the amygdala play an important role in regulation of these behavioral and neurochemical outputs (Wrynn et al., 2000). Although both olfactory bulb (Granados-Fuentes, Tseng, & Herzog, 2006) and amygdala (Lamont et al., 2005) express clock genes, only the olfactory bulb fulfills all the criteria to act as a self-sustained master pacemaker (Abraham, Prior, Granados-Fuentes, Piwnica-Worms, & Herzog, 2005; Granados-Fuentes et al., 2006). Olfactory bulbectomy in rats causes modifications in the circadian amplitude of locomotor activity, heart rate, and body temperature (Vinkers et al., 2009), and similar impairments in these circadian outputs have been observed in humans during depressive episodes. An earlier study reports a dampening of daily body temperature and locomotor activity rhythms combined with a morning increase of corticosterone in olfactory bulb-lesioned rats (Marcilhac et al., 1997). Not only in rodents, but also in the nocturnal primate gray mouse lemur olfactory bulbectomy markedly modified the circadian system (Perret, Aujard, Seguy, & Schilling, 2003). Taken together, these observations suggest that the olfactory bulb may be a critical component in terms of linking circadian rhythms to depressive symptoms.

The Impact of Neurogenesis on Depressive-Like Behavior

Neurogenesis appears to be related to depressive behavior and vice versa. The neurogenesis hypothesis of depression postulates that formation of new neurons in the adult brain is essential for mood control and may be responsible for the beneficial effects of antidepressants (Samuels & Hen, 2011). Different studies report a reduction of hippocampal gray matter volume accompanied by decreased Brain-Derived Neurotrophic Factor (BDNF) levels in depressed patients, who can be partially treated by antidepressant medication (Arnone et al., 2013; Sen, Duman, & Sanacora, 2008).

Neurotropic factors, like BDNF and Vascular Endothelial Growth Factor (VEGF), may be involved in antidepressant neurogenesis (Duman & Monteggia, 2006), but serotonin signaling is also considered as an alternative explanation (Santarelli et al., 2003). Adult neural stem/progenitor cells (NPCs) persist predominantly in the DG of the HPC (see Figure 1) and the subventricular zone (SVZ) of the lateral ventricle where they give rise to newly formed neurons. Progenitor cells from the SVZ migrate along the rostral migratory stream to the olfactory bulb and differentiate into interneurons. Interestingly, it has been suggested that adult neurogenesis is enhanced in a time-of-day-dependent manner, since M-phase cells show a significant increase during the night, whereas S-phase progenitors remain unchanged (Tamai, Sanada, & Fukada, 2008). Other studies confirmed that neurogenesis occurs mainly during the night in LD conditions and appears to be enhanced by physical exercise (Garrett, Lie, Hrabe de Angelis, Wurst, & Holter, 2012; Holmes, Galea, Mistlberger, & Kempermann, 2004). In the DG, *Per1* expression shows daily rhythmicity, which is specifically dampened by corticosterone (Gilhooley et al., 2011). Since GR-receptors are widely expressed in the DG (Maurel, Sage, Mekaouche, & Bosler, 2000) and corticoids control the levels of neuronal progenitors, these results suggest that daily corticosterone rhythms control neurogenesis (Gilhooley et al., 2011). A study in rats showed diurnal rhythms of the PER2 protein expression in the pyramidal cell layer of the DG and in nuclei of the amygdala, that appears to depend on a functional SCN (Lamont et al., 2005). Borgs and colleagues found expression of PER2 in the DG of mice, although with a constitutive profile (Borgs et al., 2009). Nevertheless, this study provides a functional link between the clock and neurogenesis. In fact Bromodeoxyuridine (BrdU) labeling in $Per2^{Brdm1}$ mutant mice revealed an increased number of newborn neurons in the DG compared to wild-type animals, meaning that PER2 is required to control proliferation of NPCs. Furthermore, there is strong evidence that PER2 regulates the NPCs differentiation into postmitotic neurons in the DG, whereas the accumulation of neurons in the $Per2^{Brdm1}$ mutants seems to be balanced by increased neuronal apoptosis (Borgs et al., 2009). However, additional studies are required to clarify and understand the role of the clock on neurogenesis in the context of depression.

The Effect of Light and Photoperiod on Mood Regulation

As previously discussed, modifications in environmental light can affect mood in humans. The effects of abnormal light exposure on mood-related behaviors have been investigated in rodents. Chronic exposure to light, which strongly affects the circadian rhythm and the sleep–wake cycle, has been demonstrated to increase depression-like behaviors and decrease spatial memory and anxiety-like responses in rats (Fonken et al., 2009; Ma et al., 2007; Tapia-Osorio, Salgado-Delgado, Angeles-Castellanos, & Escobar, 2013). These studies suggest that light affects mood via a modification of the circadian timing system and/or the sleep pathways. However, LeGates and colleagues (2010) recently demonstrated that light could also directly influence mood-related behaviors in mice. In fact, wild-type mice subject to a 7-h LD cycle (3.5 h of light followed by 3.5 h of darkness), displayed increased depression-like behaviors and learning impairments, but no significant disruption in their circadian timing system or sleep. This light effect was associated with the melanopsin-expressing photoreceptors ipRGCs, since the aberrant 7-h LD cycle did not cause any mood-related or learning deficits in ipRGC-defective mice (LeGates et al., 2012).

SAD appears to be strongly influenced by changes in the photoperiod, showing recurrence of severe episodes of depression during short days in winter. Given the link to the photoperiod, SAD is nowadays studied using diurnal species in addition to the more conventional and better-known nocturnal models, such as rats and mice. Different studies demonstrated that shortening of photoperiod leads to depression and anxiety-like behaviors in both nocturnal species, like Wistar rats and Siberian hamsters (*Phodopus sungorus*) (Prendergast & Kay, 2008; Pyter, Reader, & Nelson, 2005; Workman, Manny, Walton, & Nelson, 2011) and diurnal rodents, such as the grass rat (*Arvicanthis niloticus*) or the ground squirrel (*Spermophilus citellus*) (Ashkenazy-Frolinger, Kronfeld-Schor, Juetten, & Einat, 2010; Einat, Kronfeld-Schor, & Eilam, 2006; Krivisky, Ashkenazy, Kronfeld-Schor, & Einat, 2011; Leach, Ramanathan, Langel, & Yan, 2013). How the short photoperiod influences neurological pathways leading to a depression-like mood state remains still unclear. Two possible mechanisms suggested to play a role in the etiology of SAD are neuronal plasticity and brain volume. In seasonally breeding rodents, short days lead to reductions in brain volume and alterations in hippocampal spine density (Pyter et al., 2005; Workman et al., 2011). Another study hypothesized that the reductions in light exposure affects the communication from the SCN to monoaminergic neurons generating a depression-like phenotype in rats (Gonzalez & Aston-Jones, 2008). Finally, it has been postulated that short photoperiods increase the time of melatonin production and it has been shown that melatonin administration increases depression-like behaviors in fat sand rats mimicking the effect of short days (Ashkenazy, Einat, & Kronfeld-Schor, 2009). However, the role of melatonin is still controversial, since acute administration doses cause a reduction of depressive-like phenotypes in mice (Kopp, Vogel, Rettori, Delagrange, & Misslin, 1999; Ramírez-Rodríguez, Klempin, Babu, Benitez-King, & Kempermann, 2009). It is worth mentioning that most mouse laboratory strains are melatonin-deficient, while others possess normal melatonin production and secretion (Kasahara, Abe, Mekada, Yoshiki, & Kato, 2010). Comparative studies using these different strains might shed light on the putative involvement of melatonin in the association between photoperiods and neurological pathways implicated in mood regulation.

Circadian Clock and Nonaffective Behavioral Outputs

Affective behaviors appear to be tightly associated with the circadian clock. But can a disrupted circadian timing system also affect behavioral outputs, without altering mood? First, locomotor activity is tightly connected to the circadian clock, and is a primary output of it. In mutant mice with a defective clock, the period of locomotor activity can be either shorter or longer compared to wild type animals. For example *Cry1* mutants show a period shorter than 24 hours, whereas *Cry2* mutants show a period longer than 24 hours (van der Horst et al., 1999). In both mutants no alterations in mood related behaviors have been reported so far.

It is interesting that cognitive performance and memory may vary over the circadian cycle (reviewed in Mulder, Gerkema, &

Van der Zee, 2013), and there is evidence that the *Cry 1* and *2* genes may be required for time-place learning (Van der Zee et al., 2008). It also appears that *Npas2* is involved in hippocampus-dependent context and cued fear memory (Garcia et al., 2000), whereas *Per1, 2* double mutants exhibit normal spatial and contextual learning (Zueger et al., 2006). Furthermore, it is known that animals remember time of day based on their circadian phase and correlate it with place and naturally occurring events, such as food availability or presence of predators. This process seems to be altered in $Per2^{Brdm1}$ mutant mice, as they lack food-anticipatory behavior (Feillet et al., 2006).

As already discussed above, hippocampal synaptic plasticity is a key event in memory formation and learning, and there are many studies that demonstrate an importance of circadian components in hippocampal function. To make a clear discrimination between cognitive and affective behaviors, however, is very difficult, since both behaviors share common pathways and affect each other. This interrelationship can also be observed in various clock gene mutant mice, such as $Per2^{Brdm1}$ mutants, which show a broad range of behavioral phenotypes. Further research is required for a better understanding of the mechanistic basis of the clock, regulating both cognitive and affective outputs.

Mood Therapies and Insights Into Mechanisms

Monoamines, the HPA axis, neurogenesis, and light control depression-like behaviors in animal models, which mimic symptoms of human patients. In all of the above-discussed models circadian rhythms play an important role. The involvement of the circadian clock becomes evident when taking a closer look at the various possibilities to treat mood disorders. The main applied treatment strategies are based on pharmacological therapy and/or chronotherapeutics, which include bright light therapy (BLT), sleep deprivation (SD) and daily routine/exercise.

Pharmacological Antidepressants and Their Effect on the Circadian System

In human patients, classical antidepressants like specific serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors and tricyclic antidepressants affect both sleep structure and circadian parameters, such as melatonin and cortisol secretion (Kronfeld-Schor & Einat, 2012). There are complex interactions between the serotonergic system and the circadian clock, and several animal studies demonstrate an effect of SSRIs on circadian rhythms. Injection of the serotonin receptor agonist Fluoxetine during the day leads to phase advances of activity rhythms and alters the expression of different clock genes in rodents (Cuesta, Mendoza, Clesse, Pevet, & Challet, 2008; Horikawa et al., 2000; Mendoza, Revel, Pevet, & Challet, 2007). A direct effect of SSRI on circadian parameters was demonstrated in rat fibroblasts expressing the *Per1*-luciferase transgene, in which the SSRI Sertraline significantly dampens and shortens *Per1* oscillation (Nomura, Castanon-Cervantes, Davidson, & Fukuhara, 2008). These results indicate that SSRIs can provide nonphotic cues to synchronize disrupted circadian clocks in depressive patients, which contributes to a reduction of depressive symptoms.

Strong evidence for the importance of the circadian clock in mood therapy emerges from the mood stabilizer lithium. Since the 1950s, lithium therapy has proven to be highly efficient in treating BD patients (Baldessarini & Tondo, 2000; Cruceanu, Alda, & Turecki, 2009), including a reduction of suicide rate (Cipriani, Pretty, Hawton, & Geddes, 2005). The clinical profile of lithium is versatile, it is used to treat different phases of BD disorder, since high plasma levels are efficient in treating the acute manic phase, whereas lower levels are beneficial during the bipolar depressive state (Malhi, Tanious, Das, & Berk, 2012). The kinase GSK3β, which is involved in the fine-tuning of circadian rhythms, is considered one of the key targets in the action mechanism of lithium. In vitro lithium treatment increases GSK3β phosphorylation, thus inhibiting its activity (Iitaka et al., 2005; Stambolic, Ruel, & Woodgett, 1996). Similar observations have been reported in BD patients after antimanic treatment with lithium (X. Li et al., 2007; X. Li, Liu, Cai, Wang, & Li, 2010; Polter et al., 2010). Moreover there is a relationship between GSK3β and mood-related behavioral disturbances in animal models. GSK3β overexpressing mice are hyperactive (Prickaerts et al., 2006), whereas selective GSK3β inhibitors and lithium treatment reduce hyperactivity in mouse models of mania (Beaulieu et al., 2004; Roybal et al., 2007). On the other hand, lithium has antidepressant and neuroprotective properties on different mouse strains (Can et al., 2011; Marmol, 2008). There is a big ongoing discussion about the downstream targets of GSK3β responsible for the benefits of the lithium therapy. Results from an in vitro study suggest that lithium's therapeutic effect might be based on the modulation of the canonical Wingless signaling, leading to increased neurogenesis. Lithium-induced proliferation of hippocampal progenitor cells was mimicked by overexpression of β-catenin (a down-stream target of GSK3β), and β-catenin knockdown abolished the neurogenic effects of lithium (Wexler, Geschwind, & Palmer, 2008). Besides β-catenin, BDNF, Inositol monophosphatase and serotonin receptors are substrates of GSK3β, but particularly interesting GSK3β-targets are several circadian clock components. Stability or subcellular localization of PER2, CRY2, BMAL1, CLOCK and REV-ERBα appears to be regulated by GSK3β mediated phosphorylation (see Figure 2) (Harada, Sakai, Kurabayashi, Hirota, & Fukada, 2005; Ko et al., 2010; Sahar et al., 2010; Spengler et al., 2009; Yin et al., 2006). It is therefore not surprising to observe a strong effect of lithium on diverse circadian parameters. The most prominently observed phenotype is a period lengthening in clock protein and RNA expression profiles as well as in locomotor activity rhythms in mice (Kaladchibachi, Doble, Anthopoulos, Woodgett, & Manoukian, 2007; J. Li, Lu, Beesley, Loudon, & Meng, 2012). Similar to GSK3β mediated phosphorylation, in mouse brain lithium treatment increases the transcription of several clock genes, such as *Per2*, *Per1* and *Cry1* (McQuillin, Rizig, & Gurling, 2007). Further investigations on the interplay between the circadian clock and lithium are necessary to unravel the impact of the clock on mood disorders. However, once again the regulation of disturbed circadian rhythms appears to be a key for the therapy of mood disorders.

A new, very promising antidepressant is agomelatine, which acts through mechanisms that differ from conventional antidepressant drugs. A vast number of clinical studies in humans demonstrate not only a rapid relief of depression symptoms, but also efficient long-term treatment and comparably few side effects in various types of mood disorders, such as major depression, BD disorder and SAD. Preclinical studies in animal models prove

antidepressant effects, reentrainment of circadian rhythms and neurogenic effects of agomelatine (Bourin, Mocaer, & Porsolt, 2004; Rainer et al., 2012). Agomelatine is an agonist of melatonin and acts synergistically on both melatonergic and serotonergic receptors (Papp, Gruca, Boyer, & Mocaer, 2003), which are expressed in the SCN and HPC and are regulated by both light and the clock (see Figure 1) (Masana, Benloucif, & Dubocovich, 2000). Similar to conventional antidepressants, agomelatine's efficacy may be due to the transactivation of these receptors, which exerts positive effects on monaminergic pathways. However, it might also affect the sleep/wake cycle and circadian rhythms through melatonergic action (Srinivasan, Zakaria, Othman, Lauterbach, & Acuna-Castroviejo, 2012). Agomelatine seems to act at an important interface between mood and circadian clock and it may become the treatment of choice in the near future. Studying its mechanisms of action may lead to a better understanding of the role of circadian clocks in mood disorders.

Chronotherapeutics: Manipulate the Clock to Treat Mood

Chronotherapeuthics is a highly effective therapeutic approach that targets biological rhythms by a controlled exposure of the patient to environmental stimuli. The main strategies are bright light therapy (BLT), sleep deprivation (SD) and daily routine/exercise.

Exposure to light, the main circadian Zeitgeber, is widely used as successful therapy to reduce depressive symptoms in several categories of mood disorders. The observation that the simple exposure to more sunlight reduces the hospitalization period of depressed patients gives an empirical indication about the benefit of light in the treatment of mood disorders (Beauchemin & Hays, 1996; Benedetti, Colombo, Barbini, Campori, & Smeraldi, 2001). BLT was initially developed for SAD (Rosenthal et al., 1984), but it has been successfully employed also in nonseasonal mood disorders, such as major depression and bipolar disorder (Goel, Terman, Terman, Macchi, & Stewart, 2005; Martiny, 2004; Pail et al., 2011). Protocols can vary in light intensities (2′500–10′000 lux), spectral composition, duration of exposure (30 min–1 h) and timing of application (morning or evening) (Wirz-Justice, Benedetti, & Terman, 2009). The best results are achieved when affected individuals are treated according to their internal circadian phase (Terman & Terman, 2005). Patients showing a phase delay are usually treated with BLT during the morning, which might help to reset their circadian rhythm. It is reported that the greater the resulting phase advance of melatonin onset, the better the response to BLT (Wirz-Justice et al., 2009). However, the direct involvement of melatonin resetting in the antidepressant effect of BLT is still controversial (Srinivasan et al., 2006).

So far only few studies investigated the benefit of BLT on mood using animal models. In rats, a 30-min light pulse during the dark phase or a single day of constant light appears to decrease immobility in the FST (Molina-Hernandez & Tellez-Alcantara, 2000; Schulz, Aksoy, & Canbeyli, 2008; Yilmaz, Aksoy, & Canbeyli, 2004). However, to our knowledge, no molecular targets for BLT have been identified and further studies using rodents will shed light on this aspect. As discussed above for SAD, the putative involvement of melatonin in the beneficial effects of light therapy might be clarified with comparative studies using melatonin-proficient and melatonin-deficient mouse strains (Kasahara et al., 2010).

SD is one of the most rapid antidepressant therapies available nowadays. Restriction of sleep for one full night (or for the second half only), markedly improves mood in approximately 60% of patients with major depression (Wirz-Justice & Van den Hoofdakker, 1999). However, although the antidepressant effect is induced rapidly, it also declines promptly and recovery sleep after SD often leads to full or partial relapse (Wirz-Justice et al., 2009). In combination with BLT and classical pharmaceuticals, SD is a potentially powerful adjuvant for clinical applications. The antidepressant response of SD seems to be well maintained in combination with serotonergic drugs (Benedetti, Barbini, Campori, Colombo, & Smeraldi, 1996) and lithium, in particular for BD patients (Szuba et al., 1994). Possible explanations for the *SD* benefit emerge from few animal studies. In mice and rats SD increases aggressive behavior (Sloan, 1972), alcohol consumption (Aalto & Kiianmaa, 1986), and reduces depressive-like behavior in the FST (Aalto & Kiianmaa, 1986; Lopez-Rodriguez, Kim, & Poland, 2004). These phenotypes are comparable to mania symptoms in humans. In addition, SD in healthy individuals induces symptoms of depression and anxiety (Babson, Trainor, Feldner, & Blumenthal, 2010). It is possible that SD causes a promanic effect, which in depressed patients is similar to an antidepressant action (Kronfeld-Schor & Einat, 2012). Other views suggest that SD helps to resynchronize a misalignment between sleep homeostasis and circadian processes, by shifting the need for sleep to a less critical phase (Wirz-Justice & Van den Hoofdakker, 1999).

The third type of chronotherapy is based on exercise, defined as a programmed, organized, and regular physical activity (Danielsson, Noras, Waern, & Carlsson, 2013). As for many other mood therapies, the mechanisms on the basis of the exercise's beneficial effect are still not clear. It has been hypothesized that the stabilization of daily routines and regularity of interpersonal social rhythms might provide a distraction from depressive thinking (Craft, Freund, Culpepper, & Perna, 2007; Lawlor & Hopker, 2001). It might also modify endorphin and monoamine levels (Greer & Trivedi, 2009) or stimulate neurogenesis in the HPC (Yau, Lau, & So, 2011). Several studies attempted to estimate the exercise effectiveness in the treatment of mood disorders. The data obtained are not conclusive, since the indication of the beneficial effect ranges from high to moderate/low levels in the different studies (Krogh, Nordentoft, Sterne, & Lawlor, 2011; Mead et al., 2009; Rimer et al., 2012). However, a recent analysis performed on 14 different trials (for a total of 1,139 individuals) suggested that this therapy has a beneficial effect in combination with pharmacological treatments (Danielsson et al., 2013).

Conclusion

The identification of the origins of mood disorders, and consequently the design of suitable therapies, is made difficult by the multifactorial nature of these diseases, determined by several and sometimes synergistic variables. Over the last 40 years, different studies both in humans and animal models have suggested a role of the circadian clock in mood regulation. Circadian clock elements are expressed in brain regions involved in mood control and for some of them, a direct role in neurological pathways important for mood regulation have been demonstrated. The circadian clock is

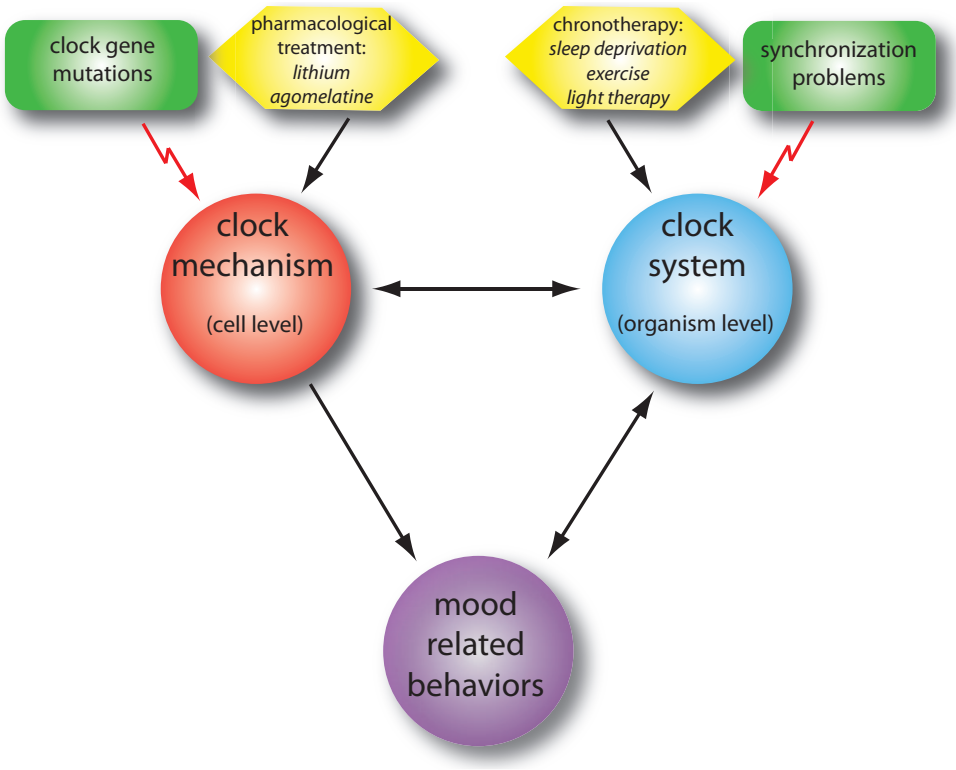

Figure 3. Model of associations between circadian clock and mood. Mutations in clock genes can affect the circadian clock mechanism (red), acting on neurological pathways involved in the regulation of mood related behaviors (purple). In vulnerable individuals, the interplay between gene and environment might also cause a misalignment of the circadian system (blue) affecting mood (purple). Therapies for mood disorders (yellow) can act on the circadian clock mechanism (pharmacological treatment) or the clock system (chronotherapy).

an extremely structured system, in which time-measuring molecular and cellular mechanisms are coordinated at the systemic level. Although further investigations are required to better understand the molecular and physiological links between the clock and mood, it seems that defects at the level of both the circadian clock mechanism and/or system might be related to a deficit in mood regulation (see Figure 3). Clock gene alleles, which cause a modification of the circadian clock mechanism, might directly contribute to the onset of mood disorders. On the other hand, different clock gene variants, with a weak or null effect in normal conditions, might elicit a misalignment or a disruption of the circadian system under environmental stress conditions. Such allelic variants may represent a risk factor in the development of mood disorders. Locating the level of the defect in the circadian clock seems therefore important to find a target strategy in the treatment of mood disorders. Pharmacological therapies, such as lithium, might in fact be effective for mood disorders associated with a perturbation in the clock mechanisms, while chronotherapeutics, such as BLT, SD, or daily exercise, might be appropriate for mood disorders related to circadian system defects.

Future experiments using tissue-specific mouse knock-out models will untangle the systemic from the tissue-specific roles of circadian clock components and thus help to dissociate the complex network of cellular and systemic defects observed in organisms with mutated circadian clock components. Using strategies to deliver clock components in specific brain regions (e.g., lentiviral vectors) will help to understand brain structure specific clock functions.

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