Most organisms (including humans) developed daily rhythms in almost every aspect of their body. It is not surprising that rhythms are also related to affect in health and disease. In the present review we present data that demonstrate the evidence for significant interactions between circadian rhythms and affect from both human studies and animal models research. A number of lines of evidence obtained from human and from animal models research clearly demonstrate relationships between depression and circadian rhythms including (1) daily patterns of depression; (2) seasonal affective disorder; (3) connections between circadian clock genes and depression; (4) relationship between sleep disorders and depression; (5) the antidepressant effect of sleep deprivation; (6) the antidepressant effect of bright light exposure; and (7) the effects of antidepressant drugs on sleep and circadian rhythms.

The integration of data suggests that the relationships between the circadian system and depression are well established but the underlying biology of the interactions is far from being understood. We suggest that an important factor hindering research into the underlying mechanisms is the lack of good animal models and we propose that additional efforts in that area should be made. One step in that direction could be the attempt to develop models utilizing diurnal animals which might have a better homology to humans with regard to their circadian rhythms.

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1. Introduction

1.1. General

In this review we explore the relationship between circadian rhythms and depression. First, we present the evolution and adaptive value of circadian rhythms, and point to possible health consequences of disruptions in this system. Then, we review a number of lines of evidence supported by human as well as animal models data indicating the involvement of circadian rhythms in depression. Some of the main interactions between depression and circadian rhythms are presented schematically in Fig. 1.

1.2. Circadian rhythms

We live in a rhythmic world. The rotation of earth around itself and around the sun causes daily and seasonal rhythms in light intensity, ambient temperature, humidity, and more. To optimally adapt to these rhythms, most organisms (including humans) developed rhythms in almost every aspect of their body, ranging from gene expression (expression levels of approximately 15% of the genes in our body show daily rhythms), physiology (e.g., heart rate, metabolism, and hormone secretion), cognitive functions (e.g., learning, memory) and activity-rest patterns.

Being active at different times, on the diel or the seasonal scale, exposes animals to very different environmental conditions. Confining activity to part of the temporal spectrum allows animal species to adapt to these conditions on an evolutionary scale (Kronfeld-Schor and Dayan, 2003, 2008; Kronfeld-Schor et al., 2000). As a consequence of these different adaptations, the environment of an organism is divided into times when it is optimal to perform a certain activity, and times when performing the same activity may even be disadvantageous. Hence, it is not surprising that most animals have a distinct activity pattern confined to a certain part of the diel cycle, which is typical to the species, and to which they are adapted behaviorally, anatomically, and physiologically (Daan, 1981; DeCoursey, 2004). The earliest mammals were nocturnal insectivores (Crompton, 1980) and although most current mammals are still nocturnal, independent evolutionary
transitions to a diurnal pattern of adaptation to the day/night cycle have occurred over the course of evolution. Humans are one of the species which developed to be active during the daytime.

As part of the adaptations to the rhythmic world, virtually all species studied so far developed an internal circadian timing system, composed of a master clock, which in mammals is located in the in the Suprachiasmatic Nucleus [the SCN (Klein et al., 1991; Moore-Ede et al., 1982)], and subsidiary clocks in nearly every body cell (Dibner et al., 2010). This internal timing system allows the individual to prepare itself, rather than respond, to the changing environment, to choose the right time for a given response or activity without being easily mislead by minor environmental changes, and to assure that a temporal order between internal processes and between them and the environment maximizes performance. A disruption of the circadian clock, or activity during the abnormal part of the diel cycle (as in the case of shiftwork, late evening activity or jet leg) may result in misalignment between the internal circadian clock and the activity pattern, which may have adverse consequences such as metabolic syndrome, obesity, insomnia, increased risk of cancer, as well as other physiological and mental disorders (Albrecht, 2010; Arble et al., 2009; Karatsoreos et al., 2011; Scheer et al., 2009).

2. The relationship between circadian rhythms and depression

Many lines of evidence in humans as well as in animal models clearly demonstrate relationship between depression and circadian rhythms. These lines of evidence stem from (A) disease patterns, mechanisms and models; (B) treatment effects in patients and in animal models. Regarding disease patterns, some important and established connections include: (1) daily patterns of depression; (2) changes in physiological and behavioral daily rhythms in depressed patients and in animal models of depression; (3) seasonal affective disorder; (4) recently established connections between circadian system genes and depression; and (5) the relationship between sleep disorders and depression. Regarding effects of treatments for depression the evidence include: (1) the antidepressant effect of sleep deprivation; (2) the antidepressant effect of bright light exposure; (3) the effects of antidepressant drugs on sleep and daily rhythms and the circadian system in animal models. In the following sections we will review the current knowledge indicating the involvement of the circadian system in depression as they emerge from human research and from animal models research.

Some of these main interactions are also schematically described in Fig. 1.

2.1. Disease patterns and mechanisms

2.1.1. Daily patterns of depression

Significant data demonstrate diurnal variations of depression symptoms in afflicted individuals. For most patients there is a regular and repetitive change in the intensity of depression symptoms across the day with generally an early morning worsening of symptoms (Gordijn et al., 1994; Tolle and Goetze, 1987; Wirz-Justice, 2008), although a minority of patients show opposite patterns (Joyce et al., 2005). A number of possible biological mechanisms were studied in this context with emphasis on the circadian rhythms of hormones such as cortisol, NE and melatonin that are implicated in affective and anxiety disorders and show circadian oscillations [for related recent reviews see (Germain and Kupfer, 2008; Monteleone and Maj, 2008; Monteleone et al., 2010)].
2.1.2. Changes in physiological and behavioral daily rhythms in depressed patients

A large body of work examined the interactions between depression and activity levels across the day/night cycle. Using methods such as actigraphy (continuous measures of activity levels) a number of studies demonstrated changes in activity patterns of depressed patients. For example, wake time activity levels were found to be reduced in depressed patients compared with healthy controls but were improved following antidepressant treatment (Raoux et al., 1994). In addition to reduced activity during the day, depressed patients also demonstrated higher motor activity during sleep (Volkers et al., 2003) and most importantly, compared to both healthy controls and to patients with schizophrenia, depressed patients had a more complex and less structured activity patterns (Berle et al., 2010; Hauge et al., 2011).

The hormone melatonin, secreted by the pineal gland, is elevated at night. Its release is controlled by the SCN, which stimulates melatonin secretion at night, and is suppressed by light, which inhibits melatonin production via mechanisms independent of the circadian time-keeping system (Moore-Ede et al., 1982). Melatonin rhythms in depressed patients were studied across the years, either as an independent factor or in combination with HPA and cortisol rhythms. One consistent finding is lower amplitude of melatonin rhythms (Beck-Friis et al., 1985; Claussrat et al., 1984). In the context of these findings, it may be worthy to note that some drugs that are frequently used by depressed patients such as benzodiazepines suppress nocturnal melatonin secretion [e.g., (Hajak et al., 1996)] and therefore, if patients in trials are not entirely drug free, such drugs may significantly affect the results. Yet, some studies suggest that depressed patients are internally desynchronized. For example, a study from 1982 demonstrates a dissociation between melatonin and cortisol secretion in depressed patients (Branchey et al., 1982) whereas a later study elegantly shows that regular daily activities in healthy individuals are associated with a decline in cortisol secretion, while daily activities and cortisol secretion are desynchronized in depressed patients (Stetler et al., 2004).

2.1.3. Circadian rhythms in animal models of depression

It is first important to note that one of the main factors hindering research into the underlying mechanisms of affective disorders is the lack of good animal models and the general difficulty in the field is highly demonstrated in the study of the interactions between circadian rhythms and depression (Cryan and Mombereau, 2004; Cryan and Slattery, 2007; Einat, 2007; Markou et al., 2009; Workman and Nelson, 2011). A variety of methods are used to induce models of depression in animals. Some of the common approaches are (1) using stress paradigms, either to naive animals or prenatally; (2) breeding for specific phenotypes (3) brain lesions and (4) genetic manipulations. A discussion of the advantages and disadvantages of these specific methods is beyond the scope of the present review but it is well understood that each of these approaches has its limitations and that all can advance our understanding of the disorder and support the development of novel treatments (Cryan and Mombereau, 2004; Cryan and Slattery, 2007; Markou et al., 2009; Willner, 1995). Interestingly, many of these models, regardless of the way they are induced, demonstrate alterations in behavioral, biochemical and molecular rhythms.

2.1.3.1. Stress based models. Chronic uncontrolled shock stress disrupts the daily temperature rhythm and markedly decreases the night–day amplitude of body temperature. However, the effect is short-lived and disappears after a few days even with the continuation of the uncontrolled shock paradigm (Kant et al., 1991). Social stress induced by repeated defeat causes a profound reduction in the amplitudes of the body temperature and activity rhythm, but without a significant phase-shift (Meerlo et al., 1997). Chronic unpredictable stress in rats results in changes in sleep architecture including in REM sleep patterns and theta activity in the hippocampus and amygdala (Hegde et al., 2011). Chronic stress in mice results in depression-like behavior in the forced swim test and the sweet solution preference test as well as increased activity level during the light phase and decreased activity level during the dark phase, and increased fragmentation of daily activity rhythms compared with control mice (Solberg et al., 1999). In rats, chronic mild stress results in reduction of nocturnal activity level and a flattening of activity rhythm amplitude (Gorka et al., 1996). Moreover, chronic unpredictable stress results in the development of depression- and anxiety-like behaviors and in a significant reduction in peak levels of Per2 expression in the SCN, which is expressed in a circadian pattern and functions as a component of the molecular mechanism of the circadian clock (Jiang et al., 2011). Behavior and Per2 expression deficits in this model are ameliorated by chronic desipramine treatment. Interestingly, 2 weeks after the termination of the chronic unpredictable stress procedure, the behavioral deficits are still apparent but Per2 expression levels show spontaneous recovery (Jiang et al., 2011).

2.1.3.2. Prenatal manipulations. Prenatal stress induces a variety of behavioral, biochemical and molecular changes in animals and this procedure is used to model aspects of depression (Maccari and Morley-Fletcher, 2007). Prenatal stress also results in changes in circadian rhythms. Prenatally-stressed rats show behavior consistent with depression including hedonic deficit and greater acquisition of learned helplessness under appropriate conditions (Weinstock, 2001). Amongst other changes, prenatal stress results in effects on daily rhythms including increased amounts of paradoxical sleep that was positively correlated to plasma corticosterone levels [(Dugovic et al., 1999); for review see (Darnaudery and Maccari, 2008)] as well as a phase-shift in their corticosterone circadian rhythm (Weinstock, 2001). Rats that are prenatally treated with clomipramine also show depression-like behaviors as adults including significant changes in the circadian rhythm of corticosterone that is reversed by chronic fluoxetine treatment (Bonilla-Jaime et al., 2010).

2.1.3.3. Selective breeding based models. A number of strains were developed by selective breeding for specific phenotypes and utilized to model facets of depression. The Flinders Sensitive Line (FSL) of rats, initially bred for cholinerigic hypersensitivity, is repeatedly demonstrated to show a variety of depression-like behaviors (Overstreet, 1993). FSL rats also show altered daily rhythms of heart rate activity and activity levels compared with control Sprague–Dawley rats and these differences disappear after treatment with chronic desipramine or paroxetine (Friedman et al., 2011). It is interesting to note that FSL rats are also phase advanced (Shiromani et al., 1991; Shiromani and Overstreet, 1994). Wistar Kyoto (WKY) rats that are hyperreactive to stress and exhibits depressive-like phenotype in several standard behavioral tests, show high plasma ACTH, corticosterone and thyroid-stimulating hormone (TSH) that remain high after the diurnal peak and for several hours compared with Wistar rats, therefore demonstrating a flattening of the daily rhythms (Solberg et al., 2001). Mice bred for spontaneous helplessness show a number of depression-like behaviors, including in the forced swim test, the tail suspension test and the sweet solution preference test. These mice also show clear alterations in sleep rhythms with lighter and more fragmented sleep, and increased REM sleep as well as alterations in corticosterone rhythms (El Yacoubi et al., 2003). Mice bred for high responsiveness to stress show behavioral changes resembling some behavioral facets of depression (Touma et al., 2011).
combined with reduced amplitude of the daily glucocorticoid rhythm, changes in sleep architecture including REM and non-REM sleep as well as slow wave activity (Touma et al., 2009). In contrast to the above mentioned strains, the Roman High-Avoidance rat line which also show a behavioral phenotype related to depression, does not demonstrate any alterations in plasma corticosterone levels or secretion patterns compared with the Low-Avoidance Line (Steimer et al., 2007).

2.1.3.4. Genetic expression factor studies. (other than Clock genes mutations, which will be discussed later). Mice heterozygote for the sodium channel Scn8a gene show emotional deficits (McKinney et al., 2008), accompanied by increased non-REM sleep, a chronic impairment of REM sleep generation and quantity, and a lowered and flattened daily rhythm of corticosterone levels (Papale et al., 2010).

2.1.3.5. Brain lesion. Bilateral olfactory bulbacotomy is a lesion based model of depression in changes in behavior, endocrine, immune and neurotransmitter systems, with high relevance to depression (Song and Leonard, 2005). These changes include disregulation of circadian rhythms. In mice, olfactory bulbacotomy results in higher morning values of plasma corticosterone and flattening of the daily rhythms of motor activity and body temperature (Magilliac et al., 1997). Olfactory bulbacotomy also results in lengthening of the free-running period of locomotor activity in golden hamsters (Pieper and Lobocki, 1991). An effect of olfactory bulbacotomy on free-running period is also demonstrated in a nocturnal primate, the gray mouse lemur (Microcebus murinus) where olfactory bulbacotomy results in shortening of the circadian periods of locomotor activity and body temperature (Perret et al., 2003).

2.1.4. Seasonal affective disorder (SAD)

2.1.4.1. Human studies. SAD was first introduced as a unique entity in 1984 in a study describing 29 patients (Rosenthal et al., 1984). These patients were characterized first and foremost by recurrent depressive episodes that occur annually in association with the changing seasons and were expressed in the fall or winter and spontaneously remitted in the spring and summer (Magnusson and Boivin, 2003; Magnusson and Partonen, 2005). Whereas summer SAD is also noted, the winter SAD is considered to be the frequent expression of seasonally dependant depression (Levitan, 2007). SAD symptoms are conceptually similar to the symptoms of major depression episodes except for their seasonal patterns and except for the frequent appearance of a few atypical depressive symptoms, including increased duration of sleep, carbohydrate craving, increased appetite and weight gain (Levitan, 2007; Magnusson and Partonen, 2005). The uniqueness of SAD had been questioned as it has significant overlap with recurrent depression that is influenced by seasons and with subsyndromal changes in mood and behavior that are not uncommon in the general population (Bauer and Dunner, 1993; Hansen et al., 2008).

However, most research supports SAD as a separate diagnostic entity and this support is reflected in both DSM and ICD criteria (Westrin and Lam, 2007). It is however important to be careful to differentiate SAD from other similar conditions such as atypical depression (Westrin and Lam, 2007).

The possible relationship between SAD and photoperiod (and therefore biological rhythms) was raised as part of the introduction of the disorder (Rosenthal et al., 1984) and was further established later. Beyond the seasonality of SAD, it is also noted that SAD patients’ mood is influenced when they travel north or south during the winter. For example, in their seminal report, Rosenthal and colleagues (Rosenthal et al., 1984) state that 83% of their patients (tested in the Northern hemisphere of the globe) reported significant improvement in mood after traveling south (thus shortening daylight) and an equal decline in mood after traveling north (thus shortening daylight). Additional support for the relationship between SAD and photoperiod comes from the demonstration that SAD frequency increases with distance from the equator, which parallels a decrease in daylight length during winter. Not all studies found such a correlation (Magnusson, 2000), but when additional factors, such as continent and heritage are controlled for, it appears that the correlation exist (Magnusson, 2000; Rosen et al., 1990).

The mechanism underlying SAD is unknown, but several theories have been suggested. These include the melatonin hypotheses suggesting that SAD might be caused by abnormal melatonin secretion (Carman et al., 1976; Wirz-Justice and Arendt, 1980), and the Phase-shift hypothesis suggesting that SAD might be caused by a phase-shift (mostly a phase delay) of the circadian system and the rhythms it controls (Lam and Levitan, 2000; Lewy et al., 2009, 2009b). Further support for the relationship of SAD with photoperiods comes from the efficacy of bright light therapy that is reviewed later in this paper.

In summary, it is now mostly accepted that SAD is a unique disorder which is strongly related to photoperiod and therefore to the circadian system. Although the underlying nature of these connections is far from being clarified, the disorder itself supports the complex interplay between depression and circadian rhythms.

2.1.4.2. Animal models for SAD. The basic demand from an animal model for SAD is possibly that it will react to short photoperiod with behavioral changes that are related to depression. Whereas originally it was thought that seasonal, photoperiodic-responsive animals would be an easy target to model SAD, the reality appears to be much more complex (Sohn and Lam, 2005; Workman and Nelson, 2011). The complexities and possibilities of animal models for SAD were recently presented in an excellent review paper (Workman and Nelson, 2011). At this time there is no ideal animal model for SAD but this is not significantly different from the state of models regarding other affective disorders (Cryan and Mombereau, 2004; Cryan and Slattery, 2007; Einat, 2006, 2007; Gould and Einat, 2007; Markou et al., 2009). However, some models are suggested to appropriately represent specific aspects of the disorder. Interestingly, whereas many models in psychiatric research utilize standard laboratory animals, mainly rats and mice, at least some of the proposed models for SAD use other species including Siberian hampsters (Phodopus sungorus), collard lemmings (Dicrostonyx groenlandicus), meadow voles (Microtus pennsylvanicus), fat sand rats (Psammomys obesus) and grass Nile rats (Arvicanthis niloticus) [for review see (Workman and Nelson, 2011)]. In some of the work from our laboratories we suggest that it is possible that some of the complexity in the identification and development of good animal models for SAD is that many studies use nocturnal rodents to model a disorder that is highly related to diurnal activity.

The earliest mammals were nocturnal insectivores (Crompton, 1980). Although most current mammals are still nocturnal, independent evolutionary transitions to a diurnal pattern of adaptation to the day–night cycle have occurred within both closely and distantly related taxa (Roll et al., 2006). Shifts of activity time may occur on an ecological or evolutionary time scale. Changes on the ecological scale may eventually lead to changes on the evolutionary scale, and therefore the mechanism of the shifts may be similar on both scales (Kronfeld-Schor and Dayan, 2008). Therefore, the neural mechanism sustaining diurnality may be diverse (Cohen et al., 2010a, 2010b; Rotics et al., 2011; Smale et al., 2003, 2008). Moreover, it is becoming apparent that diurnality is not a precise term, and may have diverse forms, and that an animals’ commitment to a given pattern may vary both between and within a species (Cohen and Kronfeld-Schor, 2006; Cohen et al., 2009, 2010b; Daan et al., 2011; Cutman et al., 2007; Hut et al., 2011; Kronfeld-Schor and Dayan, 2003, 2008; Kronfeld-Schor...
et al., 2001; Levy et al., 2007; Refinetti, 2008; Roenneberg et al., 2011; Rotics et al., 2011). In spite of the extraordinary advancement in our understanding of the circadian clock mechanism, it is still unclear how are the temporal signals from the clock translated into activity patterns, and how do they differ in diurnal and nocturnal mammals. Nevertheless, it is clear that some fundamental differences exist between nocturnal and diurnal mammals. The hypothesis for these differences that is supported by the strongest evidence is that the differences between nocturnal and diurnal mammals timing systems emerge from multiple processes operating primarily, perhaps even exclusively, downstream of the SCN, which translate the information emanating from the SCN in an opposite way (Smale et al., 2008). An additional important difference between nocturnal and diurnal animals stems from the actions of melatonin. Melatonin is secreted during the night and suppressed by light in both diurnal and nocturnal mammals; diurnal species are active when melatonin levels are low, while nocturnal mammals are active when melatonin levels are high. For example, melatonin treatment lowers body temperature in diurnal mammals and elevates it in nocturnal ones (humans - (Cagnacci et al., 1992), rats - (Roseboom et al., 1996), golden spiny mice (Acomys rufus) (Zisapel et al., 1998), Degu (Octodon degus) (V-Frinse et al., 2007)). The effects of sleep on the nocturnal species’ melatonin levels (Arendt, 2000; Zhdanova and Giorgetti, 2002), while in nocturnal mammals it increases activity levels, sleep latency, waking, and sleep fragmentation (Hastings et al., 1992; Huber et al., 1998; Mendelson, 2002; Mendelson et al., 1980). Moreover, intake of tryptophan (the precursor of the synthesis of melatonin and serotonin) causes a short term increase in activity in the nocturnal rat, while decreasing it in the diurnal dove (Aparicio et al., 2006). An important and relevant observation is that several hormones show phase opposition between nocturnal and diurnal species, including cortisol, leptin, and hippocampal serotonin (Cuesta et al., 2009).

Another difference between nocturnal and diurnal species is the masking effect of light (an immediate effect of a stimulus that overrides an animal’s endogenous clock), which is very different in nocturnal and diurnal species: light increases activity in diurnal mammals (positive masking) and suppresses it in nocturnal ones (negative masking), while darkness acts in the opposite way (Aschoff and von Goetz, 1988; Cohen et al., 2010b; Redlin et al., 2005; Redlin and Mrosovsky, 1999; Rotics et al., 2011).

To explore the possibility that diurnal rodents might be appropriate model animals for SAD, we tested the effects of short photoperiod acclimation in the diurnal fat sand rat and the diurnal grass Nile rat. Our results show that short photoperiod acclimation in these species result in the development of depression- and anxiety-like behaviors (Ashkenazy-Frolinger et al., 2009; Ashkenazy et al., 2009b). More recently, it has been observed that the effects of sleep on the diurnal grass Nile rat (Aschoff and von Goetz, 1988; Cohen et al., 2010b; Redlin et al., 2005, 2007; Rotics et al., 2011). These conflicting results suggest that such models might be valuable in the study of specific components of SAD, but we propose that additional exploration using diurnal rodents could be a promising research direction.

2.1.5. Clock genes and depression

The circadian system of mammals is comprised of a central circadian clock located in the SCN, and peripheral clocks, located throughout the body, which are normally synchronized to the SCN central clock (Dibner et al., 2010). Circadian rhythms are controlled by a well-known transcriptional-translational negative feedback network. In mammals, the primary clock loop includes the clock genes Clock, Bmal, Per, and Cry, and their products (Zhang and Kay, 2010).

2.1.5.1. Human studies. Alternations in clock genes and their promoters appear to predispose humans to develop mood disorders (Desan et al., 2000). Utge and colleagues analyzed depressed patients in comparison with healthy controls for 113 single-nucleotide polymorphisms of 18 genes of the circadian system (Utge et al., 2010). Their results indicate significant association between TIMELESS gene variants and depression with fatigue as well as additional associations between TIMELESS and Per1 and Per3 and depression in females with seasonal changes in mood, sleep duration, energy levels, and social activity, and with early morning awakening or fatigue in males (Utge et al., 2010). A small study (Nievregelt et al., 2006) suggests that haplotypes in ARNTL and Per3 gene polymorphisms are significantly associated with bipolar disorder with Per3 being the most suggestive. Although the data do not provide statistically significant evidence for association, the trends for ARNTL and Per3 are suggestive of their involvement in bipolar disorder and warrant further study in a larger sample (Nievregelt et al., 2006). Soria and colleagues (Soria et al., 2010) examined 209 single-nucleotide polymorphisms covering 19 circadian genes in a sample of 335 patients with major depression, 199 patients with bipolar disorder and 440 healthy controls. Significant associations were found in major depression with SNPs in Cry1 and Npas2, whereas significant associations in the bipolar disorder subsample were with the CLOCK and VIP SNPs (Soria et al., 2010). Additionally, individuals with a history of depression had higher expression of CLOCK, Per1, and BMAL1 mRNA levels, compared to non-depressed participants when measured in the morning (Gouin et al., 2010). A couple of studies also examined genetic associations of SAD. An early study identified a polymorphism in Npas2 as significantly associated with the disease (Johannson et al., 2003) and a later study identified variations in three circadian CLOCK genes, Per2, ARNTL, and Npas2 (Partonen et al., 2007).

Additional evidence for the relationship between clock genes and depression come from data related to the action of antidepressant drugs and will be discussed below.

2.1.5.2. Animal models. Loss or reduced function of clock genes results in diverse consequences including behavioral changes that are directly related to affective disorders. These effects, including altered sleep architecture and behavioral abnormalities, had been recently described in a number of excellent comprehensive reviews (Albrecht, 2010; Desan et al., 2000; Katzenberg et al., 1998; Kennaway, 2010; Lamont et al., 2010, 2007; McClung, 2007; Mendlewicz, 2009). We will therefore concentrate on mostly new data.

The involvement of the circadian clock system in sleep architecture and activity patterns have been repeatedly demonstrated by manipulating genes involved in the circadian clock mechanism. For example, heterozygous and homozygous Clock mutants mice (which produce dominant-negative protein that cannot activate transcription) showed altered sleep architecture including less
sleep compared with WT mice, and changes in REM sleep amount (Naylor et al., 2000). Transient suppression of Per2 in the SCN of rats using siRNA techniques disrupted free-running locomotor activity rhythms for up to 10 days (Gavrila et al., 2008). Beyond issues of sleep and activity rhythms, some recent work clearly demonstrate that manipulating clock genes have effects that are more directly related to affective disorders although many of these behavioral changes might be more strongly associated with bipolar disorder than to major depression as described below.

An interesting study by Nakamura and colleagues (Nakamura et al., 2008) found quantitative similarities in the breakdown of behavioral organization of activity between people suffering from major depression and mice with a targeted disruption of the Per2 gene (Nakamura et al., 2008). The Clock mutants display an overall behavioral profile similar to mania, including hyperactivity, decreased sleep, lowered depression-like behavior, lower anxiety, and an increase in the reward value of cocaine, sucrose, and intracranial stimulation (Roybal et al., 2007). Interestingly, these mice also show increased dopaminergic activity in the ventral tegmental area (VTA) (Coque et al., 2011). Lithium reduces the increased DA activity in the mutant mice but has no effects in wild-type mice (Coque et al., 2011). Moreover, knockdown of Clock using siRNA infusion into the VTA results in altered circadian period and amplitude as well as hyperactivity and a reduction in anxiety-related behavior similar to the phenotype of the Clock knockout mice (Mukherjee et al., 2010). Interestingly, this specific disruption of the Clock gene also results in an increase in depression-like behavior, creating a more complex behavioral phenotype with components of manic- and depression-like behaviors (Mukherjee et al., 2010). Targeted mutations in related genes also result in behavioral changes that are related to affect. Mice with a deficiency of the circadian transcription factor Bmal1 display hyperactivity in novel environments and impaired habituation, and mice double-deficient for the circadian proteins Cry1 and Cry2 (repressors of the Bmal1-mediated transcription) demonstrate reduced activity and accelerated habituation when compared to wild-type mice (Kondratova et al., 2010). Mice with a homozygous deletion of D-box binding protein (DBP) demonstrate a behavioral phenotype relevant to major depression including lower locomotor activity and blunted responses to stimulants (Le-Niculescu et al., 2008). These mice exhibit a behavioral switch after exposure to stress suggesting that this mutation might be related to bipolar disorder (Le-Niculescu et al., 2008). These experiments and many more [for reviews see (Albrecht, 2010; Desan et al., 2000; Katzenberg et al., 1998; Kennaway, 2010; Lamont et al., 2010, 2007; McClung, 2007; Mendlewicz, 2009)], clearly demonstrate the involvement of the genetic machinery of the circadian clock system in affective disorder.

2.1.6. Sleep disturbances

2.1.6.1. Human studies. In a study done approximately 50 years ago, Hinton (Hinton, 1962, 1963) examined the duration of sleep and the motility during sleep of patients with depression and compared them with previously depressed but recovered patients. The findings clearly demonstrated that the depressed individuals slept less hours and were significantly more restless compared to recovered patients (Hinton, 1962, 1963). Numerous studies have been conducted since that time in an attempt to decipher the complex relationship between sleep, sleep architecture and depression. Based on many of these studies there is a general agreement today that sleep disturbances are a core feature of depression, and insomnia or hypersomnia are diagnostic criteria for depression (Sadock and Kaplan, 2002). Subjective reports suggest that as many as 90% of depressed patients describe a variety of sleep problems including difficulties falling asleep, frequent awakenings and early morning awakening (Almeida and Pfaff, 2005; Riemann et al., 2001). Objective measures of sleep are also disturbed in depression with reduced latency between sleep onset and first episode of REM, increased duration of REM sleep, increased number of eye movements during REM sleep and decrease in slow-wave sleep (Riemann and Voderholzer, 2003; Thase et al., 1997).

Initially, sleep disturbances were considered a symptom of depression. Additional studies suggest that this is not a one way relationship where depression results (in part) in sleep disturbances, but that in fact sleep disturbances might be an independent risk factor for the development of depression, and the relationship constitutes a bidirectional linkage (Riemann et al., 2001). Significant data suggest that irregularity of sleep patterns or sleep disturbances might be a risk factor for depression and possibly also a marker that can predict the appearance of depression (Perlis et al., 1997; Riemann et al., 2001; Roberts et al., 2000). Generalized sleep disturbances are demonstrated to be associated with the development of depression [e.g., (Breslau et al., 1996; Dryman and Eaton, 1991; Mallon et al., 2000; Weissman et al., 1997)]. For example, patients with insomnia are three times more likely to develop depression within a one year period compared with patients without insomnia (Ford and Kamerow, 1989) and sleep disturbances preceded the recurrence of depression in remitted patients (Perlis et al., 1997). In a study of the general population, only 2.6% of those with no sleep complaints were classified as depressed, whereas 71.9% of those with sleep complaints were depressed (Roberts et al., 2000).

Some researchers go as far as suggesting that sleep irregularities might be a prodromal symptom to depression and more detailed insomnia markers were in fact suggested as possible biomarkers for depression (Rao et al., 2009; Szklo-Coxe et al., 2010). For example, in a prospective study, Rao and colleagues compare adolescents with family history of depression to ones without family history and show that (1) individuals with family risk for the disorder have a shorter latency to REM sleep, increased phasic REM sleep and more REM sleep (Rao et al., 2009). Moreover, in a 5 years follow-up, these researchers show that shorter latency to REM sleep and higher REM density are associated with the development of depression (Rao et al., 2009).

Despite the accumulating evidence, a direct causal relationship between sleep disturbances and depression is not yet established and the relationship between the two can be explained otherwise. Some possible alternative explanations suggest that both sleep disturbances and depression are the consequences of a more basic interference in the circadian system or that sleep disturbance and depression both represent a dissociation of feedback mechanisms governing physiological rhythms and affect (Pandi-Perumal et al., 2009).

Whereas the nature of the connections between sleep disturbances, circadian rhythms and depression and the underlying biological mechanisms that might be responsible for these connections are not completely clear, the existing data clearly indicate that there is a bidirectional relationship between them.

2.1.6.2. Animal models. As presented above in the section on animal models for depression and circadian rhythms, many of the models that were developed in the context of depression research also demonstrate changes in sleep patterns and sleep disturbances therefore supporting the relationship between depression and sleep. Such examples are available regardless of the way the model is induced.

2.1.6.3. Stress-induced models. Chronic unpredictable stress in rats results in changes in sleep architecture including in REM sleep...
patterns and theta activity in the hippocampus and amygdala (Hegde et al., 2011) and prenatal stress results in increased amounts of paradoxical sleep ([Dugovic et al., 1999]; for review see [Darnaudery and Maccari, 2008]).

2.1.6.4. Breeding-induced models. Mice bred for spontaneous helplessness show alterations in sleep rhythms with lighter and more fragmented sleep, and increased REM sleep (El Yacoubi et al., 2003). Mice bred for high responsiveness to stress show changes in sleep architecture including REM and non-REM sleep as well as slow wave activity (Tourna et al., 2009).

2.1.6.5. Mutation-based models. Mice heterozygote for the sodium channel Scn8a gene show a chronic impairment of REM sleep generation and quantity (Papale et al., 2010). Clearly all animals with mutations in Clock and related genes show altered sleep architecture and rhythm (see Section 2.1.5).

2.2. Effective treatments of depression affecting circadian rhythms

2.2.1. Sleep deprivation

2.2.1.1. Human studies. A number of case studies were published toward the end of the 1960’s indicating the effects of sleep deprivation to ameliorate depression symptoms in patients [summarized in (van den Burg and van den Hoofdakker, 1975)]. These anecdotal reports were followed by a number of clinical trials in the early 1970’s. The general results of these trials indicate that one night total sleep deprivation results in partial to substantial remission of depression but that the remission is temporary and with immediate relapse following subsequent sleep (van den Burg and van den Hoofdakker, 1975). For example, Post and colleagues (Post et al., 1976) tested the effects of one night total sleep deprivation in 19 depressed patients hospitalized at the NIH and showed that 10 of these patients had a significant improvement after one night sleep deprivation with relapse after sleep. Interestingly, the symptomatic change did not correlate with any biochemical changes that were measured at that time, mostly biogenic amines and their metabolites (Post et al., 1976).

Numerous studies were performed since that time trying to identify the specific effects of sleep deprivation as well as to explore the possibility that the antidepressant effect can be achieved by partial sleep deprivation or at specific sleep phases. Initial studies suggest that REM sleep might be the core of the effect and therefore REM phase deprivation could be enough to induce antidepressant effects. A highly cited, early study (Vogel et al., 1975) demonstrates that chronic REM sleep deprivation is efficacious to reduce depression symptoms compared with partial sleep deprivation of non-REM phases. Although this study had a significant impact, later studies cast doubt on the utility of REM sleep deprivation as an antidepressant and on the differences between REM and non-REM deprivation (Giedke and Schwarzzier, 2002; Grozinger et al., 2002). An additional line of investigation compares the effects of total sleep deprivation to partial (early or late) sleep deprivation procedures. The results of these studies are not clear with some suggesting that partial sleep deprivation can be as effective as total deprivation (Giedke et al., 1992, 1990) but later studies showing only minimal effects of partial sleep deprivation compared with total sleep deprivation (Giedke et al., 2003). Interestingly, some studies show that utilizing partial sleep deprivation as an additive treatment to antidepressant drugs results in a faster onset and more persistent improvement in patients’ status (Caliyurt and Guducu, 2005; Kuhls et al., 1996).

One interesting issue related to the antidepressant effects of sleep deprivation in patients is that it stands in clear contrast to the effects of sleep deprivation in healthy people which results in a set of negative effects including the development of depression and anxiety symptoms (Babson et al., 2010). The discrepancy between the effects in depressed patients and in healthy individuals can be partially explained by differences in the effects of sleep deprivation on brain activity. For example, a recent proton magnetic resonance spectroscopy study shows that sleep restriction (partial sleep deprivation) results in increased metabolic rate in the frontal cortex of depressed patients but not healthy controls and a correlation between the metabolic change and mood improvement in patient (Bernier et al., 2009).

Despite significant research efforts, our knowledge today is still far from complete. It is clear that sleep deprivation has a significant but transient therapeutic effect in depression but the specifics and the mechanisms related to these effects are still far from being understood. However, regardless of mechanisms, the antidepressant effects of sleep deprivation bring additional support to the complex interactions between circadian rhythms, sleep and depression.

2.2.1.2. Animal models. Early studies in sleep deprivation in animals used extreme conditions and chronic total sleep deprivation (Webb, 1962) and therefore their results might not be of high relevance to affective disorders. Substantial research also explored the effects of sleep deprivation or REM sleep deprivation on rebound sleep and the architecture of sleep at the end of deprivation [For review see (Rechtschaffen et al., 1999)] but the direct connection between these studies and affective disorders is also not clear.

Some early studies explored the effects of sleep deprivation on brain biogenic amines, an area of study with a higher relevance to affective disorders. In general, these studies show that sleep deprivation results in increase in biogenic amines (Tsuchiya et al., 1969), however, the increase is not different than the one observed after the application of other stressors and may not therefore reflect specific effects of sleep deprivation (Stern et al., 1971). Behavioral consequences of sleep or REM sleep deprivation that might have more relevance to affective-like changes were also reported. For example, REM sleep deprivation in rats resulted in a significant increase in aggressive behavior (Peder et al., 1986; Sloan, 1972), abolition of daily rhythms of locomotor activity (Elomaa and Johansson, 1980) and increased alcohol consumption (Aalto and Kiiimmaa, 1986). One behavioral effect of REM sleep deprivation with significant relevance to depression is the reduction of immobility time in variations of the forced swim test, a highly utilized test for screening antidepressant action [e.g., (Hodgson, 1984; Lopez-Rodriguez et al., 2004)]. REM sleep deprivation also increases reward seeking behavior as shown in the sweet solution preference test (Anderson et al., 2009). The accumulation of data regarding the effects of sleep deprivation on affective-like behaviors lead to the suggestion that depriving animals of sleep may be a way to model mania (Gessa et al., 1995).

Specifically, the combination of behaviors that is apparent immediately at the end of a sleep deprivation period includes insomnia, hyperactivity, irritability, aggressiveness, hypersexuality and stereotypy, all related to the behavioral domains of mania in people [for review see (Gessa et al., 1995)]. Additionally, these manic-like behaviors are ameliorated in animals that received lithium during the sleep deprivation period, further supporting the model [for review see (Gessa et al., 1995)]. Similar effects were also demonstrated in mice where sleep deprivation (but not stress control) induced increased motor activity and aggression (Benedetti et al., 2008). In summary, sleep deprivation in animals result in affective-like behavioral changes but it is not clear whether these changes are similar to antidepressant action or to a pro-manic effect.
2.2.2. Bright light therapy

2.2.2.1. Human studies. As mentioned above, a number of manipulations affecting the circadian system were offered as possible treatments for depression, but the most established one is clearly exposure to bright light (Even et al., 2008; Golden et al., 2005; Prasko, 2008; Terman and Terman, 2005). Initially devised as a method to treat SAD, some data also support the utility of bright light to ameliorate symptoms of major depression, either alone or in conjunction with antidepressant medication (Dietzel et al., 1986; Even et al., 2008; Kripke, 1998; Lieverse et al., 2011).

The original idea that led researchers to explore the effects of bright light therapy in SAD was related to the phenotype of the disorder that develops when days get shorter. The idea was to use artificial light to extend the light period. Early studies (Kripke, 1985; Rosenthal et al., 1985, 1984) demonstrate that SAD patients improve after exposure to bright full-spectrum light before dawn and after dusk, but there is no effect of exposure to dim lights (Rosenthal et al., 1985, 1984). However, later studies show that bright light administered in the morning (after sunrise) also results in improvement in SAD patients. Additional preliminary studies from the same time also suggest similar effects for patients with major depression (Kripke et al., 1983) but the results of that last study may have also been related to a reduction in the number of sleep hours (partial sleep deprivation).

The mechanism through which bright light treatment affects SAD is yet unknown. One assumption is that morning bright light treatment causes a phase advance of the circadian clock (Lewy et al., 2006b). In line with this hypothesis, giving melatonin to patients in the morning (which causes phase delay) made them feel worse while giving melatonin in the afternoon (which causes phase advance) made patients feel better (Bhattacharjee, 2007; Lewy et al., 2006a, 2006b). These positive effects were however limited to SAD patients who have a phase delay and not to patients who have a phase advance (Lewy et al., 2006b). Some support for phase advance theories come from a study on the effectiveness of sleep deprivation and bright light in bipolar depressed patients (Benedetti et al., 2007). In this study, responders to treatment show a 57 min phase advance of the activity-rest rhythm compared to the pre-treatment baseline whereas Non-responders do not show significant changes in the parameters of their activity-rest rhythm (Benedetti et al., 2007). Another possibility is that morning bright light treatment helps SAD patients by reducing and timing the secretion of melatonin, as bright light suppresses melatonin secretion, and more so in the morning (Rosenthal et al., 1984). It is also possible that the effectiveness of bright light treatment results from a combination of these two effects.

Studies have been conducted to evaluate the best “dose” and timing and the mechanism of bright light treatment. For example, 4 h exposure is not better than 2 h exposure (Doghramji et al., 2005) but 30 min exposure are not effective while 2 h exposure are (Wirz-Justice et al., 1987). Some studies show no differences between morning and evening bright light exposure (Wirz-Justice et al., 1993), but other studies show an advantage to morning exposure (Lewy et al., 1998; Terman et al., 2001). Although the accumulated data suggests that morning bright light is more efficacious than evening exposure, the fact that evening exposure also has some efficacy should not be ignored as it sheds doubt on the hypothesis that the antidepressant effect is dependent on phase advance (Wehr et al., 1979). The improvement of SAD patients seen at least in some studies after bright light exposure at different circadian phases weakens the circadian phase delay hypothesis of the disorder and the phase advance basis of treatment (Wirz-Justice et al., 1993).

An additional recent discussion regarding bright light exposure is whether it is the intensity of the light (LUX) or the specific wavelengths that are responsible to the therapeutic effects. Some recent studies suggest that wavelengths are of a significant importance and that lower intensities of blue enriched lights might be as efficacious as high intensities of the standardized full-spectrum light treatments (Anderson et al., 2009; Meesters et al., 2011).

In summary, bright light administration has clear therapeutic effects in the treatment of SAD and possible effects in the treatment of major, non-seasonal depression, indicating again a connection between depression and circadian rhythms. The mechanism of the effects of light to alleviate depression is yet to be clarified.

2.2.2.2. Animal models. The scarcity of studies using animal models to gain further understanding of the mechanisms of therapeutic action of bright light treatment is surprising. However, this lack of data might be related to some major issues with standard laboratory model animals as discussed above.

Some minimal data indicates that continuous bright light (but not dim light) blunted the hypothermic response of rats to a muscarinic agonist and the supersensitivity to such agonists that is induced by chronic stress (Dilsaver and Majchrzak, 1987; Flemmer et al., 1990). Similar results relating to effects of bright light on cholinergic supersensitivity are also demonstrated in the Flinders sensitive line (FSL), a line of rats that has significant deproteinaization as a model for depression (Oversreet et al., 1999), but bright light effect did not extend into a more direct model of antidepressant action and did not reduce the exaggerated immobility time of FSL rats in the forced swim test (Oversreet et al., 1995).

One major complexity regarding the possible modeling of bright light effects is highlighted in an interesting study comparing the effects of chronic bright light administration on brain monoamines and neuropeptides in albino Sparague Dawley and pigmented Brown Norway rats (Humpel et al., 1992). The results of this study demonstrate that bright light induces retinal lesions in albino rats as well as significant changes in neurotransmission in a number of brain areas. However, bright light exposure in pigmented rats had no effect on the retina or on brain biogenic amines and neuropeptides. The authors therefore suggest that the effects seen in the albino rats are directly related to retinal damage and that such strains might be less adequate for the study of the neurochemical effects of bright light (Humpel et al., 1992).

An additional complexity stems from the aversive and stressful effects of bright light in rats and mice. As mentioned above, the masking effect of light is very different in nocturnal and diurnal species: light increases activity in diurnal mammals (positive masking) and suppresses it in nocturnal ones (negative masking), while darkness acts in the opposite way (Aschoff and von Goetz, 1988; Cohen et al., 2010b; Redlin et al., 2005; Redlin and Mrosovsky, 1999; Rotics et al., 2011). In fact, in laboratory mice and rats bright light is used in many variations to induce anxiety-like behavior such as in the light/dark box test (Bourin and Hascoet, 2003), the elevated plus-maze (Morato and Castrechini, 1989), conditioned avoidance (McQuade et al., 1999) and defensive withdrawal test (Roman and Arborelius, 2009). Resulting from these complexities, and to the best of our knowledge, the effects of bright light as an antidepressant were never demonstrated in an animal model except in some preliminary studies from our work with diurnal rodents (Ashkenazy et al., 2009a). In our preliminary studies we thought to overcome the challenges of albino animals and of the aversion of nocturnal rodents by utilizing a diurnal rodent. Our results suggest that indeed, in the diurnal fat sand rat, morning administration of bright light in a design that is similar to the clinical treatment of SAD patients, results in the amelioration of depression-like behavior in the FST and anxiety-like behavior in the elevated plus-maze (Ashkenazy et al., 2009a). We are now attempting to utilize this new model to...
gain additional understanding of the mechanism of action of bright light treatment.

2.2.3. Antidepressant drugs

2.2.3.1. Human studies and animal models. Most antidepressant and mood stabilizing drugs have effects on measures related to circadian rhythms. Lithium, lengthens the circadian period in several species, and therefore causes a phase delay, an effect that may underlie, at least in part, its mood stabilizing activity (Kлемfuss, 1992; McCleod et al., 1985; Stewart et al., 1991). It was suggested that the therapeutic effect of lithium is mediated by its effect on GSK-3β, which is responsible for Rev-Erbα phosphorylation in the secondary feedback loop of the clock (Iwahana et al., 2004; Yin et al., 2006). Some evidence suggests that antidepressants from the specific serotonin reuptake inhibitors (SSRIs) group also directly alter circadian rhythms. The complex interactions between the serotonin system and circadian rhythms had been studied for many years (e.g., [Morin, 1999]) and is outside the scope of the present review. In brief, the SCN entrains to the environmental light dark cycle, according to photic information arriving to it via the retinohypothalamic tract. However, non-photic cues can also entrain the SCN clock (Challet, 2007; Challet and Pevet, 2003; Mallman and Mrosowsky, 2007; Mrosowsky, 1998), and at least some of the information from these cues arrive to the SCN by a serotonergic pathway via the raphe nuclei (Mistlberger et al., 2000). Based on these interactions, some studies explored the role of antidepressant drugs, with emphasis on SSRIs, on circadian clock function. The results of these studies demonstrate that antidepressants have physiological and molecular effects in the SCN but the nature of these effects is still unclear. In-vitro studies show that adding the SSRI fluoxetine to SCN neurons result in a robust phase advance of the cellular circadian rhythmicity, albeit only in the presence of L-tryptophan (Sprouse et al., 2006). Molecular studies also show that SSRIs significantly shorten the period of Per1-bioluminescence rhythms in rat-1 fibroblasts expressing the Per1-luciferase transgene, therefore suggesting direct effect on circadian rhythmicity (Nomura et al., 2008). An in-vivo study demonstrates that repeated but not single treatment with fluoxetine results in increased expression of Clock, Bmal1, and NPAS2 genes but suppression of Per1 gene expression in the hippocampus of mice (Uz et al., 2005). However, in Sudanian grass rat (Arvicanthis ansorgei), a diurnal rodent, fluoxetine does not change the expression of Per1 and Per2 in the SCN but alters the expected change in gene expression in response to light (Cuesta et al., 2008). In hamsters, rats and mice, injection of 5-HT receptor agonist (systemically or directly to the SCN) during the day causes a phase advance of activity rhythms and reduction in Per1 and Per2 expression within the SCN [reviewed by (Cuesta et al., 2009)]. However, injections of a 5-HT receptor agonist, an SSRI (citalopram, fluvoxamine, paroxetine, and fluoxetine) or a serotonin/noradrenaline reuptake inhibitor venlafaxine, during the day, decrease light-induced phase advances, but have no effects by themselves (Cuesta et al., 2009; Gannon and Millan, 2007). Interestingly the noradrenaline reuptake inhibitor reboxetine and the dopamine/noradrenaline reuptake inhibitor bupropion did not exert significant effects (Gannon and Millan, 2007). Although these results show direct effects of SSRIS on circadian rhythms, a later study, also in Syrian hamsters, shows that chronic administration of the SSRI fluoxetine result in a general decrease in total daily wheel running but has no effects on the phase of the circadian wheel running rhythm (Duncan et al., 2010).

The most studied parameter related to effects of antidepressants on rhythms is sleep. The subjective effects of antidepressants from all classes (with very few exceptions) on sleep are initially negative and later in the treatment become positive (Argyropoulos and Wilson, 2005; Tsuno et al., 2005). However, at least a partial discrepancy was identified between subjective and objective measures of sleep under antidepressants treatment (Argyropoulos et al., 2003; Argyropoulos and Wilson, 2005). Using objective measures such as polysomnography suggest a general improvement in sleep after chronic treatment (Argyropoulos and Wilson, 2005). However, antidepressants have different effects on different phases of sleep with the most noted one being REM sleep suppression (Argyropoulos and Wilson, 2005; Tsuno et al., 2005). Antidepressants from the monoamine oxidase inhibitors (MAO-I) group were noted to suppress REM sleep over 40 years ago (Wyatt et al., 1969) and these findings are repeatedly confirmed (Sander and Shapiro, 1994; Steiger et al., 1994). Tricyclic antidepressants including amitriptyline, nortriptyline, trimipramine and imipramine are also demonstrated to suppress REM sleep (Feuilade et al., 1992; Kupfer et al., 1978, 1982; Sonntag et al., 1996; Ware et al., 1989). Antidepressants from the specific serotonin reuptake inhibitors (SSRIs) group, including paroxetine, fluoxetine and citalopram lower REM sleep and increase REM latency (Rush et al., 1998; Sharpley et al., 1996; Wilson et al., 2004).

Some of the atypical antidepressants do not suppress REM. For example, nefazodone was not noted to have any effects on REM sleep (Rush et al., 1998; Sharpley et al., 1996) and bupropion was demonstrated to either not have long term effects on sleep parameters or even to shorten REM latency and increase total REM time (Nofzinger et al., 1995; Ott et al., 2002).

Effects of antidepressant drugs are also demonstrated on other sleep parameters [for reviews see (Argyropoulos and Wilson, 2005; Duncan, 1996)] and on other circadian rhythms such as body temperature, melatonin and cortisol secretion (Goetze and Tolle, 1987; Michelson et al., 1997; Monteleone et al., 1995). However, these effects were not as thoroughly studied as the effects on sleep. A new drug, agomelatine, is the first antidepressant that was developed based on hypotheses relating circadian rhythms and depression. Agomelatine is a melatonin MT1 and MT2 receptor agonist and a 5-HT-2C antagonist (Fornaro et al., 2010). It is demonstrated to have antidepressant efficacy compared with placebo and equal or superior efficacy compared with SSRIs (Eser et al., 2010). Two possible advantages of agomelatine compared with other antidepressants are its faster onset of action and its advantage as it relates to sleep quality of patients, however the number of trials directly comparing agomelatine to other antidepressant drugs is still limited (Hale et al., 2010; Kasper et al., 2010; Lemoine et al., 2007) so far reaching conclusions are not possible. Agomelatine is authorized for by the European Commission for marketing for the treatment of depression as of July 2009 but is not approved yet by the FDA for USA marketing. Agomelatine and its effects are the center of significant research interest, and are described in detail in a number of recent reviews and will not be reviewed here (Eser et al., 2010; Fornaro et al., 2010; Goodwin, 2009; Lam, 2010; Llorca, 2010). Yet, the fact that agomelatine, which directly targets the circadian system, is an effective drug for treating depression, strongly support the connections between depression and the circadian system. Interestingly, there is a lack of knowledge regarding the effects of an additional melatonin agonist drug, ramelteon, in depression. Ramelteon is a synthetic analog of melatonin with high affinity for MT1 and MT2 receptors and has been reported to be effective for initiating and improving sleep without showing hangover, dependence, or cognitive impairment (Sriniwasan et al., 2011). We were not able to locate any clinical or preclinical studies examining its possible effects in depressed patients. The lack of publications may indicate that the drug was not yet tested in this context or that there were preliminary negative results that did not encourage additional work. It would be interesting to evaluate the effects of ramelteon in the context of depression.
3. Conclusion

The connections between circadian rhythms and depression are now well established and supported by several unrelated lines of evidence in humans with at least some support from work with animal models. Nevertheless, the mechanisms underlying the specific biology of the interactions between circadian rhythms and affect are yet to be studied. In the current review we suggest that the identification of better animal models with better homology to the circadian rhythms of humans may be a significant development we that will permit better mechanistic studies and understanding.

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