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REVIEW ARTICLE

Circadian rhythm disturbances in depression†

Anne Germain* and David J. Kupfer

Department of Psychiatry, University of Pittsburgh School of Medicine, Pennsylvania, USA

Objective The aim of this article is to review progress in understanding the mechanisms that underlie circadian and sleep rhythms, and their role in the pathogenesis and treatment of depression.
Methods Literature was selected principally by Medline searches, and additional reports were identified based on ongoing research activities in the authors' laboratory.
Results Many physiological processes show circadian rhythms of activity. Sleep and waking are the most obvious circadian rhythms in mammals. There is considerable evidence that circadian and sleep disturbances are important in the pathophysiology of mood disorders. Depressed patients often show altered circadian rhythms, sleep disturbances, and diurnal mood variation. Chronotherapies, including bright light exposure, sleep deprivation, and social rhythm therapies, may be useful adjuncts in non-seasonal and seasonal depression. Antidepressant drugs have marked effects on circadian processes and sleep.
Conclusions Recent progress in understanding chronobiological and sleep regulation mechanisms may provide novel insights and avenues into the development of new pharmacological and behavioral treatment strategies for mood disorders.

KEY WORDS — circadian rhythms; sleep; sleep disturbances depression; chronotherapy; melatonin

INTRODUCTION

Living organisms show a wide range of cyclical physiological changes across the 24-h period. In mammals, including humans, the sleep–wake cycle is the most obvious daily rhythm. Physiological rhythms are also observable in core body temperature, secretion of hormones such as cortisol, and activity of many organ systems. In humans, mood also exhibits changes across the 24-h cycle. Mood disorders, especially, are associated with changes in various circadian rhythms. Our understanding of the molecular and cellular mechanisms involved in the generation and synchronization of circadian rhythms has progressed tremendously in recent years. Recent findings provide novel insights into the pathophysiology of mood disorders, as well as new avenues for chronotherapeutic approaches. This article focuses primarily on circadian anomalies reported in unipolar depression. Circadian anomalies found in seasonal affective disorder (SAD) or bipolar disorder and other mood disorders have been reviewed extensively elsewhere (Goodwin and Jamison, 2007; Levitan, 2007; Lewy *et al*., 2007), and are only briefly presented here. We briefly review recent advances into circadian clock mechanisms, with a special emphasis on the physiological underpinnings of normal sleep–wake regulation. Convergent evidence supporting the role of circadian and sleep disturbances in the pathophysiology of mood disorders with a specific focus on unipolar depression is then

* Correspondence to: Dr A. Germain, Department of Psychiatry, University of Pittsburgh School of Medicine, 3811 O'Hara Street, Room E-1124, Pittsburgh, PA 15213, USA. Tel: 412-246-6436. FAX: 412-246-5300. E-mail: germaina@upmc.edu
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presented. Effective and novel therapeutic approaches that directly affect circadian and unipolar depression are also discussed.

GENERATION AND SYNCHRONIZATION OF BIOLOGICAL RHYTHMS IN MAMMALS

Central and peripheral oscillators

All living organisms are characterized by endogenous, cyclic rhythmicity of a wide variety of biological and behavioral processes. Cyclic rhythmicity of a given molecular or biological process is produced by an oscillator, or a system of components that interact to generate a rhythmic output (Bell-Pedersen *et al*., 2005). Oscillators have been studied in detail at the cellular and molecular levels in organisms as diverse as cyanobacteria (Ishiura *et al*., 1998), the fungus *Neurospora* (Dunlap, 2008; Loros *et al*., 1989), *Drosophila* (Bargiello *et al*., 1984; Konopka and Benzer, 1971; Reddy *et al*., 1984; Rosato *et al*., 2006; Young *et al*., 1985), and more recently in the mammalian brain (Gekakis *et al*., 1998; Hastings *et al*., 2007; King *et al*., 1997; Shearman *et al*., 2000; Tei *et al*., 1997; Vitaterna *et al*., 1994). Recent studies have shown that circadian oscillators can also be found in mammalian peripheral tissues, such as the liver (Matsuo *et al*., 2003), kidney (reviewed in Ikonomov *et al*., 1998), heart (Stoynev *et al*., 1996), and fibroblasts (Nagoshi *et al*., 2004; Yagita *et al*., 2001). Rhythms that approximate the 24-h dark-light cycle are called circadian (from *circa diem*) rhythms, whereas cycles that are shorter or longer that the 24-h cycle are referred to ultradian and infradian rhythmicity, respectively. These biological cyclic processes are endogenously generated and maintained. Human subjects kept isolated from external timing cues continue to show robust cycles in physiological processes for long lengths of time. However, most of these cycles oscillate with periods that differ slightly from 24 h (usually longer) and so lose synchrony with the earth's day-night cycle. Furthermore, synchrony may be lost among some cyclic functions, producing a degree of ''internal desynchronization'' (Aschoff, 1967; Aschoff and Wever, 1976; Mills, 1964; Mills *et al*., 1974). Synchronization of multiple endogenous processes among each other enhances survival of all living organisms, and it is now clear that orchestration of the multiple oscillator systems in mammals is managed by a central pacemaker. To further enhance survival, the pacemaker is adaptable; it can be entrained to respond directly or indirectly to external time givers, or zeitgebers.

In mammals, the suprachiasmatic nucleus (SCN) of the hypothalamus is the central pacemaker, or the master clock (Klein *et al*., 1991; Nishino *et al*., 1976; Stephan and Zucker, 1972; Stetson and Watson-Whitmyre, 1976). As described below, light is a powerful zeitgeber that directly influences the output of multiple oscillator systems, via entrainment of the master clock. Feeding (or absence thereof) is an important zeitgeber for peripheral oscillators (Damiola *et al*., 2000; Schibler *et al*., 2003; Stokkan *et al*., 2001). Lesions of the SCN disturb circadian rhythmicity in a variety of behavioral, endocrine, and biochemical processes (Moore and Eichler, 1972; Stephan and Zucker, 1972; Turek, 1985). Alternatively, SCN cells transplanted to SCN-lesioned animals restore circadian rhythms (Drucker-Colin *et al*., 1984; Ralph *et al*., 1990; Sawaki *et al*., 1984). Of note, the transplanted animals adopt characteristics of the donor's biological rhythms (Sollars *et al*., 1995). While recent studies show that lesions of the SCN do not abolish peripheral circadian rhythms (e.g., Grundschober *et al*., 2001; Guo *et al*., 2005), peripheral oscillators show disrupted phase synchrony in the absence of SCN influence. Thus, SCN appears to be required for the coordination, but not for the maintenance, of peripheral circadian oscillations.

The SCN can maintain rhythmic activity in the absence of neuronal input from other parts of the brain. If lesions are made to create an ''island'' of hypothalamic tissue containing the SCN, but with all afferent and efferent pathways severed, circadian rhythmicity is lost at other brain locations but persists within the island (Inouye and Kawamura, 1979). The SCN can maintain circadian behavior when isolated and maintained *in vitro* (Gillette and Reppert, 1987), in brain slices (Shibata and Moore, 1988), dispersed cell cultures (Honma *et al*., 1998; Murakami *et al*., 1991; Watanabe *et al*., 1993), or as immortalized cell lines (Earnest *et al*., 1999). Furthermore, individual SCN neurons in dispersed cultures show prominent circadian rhythms in their firing rate that are not synchronized with others in the same culture (Welsh *et al*., 1995). Thus, individual SCN cells can function as autonomous circadian oscillators. However, in intact SCN tissue, the activity of the individual cellular oscillators is closely coordinated, although not all cells oscillate in unison. Phase differences have been observed between groups of cells (Inagaki *et al*., 2007; Quintero *et al*., 2003) that show a topographic arrangement across the SCN (Yamaguchi *et al*., 2003). Interneuronal peptidergic signaling appears

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to be necessary for synchronization between SCN cells (Maywood *et al*., 2006).

The molecular mechanisms underlying the generation of circadian oscillations are thought to be similar in both the SCN and peripheral oscillators. While an extensive review of the genetic underpinnings of circadian systems is beyond the scope of this paper (see Bell-Pedersen *et al*., 2005; Gachon *et al*., 2004; Hastings *et al*., 2007 for more extensive review), all circadian rhythms appear to rely on a common mechanism. Specifically, multiple ''clock-related'' genes produce proteins, which inhibit the activation of their own genes when a concentration threshold is reached. An endogenous, inhibitory loop thus regulates regular oscillations. However, the accurate alignment of these mechanisms with the 24-h geophysical day and other rhythms requires entrainment by external zeitgebers.

Inputs and outputs of the central pacemaker

In small and simple organisms, light may act directly as a zeitgeber at peripheral oscillators. For example, in *Drosophila*, many different tissues are photoreceptive and show circadian oscillations that can be entrained by light when explanted and maintained in culture (Plautz *et al*., 1997). In such a system, light acts as the master coordination signal and there is no need for a central pacemaker. In animals of greater complexity and size (and opacity), most tissues are not exposed to light, and the range of cells and tissues responsive to light is reduced.

Although light is the main zeitgeber of the master clock in mammals, only the retina is light responsive, and the SCN receives direct photic (light) information from the retina. Lesion studies in rats have clarified the roles of retinal inputs to the SCN. Lesions of the SCN itself abolish the circadian sleep/wake rhythm. Elimination of retinal input by enucleation of both eyes allows a circadian sleep/wake rhythm to continue but it becomes ''free running,'' gradually losing synchronization with the geophysical day. However, lesions of the primary optic tract do not prevent synchronization of the sleep/wake cycle (Ibuka *et al*., 1977; Sisk and Stephan, 1982). It is now clear that light information from the retina is conveyed to the SCN via a specific monosynaptic pathway, the retinohypothalamic tract, that originates from a distinct population of light-sensitive retinal ganglion cells (Berson *et al*., 2002) containing the novel photopigment melanopsin (Hannibal and Fahrenkrug, 2002; Hattar *et al*., 2002), and releasing the neurotransmitter glutamate. Application of glutamate or glutamate agonists to the SCN can mimic light-induced phase shifts of the clock (Hannibal, 2002; Mintz *et al*., 1999).

In addition to the glutamatergic input carrying photic information from the retina, the SCN also receives a dense serotonergic innervation from the median raphe nucleus (Moore and Speh, 2004). Application of serotonin agonists to the SCN induces circadian phase shifts (Prosser, 2003), and it has been suggested that the serotonergic pathway conveys non-photic timing stimuli to the SCN. These two major inputs appear to act on the SCN in a mutually inhibitory manner; each can inhibit the phase changes induced by the other (Muscat *et al*., 2005; Prosser, 2001; Smith *et al*., 2001). The SCN is divided into two anatomical and functional compartments. Retinal and serotonergic inputs terminate in a core region (Moga and Moore, 1997; Moore and Speh, 2004) in which the SCN cells do not show endogenous rhythmicity. Rather, their expression of clock genes is gated by light. By contrast, cells in the surrounding shell region, which do not receive direct retinal input, show endogenous rhythmicity in clock gene expression (Hamada *et al*., 2001, 2004).

Light also directly reduces melatonin, often thought of as a ''sleep'' hormone, but is perhaps more correctly viewed as a ''darkness'' hormone. Melatonin production by the pineal gland is minimal during the day and increases dramatically at nightfall in both diurnal and nocturnal mammals. Lesions to either the SCN or the paraventricular nucleus (PVN) eliminate the day/night difference in pineal melatonin synthesis (Perreau-Lenz *et al*., 2003). Melatonin has diverse effects on mammalian physiology. It is used as a signal of relative light/dark duration in species that show marked seasonal behavior, although the importance of such a mechanism in humans, especially in the modern era of artificial lighting, is less clear (Macchi and Bruce, 2004; Wehr, 2001). Melatonin is involved in regulation of several circadian rhythms, including the sleep/wake cycle (Claustrat *et al*., 2005). In humans, the dim light onset of melatonin production is regarded as the most useful marker of circadian phase position (Lewy, 1999). Some human circadian rhythms, such as those in core body temperature and sleep propensity, coincide closely with the onset and offset of melatonin production, while others, such as cortisol levels and actual sleeping and waking, appear to lag 1–3 h behind the melatonin rhythm (Wehr *et al*., 2001). In many blind individuals, metabolic, endocrine, and sleep/wake rhythms are free-running, that is, these systems are not synchronized to environmental timing cues. The lack of

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synchrony among circadian systems and with exogenous light–darkness cycles has been described as almost as burdensome as not having vision (Lewy *et al*., 2005). Administration of melatonin at physiological doses produced a dose-dependent entrainment of these free-running rhythms, suggesting a key role for melatonin in light-dependent synchronization of circadian function (Lewy *et al*., 2005; Sack *et al*., 2000). In addition, there is evidence that administration of melatonin at physiological meaningful circadian times can have beneficial effects on mood symptoms in patients with SAD (Lewy *et al*., 2006).

Timing information is relayed from the SCN to peripheral oscillators by a range of humoral and neuronal pathways. The importance of both types of output signaling has been elegantly demonstrated recently using the technique of parabiosis, in which pairs of animals share a common blood circulation. SCN-lesioned mice that are linked parabiotically with intact mice show normal circadian rhythms of gene expression, in phase with those of their partner, in some organs, notably the liver and kidney, but not in others, such as the heart, skeletal muscle, and spleen (Guo *et al*., 2005). Thus, for some oscillators, blood-borne cues are sufficient to entrain circadian rhythms, while others require additional, presumably neuronal, cues. Major output targets of SCN neurons include the PVN, the subparaventricular zone, and the dorsomedial hypothalamic nucleus (DMH) (Buijs *et al*., 2003; Chou *et al*., 2003; Lu *et al*., 2001; Moore and Danchenko, 2002). The DMH plays a major role in circadian rhythms of corticosteroid and other endocrine secretion, locomotor activity, and sleep. Neuroendocrine neurons of the PVN are involved in the control of pituitary hormones, while other PVN neurons project to the pineal gland, which is important in regulating the secretion of melatonin, and to the sympathetic and parasympathetic arms of the autonomic nervous system, which relay information to numerous tissues and organs throughout the body. Lesion studies have shown that separate populations of SCN neurons, projecting via discrete pathways, are important in regulating different circadian rhythms (Lu *et al*., 2001; Moore and Danchenko, 2002).

The human circadian system is highly complex and regulates numerous processes, many of which maintain characteristic phase differences from each other and from the earth's day–night cycle. It involves a large number of autonomous oscillators entrained by a master clock and a range of different zeitgebers. The regulation of a given process will be determined by an integration of multiple internal and external timing influences, which may allow sophisticated control in the face of changing circumstances.

NORMAL SLEEP–WAKE REGULATION

Sleeping and waking are the most overt manifestations of the mammalian circadian system. Control of the sleep/wake cycle is complex and involves numerous brain areas and pathways (for review, see Saper *et al*., 2005). Cortical arousal and wakefulness are maintained via sustained neuronal activity of cholinergic and aminergic pathways from the pontine tegmentum, locus coeruleus, and raphe nuclei. The dorsal cholinergic pathway originates from the pontine tegmentum, through the thalamus, and to the cortex. The ventral pathway originates from the locus coeruleus and raphe, ascends to the periaqueducal gray matter and tuberomammilary nucleus, lateral hypothalamus, and basal forebrain. Activity of these wakefulness-promoting systems is mediated by orexin/hypocretin (Chemelli *et al*., 1999; de Lecea *et al*., 1998; Lin *et al*., 1999; Sakurai *et al*., 1998), a neuromodulator produced by the lateral hypothalamus critical for the maintenance of wakefulness. Orexin/hypocretin deficiencies are associated with impaired ability to maintain wakefulness, such as observed in narcoleptic patients.

Neurons of the ventrolateral preoptic area (VLPOA) are one group of the few brain cells dedicated to generating and maintaining sleep. The VLPOA has outputs to hypothalamic and brainstem arousal centers via pathways directly to the thalamus, and γ-aminobutyric acid (GABA)- and galanin-mediated inhibition of the brainstem monoamergic system and hypothalamic orexin/hypocretin system (Saper *et al*., 2005). The VLPOA shares reciprocal inhibitory connections with orexin neurons of the lateral hypothalamus, and with the aminergic ascending arousal system. These inhibitory interconnections between the lateral hypothalamus and VLPOA have been proposed as a ''sleep switch'' mechanism, by which sharp transitions between sleep and wakefulness are regulated (Saper *et al*., 2005). In the normal sleeping animal or human, the ''on'' switch position triggers and maintains wakefulness; the ''off'' position triggers and maintains sleep.

Summary

Findings presented here highlight the complexity of the multi-level control systems that regulate and orchestrate central and peripheral circadian processes, including sleep and wakefulness. While the specific

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regulatory genetic, molecular, and biochemical pathways underlying individual biological rhythms, their entrainment, their interaction, and their integration by the SCN remain largely elusive, these recent advances nevertheless raise the possibility that dysfunction of central and/or peripheral oscillators, or misalignment of the multiple endogenous oscillators, and attenuated responsiveness to zeitgebers may profoundly and adversely affect both physical and mental health. Evidence for the role of circadian and sleep disturbances in the pathophysiology of mood disorders is presented in the following sections.

CIRCADIAN RHYTHM AND SLEEP DISTURBANCES IN DEPRESSION

Circadian rhythm disturbances and depression

Circadian disturbances have been observed in a variety of psychological and physiological domains in depressed patients. Many patients with non-seasonal depression show a regular daily pattern of symptoms, usually with more severe symptoms in the morning (Gordijn *et al*., 1994; Tolle and Goetze, 1987), while a minority show the opposite pattern known as ''reversed diurnal variation'' (Joyce *et al*., 2005). Healthy subjects typically report deterioration of mood in the evening compared to the morning (Gordijn *et al*., 1994; Tolle and Goetze, 1987; Buysse *et al*., 2004; Boivin *et al*., 1997). In ''winter depression,'' the most common form of SAD, patients experience major depressive episodes beginning with the onset of winter, followed by remission or even hypomania in the spring (Magnusson and Partonen, 2005; Saeed and Bruce, 1998). Suicide rates also show both diurnal and seasonal variations (Chew and McCleary, 1995; van Houwelingen and Beersma, 2001; Preti *et al*., 2000), increasing with the amount of bright sunlight, even in parts of the world with very different climates such as southeastern Australia (Lambert *et al*., 2003) and Western Greenland (Bjorksten *et al*., 2005). In healthy subjects, mood variation across the 24-h cycle depends on the interaction between circadian phase and the duration of prior wakefulness (Boivin *et al*., 1997). If circadian and sleep processes directly affect mood regulation in healthy subjects, it is not surprising the circadian and sleep disturbances associated with depression can have profound detrimental effects on mood in depressed patients.

A recent study explored the neuroanatomical correlates of diurnal mood variation in depressed compared to healthy subjects, and found that depressed patients exhibit different patterns of variation of regional brain glucose metabolism across times of day compared to healthy subjects. Specifically, evening mood improvement in depressed patients appears to be associated with increased activation of a dorsal neural network involved in affect regulation (Germain *et al*., 2007). Furthermore, depressed patients showed sustained activity in brainstem and hypothalamic regions involved in the maintenance of wakefulness across times of day, whereas healthy subjects showed increased brain glucose metabolism in the evening relative to the morning (Buysse *et al*., 2004).

Increased mean core temperature and decreased period amplitude are relatively robust findings in depressed patients (Avery *et al*., 1982; Monk *et al*., 1994a; Posener *et al*., 2000; Souetre *et al*., 1989). Recent studies have shown that oscillations in plasma cortisol and norepinephrine are phase-advanced in depressed patients compared to healthy subjects (Koenigsberg *et al*., 2004). Twenty-four-hour cortisol secretion appears to be more variable (Peeters *et al*., 2004) and less strongly related to social zeitgebers (Stetler *et al*., 2004) in depressed patients. Social zeitgebers (time givers) refer to social and occupational routines, demands, and tasks that can entrain the master clock. Cortisol response to negative events is attenuated in depressed patients compared to healthy subjects (Peeters *et al*., 2003). Abnormal levels and patterns of melatonin secretion have also been observed in depressed patients in some (Claustrat *et al*., 1984; Karadottir and Axelsson, 2001; Rabe-Jablonska and Szymanska, 2001; Wetterberg *et al*., 1992), but not all studies (Thompson *et al*., 1988). It is important to note that the circadian controls of cortisol, temperature, and melatonin differ and that alterations in any one control is likely to have significant impacts on other circadian controls. Discrepant findings may also arise from the complexity and multifactorial nature of circadian mechanisms, and/or heterogeneity of symptoms in mood disorders. For example, a reduction in amplitude of 24-h cortisol levels is apparent in non-psychotic depressed patients, but not in patients with the psychotic subtype of depression (Posener *et al*., 2000). Additionally, a growing number of studies indicate that genetic vulnerability moderate the nature of circadian disturbances in mood disorders.

Sleep disturbances and depression

Among the circadian disturbances associated with depression, sleep disturbances are by far the most

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common and robustly observed. Subjective sleep complaints are common in mood-disordered patients. As many as 90% of depressed patients endorse difficulty falling asleep, staying asleep, and early morning awakenings (Almeida and Pfaff, 2005; Tsuno *et al*., 2005), whereas fewer (6% to 29%) endorse hypersomnia complaints (Roberts *et al*., 2000). Of note, winter-onset SAD is typically associated with hypersomnia, whereas less common summer-onset SAD is associated with insomnia (Saeed and Bruce, 1998). In bipolar disorder, insomnia often precedes and persists during manic episodes, whereas both insomnia and hypersomnia can precipitate and perpetuate depressive episodes and symptoms (Goodwin and Jamison, 2007).

Objective measures of sleep are also disturbed in mood disorders (Thase *et al*., 1997; see also Riemann *et al*., 2001 for review). The latency between sleep onset and the first episode of REM sleep is typically shortened in depressed compared to healthy subjects. Depressed patients exhibit increased duration of REM sleep, increased number of eye movements during REM sleep, and decreases in slow-wave sleep (SWS) compared to healthy subjects (Shaffery *et al*., 2003; Tsuno *et al*., 2005). Based on this finding, Kupfer and colleagues proposed that shortened REM latency may be a dependable marker for depressive disease, which could even be used to distinguish primary from secondary depression (Kupfer, 1976), although later studies challenged this hypothesis (Thase *et al*., 1984). Nevertheless, shortened REM sleep latency appears to be a common marker of mood disorders (Benca *et al*., 1992).

There is clinical and epidemiological evidence that sleep disturbances in depression constitute a risk factor for poor clinical outcomes. Specifically, insomnia complaints precede the onset and recurrence of depression (Cole and Dendukuri, 2003; Perlis *et al*., 1997; Riemann and Voderholzer, 2003) in as many as 40% of cases (Ohayon and Roth, 2003). The risk of developing major depression is significantly increased in individuals complaining of insomnia (e.g., Breslau *et al*., 1996; Dryman and Eaton, 1991; Mallon *et al*., 2000; Weissman *et al*., 1997). Furthermore, insomnia and hypersomnia complaints are associated with increased suicidality (Agargun *et al*., 1997a, b). Sleep disturbances in depression also predict treatment outcomes. Specifically, poor sleep quality predicts poor response to non-pharmacological treatments of depression (Buysse *et al*., 1999; Dew *et al*., 1996). The persistence of REM sleep anomalies and of poor sleep quality post-psychotherapy treatment for depression is associated with non-response (Buysse *et al*., 1999), and recurrence (Buysse *et al*., 1997). Finally, subjectively reported better sleep quality post-treatment is associated with lower rates of recurrence of depression (Buysse *et al*., 1997). Together, these observations suggest a critical role for circadian and sleep disturbances in the pathophysiology of depression.

Circadian hypotheses of depression

Based on the aforementioned observations, several circadian hypotheses of depression have been proposed. The phase-shift hypotheses of depression proposed that mood disturbances result from a phase advance or delay of the central pacemaker and related circadian rhythms that regulate temperature, cortisol, melatonin, and REM sleep relative to other circadian rhythms, and with a marked phase-shift relative to the sleep-wake rhythm. Findings indicative of advanced circadian phase such as early morning awakenings, earlier occurrence of REM sleep relative to sleep onset, and melatonin secretion shift in patients with depression compared to non-depressed subjects were thought to reflect a phase shift in the circadian oscillator that controls these parameters. Phase shift hypotheses have motivated therapeutic approaches with bright light exposure and melatonin to resynchronize the endogenous rhythms and the sleep-wake cycle and have yielded positive and encouraging findings mostly in patients with ‘‘winter depression’’ (e.g., Lewy *et al*., 1987, 1988, 2006; Lam and Levitan, 2000).

An alternative model, the internal phase coincidence model, postulated that depression arises when awakening from sleep occurs at a sensitive phase of the circadian period (Borbély and Wirz-Justice, 1982). Furthermore, the finding that advancing sleep episodes in depressed patients, thereby reducing the mismatch in circadian and sleep phases, was associated with improvements in mood also supported this hypothesis (Wehr *et al*., 1979). Similarly, antidepressant medications, such as monoamine oxidase inhibitors (MAOIs) and mood stabilizers, were found to extend the endogenous circadian period in mood disordered patients (Kripke, 1983). However, more thorough comparisons of the circadian periods in depressed and healthy subjects failed to consistently support the phase-advance hypothesis. For instance, the distribution of REM sleep across the 24-h cycle, and core temperature or cortisol secretion rhythms are not consistently advanced in depressed patients (Avery *et al*., 1982; Buysse *et al*., 1990; Lund *et al*., 1983). Nevertheless, the phase advance hypotheses have

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stimulated the development and testing of interventions based on circadian principles.

Another circadian hypothesis of depression was based on the early observation that REM sleep latency is shortened in depression (Argyropoulos and Wilson, 2005; Benca *et al*., 1992; Kupfer, 1976), and that suppression of REM sleep either pharmacologically or behaviorally was associated with mood improvements (Vogel *et al*., 1980, 1990). However, shorted REM latency is not specific to depression (Benca *et al*., 1992; Thase *et al*., 1984), and REM sleep suppression is not necessary for mood improvements (Argyropoulos and Wilson, 2005; Grözinger *et al*., 2002).

It has also been suggested that the apparent intensification of REM sleep in depression relates to a deficiency in SWS and slow-wave activity (SWA) (Borbély, 1982; Borbély and Wirz-Justice, 1982). As such, the antidepressant effects of sleep deprivation can be attributed to the enhancement of the S process, and the relapse of depression following recovery sleep to return to baseline levels of the abnormal S process (Borbély and Wirz-Justice, 1982). However, antidepressant medications do not typically enhance SWS or SWA, and may even further reduce both parameters (Sharpley and Cowen, 1995).

The social rhythms hypothesis of depression emphasizes the role of disruption of social rhythms in the etiology of depression and associated changes in physiological rhythms (Ehlers *et al*., 1988, 1993). This circadian hypothesis of depression suggests that vulnerable individuals exhibit more severe circadian and sleep disturbances with the disruption of social rhythms, and that the resulting disruption of nonphotic zeitgebers which normally entrain physiological circadian rhythms triggers depressive episodes. Several studies have indeed shown that social rhythms are disrupted and less regular in patients suffering from mood and anxiety disorders as well as in individuals undergoing stressful life events (Frank *et al*., 1995, 1997; Prigerson *et al*., 1994; Shear *et al*., 1994). Increased regularity of social rhythms is associated with better sleep quality and reduced severity of depressive symptoms (Brown *et al*., 1996; Monk *et al*., 1994b; Szuba *et al*., 1992). Nevertheless, there is limited evidence that disruption of social rhythms disrupts physiological rhythms in depression.

Clock gene polymorphisms and depression

Polymorphisms in clock-related genes may constitute a critical mechanism by which circadian and sleep disturbances predispose individuals to depressive illnesses (Bunney and Bunney, 2000). While this hypothesis provides innovative research and clinical avenues, this promising area is in an early stage of development and further research is necessary to understand the relationships between clock gene polymorphisms, depressive illnesses, and treatment response.

The occurrence of one particular single nucleotide polymorphism in the human clock gene, T3111C, has not been found to be associated with susceptibility to unipolar depression or bipolar disorder (Bailer *et al*., 2005; Desan *et al*., 2000). Nevertheless, clock gene polymorphisms have been associated with disease chronicity in patients with bipolar disorder (Benedetti *et al*., 2003b), and relapse in recurrent major depression (Serretti *et al*., 2004). Similar polymorphisms may more specifically affect sleep and the occurrence of insomnia in depressed patients (Serretti *et al*., 2003), and insomnia in response to antidepressant treatment (Serretti *et al*., 2005). Another clock gene polymorphism, NPAS2 471, was found to be associated with susceptibility to SAD in a case-control study (Johansson *et al*., 2003), and awaits replication. There is also some preliminary evidence suggesting that circadian and sleep disturbances in mood disorders may involve multiple gene polymorphisms. For instance, "reverse" diurnal mood variation in depressed patients, that is, worsening of mood in the evening, has been associated with polymorphism of the promoter region of the serotonin transporter (Joyce *et al*., 2005).

CHRONOTHERAPIES FOR DEPRESSION

Light therapy is now an accepted and recommended therapy for the winter-onset form of SAD (Depression Guideline Panel, 1993; Lam and Levitt, 1999; Rosenthal, 1995). Morning and evening light exposure is associated with greater SAD remission rate, defined as a 50% decrease in depression severity scores and post-treatment scores below clinical threshold, after three weeks compared to placebo (Eastman *et al*., 1998). Light therapy has also been associated with reduced suicidal ideation (Lam *et al*., 2000). Side effects associated with light therapy include eyestrain, headache, nausea, and agitation, and are generally milder than those reported with antidepressant medications. Hypomania can occur as a potential adverse effect (Terman and Terman, 1999; Tuunainen *et al*., 2004), although the latter adverse effect may in fact be uncovering latent bipolarity traits rather than inducing them. Exposure to light in the early morning is more effective than in the evening (Lewy *et al*., 1998; Terman *et al*., 1998). Morning light

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therapy produces an advance in the timing of the circadian melatonin rhythm, and the magnitude of the phase advance produced is correlated with the improvement in depression symptoms (Terman *et al*., 2001). Light therapy is moderately effective in relieving the symptoms of non-seasonal depression (Wirz-Justice *et al*., 2005). A meta-analysis of 20 randomized, controlled studies concluded that light therapy shows modest but promising antidepressant efficacy in non-seasonal depression (Tuunainen *et al*., 2004). Positive findings regarding the efficacy of light therapy have been reported in recent controlled studies (Epperson *et al*., 2004; Goel *et al*., 2005), although it appears to be relatively ineffective in older adults (Loving *et al*., 2005). Nevertheless, light therapy may be used as an adjunct to other antidepressant interventions, and provides a viable alternative in drug resistant depression and in cases where drug treatment may be inappropriate (Wirz-Justice *et al*., 2005), as during pregnancy (Epperson *et al*., 2004). Light therapy also reduces depression in institutionalized older adults, who may experience little natural sunlight (Sumaya *et al*., 2001). Hypomania is a potential adverse effect of light therapy in SAD and non-seasonal depression (Tuunainen *et al*., 2004). In bipolar patients, artificial prolongation of darkness (''dark therapy'') is associated with a reduction of manic symptoms (Barbini *et al*., 2005). This is consistent with the observation that some bipolar patients may be hypersensitive to the melatonin suppressing effects of light (Lam *et al*., 1990; Lewy *et al.*, 1981, 1985; Nurnberger *et al*., 2000). Results also support the suggestion that light/darkness exposure can be an important mood regulator. A careful titration and combination of melatonin and timing of light therapy may optimize clinical benefits in patients with mood disorders.

Sleep deprivation (''wake therapy''), usually consisting of total sleep deprivation for one night or for the second half of one night, has been described as the most rapid antidepressant available today, producing marked improvement within hours in approximately 60% of patients (see Wirz-Justice *et al*., 2005 for review). However, depressive symptoms generally return after subsequent recovery sleep (Wu and Bunney, 1990), so wake therapy is not widely used as monotherapy (Wirz-Justice and Van den Hoofdakker, 1999). Combination of wake therapy with other treatments, including lithium, SSRIs, and light therapy shows promise in achieving a rapid and maintained therapeutic response (Benedetti *et al*., 1997, 1999, 2003a; Colombo *et al*., 2000; Loving *et al*., 2002).

Social rhythm therapy (SRT) is another promising approach that targets the regularization of circadian rhythmicity in patients with bipolar disorder (Frank *et al*., 1997, 2005). This intervention is based on the hypothesis that genetic vulnerability, psychosocial stressors, and circadian rhythmicity are intricately related, and directly influence adherence to pharmacotherapy. The SRT first involves the identification of unstable rhythms, and the identification of stabilizing goals (e.g., stable sleep–wake schedule, stable non-shift employment). However, the efficacy of SRT has not yet been formally evaluated in unipolar depressed patients.

Emerging evidence suggests that standard behavioral interventions shown to be effective to reduce primary insomnia can also effectively reduce insomnia occurring in the context of depression and other chronic medical conditions associated with depressive symptoms, and have direct beneficial effects on daytime symptoms of depression (Edinger *et al*., 2005; Germain *et al*., 2006; Taylor *et al*., 2007). Behavioral treatments such as stimulus control and sleep restriction are thought to enhance circadian rhythmicity and sleep homeostasis, respectively. Stimulus control aims at restricting the use of the sleep environment (bed, bedroom) to sleep (and sexual activity), and may directly address sleep avoidance and compensatory behaviors that disrupt circadian sleep–wake regulation mechanisms (Bootzin and Nicassio, 1978). Sleep restriction involves the implementation of a regular sleep–wake schedule, which limits the time spent in bed while awake and favors sleep consolidation (Spielman *et al*., 1987). Stimulus control and sleep restriction allow for the normalization of the two processes that control sleep by aligning the timing and duration of sleep.

EFFECTS OF ANTIDEPRESSANT TREATMENTS ON CIRCADIAN AND SLEEP RHYTHMS

Given the close relationships between circadian processes and mood, and the involvement of common neurotransmitter systems, including the serotonin and noradrenergic systems, effective antidepressant treatments have marked effects on circadian processes, and especially on sleep (for reviews see Tsuno *et al*., 2005; Wilson and Argyropoulos, 2005; Winokur *et al*., 2001).

Although there is variation between individual drugs, tricyclic antidepressants (TCAs) generally shorten sleep latency and improve sleep continuity

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in depressed patients, and may be associated with daytime drowsiness. Most TCAs suppress REM sleep, increasing REM latency and reducing the percentage of REM sleep, thus tending to normalize the disturbed sleep architecture found in depressed patients. Furthermore, reduced REM latency at baseline predicts a positive response to TCA treatment (Rush *et al*., 1989). An increase in REM sleep latency was found to predict clinical response in patients treated with amitryptyline (Kupfer *et al*., 1981), and antidepressant activity across different drugs was found to be related to their capacity to suppress REM sleep (Vogel, 1983). These observations led to the suggestion that suppression of REM sleep is the key mechanism of action of antidepressant drugs (Vogel, 1983). However, subsequent studies have infirmed the hypothesis that REM sleep is depressogenic. At best, REM sleep changes with antidepressant medications may reflect underlying circadian effects.

Insomnia is often reported with administration of MAOIs, selective serotonin reuptake inhibitors (SSRIs), and serotonin-norepinephrine reuptake inhibitors (SNRIs). As many as 35% of patients treated with a selective SSRI are also prescribed hypnotic drugs to relieve medication-induced anxiety and sleep difficulties (Rascati, 1995). MAOIs and some SSRI also suppress REM sleep. REM sleep suppression has also been observed with newer antidepressants, such as venlafaxine, trazodone, and bupropion. There is little evidence that circadian processes mediate the antidepressant effects of these different agents.

New antidepressants, such as agomelatine, which has both melatonergic and serotonergic receptor action profiles (Millan *et al*., 2003), can advance the circadian phase in both rats and humans (Kräuchi *et al*., 1997; Leproult *et al*., 2005; Van Reeth *et al*., 2001; Weibel *et al*., 2000). Agomelatine can entrain free-running circadian rhythms in rats kept in total darkness in a similar way to melatonin (Martinet *et al*., 1996), and this effect requires an intact SCN (Redman and Francis, 1998). Administration of agomelatine and melatonin 5 h prior to bedtime both increased REM sleep duration and REM sleep percentage in the first part of the night compared to placebo (Cajochen *et al*., 1997). In both rats and humans, administration of agomelatine is associated with significant circadian phase advances (Kräuchi *et al*., 1997; Leproult *et al*., 2005; Van Reeth *et al*., 2001; Weibel *et al*., 2000). Whether mood improvements in depressed patients associated with agomelatine directly relate to normalization of circadian and sleep alterations remains to be determined.

Both electroconvulsive therapy (ECT, Coffey *et al*., 1988) and transcranial magnetic stimulation (Cohrs *et al*., 1998) produce significant increases in REM latency. ECT also normalizes the timing and increases the amplitude of circadian temperature rhythm in depressed patients (Szuba *et al*., 1997), and reduces 24-h melatonin production (Krahn *et al*., 2000). Thus, these non-pharmacologic antidepressant treatments may also act on sleep and other circadian systems.

CONCLUSIONS

The control of circadian rhythms and sleep is complex and involves the fine orchestration of multiple molecular, biochemical, physiological, and behavioral mechanisms. While this complexity promotes adaptability and survival, this complexity also gives rise to potential internal conflicts. The current industrialized society where artificial light is available at all times and extended and irregular sleep–wake schedules are common may impose profound strain on the circadian systems, and expose their vulnerabilities.

Several lines of evidence briefly reviewed here converge and support the hypothesis that circadian and sleep disturbances may play a critical role in the pathophysiology of mood disorders. Recent progress in understanding the molecular and cellular chronobiological mechanisms opens exciting avenues to research to elucidate the underpinnings of the relationships between circadian rhythm disturbances, including sleep disturbances, and clinical mood disorders. A variety of pharmacological and behavioral strategies, as well as novel agents, can be used to further probe these relationships. Clarifying the relationships between biological clock functions and mood regulation will provide novel insights and new avenues into the development of effective treatment strategies.

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