Biological rhythm disturbances in mood disorders

Anna Wirz-Justice

From earliest times, psychiatrists have described biological rhythm disturbances as characteristic of mood disorders. The present flourishing of circadian biology has revealed the molecular basis of 24-h rhythmicity driven by 'clock' genes, as well as the importance of zeitgebers (synchronisers). Winter depression was first modelled on regulation of animal behaviour by seasonal changes in daylength, and led to application of light as the first successful chronobiological treatment in psychiatry. Light therapy has great promise for many other disorders (e.g. sleep–wake cycle disturbances in Alzheimer's dementia, bulimia, premenstrual disorder, depression during pregnancy) and, importantly, as an adjuvant to antidepressant medication in major non-seasonal depression. The pineal hormone melatonin is also a zeitgeber for the human circadian system, in addition to possessing direct sleep-promoting effects. Chronobiology has provided efficacious non-pharmaceutical treatments for mood disorders (such as sleep deprivation or light therapy) as well as novel approaches to new drugs (e.g. agomelatine). ***Int Clin Psychopharmacol*** **21 (suppl 1):S11–S15 © 2006 Lippincott Williams & Wilkins.**

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Introduction

Observers of melancholia have linked many of its clinical symptoms to abnormal biological rhythms (Menninger-Lerchenthal, 1960; Richter, 1965; Papousek, 1975): 'Of the seasons of the year, the autumn is most melancholy' (Burton, 1621). Diurnal variation of mood and early morning awakening in depression have been incorporated into established diagnostic systems, as has the seasonal modifier defining winter depression (seasonal affective disorder, SAD) (American Psychiatric Association, 1994). Not only is sleep disturbed, but also many circadian rhythms measured in depressive patients are abnormal: earlier in timing, diminished in amplitude or of greater variability (Wirz-Justice, 1995, 2003). Bipolar patients, and particularly rapid cyclers, undergo remarkably precise periodic switches between clinical states. Whether these circadian rhythm disturbances are of aetiological significance with respect to mood disorders or whether they are a consequence of altered behaviour is still not clear.

The circadian system

The characteristics of the circadian system are remarkably similar in all mammalian species (Klein *et al.*, 1991). The biological clock in the suprachiasmatic nuclei (SCN), a master pacemaker driving circadian rhythms in brain and body, is synchronised to the external light–dark cycle via retinal light input. New findings in the past few years have added complexity to this system. Classic cones and rods participate in, but are not the major transducer of, 'non-visual' circadian photic input: the main photoreceptor pigment for circadian timing appears to be melanopsin in the retinal ganglion cells (Hattar *et al.*, 2003). A specialised retinohypothalamic tract provides direct neuronal connection to the SCN, which also receives indirect non-photic input (e.g. from the raphé nuclei) (Moore and Speh, 2004). Nocturnal synthesis of the pineal hormone melatonin is driven by the SCN; melatonin also feeds back on melatonin receptors in the SCN (Stehle *et al.*, 2003). Furthermore, even though the SCN is the so-called master clock, circadian oscillators are found in every organ and, indeed, in every cell (Schibler *et al.*, 2003). Moreover, each organ has its own appropriate zeitgeber to synchronise these clocks. Although light is the major zeitgeber for the SCN, it does not affect clocks in the liver; the zeitgeber for the latter is food, but food is not a zeitgeber for the SCN (Schibler *et al.*, 2003).

Clock genes and depression

Individuals have different preferences for timing their sleep (Roenneberg *et al.*, 2003b). This characteristic of chronotype ('larks' or 'owls') is partially determined by clock genes, of which 10 have been cloned to date (Roenneberg and Merrow, 2003a). Familial forms of circadian sleep disorders (such as advanced or delayed sleep phase syndrome) manifest allelic mutations on one or other of the clock genes (Jones *et al.*, 1999; Ebisawa *et al.*, 2001; Iwase *et al.*, 2002). Studies of the *clock* gene in major depression (Desan *et al.*, 2000; Bailer *et al.*, 2005) and the *per2* gene in bipolar disorder (Shiino *et al.*, 2003) have so far been negative. Circadian clock-related polymorphisms may be related to susceptibility to SAD together with evening chronotype (Johansson *et al.*, 2003).

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It is unlikely that affective disorders will be characterised as simple clock gene mutations. However, individual genetic characteristics of the molecular mechanisms of the biological clock are also determinants of core features of mood disorders, including age at onset (Benedetti *et al.*, 2004), recurrence (Benedetti *et al.*, 2003b), symptoms of insomnia and its treatment (Serretti *et al.*, 2003, 2005) and response to sleep deprivation (Benedetti *et al.*, 2004). Such parallel findings point to an intimate relationship between the neurotransmitter systems targeted by drugs and the circadian rhythms targeted by chronotherapeutics.

Circadian rhythm desynchronisation

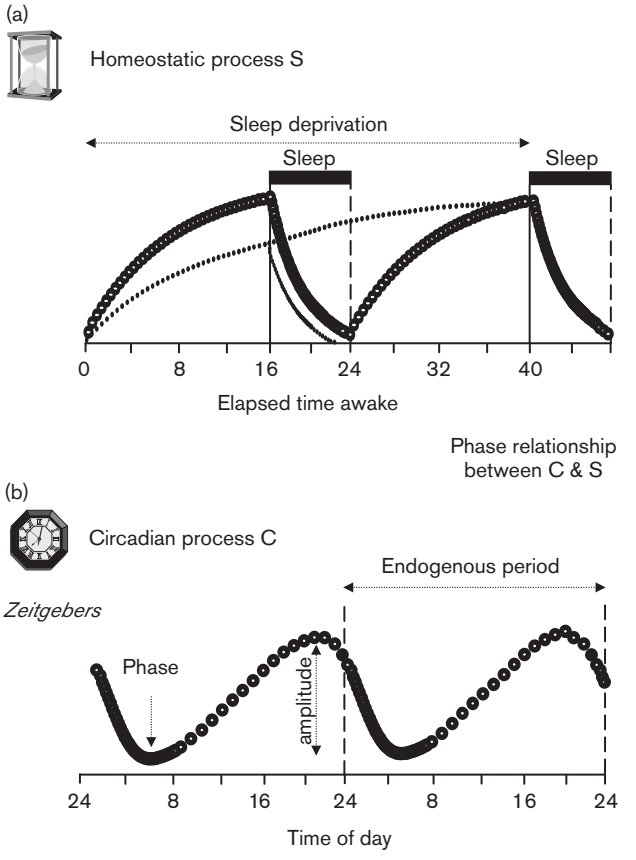
Because the timing of sleep appears relevant for determining mood state, these genetic factors may provide a chronobiological vulnerability for depression, in that wrong or poor alignment of internal phase with the outdoor world increases susceptibility to depressive mood swings. New findings on desynchronisation in clock gene expression illustrate this vividly. The clock genes in the SCN gradually adapt to a phase shift of the light–dark cycle (as found in shift work, transmeridian flight), whereas clock genes in the muscle, liver and lung resynchronise at their own rates (Yamazaki *et al.*, 2000). This results in a 'double desynchronisation'–'internal desynchronisation' between different clocks in the body and brain, and 'external desynchronisation' between the timing of body rhythms with respect to the light–dark cycle. The temporal orchestra can get quickly out of tune. The problems of a shift worker who is awake, active and eating main meals at night, although he receives daylight on the way home, are abundantly clear. Complete adaptation to night work is almost impossible, and the desynchronised status can rarely be overcome. This misalignment has profound effects on mood, sleep and health.

Genetic vulnerabilty and stress influence circadian rhythms and sleep patterns, leading to symptoms characteristic of affective disorders (Nestler *et al.*, 2002). Circadian regulation interacts with, and is determined by, neurotransmitter function; for example, the highest concentrations of central nervous system (CNS) serotonin are in the SCN (Moore and Speh, 2004). CNS serotonin turnover undergoes marked circadian and seasonal rhythmicity (Carlsson *et al.*, 1980) and is rapidly stimulated by light exposure (Lambert *et al.*, 2002). This links the important role of light as zeitgeber or synchroniser of the circadian system, to the role of serotonin in mood disorders, indirectly supported by combination therapies of light and selective serotonin reuptake inhibitors (SSRIs) (Benedetti *et al.*, 2003a; Martiny, 2004).

Sleep regulation

The two-process model of sleep regulation considers the timing and architecture of sleep to be a consequence of interactions between a homeostatic process of rising sleep pressure (Process S; Fig. 1a), dependent on the duration of prior wakefulness, that is dissipated during the sleep period, and a circadian pacemaker (Process C; Fig. 1b) that ticks along independent of sleep (Daan *et al.*, 1984). This model has proved remarkably fruitful in explaining (and predicting) many aspects of sleep–wake cycle behaviour and physiology. It is also most useful to conceptualise possible abnormalities in mood disorders. A deficit in Process S could manifest itself in a slower build up of sleep pressure during wakefulness or a different rate of decline during sleep; a full night's sleep deprivation would raise it nearer to normal values (Fig. 1a, dotted line). A deficit in Process C could be manifested in changed amplitude, phase, or endogenous period (Fig. 1b). Shifting phase relationships between

Fig. 1



Schematic representation of the two-process model of sleep regulation. (a) Depicting a homeostatic Process 'S' which builds up exponentially during time awake and declines exponentially during sleep. The dotted line symbolises a putative disturbance in depression with lower build up rate, that only attains normality after 40 h of total sleep deprivation. (b) The circadian process 'C' follows a 24-h rhythm independent of duration of prior wakefulness. In depression, the circadian system might have altered endogenous periodicity, advanced or delayed phase, and/or diminished amplitude. Additionally, the phase relationship between circadian and homeostatic processes could be abnormal.

C and S can cause, in vulnerable individuals, decrements in mood (Wirz-Justice, 1995, 2003). As yet, there is insufficient evidence of sufficient quality to determine such putative aetiological factors in major depression.

Two important protocols have been developed over the last decade to investigate circadian and sleep homeostatic processes in humans (Duffy and Dijk, 2002). Under stringently controlled conditions of a 'constant routine protocol' (very dim lighting < 10 lux, semi-recumbent posture, small isocaloric meals and water), the amplitude and phase of many circadian rhythms can be elucidated without the 'masking' effects of activity, meals and lighting conditions. In a longer, more complicated experiment (the 'forced desynchrony protocol'), subjects live on artificially very long or very short days, so that the circadian system is no longer entrained by the sleep–wake cycle. The desynchronised subjects thus sleep at different circadian phases, covering the entire 24-h cycle, and resultant analyses can dissect out the relative contribution of the sleep homeostat or the biological clock to a given variable (Dijk *et al.*, 1997). For example, the circadian rhythm of core body temperature or melatonin is hardly affected by sleep, whereas electroencephalogram slow-wave activity is mainly dependent on the sleep homeostat with little circadian contribution (Dijk *et al.*, 1997). However, most variables show varying degrees of interaction. Both factors contribute substantively to such subjective measures as mood (Koorengevel *et al.*, 2003) or performance (Cajochen *et al.*, 1999). These are the protocols required for a new generation of studies of circadian disorders in depression (Wirz-Justice, 2003). Most previous studies have not been sufficiently controlled to unmask the contribution of the clock; the biological rhythm disturbances described therein are mostly a consequence of behaviour and say little about causative factors.

Chronobiological treatments

The two-process model is additionally useful to understand chronobiological treatments acting on the sleep homeostat or the circadian system.

Manipulations of the sleep–wake cycle, whether of duration (total or partial sleep deprivation) or timing (partial sleep deprivation, phase advance), have profound and rapid effects on depressed mood in 60% of all diagnostic subgroups of affective disorders (Wirz-Justice and Van den Hoofdakker, 1999). The therapeutic effect of sleep deprivation is postulated to be linked to an increase in homeostatic sleep pressure; additionally, sleep deprivation–induced sleepiness may counteract the hyperarousal state in depression (Wirz-Justice, 2003).

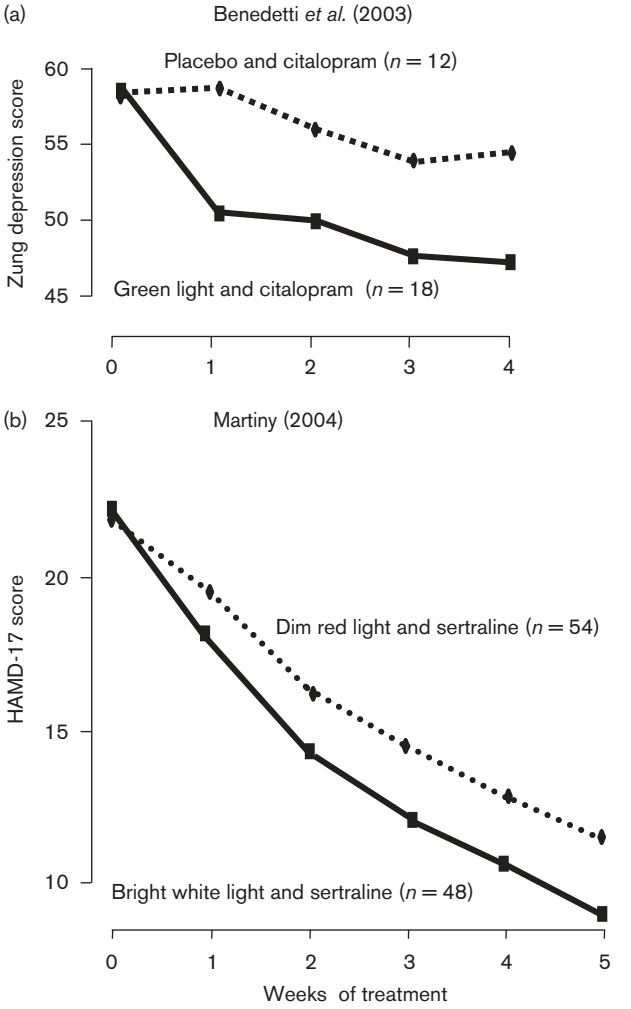
By contrast, light therapy was specifically developed as a 'zeitgeber' treatment for SAD patients, who become depressed as the days shorten and spontaneously remit during the longer days in spring and summer (Lam and Levitan, 2000). Bright light has three major effects on the circadian system: it increases circadian amplitude, shifts circadian phase (depending on the time of application) and thereby modifies the phase relationships between the internal clock and sleep, and the external light–dark cycle (Wirz-Justice, 2003). Any of these might alone suffice for the mood-elevating effects (as well as the above-mentioned serotonin connection). Light therapy has been applied in many other psychiatric disorders, from bulimia to the sleep–wake cycle disturbances of Alzheimer's dementia and antepartum depression (Lam, 1998). Recently, two research groups have demonstrated, in double-blind, placebo-controlled studies, that light therapy combined with an SSRI leads to more rapid (within 1 week) and more profound (by approximately 30%) improvement in patients with non-seasonal major depression (Benedetti *et al.*, 2003a; Martiny, 2004) (Fig. 2), suggesting an advantage of using combined approaches, which may not be limited to this category of antidepressants.

Melatonin, exogenously administered, also acts as a zeitgeber to synchronise circadian rhythms and sleep (e.g. in blind persons) (Arendt, 2003). Its direct effects inducing sleepiness occur via thermoregulatory changes; melatonin increases distal vasodilatation and hence heat loss, with a consequent hypothermia (Cagnacci *et al.*, 1997). Melatonin does not appear to have any major effects on mood.

The specific pharmacological profile of agomelatine, as an agonist of melatoninergic MT_1 and MT_2 receptors, as well as an antagonist of 5-HT_{2c} receptors, uniquely combines zeitgeber with neurotransmitter augmentation properties, with evolving evidence for robust antidepressant efficacy (Lôo *et al.*, 2002). Agomelatine has identical physiological actions to melatonin when administered in the evening, to advance circadian phase and directly increase sleepiness through thermoregulatory mechanisms (Cajochen *et al.*, 1997; Kräuchi *et al.*, 1997). This promotes a rapid sleep onset but is without after-effects on the following day.

Thus, what is important in the connection of circadian rhythms with depression? Stable internal and external phase relationships appear to be crucial for a stable and euthymic mood state (i.e. the timing between core body rhythms such as cortisol and temperature as well as the timing of sleep with respect to the day–night cycle). Any misalignment brings with it the propensity for mood fluctuation, particularly in vulnerable individuals. Chronobiological concepts emphasise the important role of zeitgebers to stabilise phase, with light and melatonin being the most important, but also paying attention to

Fig. 2



Two randomised controlled studies of adjuvant light in major non-seasonal depression showing a more rapid improvement and a greater diminution of symptoms over the clinical trial than with 'placebo'. Differences between groups are highly significant. (a) The upper panel (redrawn from Benedetti *et al*., 2003a) compares depressive patients treated with citalopram (40 mg) and additional morning green light (400 lux, 30 min/day) or a placebo (deactivated negative ion generator). (b) The lower panel (redrawn from Martiny, 2004) compares depressive patients treated with sertraline and adjuvant morning bright white light (10 000 lux, 1 h/day) or dim red light (50 lux, 30 min/day).

other zeitgebers, such as dark (and rest) periods, regularity of social schedules and meal times. Regular dark phases themselves appear to regulate the mood swings of rapid cyclers (Wehr *et al*., 1998; Wirz-Justice and Van den Hoofdakker, 1999), and a preliminary trial of 'dark therapy' can diminish manic symptoms as rapidly as the conventional antipsychotics generally used (Barbini *et al*., 2005).

In summary, circadian rhythm and sleep research have led to non-pharmaceutical therapies of depression (sleep deprivation, light therapy) that can be (and should be) used in everyday practice (Wirz-Justice *et al*., 2004, 2005). The rationale for attempting to resynchronise disturbed phase relationships between the clock and sleep is the concomitant improvement in mood. Chronobiological concepts emphasise the importance of zeitgebers and provide psychopharmacology with a novel approach for developing light (or dark) 'in a pill'.

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