Depression symptoms: significance of the circadian rhythms. Review of literature

Depresijos simptomai: cirkadinių ritmų reikšmė. Literatūros apžvalga

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SUMMARY

The circadian rhythms act like a multifunctional timer to adjust the homeostatic brain system, including sleep and alert states, locomotor activity, to approximately 24 hour cycle and allow organisms to adapt to enviromental changes.The endogenous circadian rhytm comes in cycles of roughtly 24–25 hour, but is unadulterated only when a person is completely isolated from the outside influenses (e.g., in a windowless basement, dark cave, etc.). It takes several days to „reset" the biological clock, e.g., after a long journey from east to west (jet lag). The mechanism by which this cycle activates subsequent neuronal actions (membrane potentials) is still unclear.

The primary molecular clock is located in the suprachiasmatic nucleus (SCN) in the hypothalamus, and consists of environmental input. The major transcriptional activator consists of a dimer between the circadian locomotor output cycles kaput protein (CLOCK) and brain and muscle ARNT–like protein1 (BMAL 1, also known as ARNTL or MOP3). Some of the major neurotransmitters that have been implicated in mood regulation, including serotonin, norepinephrine and dopamine, have a circadian rhythm in their levels, release, and synthesis related enzymes. It seems likely that disruptions in the normal rhythms in these circuits (either continuous or abrupt) could have major effects on mood and motivational states. Some of these modulations seems to occur through connections between the SCN and other brain regions. Melatonin is synthesized from tryptophan by pineal gland, and is under direct control of the central circadian pacemaker that is located in the SCN of the hypothalamus. Melatonin can bind to the G-protein coupled receptors M1 and M2. These receptors are expressed at high levels in the SCN, and upon stimulation, modulates SCN transmission and circadian activity. The expression of the 5–HT_{5A} receptor in raphe nuclei and in higher brain areas, such as the cerebral cortex and hippocampus, suggests a potential autoreceptor function whilst localisation in the SCN suggests a role in circadian rhytm control. Abnormal sleep is a core symptom of major depressive disorder, with sleep disruption seen at all stages in the sleep cycle. Studies suggest a potential role of the 5–HT_{5A} receptor in the control of circadian timing. Clinical findings have provided evidence for a relationship between disturbances in circadian rhythms and sleep architecture, including rapid eye movement (REM) sleep. For many years it is considered that abnormalities in circadian rhythms may underlie the development of mood disorders such as bipolar disorder, major depression and seasonal affective disorder (SAD). There is reason to suspect that many of the mood stabilizers and antidepressants used to treat these disorders may exhibit at least some of their therapeutic efficacy by affecting the circadian clock. For treating mood disorders by altering the circadian cycle are used: sleep deprivation therapy, bright light therapy or dawn simulation; pharmacological treatments. Efficiency of drugs used for treatment of mood disorders partially or essentially depends on their effect on human circadian rhythms.

Key words: circadian rhytms, cycle, neurotransmitters, mood regulation, melatonin, receptors, treatment.

SANTRAUKA

Cirkadiniai ritmai veikia kaip daugiafunkcinis laikmatis, kuris pritaiko homeostazines smegenų sistemas, taip pat miego bei būdravimo būsenas ir lokomotorinį aktyvumą prie dvidešimt keturių valandų ciklo ir taip leidžia organizmui prisitaikyti prie aplinkos pokyčių. Endogeniniai cirkadiniai ritmai susideda iš reguliarių 24–25 val. ciklų, tačiau taip yra, tik jei asmuo visiškai izoliuotas nuo aplinkos veiksnių įtakos (vėjuotos aplinkos, tamsos ir pan.). Pvz., po ilgos kelionės iš rytų į vakarus prireikia keletos dienų vidiniam laikrodžiui „persukti". Tačiau iki šiol nėra žinoma mechanizmo, kuriuo šis ciklas aktyvina membraninius potencialus (neuronų aktyvumą). Pirminis molekulinis laikrodis lokalizuotas pogumburyje, suprachiazminiame branduolyje (SChB), ir susideda iš atgalinio ryšio perrašymo kilpų, kurių kurso ciklišKumas be aplinkos įtakos yra 24 val. Kai kurie pagrindiniai neurotransmiteriai – serotoninas, norepinefrinas ir dopaminas, dalyvaujantys nuotaikos reguliacijoje, turi savo kiekio, atpalaidavimo bei su sintetinimu susijusių fermentų cirkadinį ritmą. Šių neurotransmiterių receptorių aktyvumas taip pat turi ciklinius ritmus, o tai rodo bendrą cirkadinę reguliaciją. Normalių grįžtamųjų ciklišKumų sutrikdymas gali stipriai paveikti nuotaiką ir motyvaciją. Iki šiol nėra tiksliai žinoma, kaip šios grandys yra kontroliuojamos cirkadinio ritmo. Kai kurios moduliacijos kyla per SChB ir kitų smegenų regionų ryšius. Melatoniną iš triptofano sintetina kankorėžinė liauka, o jo gamyba tiesiogiai kontroliuojama centrinio cirkadinio aktyvatoriaus, kuris yra pogumburyje, SChB. Melatoninas gali jungtis prie G-proteino porinių receptorių MT1 ir MT2, kurių gausiai yra SChB, o, juos stimuliuojant, daroma įtaka SChB transmisijai ir cirkadiniam aktyvumui. 5–HT_{5A} receptorių kiekis *raphes* branduolyje ir aukštesnėse smegenų srityse, tokiose kaip smegenų žievė ir hipokampas, siejamas su cirkadinių ritmų kontroliavimu. Didžiosios depresijos metu sutrikęs miegas yra vienas šerdinių simptomų. Klinikinių tyrimų rezultatai rodo, kad yra ryšys tarp cirkadinių ritmų sutrikimo ir miego architektūros, apimant ir REM (angl. *rapid eye movement*) miegą. Jau keletą metų manoma, kad cirkadinių ritmų sutrikimai gali daryti įtaką nuotaikos sutrikimų, tokių kaip bipolinis afektinis sutrikimas, didžioji depresija ir sezoniniai afektiniai sutrikimai, vystymuisi. Galima įtarti, kad dauguma nuotaikos stabilizatorių ir antidepresantų, vartojami nuotaikos sutrikimams gydyti, terapinį aktyvumą pasiekia paveikdami cirkadinį laikrodį. Nuotaikos sutrikimams gydyti, paveikiant cirkadinį ciklą, skiriama miego deprivacijos terapija, ryškios šviesos terapija arba sutemos simuliacija bei farmakologinis gydymas. Nuotaikos sutrikimų medikamentinio gydymo efektyvumas iš dalies priklauso nuo jų poveikio žmogaus cirkadiniams ritmams.

Raktažodžiai: cirkadiniai ritmai, ciklas, neurotransmiteriai, nuotaikos reguliacija, melatoninas, receptoriai, gydymas.

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INTRODUCTION

The circadian rhythms act like a multifunctional timer to adjust the homeostatic brain system, including sleep and alert states, locomotor activity, to approximately 24 hour cycle and allow organisms to adapt to environmental changes [1].

The endogenous circadian rhythm comes in cycles of roughly 24–25 hours, but is unadulterated only when a person is completely isolated from the outside influences (e.g., in a windowless basement, dark cave, etc.). External zeitgebers (incoming signals) synchronize the biological clock to precise 24–hour cycles. It takes several days to "reset" the biological clock, e.g., after a long journey from east to west (jet lag). The mechanism by which this cycle activates subsequent neuronal actions (membrane potentials) is still unclear. The main external zeitgeber for 24–hour synchronization of the sleep–wake cycle is bright light (photic input). Light stimuli are directly sensed by a small, melanopsin-containing fraction of retinal ganglion cells and conducted to the suprachiasmatic nucleus (SCN) via the retinohypothalamic tract. The coupled cells of the SCN generate circadian rhythms of hormone secretion, core temperature, and sleep–wake cycles by various effector systems of the CNS. The zeitgeber slows or accelerates the rhythm, depending on which phase it is in. Signals from the zeitgeber also reaches the epiphysis (pineal body, pineal gland) where it inhibits the secretion of melatonin which is high at night. Since it exerts its effects mainly on the SCN, administration of melatonin before retiring at night can greatly reduce the time required to "reset" the biological clock. The main reason is that it temporarily "deactivates" the SCN (via MT2 receptors), thereby excluding most nocturnal neuronal input (except light stimuli) [2].

MOLECULAR CLOCK

„Inner clock"

The primary molecular clock is located in the suprachiasmatic nucleus (SCN) in the hypothalamus, and consists of a transcriptional feedback loop which cycles over the course of ~24 hr in the absence of environmental input. The major transcriptional activator consists of a dimer between the circadian locomotor output cycles kaput protein (CLOCK) and brain and muscle ARNT-like protein 1 (BMAL1, also known as ARNTL or MOP3). This complex binds to E–box sequences in the promoters of many genes including the Period (Per) and Cryptochrome (Cry) genes. The PER and CRY proteins are translated in the cytoplasm, and are phosphorylated by casein kinase 1 (CK1) ε and δ and glycogen synthase kinase 3β (GSK3β), leading to changes in their stability, association and nuclear entry. Upon entering the nucleus, they can repress the actions of CLOCK/BMAL1, thus creating a negative feedback loop. In addition, there is an adjoining loop in which CLOCK/BMAL1 activates the transcription of Rev–erbα and Rorα. Once translated, these proteins can bind to the promoter of the Bmal1 gene and both positively and negatively affect its transcription. Selectively in forebrain regions, neuronal PAS domain protein 2 (NPAS2), a protein very similar to CLOCK, can bind BMAL1 and induce Per and Cry gene expression. NPAS2 may also function in the place of CLOCK in the SCN if the CLOCK protein is genetically defective. Though the central circadian pacemaker is located in the SCN, all of these genes are expressed throughout the brain and in other organs where they function as peripheral clocks that respond to non–photic stimuli, and likely also in other processes unrelated to circadian rhythms [3, 4].

Influence of the molecular clock on mood–related neurotransmitter systems

The biological factors that underlie the relationship between circadian rhythms and mood disorders are still unknown, but probably could be related with the influence of the molecular clock on certain neurotransmitters and their receptors. Indeed some of the major neurotransmitters that have been implicated in mood regulation, including serotonin, norepinephrine and dopamine, have a circadian rhythm in their levels, release, and synthesisrelated enzymes. There are also circadian rhythms in the expression and activity of several of the receptors that bind these neurotransmitters, suggesting that these entire circuits are under circadian control. It seems likely that disruptions in the normal rhythms in these circuits (either continuous or abrupt) could have major effects on mood and motivational states. How these circuits are controlled in a circadian manner is still uncertain. Some of this modulation seems to occur through connections between the SCN and other brain regions. For example, an indirect projection from the SCN to the locus coeruleus appears to regulate the circadian rhythm in noradrenergic neuronal activity. Furthermore, circadian gene expression outside of the SCN, in these specific regions, may contribute to their rhythmic activity. Circadian activity rhythms in rodents can be entrained to daytime methamphetamine injections, even in SCN lesioned animals. This treatment shifts the expression of the period genes in striatal regions typically associated with movement control in a manner that matches the shift in activity rhythms. This same shift in period gene expression does not occur in the SCN with methamphetamine treatment, thus there is a disconnect between the SCN, molecular rhythms in the striatum and locomotor activity rhythms. This suggests that the period gene expression and rhythms in striatal regions is important in producing rhythms in locomotor activity. Therefore, the circadian genes both in the SCN and in these specific circuits may be involved in regulating this rhythmic activity in neurotransmission. Future studies are needed to determine exactly how these rhythms in dopamine, serotonin and other neurotransmitters are involved in mood regulation [3].

SYNTHESIS OF MELATONIN

Melatonin is synthesized from tryptophan in a series of four enzymatic steps. First, tryptophan hydroxylase (TPH) converts tryptophan to 5–hydroxytryptophan, which is then converted to 5–hydroxytryptamine (serotonin) by aromatic amino acid decarboxylase. Serotonin is then converted to N–acetylserotonin by arylalkylamine N–acetyltransferase. N–acetylserotonin is converted to melatonin (N–acetyl–5–methoxytryptamine) by hydroxyindole–O–methyltransferase. The enzyme activity and mRNA encoding TPH and AANAT display circadian rhythms of expression, with highest levels occurring at night. Melatonin is a highly lipophilic molecule, and presumably diffuses out of the cells as soon as it is synthesized, into the neighboring cells and tissues [5].

Melatonin is synthesized by the pineal gland and its synthesis is under direct control of the central circadian pacemaker that is located in the suprachiasmatic nucleus (SCN) of the hypothalamus. Previous studies have shown that at night, norepinephrine (NE) is released from the sympathetic nerve endings and activates the adrenergic receptors located in the pineal gland, the activation of adrenergic receptors leads to the transcriptional activation of the arylalkylamine N-acetyltransferase (Aanat, the rate limiting enzyme of melatonin synthesis) gene via CRE (cyclic AMP response element) and thus to the activation of circadian melatonin synthesis. The adrenergic mechanisms also regulate circadian Period1 gene expression, further suggesting that the SCN via the adrenergic mechanism is responsible for circadian events in the pineal gland. In the recent years, the DNA microarray technique has been successfully used to study circadian gene expression in the SCN, liver, heart, kidney, and fibroblasts. The emerging evidence indicates that a certain number of genes (approximately 2–10%) in each tissue or organ are under circadian control [6].

Melatonin is released primarily by the pineal gland and can bind to the G–protein coupled receptors, MT_1 and MT_2. These receptors are expressed at high levels in the SCN, and upon stimulation, modulate SCN transmission and circadian activity. Melatonin is suppressed by light, participates in sleep, and varies seasonally in many mammals [3].

ROLE OF THE 5–HT_{5A} RECEPTORS

The 5–HT_{5A} receptor is enigmatic among 5–HT receptors since, although the human receptor was cloned in 1994, until recently, very little has been learned about the function of the receptor in native tissues. Findings from 5–HT_{5A} receptor mRNA localisation and immunolabelling studies have revealed widespread expression in the CNS, and have provided pointers to the potential functional role(s) of the receptor. The expression of the 5–HT_{5A} receptor in raphe nuclei and in higher brain areas, such as the cerebral cortex and hippocampus, suggests a potential autoreceptor function whilst localisation in the suprachiasmatic nucleus (SCN) suggests a role in circadian rhythm control [7].

CIRCADIAN RHYTHM AND SLEEP DISORDERS IN DEPRESSION

Circadian Dysregulation

Abnormal sleep is a core symptom of major depressive disorder, with sleep disruption seen at all stages in the sleep cycle. Symptoms include difficulty falling asleep, or staying asleep, as well as early-morning awakening. Hypersomnia is also described. Electroencephalography (EEG) abnormalities in depressed patients include prolonged sleep latency, decreased slow-wave sleep, and reduced rapid eye movement (REM) latency with disturbances in the relative time spent in both REM (increased) and non–REM sleep (decreased slow-wave sleep). Reduced REM latency probably is the best studied and most reproducible sleep-related EEG finding in depressed patients, and this abnormality is reversed by most antidepressants. Sleep deprivation, particularly if induced in the second half of the night, has a similar effect, although the rapid, dramatic improvement in depressive symptoms is short lived. Changes in nocturnal body temperature and attenuation of the normal fluctuations in core body temperature during sleep further suggest a more generalized dysregulation of normal circadian rhythms in patients with depression. To date, however, none of these markers have proven to be specific to depression [8].

As described above tissue localisation studies and pharmacological studies suggest a potential role of the 5–HT_{5A} receptor in the control of circadian timing. Although further studies are required to substantiate this concept, these findings raise the preclusion that 5–HT_{5A} receptor-selective ligands might exhibit therapeutic action in circadian rhythm disorders. Furthermore, a number of experimental and clinical findings have provided evidence for a relationship between disturbances in circadian rhythms and sleep architecture, including rapid eye movement (REM) sleep [7].

As mentioned previously the circadian clock is responsible for controlling sleep patterns. Melatonin secretion from this region of the brain actually induces sleep. Depressed patients often experience a wide variety of sleep disorders. It could look surprising that there is a connection between disruptions of the circadian cycle and depressive disorders. Generally a decreased amount of deep sleep per night comes just before the onset of depression. Therefore a drastic change in sleep schedule caused by jet lag, or multiple shift changes may result in a disruption of circadian rhythm function. In these instances it is possible for the circadian clock to induce REM sleep 15 to 20 minutes earlier in the sleep cycle, resulting in decrease in the amount of deep sleep, and ultimately leading to the beginning stages of depression.

Circadian rhythm sleep disorders (CRSD) manifest as misalignment between the sleep period and the physical/social 24–h environmental cycle. The two most prevalent circadian rhythm sleep disorders are delayed sleep phase (common in adolescents) and advanced sleep phase (common in the elderly), situations in which the sleep period is displaced to a later or earlier time, respectively. It is important to keep these two disorders in mind, since they can be confused with insomnia and excessive sleepiness. However, there are nine possible diagnoses, and all nine are of clinical interest. Since light is the principal cue used in synchronizing the biological clock, blind individuals and night-shift/swing-shift workers are more prone to develop circadian rhythm sleep disorders. Martinez et al. review the new international classification of circadian rhythm sleep disorders [9].

Primary disorders:
1) Delayed sleep phase
2) Advanced sleep phase
3) Sleep-wake cycle irregular pattern
4) Non–24–h sleep–wake cycle
Secondary disorders
5) Jet lag
6) CRSD secondary to work at irregular hours
7) CRSD secondary to diseases
8) CRSD secondary to the use of drugs or medications
Other
9) Other CRSDs

A diagnosis of CRSD can be made under certain conditions. First, the disorder must be accompanied by insomnia, excessive sleepiness or both, with social/occupational impairment or jeopardizing other areas. Second, the pattern of the disorder should be persistent or recurrent. Finally, the cause should be either an alteration in the timing mechanism or the lack of synchronization between the endogenous circadian rhythm and exogenous factors that affect the hours or the duration of sleep [9].

In order to help prevent disruptions in the circadian sleep cycle it is important to maintain a regular sleep schedule, which includes retiring and waking at approximately the same time each day, and sleeping a consistent number of hours each night. This is especially important for people with morningness tendencies because their circadian cycles are less adaptable to changes in behavior.

Circadian rhythm and mood disorders

For many years it is considered that abnormalities in circadian rhythms may underlie the development of mood disorders such as bipolar disorder (BPD), major depression and seasonal affective disorder (SAD). Furthermore, some of the treatments that are currently employed to treat mood disorders are thought to act by shifting or "resetting" the circadian clock, including total sleep deprivation (TSD) and bright light therapy. There is also reason to suspect that many of the mood stabilizers and antidepressants used to treat these disorders may exhibit at least some of their therapeutic efficacy by affecting the circadian clock. Recent genetic, molecular and behavioral studies implicate individual genes that make up the clock in mood regulation. As well, important functions of these genes in brain regions and neurotransmitter systems associated with mood regulation are becoming apparent. Current evidence about the linkage between circadian rhythms and mood disorders, underlying biological factors of these relationships is presented in the review by McClung and colleagues [3].

The circadian rhythms act like a multifunctional timer to adjust the homeostatic brain system, including sleep and wakefulness, locomotor activity, to approximately 24-h cycle, and allow organisms to adapt to environmental changes. Different paradigms can be used to explain the disruptions of the circadian rhythms, including chronic constant light exposure (CCL), phase shifting of the light–dark cycle, bilateral lesions of the master clock in the suprachiasmatic nucleus and clock gene mutant, etc. Among these paradigms, CCL is a simple, chronic way to influence circadian rhythms which may occur during shift work, hospital intensive care units or future space travel. Furthermore, evidence suggests that disruption of biological rhythms increases plasma corticosterone levels, and evokes stress. Stress is defined as adaptive syndromes in response to negative life-events and tactically indicated by plasma levels of glucocorticoids [1].

SEASONAL AFFECTIVE DISORDER

In recent years psychiatrists have recognized the impact of seasonal changes on mood and behavior. Seasonal affective disorder (SAD) is a unipolar mood disorder in which patients are highly responsive to the total amount of light available in the environment [10]. SAD, characterized by recurring fall and winter depressions (with remissions during spring and summer), affects approximately 5% of the population [11]. SAD is not recognized as a distinct disorder in ICD–10, but it is included in DSM–IV as recurrent mood disorder with seasonal pattern. Individuals who suffer from seasonal affective disorder show signs of depression during the fall and winter months when there are less hours of natural sunlight. Disturbances in mood are the main psychological component of seasonality [12]. Persons suffering from seasonal depression generally show an increase in appetite and hypersomnia, which oddly is opposite of the behavior normally associated with most other forms of depression. This behavior is consistent with research conducted on animals and may be related to basic survival instincts. The explanation behind this theory is that people like some animals may have a natural tendency towards increasing fat stores in the body during the winter, as well as sleeping more often in order to preserve energy levels. Several more recent studies suggest that suffers of seasonal affective disorder display disturbances in their circadian cycles, as indicated by less consistent rhythm patterns. A common therapy used to treat seasonal affective disorder is light exposure therapy [10]. Though the effects of light exposure are not completely understood it has been shown that the presences of either natural or artificial light seems to work towards correcting circadian disturbances caused by seasonality.

Symptoms of seasonal depression

The characteristic feature is the recurrent episodes of depression with an onset in autumn or winter, and remission over the spring and summer months. Features shared with non-seasonal depression include:

- low mood (often worst in the morning)
- anhedonia
- low libido
- irritability
- impaired concentration.

Features more specific to SAD than non-seasonal depression include:

- hypersomnia (often with prominent daytime sleepiness and fatigue)
- chocolate/carbohydrate craving
- weight gain.

These symptoms have given rise to analogies with hibernation and may have been advantageous at an earlier stage of man's development [13].

The pathophysiology of SAD is not fully understood, although it is assumed to be associated with altered circadian rhythms. Basic circadian rhythms are regulated by several endogenous or exogenous pacemakers. The major endogenous pacemaker is probably located in the suprachiasmatic nucleus (SCN) of the hypothalamus. One of the major exogenous pacemakers is the light–dark cycle, in which different durations of light or dark hours affect the timing of sleep induction, hormone secretion, and many other biological rhythms. In healthy, euthymic subjects, the ratio of light to dark hours triggers the SCN to induce certain activities, including sleep, hormone secretion, and the secretion of melatonin via stimulating the pineal gland. SAD is characterized, among other things, by a basic state of 'phase-delay' circadian rhythm.

This means that the same triggered activities (by the SCN) are induced at a later time in the day (24–hour clock) than in non SAD patients. Empirical data suggest that when a person is exposed to bright light during the light hours, the SCN is stimulated to induce its activities at an early time in the 24–hour cycle. This is termed 'phase-advance' circadian rhythm. If it is administered to a SAD patient, the 'phase-advance' is superimposed on a 'phasedelay' status, which may bring the system (e.g. the SCN) to an equilibrium, normalizing circadian rhythms, and at the same time ameliorating the depressive symptoms of SAD [14].

TREATING MOOD DISORDERS BY ALTERING THE CIRCADIAN CYCLE

Sleep deprivation therapy

Treatment with sleep deprivation may offer valuable clues to the mechanisms that underlie rapid treatment of depression. Sleep deprivation has been used to treat more than 1000 depressed patients worldwide in more than 60 studies and is consistently reported to produce rapid (within 24–48 h) reversal of depressive symptoms in approximately 40–60% of depressed patients [15]. Sleep deprivation protocols vary, but essentially, the depressed patient is kept awake all night (total sleep deprivation) or part of the night (partial sleep deprivation). By the next morning, approximately half of depressed patients experience a dramatic improvement in mood which continues throughout the day. Relapse is common following recovery sleep; however, recent studies suggest that the response can be prolonged with adjunctive treatments which include antidepressant medications and mood stabilizers (e.g. lithium) and chronobiological (e.g. light therapy, sleep phase advance) interventions. Even the most difficult to treat patients (treatment resistant) may respond to sleep deprivation [16].

Bright light therapy or dawn simulation

Brigzt light therapy is an effective treatment for some depressed patients. This circadian use of brightlight therapy for depression activates the SCN, inhibiting corticotrophin-releasing hormone release and suppressing hypothalamic–pituitary–adrenal activity [17]. Impairment in the normal mechanisms that 'turn off' hypothalamic–pituitary–adrenal activation can produce behavioural manifestations and neuro–vegetative responses similar to those seen in major depressive disorder including changes in sleep, appetite, concentration, motivation, pleasure seeking and psychomotor alterations [18].

Twenty three studies met inclusion criteria, and 20 provided sufficient data for meta-analysis. Compared to placebo, bright light treatment reduced the symptoms of seasonal affective disorder (eight RCTs; 360 people; effect size: 0,84, 95% CI 0,60 to 1,08; p<0,0001) and non-seasonal depression (three RCTs; 127 people; effect size: 0,53, 95% CI 0,18 to 0,89; p<0,003). Remission of seasonal affective disorder was almost three times more likely after bright light therapy than with placebo (four RCTs; OR 2,9, 95% CI 1,6 to 5,4). Dawn simulation also improved the symptoms of seasonal affective disorder (five RCTs; 133 people; effect size: 0,73, 95% CI 0,37 to 1,08, p<0,0001). No additional benefit was found for bright light therapy in conjunction with drug therapy in non-seasonal depression (five RCTs; 135 people; effect size: 20,01, 95% CI 20,36 to +0,34, p>0,95) [19]. As also showed by Lee, Chan and colleagues in their study, phototherapy (bright light therapy or dawn simulation) is an effective treatment for seasonal affective disorder. Although bright light therapy reduces the symptoms of non-seasonal depression, it does not provide additional benefits when used as an adjunct to drug therapy. 39 studies met the selection criteria. Studies were grouped according to timing of treatment and the intensity of light used: strong light (≥6000 lux), medium light (1700–3500 lux), and dim light (≤ 600 lux). The fixed effects model was used to combine the results in metaanalysis. In the morning, strong light was more effective than medium or dim light ($p < 0,05$) and medium light was more effective than dim light ($p < 0,05$) for reducing depressive symptoms measured with the HDRS. In people with seasonal affective disorder, a dose response relation exists between the intensity of light and reduction in typical depressive symptoms. No dose response relation exists for atypical symptoms [20].

Pharmacological treatments

Mood stabilizers like lithium and valproate are commonly used for treatment of bipolar patients. Interestingly, both of these drugs have been repeatedly shown to alter the circadian period, leading to a long period in Drosophila, nonhuman primates, rodents and humans. This effect on circadian rhythms could involve the inhibition of GSK3β which modifies multiple members of the molecular clock. It is thought that this action of lithium on the circadian clock is important in its therapeutic efficacy. Lithium is able to slow the abnormally fast circadian rhythms found in many bipolar patients. Furthermore, patients that have a shift in rhythms respond positively to lithium treatment in terms of mood stabilization, whereas those few bipolar patients that begin with an abnormally slow clock do not respond to lithium treatment. Furthermore, lithium treatment is able sustain and enhance the phase-shifting and mood-altering effects of TSD. Similar to morning bright light therapy, the antidepressant, fluoxetine, also affects circadian output by producing a phase advance in the firing of SCN neurons in rat slice culture. Indeed, serotonin neurons from the midbrain raphe nuclei innervate the SCN, and local applications of 5–HT or 5–HT_{1A} and 7 receptor agonists to the SCN will also produce a phase advance in circadian activity. Thus antidepressants of the selective serotonin reuptake inhibitor (SSRI) class may also exert some of their effects on depression through modulation of the circadian clock. Interestingly, SSRI and mood stabilizers can have opposing therapeutic actions in bipolar patients. This could be linked to their opposing actions on rhythms since SSRI cause a phase advance in rhythms while lithium can cause a phase delay.

Recently, agomelatine, a potent agonist of the melatonin receptors and an antagonist at the serotonin 5–HT_{2C} receptor has proven to be highly effective in animal models of depression, and in several on-going clinical trials involving patients with MDD. Agomelatine also seems to produce fewer adverse side effects than some of the other antidepressant medications, and it alleviates many of the sleep problems associated with depression that are typically exacerbated by SSRI treatment,

making it a potentially valuable new treatment for depression. As expected by its pharmacologic profile, agomelatine has been shown to resynchronize circadian rhythms in body temperature, cortisol and other hormones in animal models and in humans, which may underlie some of its therapeutic effects. Interestingly, agomelatine is much more effective than melatonin in reversing depression-like behavioral responses in animal models, suggesting that the therapeutic actions of agomelatine are not exclusively due to its actions at the melatonin receptors. However, the kinetics of agomelatine, and actions at the melatonin receptors, may differ greatly from those of melatonin, so this action may still underlie at least part of its efficacy as an antidepressant. Though the latency to action is similar between agomelatine and the SSRIs, agomelatine seems to have no effect on central serotonin transmission or the density and function of 5–HT_{1A} receptors. However, its actions at the 5–HT_{2C} receptors enhances mesolimbic dopaminergic and noradrenergic transmission, an effect also seen with SSRIs. Furthermore, chronic, but not acute, treatment with agomelatine also induces neurogenesis in the hippocampus similar to other antidepressants. Interestingly, specific antagonists at the 5–HT_{2C} receptor have potent anxiolytic-like activity in animal models, but they seem to have no effect in models of depression. Therefore, the therapeutic actions of agomelatine in the treatment of depression are still uncertain and may involve both the 5–HT_{2C} and melatonin receptors [3].

The current review reveals obviuos connection between circadian rhythms and mood disorders. Efficiency of drugs used for treatment of mood disorders partially or essentially depends on their effect on human circadian rhythms.

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