Sleep and biorythm disturbances in schizophrenia, mood and anxiety disorders: a review

Disturbi del sonno e dei bioritmi nella schizofrenia, nei disturbi d'ansia e dell'umore: una review

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SUMMARY. Sleep problems and circadian rhythms disturbances are common in many psychiatric disorders, with the most-often-reported sleep problem in most cases being insomnia. In this paper, the main findings about sleep disturbances (features and therapy) and other biorhythm disturbances (biological timekeepers, CLOCK genes, GSK3, melatonin, hypothalamo-pituitary-adrenal axis, body temperature) are reviewed in relation to schizophrenia, mood and anxiety disorders.

KEY WORDS: sleep disturbances, insomnia, circadian rhythms, biorhythms, GSK3, melatonin, schizophrenia, depression, bipolar disorder, post traumatic stress disorder, general anxiety disorder, panic disorder.

RIASSUNTO. Disturbi del sonno e disordini dei ritmi circadiani sono frequenti in diversi disturbi psichiatrici. L'obiettivo dell'articolo è presentare una revisione delle principali nozioni relative ai disturbi del sonno (le loro caratteristiche e la loro terapia) e dei ritmi circadiani (timekeepers biologici, geni CLOCK, GSK3, melatonina, asse ipotalamo-ipofisi-surrene, temperatura corporea) in relazione alla schizofrenia, ai disturbi d'ansia e dell'umore.

PAROLE CHIAVE: disturbi del sonno, insonnia, ritmi circadiani, bioritmi, GSK3, melatonina, schizofrenia, depressione, disturbo bipolare, disturbo da stress post-traumatico, disturbo d'ansia generalizzato, disturbo di panico.

INTRODUCTION

More than 40 epidemiological studies have explored the prevalence of insomnia in the general population since the end of the 1970s (1). Sleep problems are common in many psychiatric disturbances, with the most frequently reported being insomnia. In mania and depression, insomnia (i) can significantly worsen the psychopathological severity, and (ii) can represent a prodromal sign of imminent relapse (early intervention aimed at improving sleep may help to prevent a relapse) (2). In addition to increased insomnia, subjects with depressive and manic symptoms can also experience an increased incidence of parasomnias, circadian rhythm disorders, and hypersomnia (2).

Sleep disturbances are related to disturbances of circadian rhythms; in mammals, including humans, the circadian pacemaker, or biological clock, is the site of generation and entrainment of circadian rhythms (3,4). It is located in the suprachiasmatic nuclei (SCN) of the anterior hypothalamus.

In the absence of temporal signals (e.g., in caverns or bunkers), circadian rhythms persist, "free run", and express their own period. In humans, the endogenous period of the circadian clock has a mean value of approximately 24.2 hours, i.e. each day human biological clock is slightly delayed compared with the environmental light/dark cycle. The circadian clock can use several synchronizers to modify the period and the phase of circadian rhythms: while the light/dark cycle is the most important synchronizing agent for circadian rhythmicity (light is therefore called a *zeitgeber* - timekeeper), social stimuli and physical activity may play a relevant role as well (5-7).

The SCN receives direct light information through the retino-hypothalamic tract and indirect light information through the retino-geniculo-hypothalamic tract (3,7). The circadian pacemaker integrates various light-related parameters (e.g. time of presentation, duration, irradiance, and wavelength), being sensitive to light along the 24-hour cycle in a dose-dependent manner (7,8). As in other species, light presented in the evening stimulates the human circadian

pacemaker to a phase delay, whereas light presented in the morning stimulates a phase advance. In addition to phase-shifting effects, ocular light exposure at night also suppresses the production of melatonin by the pineal gland (7,9).

The circadian oscillator is also sensitive to the phase-shifting changes induced by chemical or pharmacological components, such as melatonin, which acts at the pharmacodynamic level through specific MT1 and MT2 receptors located in the SCN (7,10). In healthy subjects, the secretion of melatonin has a circadian pattern. Melatonin is involved in the synchronization of the circadian clock by signaling day-night information to the endogenous circadian pacemaker, and it also affects the circadian rhythm of body temperature. Melatonin synthesis pattern is characterized by elevated levels during the night (7).

The timing of biological pacemakers in humans is also dependant on particular genes (i.e. the so-called clock genes), most of which are common to fruit files, mice, and primates, and probably many other species (11). Polymorphisms of these genes that lead to an altered circadian rhythm are easy to identify in fruit flies, and similar variants of these genes have been found in people with certain disorders of circadian rhythm (2,11).

The products of some of these clock genes regulate their own expression, this resulting is an oscillation in the levels of messenger ribonucleic acids (mRNAs) and proteins. As described by Lamont et al. in 2007 (11), "in mammals, *Clock* and *Bmal1* encode transcription factors CLOCK and BMAL1, which form heterodimers that activate the transcription of three *Period* genes (*PER1, 2* and *3*) and two *Cryptochrome* genes (*CRY1* and *2*), *Rora* and *Rev-Erba*. PER and CRY proteins form complexes that are translocated back into the nucleus and inhibit their own expression. ROR*a* and REV-ERB*a* act on *Bmal1* to activate and repress transcription respectively. NPAS2 is an alternate dimerization partner for BMAL1 that may also regulate circadian rhythmicity in the forebrain, but it has not been consistently found in the SCN. Clock proteins are phosphorylated by casein kinase I epsilon (CKIε) and delta (CKIδ), and possibly also by the *Drosophila shaggy* homologue glycogen synthase kinase 3 (GSK3). They are targeted for degradation by components of ubiquitin ligase complexes like FBXL3 and β-TR-CP1, which together regulate the period of circadian oscillation by controlling the rate of accumulation, association and translocation of PER and CRY".

These molecular pathways work together to regulate clock functioning; abnormalities in such genetic elements can have deep consequences for the synchronization of psychological, emotional, physiological, cognitive, behavioural and sleep-related processes.

DEPRESSION

Sleep disturbances

Sleep disorders have long been considered as a cardinal symptom of depressive disorders (12); subjects with insomnia exhibit symptoms of depression in 40% to 60% of the cases and have a clinical depression in 10% to 25% of cases (1). Depressive symptoms may reflect sleep disturbances, including phase shift of sleep-wake cycles, reduced amplitude, or disturbance of sleep-wake-dependent processes (13,14).

Cyrcadian rhythms of sleep in subjects with clinical depression is often charachterized by a phase advancement; polysomnographic recordings have evidenced that the internal sleep organization of subjects with clinical depression is impaired, with (i) specifically, a reduced latency of the first Rapid Eye Movement (REM) sleep episode of the night, (ii) increased density of rapid eye movements, (iii) an increase in total percentage of REM sleep, (iv) a reduction in deep Slow Wave Sleep (SWS), and (v) an increase in night awakenings (15). As discussed b Gorwood in 2007, these observations, together with the fact that most antidepressant medications inhibit REM sleep, have led to the theory that short REM sleep latency is increased in depressed patients and is part of the pathological processes associated with such condition (15,16).

Alterations in REM and SWS appear linked to sleep-related dysfunctional arousal in primary limbic and paralimbic structures, and hypofunction in frontal cortical areas (17). Preliminary studies in insomnia in depression indicate subcortical hyperarousal and failure of sleep to provide normal restoration of function in the prefrontal cortex, leading to chronic sleep deprivation.

Subjects with clinical depression also complain of insomnia (i.e. difficulty in falling asleep, frequent nocturnal awakenings, and/or early waking up) and non-refreshing sleep. However, as discussed by Gorwood in 2007, one should dissociate insomnia from decreased REM sleep latency: "indeed, while short REM sleep latency is a pathogenic process, insomnia induces an improvement in mood. In insomniac patients who are at risk for depression, sleep loss might represent an efficient adaptive mechanism to counteract the underlying depressive mood, and therefore, prolonged sleeping appears as an important risk factor for depression" (15).

Treatment of sleep disturbances

From a clinical perspective, the subjective perception of sleep is more meaningful than polysomnographic findings. In most of the studies on sleep disturbances during antidepressant treatment, improvements are observed over weeks as the depression lifts. This is seen with both drug and cognitive therapies (2,18).

However, the ability of medications to improve sleep early in treatment is important for patients (i) if insomnia is causing significant distress, and (ii) as early improvement of sleep symptoms may encourage them to carry on with medications. 5HT2 blockers such as mirtazapine and agomelatine have been suggested to improve subjective sleep quickly in depression; tricyclic antidepressant (TCAs) such as trimipramine and doxepine can lead to similar outcomes due to potent histamine H1 antagonistm, but with more unwanted effects (e.g. sedation and dry mouth) (2).

Objectively, selective serotonin reuptake inhibitors (SSRIs), alerting TCAs and mixed uptake blockers antidepressants have been shown to decrease REM sleep and REM latency but also to increase waking in sleep early in treatment (2,19,20). Mirtazapine, mianserin, trazodone and trimipramine have been shown to smaller effects on REM but to decrease waking in sleep in the first week of treatment (2).

Treatment with melatonin in depression give still unclerar

results; melatonin, however, may be helpful when insomnia is related to shift work and jetlag (21,24).

There has been some recent evidence suggesting that biological interventions targeting the dopaminergic and serotonergic systems (including medications as well as other non-pharmacolgical interventions) may have a common mode of action either via the direct inhibition or increased phosphorylation of the GSK3 enzyme (11,25-27). GSK3 is involved in many cellular functions; therefore the therapeutic action may be via a number of possible routes, including regulation of monaminergic signaling, neuroprotection, neuroplasticity, hormonal activity, brain metabolism and circadian system (11,28).

Exposure to bright light at appropriate times, traditionally used to alleviate the depression associated with seasonal affective disorder, can help realign the circadian rhythm in patients whose sleep-wake cycle has shifted to undesirable times (19,20,29).

The rapid short-lasting mood improvement following total sleep deprivation, and rapid return of depressive symptoms after subsequent recovery sleep, is well documented in the literature, and suggests that the depressive and sleep processes are strongly associated (15). As discussed by Gorwood in 2007, "prolonged manipulations of the sleep-wake cycle, such as phase advancing, could maintain the effects of total sleep deprivation, both in the presence or absence of combined antidepressant drug treatment. In insomniac patients at risk for depression, sleep loss might represent an efficient adaptive mechanism to counteract the underlying depressive mood and, therefore, prolonged sleeping appears as an important risk factor for depression, as discussed above. However, the antidepressant effect of sleep deprivation is very short-lived and cannot be considered as long-term antidepressant therapy" (15).

Other biorhythm disturbances

A range of physiological variables can show circadian abnormalities in individuals with clinical depression (30).

Body temperature: Patients with major depression can exhibit a flattened core body temperature rhythm (31,32); subjects with Seasonal Affective Disorder (SAD) as well have been shown to exhibit a significant delay in temperature rhythm (15). Lewy et al. documented that morning phototherapy was effective in treating patients with SAD by phase advancing endogenous circadian rhythms of core body temperature (15,33).

Hormones: A meta-analysis of Van Cauter et al on cortisol findings in clinical depression showed an overall increased glucocorticoid secretion with the largest effect at the nadir of the circadian rhythm (34). Linkowski et al. showed hypercortisolism, early timing of the nadirs of the ACTH-cortisol rhythms, shorter nocturnal periods of quiescent cortisol secretion and hypersecretion of GH during wakefulness in depressed patients compared to controls (35).

Melatonin: Both decreases (36) and increases (37) in melatonin levels have been reported in depressed patients. Brown et al. (38) reported lower serum melatonin concentrations in patients with melancholia than in healthy volunteers, as well as inverse correlations of melatonin concentration with certain factors of the Hamilton Depression Rating Scale (HDRS) (39). Lower nocturnal concentrations of a metabolite of melatonin were reported in subjects with depression

by Boyce et al. (40), although Rubin et al. did not confirm this finding (24). A trend toward a later nocturnal melatonin peak has been reported in patients with unipolar depression (41). Tuunainen et al. hypothesized a familial vulnerability in the endogenous melatonin signal in subjects prone to depression, and an abnormality in the duration of the melatonin signal in subjects with current major depression (42).

Clock genes: To date there has been no clear evidence of clock gene mutations associated with Major Depressive Disorder. The T3111C polymorphism of *CLOCK* has been investigated but no significant differences emerged in allelic frequencies in a study involving a group of 143 people with a history of major depression and 195 controls (11,43).

BIPOLAR DISORDER

Sleep disturbances

Sleep in BD is state-dependant, with manic phases usually being preceded by a shortened duration of sleep, and depressive phases often being characterized by longer duration of sleep and increased amount of daytime sleepiness; objective sleep changes in bipolar depression are similar to those in unipolar depression (2).

As pointed out by Lamont et al. in 2007, the relationship between the sleep-wake cycle and changes in mood appears to be important in patients with frequent and rapid changes in mood state, i.e. the so-called "rapid cyclers," in which the switch from mania/hypomania to depression/euthymia tends to occur during or after sleep, while the changes in mood from depression to hypomania/mania are more likely to occur after a period of wakefulness (11,44,45).

Treatment of sleep disturbances

Certain psychopharmacological approaches to treat sleep disorders in BD patients have shown some effectiveness, including (i) avoid the antidepressant medications, even those with good efficacy on sleep, (ii) avoid long-term use of benzodiazepines, in particular on patients with a history of substance abuse, and (iii) preferentially prescribe one or more mood stabilizers (46).

Recent evidence suggests that the therapeutic action of lithium may be related to direct effects on the circadian clock. As reported by Lamont et al. (11), (i) lithium has been shown to lengthen the period of circadian rhythms in animal models (rodents), (ii) lithium can lengthen the period of neuronal firing of cultured SCN neurons, and (iii) a delay of the circadian rhythm of temperature and of REM sleep has been shown in a BD patient. This suggests that the therapeutic action of lithium could be due, at least in part, phase adjustments on the circadian systems.

One proposed molecular mechanism is via the inhibition of GSK3 (11,47); this issue has been summarized by Lamont et al. as follows (11): "although this enzyme has a number of functions that could potentially mediate the therapeutic effects of lithium, one likely possibility is via its function as a central regulator of the circadian clock. Numerous lines of evidence support this idea; both lithium and GSK3 knockdown produce a lengthening of *mPer2* period in mouse fibroblasts, and GSK3 phosphorylates PER2 and REV-ERBα

and regulates their localization and stability, respectively. Even more interesting are findings that inhibition of GSK3 may be common to other mood-stabilizing agents such as valproate, and may even be a target of antidepressant therapies, including drugs which target the serotonergic and dopaminergic systems as well as electroconvusive therapy. There is also evidence for effects of allelic frequency of the *GSKβ-50* T/C SNP. Bipolar patients with the T/T allele of *GSK3β* show an earlier age on onset of BD and enjoy less improvement from lithium therapy than patients with the T/C or C/C alleles. Together these results are persuasive, making GSK3 a promising target for the future development of pharmotherapeutic agents".

Other biorhythm disturbances

A phase advance of the diurnal rhythm of plasma cortisol has been suggested to occur in BD (48), although negative results have also been reported (49).

Beck-Friis et al. (21) reported that BD patients had lower nocturnal melatonin concentrations than healthy individuals. Nurnberger et al. (50) also found atypicality in melatonin secretion abnormalities among BD patients. On the other hand, Rubin et al. (24) did not find significant associations between melatonin levels and bipolar depression.

The evidence for genetic abnormalities associated with clock genes is consistent in BD: the C/C allele of *CLOCK* has been associated with greater severity of insomnia during antidepressant treatment, with higher recurrence rate of bipolar episodes and with reduced need for sleep (11). Support for a role of *Clock* mutation in BD also come from animal models, where behavioural studies using *CLOCK* mutant mice suggest a phenotype similar to mania (11,51). Further, a Mendelian transmission distortion analysis preliminarily revealed associations of *BMAL1* and *TIMELESS* with BD (11).

GENERALIZED ANXIETY

Sleep disturbances

Sleep onset insomnia is experienced by about 20-30% of patients with generalized anxiety disorders (GAD), and sometimes sleep is the most distressful symptom of anxiety; GAD patients may also have increased night-time awakening and poor sleep quality (2). Specific objective sleep abnormalities apart from reduced sleep continuity have not been identified in GAD (2).

Treatment of sleep disturbances

The SSRIs have shown effectiveness in improving sleep in GAD (2). In large clinical trials, it has been shown that sleep disturbances in GAD improve along with other symptoms after effective anti-anxiety treatment involving both medications (antidepressants and benzodiazepines) and cognitive behavioural therapy (CBT) (2).

Other biorhythm disturbances

Monk et al. (52) recently assessed that behavioural circadian regularity at the age of 1 month predicts anxiety levels during school-age years (more regular=less anxious). Apart from this, There is relatively little evidence suggesting specific circadian disturbances or a role for clock genes in anxiety disorders (11,53) . There are however a few interesting results from research on animals, as (i) one study showed a reduction of *Per1* mRNA levels in mouse cerebellum by antianxiety medications, suggesting that altering circadian clock genes could potentially contribute to the therapeutic action of these drugs, and (ii) a reduction of anxiety has been observed in mice with a mutation of the *Clock* gene (11).

POST-TRAUMATIC STRESS DISORDER (PTSD)

Sleep disturbances

Almost all sleep disturbances are highly represented in PTSD; among PTSD patients, 70-90% have difficulty falling or staying asleep, and 20-70% experience nightmares (2,54). Sleep-disordered breathing, sleep movement disorders, sleepwalking and night terrors are more common among PTSD subjects than that in the general population (2).

Koren et al. performed a study on car accident survivors finding that sleep complaints at 1 month after the trauma were higher in the group who had PTSD a year later, thus suggesting that there may be some predictive value in assessing sleep (55).

Objective measures of sleep disturbances include (i) decreased sleep efficiency, (ii) REM decreases or increases, , and (iii) increased awakenings during REM episodes (2).

Treatment of sleep disturbances

Both CBT and medications used for PTSD symptoms (e.g. SSRIs, trazodone and mirtazapine) have been shown to improve sleep and nightmares; preliminary encouraging reports have recently emerged in relation to a range of medications including prazosin, buspirone, gabapentin and tiagabine, while some evidence suggests that benzodiazepines, TCAs and monoamine oxidase inhibitors (MAOIs) are not useful for the treatment of PTSD-related sleep disorders (2).

PANIC DISORDER (PD)

The most specific association between PD and sleep disorders is related to the experience of night-time panic attacks, which occur in up to 50% of PD patients and are usually vividly recalled (2). Polysomnographic studies have showed that nocturnal panic attacks usually follow a sudden awakening at the transition between stages 2 and 3 sleep, i.e. when the subject is descending into deep sleep (2). Apart from the nights with panic attacks, patients with PD do not show specific differences in sleep architecture compared to healthy controls.

Other biorhythm disturbances

Findings about the relation of circadian rhythms and PD are still fragmentary. Hypothalamic-pituitary-adrenal func-

tionality is thought to be disturbed in PD patients as (i) several studies found that patients with PD had elevated overnight cortisol secretion and greater amplitude of ultradian secretory episodes (56-58), and (ii) alprazolam has been shown to induce substantial improvements in clinical status accompanied by nearly full resolution of pre-treatment hypercortisolemia (59). McIntyre et al. found melatonin to be elevated in patients with PD (60).

Seasons seem to play a role in panic exacerbation, given the observation that panic attacks are more frequent during the summer (61,62). Limpido et al. found alterations of diurnal 24-h cycle rhythm of sleep and wake cycles sleep, appetite, and other bodily functions in patients with PD in comparison to healthy controls (63).

SCHIZOPHRENIA

Sleep disturbances

Patients with schizophrenia (SCZ) experience a range of sleep-related symptoms including poor sleep initiation and consolidation, prolonged sleep and excessive napping in the day, as well as impaired sleep homeostasis expressed as low levels of SWS, absence of stage 4 sleep, shortened REM sleep latency with frequent sleep onset REM periods, and reduced sleep spindles in electroencephalogram (2). Taken together, these observations suggest an impaired homeostatic regulation of sleep associated with the disease.

Actigraphic recordings of SCZ subjects have revealed phase delays, longer periods of activity, or circadian rest-activity patterns (11). The causes of the disturbed circadian regulation of sleep observed in SCZ are unknown, but they presumably reflect some biological perturbations in the brain leading to a loss of normal sensitivity in the *zeitgebers* (64,65); environmental factors may also play a key role as the lifestyle of many SCZ patients can expose them, for example, to inadequate habits related to sleep, light, and physical activity (2).

Treatment of sleep disturbances

Psychopharmacological therapies based on the administration of medications with both antipsychotic and hypnotic have shown some effectiveness to treat sleep disturbances in SCZ patients (46,66-68). Recent studies found that certain atypical antypsichotics can regulate GSK3 and inhibit its circadian regulatory activity (69).

Interventions with environmental entraining processes, e.g. light and exercise, are usually difficult in these patients due to disease-related low levels of compliance and engagement (2).

Other biorhythm disturbances

Circadian disturbances have been reported in SCZ patients, but the results are inconsistent (70). Madjirova et al. reported desynchronization of body temperature, pulse and blood pressure rhythms in SCZ patients compared to controls (71). Some experiments reported blunted circadian variation of melatonin secretion (72-74); this may be partially explained by the precox pineal calcification that occurs in

patients with SCZ (75-78). Phase advances of body temperature (79), prolactin and melatonin (80) have also been recorded, while actigraphic studies have revealed disturbed rest-activity cycles (81,82). Levels and ultradian rhythms of nerve growth factor can also be affected in SCZ (83,86) and antipsychotics such as clozapine or haloperidol may regulate them (87-89). SCZ patients also show a greater tendency towards eveningness than controls (70,90).

Evidence linking circadian clock gene polymorphisms or deregulation with schizophrenia is limited. Takao et al. demonstrated that the T3111C *CLOCK* polymorphism showed a transmission bias in a sample of 145 Japanese SCZ subjects relative to healthy controls, suggesting that this polymorphism may underlie certain aspects of the pathophysiology of schizophrenia (11,91). Studies have shown decreased expression of the *PER1* mRNA in the temporal lobe of SCZ subjects compared with age-matched controls, as well as associations of *PER3* and *TIMELESS* with SCZ and BD (11). The *CRY1* gene has been hypothesized to be a candidate gene for SCZ based on its location near a linkage hotspot for SCZ on chromosome 12q24 (11,92).

Acknowledgments

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