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Review article

Sleep and circadian rhythm dysregulation in schizophrenia

Jaime M. Monti [a], Ahmed S. BaHammam [b], Seithikurippu R. Pandi-Perumal [c], Vivien Bromundt [d], D. Warren Spence [e], Daniel P. Cardinali [f], Gregory M. Brown [g,*]

[a] Department of Pharmacology and Therapeutics, Clinics Hospital, Montevideo, 11600, Uruguay
[b] University Sleep Disorders Center, King Saud University, Riyadh, Saudi Arabia
[c] Somnogen Canada Inc., College Street, Toronto, ON, Canada M6H 1C5
[d] Centre for Chronobiology, Psychiatric Hospital of the University of Basel, Wilhelm Klein-Str. 27, 4012 Basel, Switzerland
[e] 323 Brock Avenue, Toronto, ON, Canada
[f] Departamento de Docencia e Investigación, Facultad de Ciencias Médicas, Pontificia Universidad Católica Argentina, 1107 Buenos Aires, Argentina
[g] Centre for Addiction and Mental Health, University of Toronto, 1001 Queen St., Toronto, Canada M6J 1H4

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ABSTRACT

Sleep-onset and maintenance insomnia is a common symptom in schizophrenic patients regardless of either their medication status (drug-naive or previously treated) or the phase of the clinical course (acute or chronic). Regarding sleep architecture, the majority of studies indicate that non-rapid eye movement (NREM), N3 sleep and REM sleep onset latency are reduced in schizophrenia, whereas REM sleep duration tends to remain unchanged. Many of these sleep disturbances in schizophrenia appear to be caused by abnormalities of the circadian system as indicated by misalignments of the endogenous circadian cycle and the sleep–wake cycle. Circadian disruption, sleep onset insomnia and difficulties in maintaining sleep in schizophrenic patients could be partly related to a presumed hyperactivity of the dopaminergic system and dysfunction of the GABAergic system, both associated with core features of schizophrenia and with signaling in sleep and wake promoting brain regions. Since multiple neurotransmitter systems within the CNS can be implicated in sleep disturbances in schizophrenia, the characterization of the neurotransmitter systems involved remains a challenging dilemma.

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1. Introduction

Schizophrenia is characterized by positive symptoms, such as delusions and hallucinations, together with negative symptoms, mainly lack of motivation and interest, flattened affect and social withdrawal. Insomnia is a common feature in schizophrenia, although it is seldom the predominant complaint (Anonymous, 2000). As comorbid insomnia, it belongs to the most frequent type of insomnia (McCrae and Lichstein, 2001). According to the

Abbreviations: AANAT, (Alkylamine N-Acetyl Transferase); ASMT, (Acetylserotonin methyl transferase formerly HIOMT); BZD, (Benzodiazepine); CRY, (Cryptochrome); N2, (Non REM Sleep Stage 2); N3, (Non REM Sleep Stage 3); PER, (Period); REMOL, (Rapid Eye Movement Sleep Onset Latency); SCN, (Suprachiasmatic Nuclei); SNP, (Single Nucleotide Polymorphism).

* Corresponding author at: Centre for Addiction and Mental Health, Mood and Anxiety Program, 1001 Queen St. Toronto, Canada M6J 1H4. Tel.: +1 416 979 6832; fax: +1 416 979 6864.
E-mail address: gregory_brown@camh.net (G.M. Brown).

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Diagnostic and Statistical Manual of Mental Disorders (Anonymous, 2000), comorbid insomnia is related to a mental disorder, to another sleep disorder, to a general medical condition, or to the effects of medication or of drugs of abuse. Studies of sleep in schizophrenia, however, have not provided consistent results (Benca et al., 1992; Keshavan et al., 1990).

As indicated by Van Kammen et al. (1986), sleep disturbances in schizophrenia can be sufficiently severe to warrant clinical attention. Ritsner et al. (2004) studied the relationship between subjective quality of sleep and perceived quality of life among schizophrenic patients; patients with insomnia reported lower mean scores on all quality of life domains and these were independent of comorbid depression, side-effects related to antipsychotic medication, or distress. Although treatment of the underlying disorder with antipsychotic drugs tends to improve insomnia in patients with schizophrenia, drug administration does not always result in better sleep (Monti, 2004). Benzodiazepine (BZD) and non-BZD hypnotics are often used adjunctively to improve sleep in this patient group.

2. Temporal disorganization and dysfunctional circadian rhythms in schizophrenia

Sleep is a prominent part of the 24-h circadian cycle and is regulated by a complex interplay of sleep and wake promoting and inhibiting brain areas. The regulation of sleep and wakefulness can be conceptualized by the two-process model (Borbély, 1982), which comprises the circadian process and the homeostatic process. The circadian component describes the intrinsic circadian timing and synchronization of body functions to the light–dark cycle of day and night. The homeostatic or evoked component regulates the "need for sleep" which builds up during wakefulness and dissipates during sleep.

Several studies have documented abnormalities in the circadian organization of sleep–wake cycles in patients diagnosed with schizophrenia, which can result in difficulties in initiating and maintaining sleep. These circadian misalignments range from delayed and advanced sleep phase, free running rest–activity patterns to irregular sleep–wake patterns (Bromundt et al., 2011; Wirz-Justice et al., 1997, 2001; Wulff et al., 2006, 2012).

Melatonin profiles, commonly used as an endocrine marker of the individual's circadian rhythm, help to detect circadian misalignments with the sleep–wake cycle or lack of entrainment, i.e. the desynchronization to the light–dark cycle. A recent ambulatory study using saliva samples to determine melatonin and wrist actimetry for assessing circadian rhythms has found circadian misalignments of sleep timing with bedtime earlier than the melatonin onset and fragmented sleep epochs in some schizophrenic patients, with the consequence of significantly worse cognitive performance than in patients with synchronized circadian rhythms (Bromundt et al., 2011). Another study in schizophrenic patients has reported markedly delayed and/or free-running melatonin phases and sleep–wake cycles, and therefore the circadian rhythms were badly entrained to the light–dark cycle (Wulff et al., 2012).

A circadian phase advance of the melatonin profile was reported by Rao et al. (1994) in schizophrenic patients, and in isolation experiments a remarkable shorter circadian period of 23.7 h was revealed in two patients suffering from schizophrenia (Mills et al., 1977). A case study under controlled "constant bed rest" laboratory conditions for more than 30 h has also shown a phase advance of melatonin secretion and core body temperature, but a delayed rhythm for sleep propensity (Wirz-Justice et al., 1997).

In a recent study including 34 schizophrenia outpatients and 34 healthy subjects, saliva melatonin was collected under dim light conditions hourly from 20:00 h to 23:00 h. Wrist actimetry recordings and a sleep diary were used for sleep–wake cycle assessment (Afonso et al., 2011). Schizophrenic patients showed a reduced sleep efficiency, longer sleep latencies and increased number of nighttime awakenings. In addition, there was a loss of the negative correlations of saliva melatonin levels with sleep latency and total sleep time and positive correlations with sleep efficiency that were present in controls indicating an interference with endogenous melatonin sleep-promoting action in schizophrenia (Afonso et al., 2011).

Thus, schizophrenic patients often show a change in the circadian phase angle, i.e. the difference among the timing of the circadian melatonin profile, the timing of the major sleep and wake episodes and the external day–night cycle. Along these lines goes the finding that schizophrenic patients can have a blunted circadian variation of melatonin secretion (Bersani et al., 2003; Ferrier et al., 1982; Monteleone et al., 1992; Robinson et al., 1991). However, these latter studies were not controlled for prior light history that may have confounded the results. It should be noted that circadian rhythm disruptions are common, but are not specific to this patient group.

The mammalian circadian timing apparatus comprises oscillators that are found universally at a cellular level and a central pacemaker generator located in the hypothalamic suprachiasmatic nuclei (SCN) (Dibner et al., 2010). Circadian rhythms are driven by the self-regulatory interaction of a set of clock genes and their protein products (Ko and Takahashi, 2006; Mazzoccoli et al., 2012). Expression of proteins from one positive and one negative loop oscillates, forming a circadian rhythm. The positive drive to the daily clock is constituted by helix–loop–helix, PAS-domain containing transcription factor genes (*Clock* and *Bmal1*). The negative loop consists mainly of *Per* and *Cry* proteins, which provide a negative feedback signal on *Clock*/*Bmal1* drive to complete the 24-h cycle (Mazzoccoli et al., 2012). Since dopaminergic signaling through D_2 receptors appears to be associated with increased *Clock*:*Bmal1* activity (Yujnovsky et al., 2006), a possible link between the dopaminergic hypothesis of schizophrenia and circadian abnormalities in these patients is worth exploration.

Evidence linking circadian clock gene polymorphisms with schizophrenia is limited. In one study, SNP analysis of the *Clock* gene demonstrated that T3111C polymorphism showed a transmission bias in a sample of 145 Japanese schizophrenic subjects relative to healthy controls (Takao et al., 2007). The authors suggested that this SNP, which may be associated with aberrant dopaminergic transmission at the SCN, presumably underlies the pathophysiology of schizophrenia. *Per3*, but not *Per2* abnormalities were associated with schizophrenia in another study (Mansour et al., 2006). Post-mortem studies have shown decreased expression of the *Per1* mRNA in the temporal lobe of schizophrenic subjects compared with age-matched normal controls (Aston et al., 2004). Another circadian gene, *Cry1* was hypothesized to be a candidate gene for schizophrenia based on its location near a linkage hotspot for schizophrenia on chromosome 12q24 (Peng et al., 2007). The fact that *Cry1* is expressed in dopaminergic cells in the retina and that its expression influences the effects of psychoactive drugs lends support to this hypothesis.

However, the association between clock genes and schizophrenia is not undisputed, since positive studies had smaller samples (around 150 patients) than those needed for genetic association studies (Mansour et al., 2006; Takao et al., 2007; Zhang et al., 2011). Moreover, larger studies have failed to confirm those initial findings (Kishi et al., 2009; Purcell et al., 2009; Stefansson et al., 2009), thus the possible association between a specific subtype of schizophrenia and any of the clock genes is far from resolution.

Another protein that has been implicated in schizophrenia is SNAP-25. Decreased levels of SNAP-25 have been reported in the hippocampus (Fatemi et al., 2001; Thompson et al., 2003a; Young et al., 1998) while increased levels have been reported in the cerebrospinal fluid (Thompson et al., 1999, 2003b). Genetic studies also implicate SNAP-25 in schizophrenia (Arinami et al., 2005; Carroll et al., 2009; Fanous et al., 2010; Lewis et al., 2003). It has been reported that in vitro treatment of rat SCN with SNAP-25 at CT (circadian time) 14 h