Sleep of Patients with Schizophrenia On and Off Melatonin Treatment: Contradictions and Hypothesis

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IN: Schizophrenia, Sleep, and Acupuncture

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Abstract. Positive symptoms in schizophrenia decrease the requirement for REM sleep and reduce its pressure, while negative symptoms increase the need for REM sleep. This need cannot be satisfied because REM sleep in schizophrenia is functionally insufficient. This insufficiency may relate to the decreased melatonin level. Melatonin treatment restores REM-sleep functional efficiency in patients with different mental disorders, probably also in schizophrenia. There are some signs that melatonin inhibits brain dopamine systems that are active in wakefulness and that stimulate the dopamine system responsible for REM sleep-dreams sufficiency.

Keywords: schizophrenia, REM, melatonin, treatment

Sleep Disorders in Schizophrenia

In this chapter I will discuss only those sleep variables that are important for the understanding of melatonin treatment outcome.

According to many investigations (Keshavan et al., 1998; Yang & Winkelman, 2006; and the previous chapter), schizophrenia is characterized by a decrease in the percentage of slow-wave sleep (SWS). Keshavan et al. (1998) emphasized that reduced delta-counts in the first non-rapid eye movement (non-REM) sleep period, reduced delta-wave accumulation in continuous non-REM minutes, and reduced delta-power suggests that a delta-sleep deficit may be related to the primary pathophysiology of illness. Unlike REM sleep alteration (see later), delta-sleep deficits are persistent. In patients with schizophrenia sleep deprivation does not cause the increase of SWS in the subsequent night sleep, which is a typical "rebound effect" seen in healthy persons (Luby & Kaldwell, 1967).

Keshavan et al. (1998) as well as Yang and Winkelman (2006) have found an inverse correlation between SWS and delta waves and cognitive disorders in patients with both
acute as well as chronic schizophrenia.

It is possible to explain these interrelationships by taking into consideration the role of SWS in the retention of information in healthy persons (Latash & Manov, 1975) as well as the critical role of prefrontal cortex in directed attention and memory consolidation and at the same time in the generation of SWS activity (Gais & Born, 2004). According to Wolkin et al. (1992) negative symptoms are characterized by the hypometabolism of the prefrontal cortex while Feinberg (1989) suggested a positive correlation between delta-wave amplitude during sleep and the metabolic rate of the cerebral cortex. Recent investigations (Huber, Tononi, & Cirelli, 2006) have shown that SWS is homeostatically increased in sleep not only as a function of the duration of the prior wakefulness (Borbely & Acherman, 2000) but mostly as a function of the quality of the prior wakefulness. In animals the amount of exploratory behavior during the preceding wakefulness predicts the extent to which brain-derived neurotropic factor is induced as well as the extent of the homeostatic SWS increase in the subsequent sleep period. This means that there is a direct link between the synaptic plasticity triggered by waking activity and the homeostatic sleep response. Slow wave activity was locally increased in a specific cortical region after a visuomotor learning task involving that region but not after a kinematically equivalent motor task that did not require learning (see Huber et al., 2006) and, thus, did not include exploratory activity. The lack of normal exploratory mental activity during wakefulness in schizophrenia, with the dominating negative symptoms and cognitive disorders, may explain the deficiency of SWS in night sleep and the absence of the SWS rebound effect after the prolonged wakefulness caused by sleep deprivation. Interestingly, Huber et al. (2006) proposed that the noradrenergic system of locus coeruleus may be involved in mechanisms of slow wave activity homeostasis during sleep. The central noradrenergic system plays an important role in exploratory (search) activity during wakefulness (see Rotenberg, 2006). When this system was chronically disturbed, slow wave activity after spontaneous wakefulness and sleep deprivation was reduced relative to controls (Cirelli, Huber, Gopalakrishnan, Southart, & Tononi, 2005).

Data on the REM sleep variables in schizophrenia are more complicated than data on SWS representation. In never-medicated patients, REM sleep latency was either decreased or normal; REM sleep was either moderately decreased or increased (see Monti & Monti, 2004; Yang & Winkelman, 2006).

We have shown that in patients with chronic schizophrenia, as well as in healthy participants, REM sleep latency correlates with the duration of wakefulness incorporated into the first sleep cycle, in contrast to patients with major depression (Rotenberg et al, 2002). This means that in patients with chronic schizophrenia, as a whole, the requirement for REM sleep is less prominent than in patients with depression.

The prominent difference in the clinical picture and in many physiological variables between patients with the predomination of positive and negative symptoms suggests that this opposition between positive and negative symptoms may also explain some differences in sleep structure. Lauer, Schreiber, Pollma-cher, Holsboer, and Krieg
(1997) did not find any significant differences in sleep structure between a group of patients with paranoid schizophrenia and a healthy control group. Mendelson, Gillin, and Wyatt (1977) emphasized that REM sleep percentage increases exactly before the exacerbation of psychotic symptoms and tremendously decreases during the exacerbation itself. Gillin and Wyatt (1975) and Zarcone et al. (1975) have shown that during acute schizophrenic episodes the rebound increase in REM sleep that normally follows REM sleep deprivation is markedly blunted. Tandon et al. (1992) have shown that short REM sleep latencies were significantly associated with more severe psychotic symptoms. On the other hand, Taylor, Tandon, Shipley, Eiser, and Goodson (1991) found that patients with sleep-onset REM sleep (which means extremely short REM sleep latency) had more negative symptoms and poorer clinical outcomes.

We have investigated 34 patients with chronic schizophrenia on neuroleptic treatment (Rotenberg et al, 1999) and selected two groups. In Group I the ratio of positive/negative symptoms was > 1 (1.4), in Group II this ratio was < 0.5 (0.38). REM% in Group I was 20%, in Group II - 25% (p < .05). In patients with REM% higher than 25% the positive/negative ratio was 0.55. However, in patients with REM% less than 20% this ratio was also less than 1 (0.8). Thus, there was no linear relationship between REM% and positive/negative ratio. This means that while the domination and prominence of positive symptoms definitely determine at least the absence of the increase of REM%, in patients with a high level and domination of negative symptoms REM% may be either increased or decreased.

Another REM sleep variable that is related to the balance between negative and positive symptoms is eye movement (EM) density. It was shown (Neylan, Van Kammen, Kelley, & Peters, 1992) that EM density is higher during the process of neuroleptic treatment in comparison to neuroleptics withdrawal (which usually causes an exacerbation of clinical symptoms, especially positive symptoms). Moreover, in previously drug-naive patients, EM density was higher immediately after drug withdrawal in comparison to patients with long-lasting drug discontinuation (Tandon et al., 1992). It is well-known that immediately after drug withdrawal the effect of neuroleptic treatment is still present for some period, thus, it is possible that in these patients positive symptoms are still less prominent than in patients with long-lasting neuroleptic withdrawal. Actually, the increased severity of psychotic symptoms after drug withdrawal correlated with the decrease of EM density (Neylan et al., 1992). According to Tandon, Shipley, Eiser, and Greden (1989), EM density in REM sleep positively correlates with the severity of negative symptoms.

We have found (Rotenberg, Hadjez et al., 1997) that in patients with low EM density (< 2.5 per minute) the mean score of positive symptoms is higher than in patients with a high EM density (> 8.1 per minute), while the scores of negative symptoms were similar in both subgroups (33.2 and 31.0, respectively). In patients with a low score of positive symptoms, mean EM density was significantly higher than in patients with high scores, while EM density was similar in patients with high and low scores of negative symptoms. These results implicate that, just like REM%, EM density decreases with the increase of positive symptoms while its relationship with negative symptoms is not linear. In patients with a positive/negative ratio higher than 0.6, EM
density was lower than in patients that had a ratio lower than 0.4. In this last group EM density achieved its maximum level in the first cycle, in other cycles it was lower and almost equal (flattened distribution), which resembles EM distribution in patients with depression (Foster, Kupfer, Coble, & McParland, 1976). A significant negative correlation was found (Rotenberg, Hadjez et al, 1997) between the score of positive symptoms and EM density in the first and third cycles (-45; -.50, p < .05). Yang and Win-kelman (2006) also found a negative correlation between EM density and positive symptoms (-0.62).

The ratio of positive vs. negative symptoms also determines the presence or absence of the "first night effect" (FNE) in schizophrenia. FNE displays itself in the increase of REM sleep latency, decrease of REM sleep percentage, increased sleep onset latency and decrease of sleep depth (increased number of awakenings, decreased sleep efficiency) during the first sleep investigation in a sleep laboratory in comparison to sleep registration on the following nights. FNE reflects the natural increase of the participant's state of vigilance in an unfamiliar environment. However, because one of the main signs of FNE is the delay of REM sleep onset and the reduction of REM sleep, especially in the first cycles, FNE is seen, not only when the vigilance is increased, but also if the REM sleep system is flexible enough. In patients with depression, who are resistant to treatment and contain psychotic features relevant to the depressed mood, FNE is absent because of the rigid and unsatisfied requirement for REM sleep (Rotenberg, Kayumov et al, 1997). Thus, FNE reflects the requirement of the person for REM sleep and the flexibility of the REM sleep system.

Neylan et al. (1992) did not find FNE in patients with schizophrenia on and off haloperidol therapy. In our investigation (Rotenberg et al, 1998), FNE was present in 35% of all patients with schizophrenia (Group I) and absent in all other patients (Group II). Negative symptoms were almost equal in both groups, while positive symptoms were significantly higher in Group I (22.1 vs. 14.1, p < .02). When the positive/negative ratio was higher than 0.6, FNE was present in 71% of cases, when this ratio was lower than 0.4 it was present only in 17%. According to the sleep variables, the FNE was even exaggerated in Group I in comparison to the control group.

Some data confirm that the domination of positive symptoms may determine the appearance of FNE: Patients with schizophrenia that have prominent positive symptoms display an exaggerated orienting reaction (Kim, Shin, Kim, Cho, & Kim, 1993) and higher reactivity to sensory and affective stimuli in comparison to patients with schizophrenia that present negative symptoms (Docherty, 1996) as well as higher response of the brain monoamine system (Wolkin et al., 1996).

In addition, psychotic features decrease REM sleep pressure and make the REM sleep system more flexible (Gillin & Wyatt, 1975; Neylan et al, 1992; Zarcone et al., 1975).

We (Rotenberg et al, 2000) have found that patients with schizophrenia are able to estimate sleep latency more correctly than healthy persons, patients with neurosis, and patients who suffer from depression: In all these groups the correlation between
objective sleep latency and its subjective estimation is absent whereas in schizophrenia it is surprisingly high: 0.83! The relevance of this correlation is confirmed by the negative significant correlation between the subjective estimation of sleep latency and objective sleep duration (-0.72). This high ability to estimate sleep delay may relate to the blunted affect of patients with chronic schizophrenia. It prevents the emotional overestimation of sleep latency typical for healthy persons and patients with neurosis.

The subjective estimation of sleep depth in the first half of the night positively correlated with SWS duration (0.42). There was also a positive correlation between the feeling of being refreshed and SWS duration in the third cycle. In healthy participants, SWS also contributed to the positive estimation of sleep.

Previously, I have mentioned that patients with schizophrenia are characterized by the decrease of SWS, probably as a result of the decreased SWS requirement. A positive correlation between SWS, a feeling of sleep depth, and a morning feeling of refreshment show that when SWS is present it is functionally efficient.

At the same time, some of the subjective-objective correlations show that REM sleep in patients with schizophrenia is functionally inefficient. We have found that the subjective duration of wakefulness during the night correlates positively with EM density in the 4th cycle (0.60, p < .01). In healthy persons the subjective estimation of the duration of wakefulness incorporated in sleep correlates negatively with sleep efficiency (-0.66, p < .05) and positively with the objective duration of wakefulness, while EM density correlates with some features of dream reports (such as self-participation in dreams; Rotenberg, 1988).

Patients display a negative correlation between EM density and dream reports. In our investigation (Hadjez et al, 2003) we found less personal involvement and less emotional expression in dreams of inpatient adolescents with schizophrenia compared with dreams of controls. In schizophrenia the negative subscale of PANSS negatively correlated with the dream parameters of emotional expression, involvement, and recall.

If REM sleep is functionally insufficient in patients with schizophrenia, it could explain some of the paradoxical interrelationships that were mentioned above, like the absence of a linear relationship between REM sleep variables and positive/negative ratio. In patients with domination of negative symptoms REM% may be either increased or decreased, and EM density was similar in patients with high and low scores of negative symptoms. It may be that the increase of REM sleep reflects the combination of the increased requirement for REM sleep (determined by the domination of negative symptoms) and the functional ability of the REM sleep system to satisfy this demand. In such cases, EM density is usually increased in comparison to healthy participants. The decrease in the amount of REM sleep may represent either the decreased requirement for REM sleep caused by the domination of positive symptoms (in this case EM sleep density is also decreased) or the inability of the REM sleep system to satisfy this requirement because of its functional insufficiency, and in this case EM density may be either high or low. It may be high if the tendency to correspond to the increased requirement is prominent but the opportunity to satisfy this
requirement is, nevertheless, less prominent than the need. When low, it obviously shows the functional insufficiency of the REM sleep system.

The presence of the FNE in patients with schizophrenia, who have a domination of positive symptoms, reflects not only the active reaction to the environment but also the decreased requirement for REM sleep.

The increased requirement for REM sleep in patients with dominating negative symptoms and its decrease in patients with dominating positive symptoms can be explained in the frame of the search activity concept (Rotenberg, 1984, 2006; Rotenberg & Arshavsky, 1979). In this chapter it is not possible to present this concept in detail, thus, I am going to discuss only its main points. Search activity (SA) is defined as the activity oriented to change the situation or the individual's attitudes toward it without definite probability forecast of the possible outcome of such activity. SA is of importance in stress resistance and in preserving mental and somatic health. A functionally sufficient REM sleep-dreams system restores SA after its temporary renunciation in preceding wakefulness. Thus, REM sleep in animals increases after restraint stress in comparison to the stress of social relationships (Meerlo, Easton, Bergmann, & Turek, 2001) when an animal has no opportunity for the overt active behavior. If wakefulness is characterized by prominent SA the requirement for REM sleep decreases. If after giving up REM sleep is functionally inefficient (which means that SA is not restored by dreams) renunciation of search becomes dominant and predisposes the person to mental and somatic disorders. Negative symptoms in schizophrenia (apathy, low social activity, poverty of speech, tendency toward stereotyped behavior) obviously are opposite to SA. Positive symptoms (hallucinations and delusions) represent a very particular, socially irrelevant and inappropriate, but very intense SA (Rotenberg, 1994) and determine a decrease of the REM sleep requirement. In positive schizophrenia, the load on the REM sleep system is decreased and it can help, at least partly, to restore the functional value of REM sleep. In addition, in positive symptoms, in contrast to negative symptoms, the right hemisphere is, relatively, less involved and the right hemisphere is responsible for image thinking in dreams and for the regulation of eye movements in REM sleep (Rotenberg, Hadjes et al, 1997).

Sleep While on Melatonin Treatment

In this part of the chapter I am going to present data on the sleep estimation and alteration of objective sleep variables in healthy participants and in patients with different mental disorders besides schizophrenia while on melatonin treatment.

Rogers, Kennaway, and Dawson (2003) have compared the outcome of melatonin (5 mg), benzodiazepine temazepam (10 mg), and placebo administration on daily sleepiness and neurobehavioral performance in healthy participants. Melatonin increased sleepiness levels between 13.00 and 17.00 pm relative to placebo. However, in the first hour following drug administration, sleepiness levels in the temazepam condition were greater than in the melatonin condition. Some previous investigations have shown a decrease in neurobehavioral performance following administration of
melatonin (Deacon & Arendt, 1995; Zhdanova et al, 1995). However, in the investigation of Rogers et al. (2003) melatonin, in comparison to temazepam, had a less prominent negative effect on neurobehavioral performance, on unpredictable tracking, and on spatial memory.

In the investigation of Cajochen, Krauchi, Mori, Graw, and Wirz-Iustice (1997) melatonin (5 mg) and melatonin agonist S-20098 (5 mg and 100 mg) were used in comparison to a placebo in healthy young men, 5 hours before bedtime. Both types of treatment advanced the core body temperature rhythm and increased REM sleep. The increase in REM sleep was most pronounced in the first REM-sleep episode. The authors emphasized that, in healthy participants, the timing of REM sleep is coupled to the circadian rhythm of core body temperature and is regulated by the circadian pacemaker. However, on the posttreatment night, where a phase advance in core body temperature was still present (although less prominent than in the treatment night), this change in REM sleep was not maintained.

It is worth stressing that, although in these healthy participants the melatonin level after its exogenous administration was seven times higher than the normal endogenous nocturnal rise at 23:00 o'clock, sleep latency was not significantly reduced. Cajochen et al. (1997) came to the conclusion that when the endogenous levels of melatonin are high application of exogenous melatonin or S-20098 does not affect EEG power density; the soporific effect of melatonin may be only demonstrable when the level of endogenous melatonin is low.

In patients with anxiety and insomnia, acupuncture increased nocturnal melatonin secretion, decreased sleep onset latency and the arousal index, increased total sleep time and sleep efficiency, and increased Stage 3. REM sleep also demonstrated a tendency to increase (Spence et al., 2004).

We have investigated SWS distribution and REM sleep EM density in Delayed Sleep Phase Syndrome (DSPS) on and off melatonin treatment (Kayumov, Ro-tenberg, & Shapiro, 2002). DSPS is a circadian rhythm disorder in which the major sleep episode is delayed in relation to the desired clock time. It typically results in chronic sleep onset insomnia. DSPS is strongly associated with depression, and in the present investigation participants had elevated depressive indices. Melatonin treatment was presented during 9 consecutive weeks. Polysomnography was performed during 2 consecutive nights at baseline and at the end of 4 weeks of treatment on either melatonin (5 mg) or placebo. As compared to placebo, melatonin caused a decrease of the sleep onset latency. In all experimental conditions, SWS decreased from the first to the last cycle, which means that there was a normal distribution of SWS.

Melatonin caused a significant increase of REM sleep duration in the last (4th and 5th) cycles (normal REM sleep distribution), while at the baseline and on placebo REM sleep did not differ in the consequent sleep cycles (flattened REM sleep distribution). Thus, melatonin improved REM sleep distribution without changing the REM%.

Moreover, melatonin caused a regular increase of EM density from the 1st to the 5th
sleep cycle with a normal EM distribution.

The level of depression in DSPS participants was elevated during baseline investigation and on the placebo but decreased after the melatonin treatment.

It is notable that because of the delayed sleep onset, sleep on the baseline night was actually shifted to the morning hours. If sleep in DSPS would correspond to the normal sleep in the second part of the night, and melatonin would only decrease sleep latency and shift sleep back to the early night, than it would be reasonable to expect the relative general increase of REM sleep variables (REM sleep duration and EM density) on the baseline night in comparison to the night on melatonin treatment. Placebo also reduces sleep latency, thus, it would be reasonable to expect the more similar distribution of REM sleep variables for the melatonin and placebo conditions than for the baseline and placebo conditions. However, the results were opposite to such expectations. It is possible to conclude that, in addition to the decrease of sleep latency, melatonin normalizes the distribution of REM sleep variables.

The inverted or flattened distribution of REM sleep variables is a typical sign of depression and may reflect the increased requirement for REM sleep combined with the functional deficiency of REM sleep as a part of the pathogenetic mechanisms of depression (Rotenberg, Kayumov et al, 1997). By taking into consideration that in DSPS depression decreased on the melatonin treatment, it is possible to suggest that melatonin improves the REM sleep system.

This suggestion is in agreement with data of the activation of REM sleep and dream activity on melatonin treatment in REM sleep behavior disorders (Kunz & Bes, 1999) characterized by vigorous, and often dangerous, involuntary behavior during sleep usually accompanied by vivid, striking dreams. In these disorders REM sleep is usually characterized by the absence of muscle atonia. Obviously, it makes REM sleep functionally inefficient when such behavior causes self-damage, or damage of the sexual partner, finally leading to awakenings. During one week, melatonin (3 mg) used 30 min before bedtime, caused dramatic clinical improvements in most of these patients. A control polysomnogram performed 6 weeks after the beginning of treatment showed a tendency toward normalization of REM%, reduction of 30-s epochs scored as REM sleep without muscle atonia, reduction of stage shifts in REM, and reduction in epochs considered as movement time in REM. Frightened dreams disappeared (Kunz & Bes, 1999, 2001). The authors suggest that melatonin increases the overall amplitude of the circa-dian pacemaker and restores circadian-driven rhythms, one of them being the circadian modulation of REM sleep. However, all the features of REM sleep improved under the melatonin treatment characterize the quality of REM sleep. The question is whether improvement of these features is only an outcome of the normalization of circadian rhythm or whether it is in parallel with rhythm normalization? It is worth emphasizing that in these investigations melatonin did not change EM density (Takeuchi et al., 2001) - it changed only those REM sleep features that caused disturbed behavior during REM sleep. If muscle atonia is present and a person does not awake during REM sleep than even very intense participation in a dream scenario (which correlates with EM density in healthy persons, see Rotenberg et
The positive effect of melatonin on REM sleep behavior disorders was confirmed in patients with different neurological diseases: dementia, Parkinsonism, and multiple system atrophy (Boeve, Silber, & Ferman, 2003). The authors stressed that the mechanism of the melatonin action is not clear.

In patients with unselected neuropsychiatric sleep disorders and reduced REM sleep duration, melatonin (3 mg), in comparison to placebo, increased REM% as a result of the increased REM sleep continuity and improved subjective measures of daytime functioning (Kunz, Mahlberg, Muller, Tilmann, & Bes, 2004). The investigated group of patients included those with very different sleep disturbances (idiopathic insomnia, restless legs syndrome, narcolepsy, REM sleep behavior disorders). Melatonin did not change REM latency or time of temperature minimum, thus, indicating that the circadian phase remained unchanged. Increases in REM sleep were primarily caused by an increase of REM sleep episode duration especially in the 3rd and 4th REM sleep episodes while REM sleep episodes were short in the first cycles. Thus, there was a normalization of REM sleep distribution.

In parallel with REM sleep normalization, total sleep time, sleep efficiency, and NREM Stage 2 were increased and wake after sleep onset decreased. Moreover, 11 of 14 patients reported improvement in (very different) clinical symptoms.

From the present author's point of view it means that it is necessary to search for a very general pathogenetic mechanism common to different disorders that is improved by melatonin treatment, and REM sleep functional inefficiency is a good candidate for this common mechanism (Rotenberg, 1984, 1988). It is suggested that one of the main melatonin functions is the maintenance of the REM sleep system in its active state and its restoration. This function maybe especially important in patients with disturbed REM sleep functional efficiency.

**Melatonin Secretion in Schizophrenia and Sleep of Patients with Schizophrenia in Melatonin Treatment**

Many investigations (Kumar, Andrade, Bhakta, & Singh 2007; Monteleone, Natale, La Rocca, & Maj, 1997; Robinson et al., 1991) have shown that in patients with schizophrenia the melatonin level is decreased in both drug-free patients as well as after neuroleptic treatment. The circadian rhythm is altered as well as the rest/activity cycle. The decreased and blunted level of nocturnal melatonin secretion in schizophrenia is not confirmed by all investigators (Rao et al, 1994). According to Sandyk and Kay (1990) melatonin secretion is decreased mostly in patients with schizophrenia, who have a subtle morphological brain abnormality (cortical atrophy) associated with enlarged cerebral ventricles. These patients display poorer performance on neuropsychological testing, more disordered smooth-pursuit eye tracking, poorer premorbid adjustment, and more negative symptoms. Sandyk and Kay suggest that it is an association between prefrontal cortical atrophy and pineal calcification, and reduced melatonin secretion may be involved in the pathophysiology of prefrontal cortical
atrophy that, during sexual maturation, predisposes the person to the clinical manifestation of schizophrenia.

In our pilot investigation of seven patients with schizophrenia who had long-term insomnia complaints (Shamir, Rotenberg, Elizur, & Zisapel, 1997), we showed that after 3 weeks of melatonin (2 mg) treatment SWS duration and EM density in the 2nd cycle were significantly higher as compared to placebo. No significant differences were found in other sleep variables.

In 19 patients with schizophrenia, sleep was investigated by means of wrist actigraphy under melatonin treatment (2 mg) and placebo (Shamir, Laudon et al, 2000). Sleep efficiency significantly improved on melatonin vs. placebo especially in those patients whose sleep efficiency with placebo was lower than the median. The initial level of melatonin before melatonin treatment was low in all patients including those who displayed relatively high initial sleep efficiency. Probably the level of melatonin does not relate directly to sleep efficiency but relates to more global mechanisms of schizophrenia. The improvement of these mechanisms with melatonin may secondarily determine sleep improvement including sleep efficiency. One such basic mechanism may be REM sleep deficiency. In this context it is interesting to take into consideration that sleep efficiency of patients with paranoia tends to be less responsive to melatonin treatment (compared to placebo) than sleep efficiency of other clinical groups. We have mentioned before that patients with dominating positive symptoms seem to be less dependent on REM sleep and display lower REM sleep requirements. As a result, the functional insufficiency of REM sleep may have less clinical consequences in this group of patients and their sleep efficiency may be less sensitive to melatonin treatment.

In the investigation of Kumar et al. (2007), 40 patients with paranoid schizophrenia that complained of sleep-onset insomnia (according to our previously presented data their complaints may be quite relevant!) were treated with melatonin (3 mg) and a placebo for 15 days. The improvement of sleep-onset latency with melatonin was not significant. However, melatonin-treated patients showed a greater reduction in the number of nighttime awakenings. This investigation, as well as the investigation of Shamir, Laudon et al. (2000), was performed without polysomnography and it was impossible to check the hypothesis that melatonin reduced awakenings in REM sleep; as happens in other sleep disorders (see Kunz et al., 2004). Nevertheless, there are some indirect confirmations of this hypothesis. Melatonin treatment was associated with significantly better mood and greater morning freshness in these patients, and our investigation performed on patients with depression (Indursky & Rotenberg, 1998) showed that a better mood after sleep is associated with the normalization of the REM sleep dynamic during the night (increase of REM sleep eye movement density from the first to the fourth cycle and the decrease of REM sleep duration in the first cycle). In the investigation of Kunz et al. (2004) melatonin performed exactly this normalization of REM sleep in sleep disorders. It is suggested that melatonin is doing the same in patients with schizophrenia.

According to the subjective reports, melatonin had no effect on the number and quality
of recalled dreams. It seems to be a contradiction to our hypothesis: Dreams would have to increase and to be more vivid. However, if the improvement of REM sleep quality was associated with the decrease of REM sleep awakenings the subjective estimation of dream number may not increase.

The hypothesis of the normalizing effect of melatonin on REM sleep functions in schizophrenia is indirectly confirmed by our data of the FNE in melatonin-treated patients with schizophrenia (Shamir, Rotenberg, Laudon, Zisapel, & Elizur, 2000). With melatonin treatment, in comparison to placebo, patients with schizophrenia demonstrated a prominent FNE. On the 2nd night, sleep variables with melatonin and placebo did not differ significantly although sleep duration, sleep efficiency, SWS%, and REM% tended to be higher on melatonin. Presumably, the restoration of REM sleep quality decreases high REM sleep pressure that in turn prevents the FNE.

**Melatonin, REM Sleep, and the Brain Dopamine System**

If melatonin restores the functional efficiency of REM sleep it is necessary to explain the biochemical mechanisms of such a restoration. REM sleep in normal persons is characterized by the domination of dopamine (DA) and acetylcholine (Ach) activity while the activity of noradrenergic and serotonergic systems is decreased (Gottesman, 2002). It was proposed that the domination of DA activity is responsible for the peculiarity of SA in dreams (Rotenberg, 2006). In this context, it is intriguing that, according to many investigations, melatonin affects the brain's DA system (Alexiuk & Vriend, 1991; Zisapel, 2001; Zisapel, Egozi, & Laudon, 1982). However, data on the effect of melatonin treatment on DA activity in the brain are very controversial. According to Alexiuk and Vriend, melatonin administration significantly inhibited daytime DA synthesis in median eminence concomitantly with suppression of pituitary and plasma prolactin. According to Sandyk and Kay (1990) melatonin inhibits limbic DA activity, and in schizophrenia, especially with dominating positive symptoms, mesolimbic and mesocortical DA tone maybe chronically increased because of diminished melatonin secretion.

On the other hand, tuberinfundibular dopaminergic neuronal activity fall can be reestablished by melatonin injection (Shieh, Chu, & Pan, 1997). Melatonin exhibits both acute and chronic effects on the secretion of prolactins, and it may act via activating the tuberoinfundibular dopaminergic (TIDA) neurons (Chu, Shieh, Yuan, & Pan, 2000). Systematic injections of melatonin and its putative agonist S-20098 stimulate TIDA neurons. TIDA spontaneous neuronal activity changes from high to low between 13:00 and 17:00 hours and from low to high between 21:00 and 01:00 hours. This increase of the TIDA neuronal activity corresponds to the natural increase of the melatonin level, and a causal connection between these two variables was confirmed: Repeated injection of S-20928 (putative melatonin antagonist) between 18:00 and 01:30 hours effectively prevented the increase in TIDA neuronal activity. Thus, increased nocturnal endogenous melatonin may be responsible for this activity. In rats whose diurnal rhythm of TIDA neuronal activity is suppressed by continuous lighting environment repeated injection of melatonin can restore the TIDA rhythm.
In rats, Zisapel et al. (1982) and Zisapel (2001) have shown an inhibition of dopamine release by melatonin in the ventral hippocampus, medulla pons, preoptic area, median and posterior hypothalamus and no inhibition in the cerebral cortex, dorsal hippocampus, and striatum. Brain sites for the inhibitory effect of melatonin on dopamine neurosecretion overlap the sites involved in its modulation on neuroendocrine functions. The results indicate that the effect of melatonin is brain-region specific. It seems that some dopaminergic neurons are activated by melatonin while activity of many other groups of dopaminergic neurons is inhibited by melatonin (Zisapel, 2001).

In natural conditions melatonin probably inhibits dopamine release in those brain zones and systems where it provides active behavior during wakefulness but does not inhibit or even activates dopamine activity in brain zones related to REM sleep function. The difference between these DA systems is overlooked in modern reviews of different brain DA mechanisms (Rye, 2004) although these systems have to be in competitive relationships: DA agonists that enhance wakefulness are doing it at the expense of REM sleep. This may explain why the inhibitory effect of melatonin on dopamine release exhibited a 24-h rhythm with a peak in the early light hours and no inhibition before lights-off. A different influence of melatonin on different DA systems in different periods of the 24-h rhythm may explain the paradox when melatonin-induced inhibition of median eminence DA activity occurred concomitantly with suppression of pituitary and plasma prolactin (Alexiuk & Vriend, 1991).

The data of Van Cauter et al. (1991), and Appelberg, Katila, and Rimon (2002) present an indirect confirmation of the proposed hypothesis. Van Cauter et al. showed increased night time prolactin secretion and normal to reduced daytime prolactin secretion in patients with schizophrenia. Prolactin secretion is inhibited by dopamine, meaning that while during wakefulness DA systems of patients with schizophrenia are active or even overactive (probably because of the presence of positive symptoms - Appelberg, Katila, and Rimon, 2000, have shown the inverse correlation between prolactin and hallucinations), at night DA system activity is decreased, probably those DA systems that are related to REM sleep quality. Appelberg et al. (2002) have shown a negative correlation between prolactin measured just after awakening (produced during sleep) and REM sleep duration in patients with schizophrenia. At first glance, all these data look paradoxical: It is known (Obal et al., 2005) that prolactin participates in the synthesis of Ach, which is responsible for the initiation of REM sleep as a physiological state. However, it is necessary to discriminate the conditions for the initiation of the physiological state and the conditions for its functional efficiency. REM sleep has to be functionally sufficient (which means: accompanied by dreams that restore SA) and, accordingly, not to be regularly disrupted during sleep, and its functional sufficiency is presumably related to the particular DA system. It has been shown (Solms, 2000) that dreaming depends on the specific (probably, dopaminergic) forebrain pathway that instigates goal-seeking behavior, and which is independent from brainstem REM mechanisms. Brainstem REM mechanisms in healthy participants only provide optimal physiological conditions for dream realization (Rotenberg, 2000).
The hypothesis, according to the crucial role of brain DA in promoting search activity in REM sleep and in wakefulness (Rotenberg, 2006), corresponds to the data that REM sleep is characterized by an increase in mesolimbic DA release (Lena et al., 2005). Novelty exposed mice with hyperdopaminergia display a wake state characterized by hippocampal neural oscillations similar to those observed during REM sleep (Dzirasa et al., 2006). Dzirasa et al. have also shown that normal REM sleep can be suppressed by diminishing dopaminergic tone.

In patients with schizophrenia, who are already characterized by REM sleep insufficiency, it is a fact that the less active this particular DA system that determines REM sleep quality is (and correspondingly the higher the prolactin secretion just in this period is) the more disrupted their REM sleep is and the less is the amount of REM sleep.

Melatonin may help to restore the quality of REM sleep.

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