

MELATONIN AND REM-SLEEP BEHAVIOR DISORDER

by Regina Patrick RPSGT



Skeletal muscles undergo atonia (i.e., loss of tone) during rapid eye movement (REM) sleep. This keeps a person from acting out his dreams. The parasomnia REM sleep behavior disorder (RBD) allows muscle tone to remain during REM sleep and, as a result, an RBD sufferer can act out his dreams. The person may get out of bed, yell, scream, or strike out against objects or people. Bedpartners may be awakened by the RBD sufferer's vocalizations and movements or may be physically attacked inadvertently by the RBD sufferer. The drug treatment of choice for RBD is the benzodiazepine clonazepam since it relieves symptoms in 90% of people with the disorder. However, side effects such as dependency, residual daytime drowsiness, and impaired cognition can be problematic. Levo-dopa and tricyclic antidepressants (TCA) are alternative medications that are sometimes used to treat RBD. Unfortunately, these drugs can worsen motor activity during sleep. But RBD sufferers for whom medication therapy has been problematic may not have to choose between suffering the symptoms of the disorder or suffering the side effects of drug therapy. Recently, the hormone melatonin has shown some promise in relieving symptoms of RBD without the side effects associated with clonazepam, levo-dopa, or TCAs.

Scientists are not sure why muscle atonia does not occur during REM sleep in people with RBD. One possibility is that dysfunctions in the locus ceruleus, basal ganglia, or pontine reticular formation may play a role. In animal studies, chemical and

electrical stimulation of these areas can induce muscle atonia but lesions in brainstem nuclei (e.g., pedunculopontine nuclei) which supply the locus ceruleus and reticular formation result in muscle tone remaining during REM sleep. These findings suggest that: 1) these areas play a role in muscle atonia during REM sleep and 2) dysfunctions in these areas can lead to the motor symptoms of RBD.

Another possible explanation for why muscle tone remains during REM sleep may be dysfunctions in the cholinergic, dopaminergic, serotonergic, or noradrenergic nervous systems. The ability of clonazepam, levo-dopa, and TCAs to reduce RBD symptoms point to the involvement of these systems in the disorder.

Clonazepam binds to benzodiazepine (BDZ) receptors on central nervous system neurons. BDZ receptors when stimulated allow calcium to flood into a neuron which hyperpolarizes it. Hyperpolarization inhibits the transmission of a signal throughout the neuron. Neuroinhibition in the reticular formation results in sedation and neuroinhibition in brainstem nuclei that innervate the spinal cord results in reduced muscular activity. Activation of BDZ receptors can modulate the activity of the cholinergic neurons. Since cholinergic neurons in the pons trigger the onset of REM sleep, activation of BDZ receptors by clonazepam may counteract dysfunctional cholinergic activity occurring during REM sleep in a person with RBD.

Tricyclic antidepressants cause the neurotransmitters norepinephrine (also called noradrenaline) and serotonin to remain outside a neuron in the synaptic cleft and exert their stimulatory effects on adjacent neurons for an extended period of time. The extended activation may restore activity in serotonergic pathways in the pons and noradrenergic pathways in the locus ceruleus and brainstem which may have improper levels of these neurotransmitters in people with RBD. Since serotonergic pontine pathways modulate sleep and noradrenergic pathways in the locus ceruleus play a role in muscle tone, stimulation of these pathways by TCAs may restore REM sleep and REM sleep muscle atonia in people with RBD.

Levo-dopa is a precursor of the neurotransmitter dopamine. Unlike dopamine which if given exogenously can not enter the brain from the bloodstream, levo-dopa can cross the blood-brain barrier. Once it enters the brain from the bloodstream, it is converted into dopamine. This conversion may restore depleted levels of dopamine in dopaminergic pathways in the areas of the brain (e.g., substantia nigra) that play a role in movement. Restored levels of dopamine may explain why levo-dopa can reduce motor activity during sleep in RBD sufferers.

In 1997, German scientists Dieter Kunz and Frederik Bes began to suspect that melatonin could reduce symptoms of RBD after treating a 64 year old male patient for insomnia. The patient also had RBD. They prescribed melatonin as an alternative to benzodiazepine drugs to treat his insomnia. After two months, a polysomnography study showed that no major changes had occurred in sleep except for two: the percentage of REM sleep during a sleep period increased by 30% and muscle atonia was better preserved during REM sleep. Five months after starting melatonin therapy, all symptoms of RBD were resolved. This meant that

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although melatonin had been prescribed for insomnia, it had somehow improved RBD symptoms.

Kunz and Bes investigated this phenomenon more in-depth in a 1999 study that involved six RBD subjects. The researchers prescribed 3.0 mg of melatonin to the subjects which was taken 30 minutes before going to bed for six weeks. Subjects underwent a baseline polysomnogram (PSG) at the outset of the study and a second at the end of the sixth week. The second PSG revealed that the percentage of REM sleep during the sleep period had increased by 48% compared to baseline; arousals during REM sleep had decreased by 33%; movement during REM sleep had decreased by 28%; and the percentage of REM sleep without muscle atonia decreased by 34%. This again verified that melatonin could improve symptoms of RBD.

Melatonin's ability to improve RBD symptoms may be related to its role in circadian rhythmicity. One's circadian rhythmicity results from an interplay between an internal circadian pacemaker (i.e., a "master pacemaker") and external cues. However, rhythms produced by one's internal circadian pacemaker can persist in the absence of external cues. It was this characteristic which led to the discovery of the "master pacemaker" in the late 20th century.

In 1968, researchers Suzanne Gaston and Michael Menaker suspected that the pineal gland was the internal circadian pacemaker after discovering that removing the pineal gland destroyed rhythmicity in birds but transplanting healthy pineal tissue in pinealectomized birds restored their rhythmicity. Other researchers were finding that the internal circadian pacemaker in mammals including humans seemed to be located in the suprachiasmatic nucleus. In 1972, two independent groups of researchers – Robert Y. Moore working with Victor B. Eichler and Friedrich K. Stephan working with Irving Zucker – reported that lesioning the SCN in rodents abolished circadian rhythmicity but transplanting healthy SCN tissue into SCN-lesioned animals restored their rhythmicity. Researchers later discovered that an avian structure that seemed to correlate with the SCN in mammals more strongly controlled circadian rhythmicity in birds than did the pineal gland. This more strongly pointed to the SCN as the "master pacemaker." Since then, scientists have discovered that neural pathways exist between the pineal gland and the SCN. These pathways allow melatonin to play a role in circadian rhythmicity.

The SCN is highly sensitive to changes in light intensity that occurs throughout the day since photic signals are relayed from the retina to the SCN. In response, the SCN transmits signals to the paraventricular nuclei located in the thalamus. From there, signals travel to a group of cells in the thoracic and upper lumbar regions of the spinal cord (i.e., the upper thoracic intermediolateral cell column). These cells relay the signals to the superior cervical ganglion, a mass of cells which gives rise to fibers that supply the pharynx, larynx, and the head. Then, finally, signals arrive from the superior cervical ganglion to the pineal gland.

The pineal gland produces melatonin but its production is influenced by intensity of photic signals that enter the SCN. Increased photic stimulation results in reduced melatonin production and, conversely, decreased photic stimulation results in increased melatonin production. Wakefulness occurs during low levels of melatonin and sleep occurs during high levels of melatonin.

The pineal gland can synchronize the rhythm of melatonin production to the external cues of daylight and nightfall due to the neural connections between it and the SCN. However, in the pres-

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ence of constant darkness or constant light, the rhythmic rise and fall of melatonin production still occurs although an organism may free run (meaning that the rise/fall shifts to a later and later time each day rather than remaining at a constant time each day). The uncoupling of the internal circadian pacemaker from external cues is called desynchronization.

Desynchronization of melatonin production may play a role in RBD. In other words, the master pacemaker controlling the rhythmic rise and fall of melatonin may not be working correctly in people with RBD leading to inappropriate levels of melatonin during REM sleep. As a result, problems with disrupted REM sleep and the maintenance of muscle tone during REM sleep can occur.

Due to the lack of muscle atonia during REM sleep, RBD is normally thought of as a REM-sleep disorder. However, the ability of melatonin to relieve symptoms is beginning to suggest that it may instead be a circadian rhythm disorder. More studies are needed to determine this. If RBD is more of a circadian rhythm disorder than previously thought, scientists may soon focus on determining how to use melatonin to effectively treat RBD.

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