Muscle atonia (i.e., loss of muscle tone) is a feature of rapid eye movement (REM) sleep. If a person is simultaneously awake and in REM sleep, muscle atonia is experienced as sleep paralysis (i.e., the person is awake but unable to move voluntarily). Which neurotransmitter in the brain is responsible for REM sleep muscle atonia has long perplexed scientists. For a long time, scientists have believed that the amino acid glycine may be responsible for REM sleep muscle atonia.1 Recent studies now indicate that glycine and another neurotransmitter, gamma-aminobutyric acid (GABA), are simultaneously needed to induce muscle atonia in REM sleep. This finding may impact treatment for narcolepsy-cataplexy and other disorders that involve a dysfunction in REM sleep (e.g., Parkinson’s disease and REM-sleep behavior disorder).

Narcolepsy-Catatpexy
Cataplexy — the sudden, temporary loss of muscle tone — is one of four symptoms of the sleep disorder narcolepsy. Other symptoms of narcolepsy are excessive daytime sleepiness, hypnagogic hallucinations (i.e., vivid dream imagery that occurs with sleep onset), and sleep paralysis. A person with narcolepsy does not have to have all four symptoms to be diagnosed with the disorder. Of all symptoms, cataplexy can be the most debilitating since it can endanger the life of the person with narcolepsy or other people. For example, the sudden loss of muscle tone while a person is driving may result in an accident.

Cataplexy is triggered by strong positive emotions (e.g., mirth) or negative emotions (e.g., anger). Affected muscles may involve all skeletal muscles (resulting in the person falling to the floor) or involve only a group of muscles (e.g., leg muscles may weaken and cause the person to stagger during the episode). Scientists believe that during a cataplexy attack, a person is simultaneously experiencing the muscle paralysis of REM sleep while fully alert.1

Parkinson’s Disease
Parkinson’s disease (PD) is a progressive neurological disorder that is associated with the degeneration of the basal ganglia. The basal ganglia are several specialized groups of neurons at the base of the brain. Certain basal ganglia play a role in movement and are dopaminergic (i.e., respond to or produce the neurotransmitter dopamine). Loss of basal ganglia neurons consequently results in decreased dopamine levels and affects movement. In people with PD, reduced dopamine levels play a role in tremor; muscular rigidity; impaired balance and coordination; slow, imprecise movements (i.e., bradykinesia); or the inability to voluntarily move (i.e., akinesia). Approximately 80 percent of dopamine-producing cells are lost before the motor symptoms of PD appear.2

REM-Sleep Behavior Disorder
For many people with PD, the sleep disorder REM-sleep behavior disorder occurs several decades before the onset of their PD symptoms. REM-sleep behavior disorder may reflect impaired dopamine transmission resulting from the loss of basal ganglia neurons. Without sufficient levels of dopamine, REM sleep muscle atonia does not occur and a person with REM-sleep behavior disorder is able to act out dreams. The dreams typically have themes of danger such as being attacked or chased. As a result, the person with REM-sleep behavior disorder may jump out of bed, shout, scream, hit, punch, run, etc. while dreaming. The person may be hurt on acting out the dreams and/or a bed partner may be hurt if the person unwittingly strikes the bed partner while acting out a dream.

Animal studies have indicated that glycine and GABA inhibit neuronal and spinal motoneuron activity.3-6 As an offshoot of this finding, scientists have examined the neurochemistry of REM sleep muscle atonia.

For example, Yoshio Nakamura7 and colleagues found that administering glycine to the reticular formation (a brain structure that plays a role in the onset of REM sleep) activated trigeminal motoneurons during non-REM sleep, but inhibited the motoneurons during REM sleep. Peter Soja8 and colleagues examined the effect of strychnine on the hyperpolarization (i.e., inhibition) of lumbar motoneurons during REM sleep in cats. Strychnine is a toxin that causes muscle contractions and antagonizes glycine. Soja hypothesized that signals originating from the brain during REM sleep would hyperpolarize spinal motoneurons. Soja applied strychnine to the lumbar motoneurons in one group of cats but not in another group of cats (i.e., the control). Soja found that, during REM sleep, the lumbar motoneurons that had not been exposed to strychnine received inhibitory signals from the brain and became hyperpolarized during REM sleep — the activity of the lumbar motoneurons decreased by 59 percent during REM sleep. In the lumbar motoneurons that had been exposed to strychnine, the inhibitory signals from the brain were blocked and therefore hyperpolarization was markedly reduced during REM sleep — the activity of the strychnine-exposed motoneurons was
Based on these and similar research findings, scientists initially concluded that REM sleep muscle atonia resulted only from the glycinergic inhibition of motoneurons. However, some researchers later demonstrated in animal studies that REM sleep muscle atonia could persist after blocking the glycine receptors on motoneurons. This indicated that REM sleep muscle atonia is triggered by an unidentified inhibitory mechanism.

Canadian researchers Patricia Brooks and John Peever aimed to identify the neurotransmitter and receptor mechanisms involved in REM sleep muscle atonia. They focused on the neurotransmitters glycine and GABA in their study for several reasons: (1) brainstem circuits that control REM sleep contain GABAergic and glycinergic neurons; (2) somatic motoneurons express GABA and glycine receptors that on activation trigger cellular hyperpolarization; and (3) conflicting reports had indicated that GABAA or GABAB receptors were responsible for REM sleep muscle atonia, which indicated that the phenomenon may be activated by specific GABA receptors.

To investigate these factors, Brooks and Peever used the following drugs to modify the activity of the GABAA, GABAB, and glycine receptors: bicuculline and CGP52432 (GABAA and GABAB receptor antagonists, respectively); baclofen (GABAB receptor agonist); and strychnine (glycine receptor antagonist). All drugs were dissolved in artificial cerebral spinal fluid and administered through a cannula to the trigeminal nucleus (i.e., the root of the trigeminal nerve [cranial nerve V] in the brain). To monitor the muscular effect of the drugs, they measured the activity of the masseter muscle (i.e., a powerful jaw muscle that is involved in chewing and is innervated by the trigeminal nerve). Each drug was perfused onto the trigeminal nucleus for 2–4 hours. After each drug treatment, the animal underwent (at minimum) a two-hour washout period with artificial cerebral spinal fluid.

To investigate the role of the GABAB receptors in REM muscle atonia, the researchers perfused baclofen (GABAB receptor agonist) into the trigeminal motor nucleus (which is a portion of the trigeminal nucleus) while measuring masseter muscle activity. They antagonized the receptor with CGP52432. To determine if glycine and GABA are simultaneously needed to induce REM sleep muscle atonia, the authors simultaneously perfused GP52432, bicuculline, and strychnine onto the trigeminal nucleus motoneurons during sleep and during wake.

Brooks and Peever found that GABAB receptors, when activated by baclofen, significantly reduced the waking masseter muscle tone by 78 percent. Despite this reduction in tone, the activity of the muscle was greater than the muscle activity during REM sleep. Because baclofen administration did not reduce muscle activity to the level that occurs in REM sleep, the researchers concluded that GABAB receptor activation alone does not completely trigger muscle atonia during REM sleep.

The simultaneous administration of GABAA, GABAB, and glycine antagonists reversed motor paralysis and resulted in a 105 percent increase in masseter muscle tone during REM sleep. The muscle tone level during REM sleep was similar to the level observed during normal non-REM sleep. This indicated that REM sleep muscle atonia is triggered by the combined activation of both GABA receptors (i.e., GABAA and GABAB) and the glycine receptor. Brooks and Peever believe their results refute the long-standing idea that only one transmitter (i.e., glycine) is responsible for REM sleep muscle atonia.

Because the finding that both glycine and GABA may be needed to induce REM sleep muscle atonia is so recent, no studies have investigated to what extent manipulating GABAergic and glycinergic systems can improve sleep disorders associated with alterations in REM sleep. A greater understanding of how REM sleep muscle atonia occurs could result in better treatment of disorders associated with a dysfunction in REM sleep. For example, altering the activity of glycine and GABA receptors, in addition to increasing the brain levels of dopamine, may more effectively improve symptoms in people with REM sleep behavior disorder or Parkinson’s disease. Simultaneously targeting the glycinergic and GABAergic systems may lead to the development of less addictive treatments for cataplexy. (The drug sodium oxybate, a form of GABA, effectively reduces cataplexy attacks in some people with narcolepsy but it is very addictive.) For now, scientists continue studies to determine the role of glycine, GABA, and other neurotransmitters (e.g., dopamine) in REM sleep muscle atonia.

REFERENCES


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