

Restless legs syndrome, insomnia and brain chemistry: A tangled mystery solved?

7 May 2013

Johns Hopkins researchers believe they may have discovered an explanation for the sleepless nights associated with restless legs syndrome (RLS), a symptom that persists even when the disruptive, overwhelming nocturnal urge to move the legs is treated successfully with medication.

[Neurologists](#) have long believed RLS is related to a dysfunction in the way the brain uses the [neurotransmitter dopamine](#), a chemical used by [brain cells](#) to communicate and produce smooth, purposeful [muscle activity](#) and movement. Disruption of these neurochemical signals, characteristic of Parkinson's disease, frequently results in involuntary movements. Drugs that increase [dopamine levels](#) are mainstay treatments for RLS, but studies have shown they don't significantly improve sleep. An estimated 5 percent of the U.S. population has RLS.

The small new study, headed by Richard P. Allen, Ph.D., an associate professor of neurology at the Johns Hopkins University School of Medicine, used MRI to image the brain and found glutamate—a neurotransmitter involved in arousal—in abnormally high levels in people with RLS. The more glutamate the researchers found in the brains of those with RLS, the worse their sleep.

The findings are published in the May issue of the journal *Neurology*.

"We may have solved the mystery of why getting rid of patients' urge to move their legs doesn't improve their sleep," Allen says. "We may have been looking at the wrong thing all along, or we may find that both dopamine and glutamate pathways play a role in RLS."

For the study, Allen and his colleagues examined [MRI images](#) and recorded glutamate activity in the [thalamus](#), the part of the brain involved with the regulation of consciousness, sleep and [alertness](#). They looked at images of 28 people with RLS and

20 people without. The RLS patients included in the study had symptoms six to seven nights a week persisting for at least six months, with an average of 20 [involuntary movements](#) a night or more.

The researchers then conducted two-day sleep studies in the same individuals to measure how much rest each person was getting. In those with RLS, they found that the higher the glutamate level in the thalamus, the less sleep the subject got. They found no such association in the control group without RLS.

Previous studies have shown that even though RLS patients average less than 5.5 hours of sleep per night, they rarely report problems with excessive daytime sleepiness. Allen says the lack of daytime sleepiness is likely related to the role of glutamate, too much of which can put the brain in a state of hyperarousal—day or night.

If confirmed, the study's results may change the way RLS is treated, Allen says, potentially erasing the sleepless nights that are the worst side effect of the condition. Dopamine-related drugs currently used in RLS do work, but many patients eventually lose the drug benefit and require ever higher doses. When the doses get too high, the medication actually can make the symptoms much worse than before treatment. Scientists don't fully understand why drugs that increase the amount of dopamine in the brain would work to calm the uncontrollable leg movement of RLS.

Allen says there are already drugs on the market, such as the anticonvulsive gabapentin enacarbil, that can reduce glutamate levels in the brain, but they have not been given as a first-line treatment for RLS patients.

RLS wreaks havoc on sleep because lying down and trying to relax activates the symptoms. Most people with RLS have difficulty falling asleep and staying asleep. Only getting up and moving around

typically relieves the discomfort. The sensations range in severity from uncomfortable to irritating to painful.

"It's exciting to see something totally new in the field—something that really makes sense for the biology of arousal and sleep," Allen says.

As more is understood about this neurobiology, the findings may not only apply to RLS, he says, but also to some forms of insomnia.

Provided by Johns Hopkins University School of Medicine

APA citation: Restless legs syndrome, insomnia and brain chemistry: A tangled mystery solved? (2013, May 7) retrieved 5 May 2021 from <https://medicalxpress.com/news/2013-05-restless-legs-syndrome-insomnia-brain.html>

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