

## Melatonin alterations in Huntington's disease help explain trouble with sleep



Study shows HD patients have decreased levels of melatonin, which may explain why so many suffer from sleep problems

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*Many people with Huntington's disease have problems sleeping. Sleep-wake cycles are controlled in part by melatonin, a hormone that makes you drowsy at bedtime. Scientists in London measured melatonin levels in HD patients, gene carriers, and unaffected individuals and found changes in the levels and timing of melatonin release. This could help to explain the sleep disruptions that occur in HD.*

### Sleep can be elusive

If you've ever been in bed with your mind racing, wishing for sleep, you know that slipping into dreamland is far less simple than it seems. In fact it requires a lot of complex coordination by different parts of the brain to get your body in tune with the darkening world, leaving you drowsy enough to fall asleep and restful enough to stay that way till morning.

We know that people with Huntington's disease sleep poorly: nearly 80% of Huntington's disease sufferers experience sleep disturbances. These can include an increase in the length of time it takes to fall asleep, changes in what the brain is doing during sleep, and decreases in the amount of truly restful sleep. It's not well understood why these disturbances occur in HD, but a new study highlights changes in levels of **melatonin**, a chemical that regulates sleep and wakefulness in relation to the rising and setting of the sun.



Sleeping problems are common in HD, and can impact on other symptoms and reduce quality of life.

### Brain control of sleep

Our predisposition for nighttime sleep and daytime activity is just one of many **circadian rhythms**, a term that refers to anything that changes within our bodies on a 24-hour cycle, and can be synchronized with what's happening in our environment. Lots of human behaviors are rhythmic or change predictably over the course of a day. Not only sleep and alertness, but also digestion, body temperature, and the immune system change depending on what time it is. We've talked about sleep and circadian rhythms in Huntington's disease before. .

These rhythms are overseen by a brain region called the **suprachiasmatic nucleus**, or **SCN**. The SCN acts as the brain's timekeeper, coordinating the body's activities over the 24-hour day. Neurons in the SCN are perfectly situated to communicate with cells from the eyes that describe how much light there is in the environment. With this information, the SCN can send out a message to other brain and body areas telling them what they need to do to keep their cycles running smoothly.

Because of the resulting circadian rhythms, levels of all kinds of substances made by the body can fluctuate normally with the amount of light outside, and melatonin is an important one. Melatonin is a hormone, a chemical messenger that circulates in the blood. It is produced by an organ deep in the center of the brain called the pineal gland. As the sun begins to go down, the SCN senses the change in light and sends a message to the pineal gland to start secreting melatonin. Melatonin helps to regulate sleep cycles by causing drowsiness and lowering the body's temperature a little in preparation for sleeping through the night. Melatonin levels are high throughout the night, but as the sun comes back up, they drop, corresponding with increased wakefulness.

## Are melatonin levels altered in HD?

Since Huntington's disease patients have problems regulating the normal sleeping/waking cycle, a group of researchers in the UK led by Prof Tom Warner wanted to ask whether the rise and fall of melatonin levels in HD patients is abnormal compared to unaffected individuals. Previous studies had measured patients' melatonin at a single time point, early in the morning, but Warner's group wanted to monitor melatonin levels throughout the 24-hour cycle to get a better sense of how the rhythm of melatonin production is affected in HD.

“ The HD patients had much lower levels of melatonin in their blood ”

They recruited 13 patients with moderate to advanced HD, and 15 people who do not have the HD gene. They also included 14 people who carry the HD gene, but had not yet shown disease symptoms. Each person involved in the study spent a day and night in a private room, under supervision by clinicians. They could walk around and do what they liked during the day, but they weren't allowed to nap, and the lights were out between 10 pm and 6 am. The researchers inserted an IV line so that they could collect a small amount of blood every hour, even in the middle of the night, with minimal interruption of the volunteers' sleep.

## Melatonin in HD and gene carriers: lower levels and improper timing

Using a sensitive type of chemical analysis, the researchers determined the amount of melatonin in each person's blood, then compared the three groups with one another using a variety of statistical methods.

They found that the HD patients had much **lower levels of melatonin** in their blood than those without HD – around 85% lower on average. Presymptomatic carriers of the HD gene also had

slightly lower melatonin levels than normal.

Another finding was that HD patients and gene carriers showed more variation in the time of day that their melatonin levels began to rise. Most of the volunteers without HD had a surge of melatonin around bedtime, while HD-affected individuals' melatonin levels rose at different times – some in the afternoon, some in the middle of the night.

## **An explanation for disrupted sleep in HD?**

By consistently monitoring blood levels of melatonin for a full 24 hours in Huntington's disease patients, presymptomatic HD carriers, and unaffected control participants, this study showed that melatonin levels are indeed altered in HD, a finding which may help to explain why patients experience disrupted sleep.

The researchers go on to suggest that a low or poorly-timed surge of melatonin from the pineal gland could mean that there's something wrong with the timekeeper neurons in the SCN. Several different types of Huntington's disease mice have shown problems in sleep and other cyclic behaviors controlled by the SCN. Abnormalities in signalling chemicals produced by the SCN have been found in HD brains, both human and mouse.

Back in 2011, we reported on a study in which melatonin treatment improved behavior and survival in Huntington's disease mice. It's not yet clear whether we can link that finding with the new discovery of decreased melatonin levels in HD patients. But sleep disruption can be a major source of stress and can worsen the symptoms of many diseases. Improving sleep through melatonin therapy, could be a positive change for the body and brain. However, it's not yet clear whether melatonin is effective in HD to improve sleep, let alone as a means of slowing down the progression of the disease.

## **A case for clinical trials of melatonin**

There hasn't been a clinical trial of melatonin as a therapy for Huntington's disease patients with sleep disturbances, but this study provides good evidence of HD-related changes in melatonin levels, and suggests that a clinical trial might be warranted. Melatonin is already an approved supplement that many people buy over-the-counter or get on prescription, to adjust their sleep patterns. Some patients appear more responsive than others to melatonin and other sleep aids; perhaps this could be explained by the variable timing of melatonin production that this study found in HD patients.



Melatonin is a hormone that helps the brain decide when to sleep and wake.

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Finally, these results don't provide any explanation for **why** changes in melatonin occur in HD. We can speculate that the SCN or its communication with the pineal gland may be disrupted, but the reasons for that are unclear. It's also fairly clear that changes in melatonin are only one of several things that can cause sleep disruption in Huntington's disease, and we're **definitely** not saying that every HD patient should take melatonin. However, these results make a solid case for a clinical trial, and importantly, the study provides one explanation for why it's so tough for many HD patients to catch some much-needed zzzs.

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*The authors have no conflicts of interest to declare. For more information about our disclosure policy see our FAQ...*

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## Glossary

**suprachiasmatic nucleus** the part of the brain that controls daily or 'circadian' rhythms

**clinical trial** Very carefully planned experiments designed to answer specific questions about how a drug affects human beings

**pineal** a gland in the brain that produces the hormone melatonin

**Melatonin** a hormone produced by the pineal gland, important for regulating sleep

**circadian** a circadian rhythm is something that repeats every day, like the body's sleep-wake cycle

**neuron** Brain cells that store and transmit information

**hormone** Chemical messengers, produced by glands and released into the blood, that alter how other parts of the body behave

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