

New roles for huntingtin: removing a healthy protein to understand its function

Completely removing normal huntingtin in adults may disrupt healthy brain function, a recent study suggests.

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Some techniques aimed at lowering mutant huntingtin can also affect the normal form of the protein. With clinical trials underway, it's all the more important to understand the role of normal huntingtin in the adult brain. Researchers recently inactivated the huntingtin gene in healthy adult mice of different ages. They found that this could cause neurological and behavioral problems. Mice aren't perfect for modelling human brains, and no huntingtin-lowering drug would remove the protein completely - but this research supports the need for continued caution as we test drugs that lower normal huntingtin.

Understanding huntingtin function

The mutation that causes Huntington's Disease alters instructions for building a protein called huntingtin. In HD, a repeated sequence of letters in this gene leads to an extra-long form of huntingtin protein that can wreak havoc in brain cells over long periods of time. One of the most exciting avenues of HD research is *huntingtin lowering* (also known as *gene silencing*), which aims to reduce levels of the huntingtin protein in cells.



Mice aren't people, but studies in mice can provide important information about the role of huntingtin.

Animal studies have revealed strong benefits of these techniques, showing that reducing mutant huntingtin in the brains of HD mice can improve their brain health and behavior. Rigorous experiments in animals have given way to clinical trials of drugs that target the HD

gene in people, and there are more techniques for decreasing or eliminating huntingtin on the horizon. Some of these approaches to attack mutant huntingtin also reduce levels of the normal protein, including the Ionis [huntingtin-lowering drug](#).

For this reason, we need to understand more about what happens to the brain when huntingtin is removed. To do this, a group of researchers recently used genetic techniques to remove huntingtin from adult mice of different ages, then studied their brains and behavior until old age.

Huntingtin during development and adulthood

When researchers want to understand the function of a gene, their first move is usually to get rid of it. By studying what goes wrong when a protein is missing, we get clues about its role in cells. If you didn't know the purpose of a belt, and then you removed your belt and found your jeans around your ankles, you'd likely realize what a belt was for.

In mice, when huntingtin is missing from the brain at conception, this causes early and severe neurological problems. When huntingtin is missing from the entire body and brain, the mice will die before birth. This led scientists to deduce that normal huntingtin is very important during development, especially in the brain.

“We need to understand more about what happens to the brain when huntingtin is removed ”

However, there is far less known about the role of normal huntingtin in adulthood. Mutant huntingtin, although altered, is still present, and most people with HD have normal huntingtin, too. What if huntingtin is around for half a lifetime, and then is suddenly eliminated? That's much more dramatic than what happens in a huntingtin-lowering treatment trial. So far, there are promising reports on the short-term safety of reducing huntingtin levels in adult humans. But continued animal studies can help to inform ongoing trials.

What happens when huntingtin is gone?

To study what happens when huntingtin is removed during adulthood, a team of researchers led by Ioannis Dragatsis at the University of Tennessee used a genetic tool to precisely time the removal of huntingtin in a large proportion of cells all over the body. This is a technique involving specially modified mice that are given a chemical injection to trigger the removal of a chosen gene. It's useful to help researchers understand the function of a gene at a specific time of life, but this particular technique is not being developed as a treatment for any human disease.

It's important to emphasise that this technique completely shuts off production of the huntingtin protein. That's not what we expect when patients are given huntingtin-lowering drugs, which might produce around 50-75% reductions in the mutant and healthy protein. Current huntingtin-lowering drugs, called ASOs, are also given as individual doses separated by several weeks, with normal protein production expected to bounce back somewhat in between.

Nonetheless, the Dragatsis team used this method to try and understand the extreme case of loss of huntingtin during adulthood. They inactivated the huntingtin gene at three different adult ages: 3, 6, and 9 months old. For context in mouse-years, 3 months is sort of like an older teen, and 9 months is about middle-aged. They examined the natural lifespan of these mice and closely studied their brains and behavior over time.



Removing Huntingtin from the brains of mice damaged the thalamus - a key relay station in the brain.

Completely removing normal huntingtin caused the mice to have a shorter lifespan, neurological problems, and trouble with movement tasks. The earlier the gene was inactivated, the more severe the behavioral issues, suggesting that huntingtin is most important in younger adults. Removing huntingtin caused the mice to have slightly smaller brains and overall signs of inflammation. Despite behavioral and neurological concerns, brain areas normally affected by HD, the striatum and cortex, did not contain damaged nerve cells. This is encouraging given that these areas are the main focus for huntingtin lowering drugs in clinical trials.

A new role for huntingtin – and conflicting results

It's difficult to determine the exact cause of the neurological problems that arose when huntingtin was removed in mice, but the researchers uncovered some interesting clues. They found that brain cells in an area called the thalamus had problems processing and using iron, leading to the buildup of iron and calcium inside cells. The thalamus is a main

relay station for the brain, often an important middleman in transmitting messages from one area to another. Iron is a mineral that's essential in the brain for generating energy and ensuring the smooth transmission of nerve impulses. It's not clear exactly how huntingtin helps with the efficient use of iron in the thalamus. However, the neurological problems caused by disrupting this pathway have alerted us to a potentially significant role for huntingtin in the aging brain.

Another recent study from Xiao-Jiang Li's laboratory at Emory University used a similar (but not exactly the same) technique to remove huntingtin in mice at 2, 4, and 8 months of age. This was dangerous in the youngest mice, leading to early death due to failure of a digestive organ called the pancreas. However, removing huntingtin in mice older than 4 months appeared to cause no neurological problems, a stark contrast to the Dragatsis lab's work.

One possible explanation is that the mice in the Dragatsis project were unusual to begin with, in that they had only one copy of the huntingtin gene, rather than the usual two. That means they produced less huntingtin throughout development, which might have left the brain more susceptible to the later switching off of the gene.

“We will need to continue to use caution when removing or lowering normal huntingtin in human studies ”

Such conflicting reports can be confusing, but it's ultimately informative to examine the differences between parallel studies. The slight discrepancies that lead to differing results allow us to gather more information about the underlying biology.

The message

Importantly, both studies suggest that we need to continue our current cautious approach when lowering normal huntingtin in human studies. Another option may be the pursuit of “allele-specific” therapies, those that specifically target mutant huntingtin while leaving the normal form intact. This approach is being used by WAVE Life Sciences, a company working on developing allele-specific huntingtin lowering drugs for HD.

However, it's essential to re-emphasise that the experimental technique used in these mice, permanently removing huntingtin all over the body and brain, is very different from the clinical approach of temporarily lowering huntingtin in selected parts of the brain. In the huntingtin-lowering trial that is currently underway, the treatment is reversible, and participants are being carefully monitored for safety. Irreversible forms of HD gene editing, like CRISPR-Cas9, will require meticulous long-term testing before they can be brought to the clinic.

As the short-term administration periods for the huntingtin-lowering drug are extended, clinicians will continue to be watchful and to collect data that is essential to determine whether the treatment is safe and effective. In the meantime, a variety of approaches in

animals can deepen our understanding of the biology behind the drugs that are already in the clinic.

This article was updated on 26th September 2017, in response to reader feedback, to clarify the important differences between total huntingtin removal in mice and partial reduction by huntingtin lowering drugs.

The authors have no conflicts of interest to declare. [For more information about our disclosure policy see our FAQ...](#)

GLOSSARY

huntingtin protein The protein produced by the HD gene.

gene silencing An approach to treating HD that uses targeted molecules to tell cells not to produce the harmful huntingtin protein

inflammation Activation of the immune system, thought to be involved in the HD disease process

Allele one of the two copies of a gene

CRISPR A system for editing DNA in precise ways

ASOs A type of gene silencing treatment in which specially designed DNA molecules are used to switch off a gene

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