A multiple sclerosis drug that works for Huntington's disease: the real deal or too good to be true?

Fingolimod, a drug used in multiple sclerosis, prevents memory problems in HD mice. Would it work in patients?

By Melissa Christianson November 24, 2015 Edited by Dr Ed Wild

Thinking problems in Huntington's disease take a huge toll from early in the disease. Now, new work suggests that a drug already approved by the FDA to treat another brain disease – multiple sclerosis – may stave off these problems in HD mice. Could these results be real, or are they too good to be true?

Although movement disturbances are the most obvious symptom of Huntington's disease, Huntington's also causes cognitive problems – like changes in memory, planning, decision-making, and communication – that take a huge toll on patients and their families early in the disease. Understanding why these cognitive changes arise and how we might prevent them is really important for treating Huntington's.

The brain's game of 'telephone'

The brain is made up of cells that talk to each other like players in a giant game of telephone. Thinking problems can arise when messages in this giant game of brain telephone get garbled.
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In Huntington's disease, thinking or 'cognitive' problems typically arise long before brain cells die. If these problems begin *before* brain cell death, though, what causes them?

One likely culprit is a change in how well brain cells communicate.

To understand this idea, remember that the brain is made up of a huge network of cells (called neurons) that talk to each other by

passing messages back and forth. You can think of brain communication like a giant game of 'telephone': one neuron (brain cell) passes a message to another, which passes it to a third, and so on down the line. Because the brain has about 86 billion neurons, however, this game is huge beyond the scale of what you probably played as a kid.

Problems occur when messages in this giant game of telephone get garbled - in other words, when neurons don't reliably hear or pass along the messages they receive.

This garbling can happen in a few different ways. First, messages can get garbled if a neuron gets sick. Just like it would be difficult for you to play telephone if you lost your voice, being sick makes it difficult for a neuron to pass messages to other neurons.

Alternatively, a neuron's environment can influence how well it hears or passes along messages. Just like it would be harder to play telephone in a room full of screaming two-year-olds than in a quiet room, certain brain environments make it harder for neurons to communicate. For example, we know that neurons in the brain are surrounded by helper cells that have a bit of a split personality. These helper cells are normally 'good guys' that make communication easier; when the brain gets damaged by injury or disease, however, helper cells can become 'bad guys' that can interfere with brain communication.

So, to keep messages flowing through the brain's giant game of telephone in Huntington's disease, we may need to protect neurons, their helper cells, or both at the same time.

An multiple sclerosis drug for Huntington's disease?

Wouldn't it be nice if a drug that's already in use, could protect both neurons and helper cells, and was already being used in humans?

One possible drug that fits the bill is **fingolimod**. It's approved around the world for treating **multiple sclerosis** (MS). MS is a disease where excessive inflammation harms the brain.

Fingolimod reduces the risk of MS attacks by altering the behaviour of the immune system. However, like many drugs, fingolimod also does a whole bunch of other things in the body - and some scientists think that two things it does in the brain could make it a valuable Huntington's therapy.

> **"**Together, the effects of fingolimod protect both neurons and helper cells in the brain – which is exactly what we want in a Huntington's therapy. ″

First, fingolimod increases the amount of a brain chemical called **BDNF**. BDNF is kind of like Miracle-Gro for brain cells: it keeps them healthy and strong. Second, fingolimod keeps helper cells in their 'good guy' mode where they help neurons communicate. Together, these two effects protect both neurons and helper cells in the brain – which is exactly what we want in a Huntington's therapy.

There's even more reason to think that fingolimod could be valuable in Huntington's disease. Last year, scientists tested fingolimod treatment in mice with Huntington's disease, and they found that treated mice had fewer movement problems, lived longer, and lost fewer brain cells.

However, no one knows yet whether fingolimod also affects the thinking problems that arise early in Huntington's disease.

Of mice and memory

To answer this question, a group of scientists from the University of Barcelona decided to test whether fingolimod could prevent thinking problems in a mouse model of Huntington's. In this model, mice are genetically altered so that their DNA contains a small piece of the human Huntington's gene. These genetically altered mice get sick early, developing motor problems and brain changes similar to those in the human disease.

Testing thinking skills in mice is a tall order, especially when you consider that the average mouse brain weighs less than a gram. How is such testing even possible?

To study 'thinking' in mice, we have to simplify our questions and use answers from what mice will do in the laboratory.

For example, let's imagine that we want to measure a cognitive skill like memory in a mouse. Obviously, we can't just ask the mouse if he remembers a toy we showed him yesterday. However, just like humans, mice will spend more time looking at exciting new things than boring familiar things. By measuring how long a mouse explores an object, therefore, we can get a sense for how familiar that object is – and thus figure out how well the mouse remembers it.

Though it's not be perfect, this type of reasoning lets us ask questions about complicated cognitive ideas like memory in mice. By asking such questions, scientists have learned that Huntington's mice develop memory problems as they age.

What did they find?

So, what happened when the University of Barcelona scientists tried to prevent these memory problems by treating Huntington's mice with fingolimod?

As much as were hoping that scientists will find a drug to prevent or improve Huntington's symptoms, we're holding our horses about fingolimod for now.

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First, in contrast to Huntington's mice given a dummy medicine, those given fingolimod preferred new objects and places instead of familiar ones. Because these mice 'remembered' familiar things, the scientists reasoned that fingolimod protected them from Huntington's-like memory problems.

Additionally, in parts of the brain important for memory, fingolimod-treated mice had lots more of the genetic recipe for making BDNF (the 'Miracle-Gro' brain chemical) than the dummy medicine-treated mice did. Mice given fingolimod also developed fewer disease-related changes in the shape and activity of their neurons, and fewer of their helper cells got stuck in the 'bad guy' mode that interferes with brain cell communication.

Based on all of these effects, the scientists concluded that fingolimod protected neurons and helper cells in the treated mice, thereby preventing Huntington's-like memory problems. They further suggested that fingolimod may offer a new therapeutic strategy for Huntington's disease – one that could be very rapidly implemented because fingolimod already has FDA approval for human use in MS.

Holding our horses

As much as were hoping that scientists will find a drug to prevent or improve Huntington's symptoms, we're holding our horses about fingolimod for now. Here's why.

First, the experiments we've talked about here are actually *really* hard. They involve measuring very, very small changes in mouse behavior or brain cell shape and activity – and in this type of experiment, it's really easy to get misleading results. Confirming that these fingolimod-based improvements are real and can be repeated, and proving that they extend to other tests of memory or thinking, will be an important next step.

Second, even if the memory improvements are real, there's still a lot more work to do before we'll know for sure **how** fingolimod caused them. In part, this is because fingolimod affects the body in multiple ways - and remember, the most well-studied of these effects involves the immune system. More research is needed to prove that fingolimod's effects on the brain, and not some other part of the body, are indeed responsible for any memory improvements observed in the Huntington's mice.

Thirdly, though fingolimod is pretty safe, it's still a serious drug with the potential for some heavy-duty side effects. Not just stuff like drowsiness or a rash – but, rarely, its effects on the immune system can allow the brain to develop a severe viral brain infection called PML, which is often fatal. If people with Huntington's disease are going to take that kind of risk, we want to be darn sure fingolimod is super-effective at relieving HD symptoms or slowing progression in most people first.

Finally, the mice in the experiments we've been talking about are just that: mice. Like any laboratory model, they can't reproduce all the complexities of human Huntington's disease. While we can still learn a lot from studying these mice, scientists will need to test fingolimod in other models before they make firm predictions about whether fingolimod could work in people.

The take-home message

It's good news that a drug already approved for human use may be beneficial in a lab model of Huntington's disease, because this drug could rapidly advance into human trials. For now, we suggest keeping the celebratory champagne corked until we know a lot more.

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- Glossary
- **multiple sclerosis** a disease of the brain and spinal cord, in which episodes of inflammation cause damage. Unlike Huntington's disease, MS isn't genetically inherited.
- **inflammation** Activation of the immune system, thought to be involved in the HD disease process
- **neuron** Brain cells that store and transmit information
- **BDNF** brain-derived neurotrophic factor: a growth factor that may be able to protect neurons in HD
- Read more definitions in the glossary

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