Is a new Huntington's Disease drug study on the right Trk?

A recent HD animal study reveals that a small molecule drug could be an effective "Trk" to target for HD therapeutics

By Joseph Ochaba | **January 02, 2014** | **Edited by Dr Jeff Carroll**

A recent headline from the Society for Neuroscience (SfN) describes work by Stanford researchers with a drug that "reduces brain changes and motor deficits associated with Huntington's disease." The drug works by mimicking a chemical that acts as brain fertilizer called "BDNF", which has an important job keeping brain cells healthy. While this new drug did improve some symptoms of HD in a mouse, it is still a long way from the clinic. What exactly was found?

What's all the hype actually about?

Scientists know that the symptoms of HD are caused by a genetic mutation that changes the shape of a protein, which they confusingly call **huntingtin**. Changes in the shape of the huntingtin protein seem to make it poisonous, and also make it less effective at doing its normal jobs in the cell.

Neurotrophic factors, like BDNF, act as growth-promoting fertilizers in the brain.

We have known for over a decade that one of the normal jobs of thehuntingtin protein that is to help cells make more of a critical brain nutrient called **brain-derived neurotrophic factor** or **BDNF**. When the huntingtin protein is mutated, one of the consequences is the

brain has lower levels of BDNF - in fact, some scientists believe these low levels ofBDNF and its effects via a receptor known as TrkB (we'll get to this later) contributes to the development of HD symptoms.

Brain Fertilizer

BDNF is what scientists call a **neurotrophic factor**, a chemical (actually a protein, for the geeks!) that helps brain cells grow more quickly and develop stronger connections. These neurotrophic factors are essentially the "Miracle-Gro" fertilizer of the brain.

An interesting feature of BDNF, in particular, is that it is made by cells in the cortex (the intricate and wrinkly, outer part of the brain) it is delivered to cells in the striatum (an deep internal area of the brain). Because the striatum is is most affected part of the brain in HD, this process of cells supporting one another with BDNF delivery is an attractive process to study in HD.

In fact, several previous studies in mice over the years have used various tricks to get the brain to make more BDNF, and these have proved beneficial to some symptoms. This makes sense - HD patients and model mice have low levels of BDNF, so replacing it might help their brain cells stay healthy longer.

Basically, BDNF improves the function of brain cells called neurons, even encouraging new neurons to grow and protecting existing ones from stress and death. When sprinkled on neurons in a petri dish, BDNF causes neurons to sprout and grow the branches required for learning and communication between brain cells, like a happily-fed plant.

> **"Delivering BDNF to the brain is easy in the lab, but really tricky in the clinic. "**

Delivering BDNF to the brain is easy in the lab, but really tricky in the clinic. A tiny mouse brain is pretty easy to pump full of the bulky chemical, but delivering it to big human brains is much harder. This has left scientists a bit stuck - getting more BDNF to the brain would probably help HD, but so far they haven't had the tools to deliver it.

Opening the right lock

Chemicals like BDNF don't just float into brain cells, they act like keys trying to find the right locks to open outside of the cell. In fact, while each cell has thousands of locks sticking out of it, only specific ones can fit the right key. A chemical like BDNF only opens certain locks if it fits in just the right way.

One of the big problems with directly delivering BDNF into the brain is that it has at least two different locks that it can open, that we know of. These different locks (called **receptors** by scientists, and made of protein) are called **TrkB** (pronounced "track-bee") and p75. Each receptor is like a lock that opens doors to different processes within the cell.

Depending on which lock BDNF interacts with, it can open totally different doors and have opposite effects in the cell! For example, when BDNF opens the TrkB lock, a signal is activated in the cell that inhibits a process of cell death. This is good news for the cell!

After BDNF arrives at the surface of a cell it can only have effects if it is received at the appropriate receptor. It works quite a bit like a key fitting into a lock.

However, when BDNF is opens the p75 lock, it opens the door and activates a protein called JNK (pronounced “junk”), which in turn passes the message on to kill the cell. Not such good news!

So, a single chemical signal (BDNF) causes two completely opposing messages inside the cell. This means that the balance between opening the TrkB and p75 locks is really important. In fact, cells with the HD mutation seem to have too many p75 and too few TrkB locks open, an imbalance which could help contribute to early cell death in the HD brain.

Because of the lack of BDNF and altered lock landscape in HD brain cells, scientists have been searching for drugs that could open the TrkB door, without also unlocking the p75 lock. This would be a neat trick, and might also lead to a smaller chemical that more easily gets into the brain.

Are they on the right Trk?

In a recent study, scientists led by HD researcher Dr. Frank Longo in Stanford, California investigated ways to boost the activity of the TrkB receptor in two different types of HD mice. Specifically, Longo’s research group tested the effects of a drug called LM22A-4 which activates the TrkB receptor on nerve cells without activating the p75 receptor.

> **“HD mice given LM22A-4 improved on several motor tasks that researchers use to look at HD movement problems in animals ”**

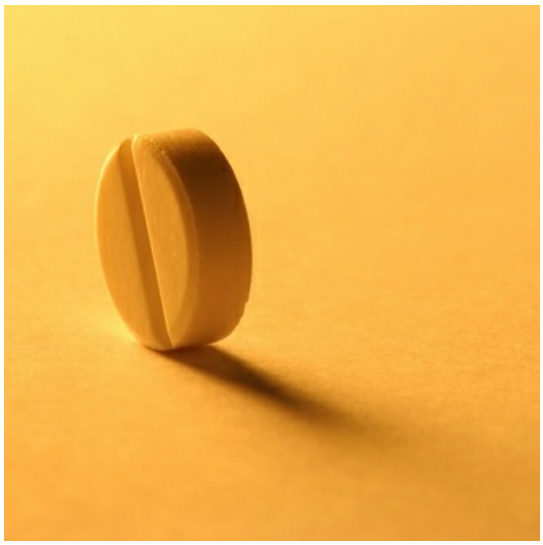
The researchers found that LM22A-4 reached the brain (a great feat for many drug studies!), and also corrected the imbalance of overcharged p75 receptors and underactive TrkB receptors. Treatment of mice with LM22A-4 boosted TrkB activity and also resulted in some improvements of HD symptoms in the brains of treated mice.

Specifically, clumps of mutant huntingtin protein that normally build up in the brain in HD were reduced in LM22A-4 treated mice. The drug reduced inflammation and prevented loss of the structural branches found on cells in the striatum that are affected in HD.

Moreover, HD mice given LM22A-4 improved on several motor tasks that researchers use to look at HD movement problems in animals. They found that mice given the drug could run down a vertical pole faster and demonstrated stronger grip when handing from a wire. However, the drug seemed to have no effect on how well animals ran on a rotating bar (picture a lumberjack trying to stay on a spinning log) or on mouse survival times.

Extra! Extra!

This work reveals a possible enticing new target for HD treatments and highlights the importance of studying BDNF and its partners in HD. As is unfortunately common, the press release headline that put out to announce this work focuses on the positive, and ignores some of the less exciting results of the study.



In the future, a drug that works like LM22A-4 might be able increase brain BDNF levels after swallowing a pill, rather than needing brain-directed gene therapy.

For example, a major result that the press release fails to mention is that the compound did not extend the mouse's shortened life span. We all hope that an effective treatment for HD would prevent early death from the disease! Also, the mice were protected from some, but not all, of the deficits in movement control caused by the HD mutation. In fact, the authors were careful to point out these concerns in their report on the study.

Should we believe the reported improvements, without worrying about the things that weren't improved? This is impossible to say without more animal work, and ideally a human trial of a drug that activates TrkB.

This research provides some support to further study of LM22A-4, or drugs like it, as a possible therapeutic for Huntington's disease. Given how much interest scientists have in BDNF in HD, you can be sure that more work is happening labs around the world to test this

approach and address the concerns raised by this study.

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.

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

Receptor a molecule on the surface of a cell that signalling chemicals attach to

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
