Phosphodiesterase inhibitors: new HD drugs entering trials soon

CHDI and Pfizer announce exciting animal work and plans for a human trial with a drug targeting 'phosphodiesterases'.

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At this year's HD therapeutics conference, Pfizer Pharmaceuticals and the CHDI Foundation announced big plans for new HD drugs that target something called 'phosphodiesterases'. What's so exciting about these new drugs, and what's the timeline for bringing them to people?

Phospho-di-what?

Most people have probably heard of the drug Viagra. However, many would be surprised to discover that the "little blue pill" was originally developed as a treatment for high blood pressure, and only during clinical trials was it discovered to have some - ahem - unexpected side-effects.

Viagra, a widely-used drug for impotence, works as a phosphodiesterase inhibitor

Viagra is just one of a series of drugs called **phosphodiesterase inhibitors** (pronounced foss-foe-die-EST-er-ayze), which have been used to treat a range of ailments such as heart disease and asthma. These drugs all work in similar ways, but have very different effects in the body. They are so variable, in fact, that select phosphodiesterase inhibitors are now being investigated for the treatment of HD.

To understand how phosphodiesterase inhibitors might benefit HD, we must first learn a

little about phosphodiesterases themselves and how they are used by our brains.

Neurons need to connect

Our neurons make it possible for us to think and move by forming many connections with other surrounding neurons, which each have distinct roles in creating and delivering messages to our body. One neuron can form many thousands of connections.

Messages are passed from one neuron to another through chemical signals called neurotransmitters. Like a relay race, when one neuron sends out a neurotransmitter to another neuron, it sets off a series of events that activate the receiving neuron, and prepare it to pass the message along.

Neurotransmitters are called 'first messengers' because they're the first message to arrive, signaling that another neuron has fired off a message. Inside neurons there are 'second messengers', including the chemicals **cyclic AMP** and **cyclic GMP**, which change the receiving neuron's behavior in response to the first message.

This process could be compared to a mailman attempting to deliver a letter. When he knocks on the door, it is answered by a child, so the mailman asks the child to pass the message along to his mother. In this example, the mailman is the neurotransmitter (or first messenger), who passes the message along from outside the house, and it is the child (or second messenger) who passes the message along to his mother from the inside.

The second messengers cyclic AMP and cyclic GMP are critical to brain function. One of the ways they work is by activating and turning off genes through their interaction with 'transcription factors'.

So, even though a burst of neurotransmitter is very brief, by changing the levels of cyclic AMP and cyclic GMP inside the cell, it can leave a lasting imprint on a neuron by interacting with transcription factors and turning genes on or off.

To grow and learn, neurons need to be shaped and moulded according to the messages they receive. Signaling by second messengers is very important for everyday learning and memory. Genes turned on by increased concentrations of second messengers cause connections with other neurons to be strengthened or lost. This flexibility in the strength of connections between neurons enables the formation of new memories and the learning of new tasks.

> **"CHDI and Pfizer have done an enormous amount of work in animals to prove that this drug does interesting things. They've also laid out a very responsible and quick pathway to clinical testing to see if the drug does what we all hope for - an effective treatment for HD "**

Having the right levels of cyclic AMP and cyclic GMP is obviously very important. Neurons that are not able to properly receive and interpret signals will lose their connections, which

can cause them to die.

What about phosphodiesterases in the brain?

And so finally, we reach the important task of phosphodiesterases. Phosphodiesterases deactivate cyclic AMP and cyclic GMP by breaking apart their chemical structure.

Because phosphodiesterases dampen second messenger signals, drugs that block phosphodiesterases -phosphodiesterase inhibitors - allow the buildup of more cyclic AMP and cyclic GMP, strengthening their message.

Normally, having phosphodiesterases active in our brains is a good thing - too much cyclic AMP and cyclic GMP message would lead to over-stimulation of neurons. And when it comes to chemicals in the brain, we must always maintain a fine balance.

The striatum, garbled messages and new hope

In HD mouse models, researchers have found that the levels of cyclic AMP in the striatum are lower than in normal mice. That may explain why this brain region is particularly sensitive to the effects of Huntington's disease.

Although neurotransmitters may be sending the correct messages to vulnerable cells of an HD-affected brain, low levels of second messengers might mean those cells can't interpret the information correctly.

A team of scientists at CHDI, led by Dr Vahri Beaumont, are very interested in measuring neuronal communication. Rather than waiting around for neurons to die, they reason, it's better to design tests for changes in how neurons talk to one another.

Working with specialists in measuring the communications between neurons, Beaumont and her team have developed tests that accurately measure the communications between neurons. Having established these tests, they've shown that communication between neurons is distinctly altered in HD brains, especially in the striatum - the region of the brain most vulnerable in HD.

Messages between neurons are communicated to the outside and inside of the cell by neurotransmitters and second messengers, like a mailman dropping off a message with a child to be delivered to mom inside.

Their consistent finding is that vulnerable neurons in the striatum of HD mice are ‘restless’ and too excitable.

New human drug trial on the way

To try and combat this hyper-excitability, CHDI launched a collaboration with Pfizer, the international pharmaceutical giant. Pfizer has well developed drugs that work as phosphodiesterase inhibitors, including Viagra, so they have a lot of experience which could prove useful for solving this problem.

One of Pfizer’s phosphodiesterase inhibitor drugs, called TP-10, blocks a particular form of phosphodiesterase found at higher levels in parts of the brain that are vulnerable in HD.

When HD mice were treated with TP-10, the results were very encouraging. Not only did the researchers observe an overall benefit to the motor skills of the mice, but they also saw less neuron loss in the striatum.

At the annual HD Therapeutics Conference, Pfizer and CHDI announced their joint efforts to testing TP-10 and a related drug in people. They are currently finishing animal studies, and plan several pilot studies in people in 2012 and 2013.

These preliminary studies are important to ensure that the drugs get where we think they should, and that they do what they’re supposed to do when they get there. If all goes as planned, look for a 6 month human study in late 2013 designed to try and prove that these drugs work in HD patients.

This is a very exciting development. CHDI and Pfizer have done an enormous amount of work in animals to prove that this drug does interesting things. They’ve also laid out a short but sensible pathway to clinical testing, to see if the drug is what we all hope for - an effective treatment for HD.

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

GLOSSARY

Phosphodiesterase a protein that breaks down cyclic-AMP and cyclic-GMP

transcription the first step in making a protein from the recipe stored in a gene. Transcription means making a working copy of the gene from RNA, a chemical messenger similar to DNA.

therapeutics treatments

neuron Brain cells that store and transmit information