

## Anti-nausea drug helps cells with the HD mutation stay healthy in a surprising way



Anti-nausea drug meclizine protects cells with the HD mutation from death by reducing cellular energy production

By Dr Jeff Carroll on February 04, 2011

Edited by Dr Ed Wild

*The connection between cellular energy levels and HD is more complicated than we previously thought, but in a way that opens a door to more possible treatments. It seems drugs that actually slow down the production of energy can rescue cells with the HD mutation from dysfunction and death.*

### Energy in HD

Energy is a big problem in HD. One of the most common symptoms in people with HD is weight loss: the emaciated facial features of HD patients are immediately recognizable to many HD family members. Surprisingly, not much is known about how and why this happens. HD patients generally eat as much as people without HD, if not more, but they have a hard time keeping on weight. So it seems that the problem is not getting enough calories, but some problem with using the energy they consume.

Scientists are beginning to understand that one of the jobs of the huntingtin protein is to regulate energy production within cells. Dr Marcy MacDonald's group of researchers have shown that in blood cells from HD patients, longer CAG repeats in the huntingtin gene go along with lower total energy levels. That's important, because longer CAG repeat counts tend to produce an earlier age of onset of the disease.

Because of that link between CAG repeats and energy, researchers have been looking at whether bolstering energy levels might be helpful in HD. Several trials underway, including those with creatine and coenzyme Q10, are based on the idea that increasing energy levels in HD will be helpful.

But symptoms in HD are complex - it can be difficult to figure out which symptoms are causing the disease, and which symptoms are the body's attempts to deal with it. It's a bit like having a fever - it's not comfortable, but it's one way the body fights infections. So, are reduced energy levels in HD causing the disease, or something the body is doing to cope with another problem



Energy usage by cells is disrupted in HD – but is that a problem or the body's solution?

we don't understand?

## Could reducing metabolism be good for cells with the HD mutation?

A surprise came about two years ago, when a team of researchers working with Dr Brent Stockwell at Columbia university were looking for drugs that rescue cells with the HD mutation from dying. They found that drugs that slow down metabolism, or energy production, made cells with the HD mutation healthier.

That caused some confusion - energy levels are low in cells with the HD mutation, and many HD patients take drugs aimed at increasing their energy levels. Despite this, Stockwell's team suggested that or slowing down metabolism can protect cells with the HD mutation. Could this be true?

Vamsi Mootha, working with Vishal Gohil and others, has been working to understand the situation. Energy levels are also important in conditions like heart attack and stroke, where important cells are not getting enough oxygen. Previously, Mootha has shown that a compound called meclizine protects heart cells from damage caused by lack of oxygen.

Meclizine works, in part, a bit like the way Stockwell's compounds worked, so he tested it in another HD cell model. Meclizine does turn out to protect cells with the HD mutation from dying, and it does so by slowing down their metabolism, in agreement with Stockwell's data.

It's not clear if the effects observed by Stockwell and Mootha will translate from cells to HD patients. In order to improve on simple cell models, Mootha examined the effects of Meclizine in worm and fly models of HD. These animal models showed some improvements when treated with Meclizine, but additional studies in mice or rats would be beneficial. Rodent studies take more resources and time to conduct, which is why scientists often study shorter-lived organisms like flies and worms first.

## Now what?

This set of unexpected findings demonstrates why we have to be very careful with drug development in HD. On the surface, it's easy to look at a problem like low energy levels and conclude that increasing energy levels would help. But, if we dig below the surface, the picture becomes more complex. It's still not clear what aspect of metabolism is damaging cells with the HD mutation, or how it's helped by Meclizine, but you can be sure that these scientists are trying to figure it out.

An interesting twist to the story is that Meclizine is already an approved drug - but not for HD. It's an anti-nausea drug that's available over the counter in many countries. It's too early for anyone to take any drug based on this research, but it's heartening to see that researchers are trying to

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use drugs in their scientific studies that could quickly translate to use in humans, once we understand them better.

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*Jeff Carroll works as a post-doctoral fellow in the lab of Marcy MacDonald, mentioned in this story. His project involves understanding metabolic alterations in HD. At the time of writing, he does not work with Meclizine or any of the other researchers mentioned directly. For more information about our disclosure policy see our FAQ...*

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## Glossary

**huntingtin protein** The protein produced by the HD gene.

**CAG repeat** The stretch of DNA at the beginning of the HD gene, which contains the sequence CAG repeated many times, and is abnormally long in people who will develop HD

**metabolism** The process of cells taking in nutrients and turning them into energy and building blocks to build and repair cells.

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