Special 'brain fat' injection helps HD mice

Directly injecting the brains of HD mice with a good type of fat called ganglioside GM1 provides dramatic benefit

By Dr Jeff Carroll | February 14, 2012 | Edited by Professor Ed Wild

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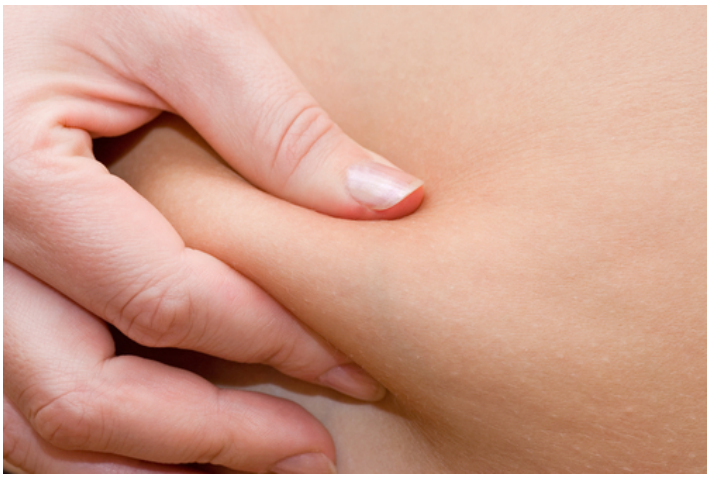
The human brain is enriched in many different types of fat. Some of these greasy molecules are reduced in HD, and a new study demonstrates that replacing one specific type, called ganglioside GM1, leads to dramatic improvements in the behavior of HD mice.

Fat molecules and the brain

'Fat' is a broad word with a bad reputation. But the word basically describes any greasy substance in cells and the body. The biology of fat is actually quite complicated - there are a number of different types of fat that have special roles, particularly in the brain.



Fat - it's not all bad news! Ganglioside fat molecules are one type of fat that's good for the brain

The brain relies heavily on fat for its normal function. Like electrical wires, the projections of the brain are coated with an 'insulator' that helps signals travel long distances without being lost. The insulators that surround these projections in the brain are made of fat - so, far from being a bad thing, fat is critical to normal brain function.

Gangliosides in HD

In 2010, one interesting type of fat called **ganglioside GM1** was shown to be reduced in HD patient cells and brains by a group lead by Simonetta Sipione at the University of Alberta.

'Gangliosides' are special types of fat that act, not just to insulate our brains' wiring, but to signal important messages themselves. We know that gangliosides are important, because terrible childhood diseases result from genetic mutations that affect the body's normal handling of them.

Brain problems are a common feature of the diseases caused by mutations affecting gangliosides, suggesting that whatever roles gangliosides play, they're critically important to brain function. When Sipione and her colleagues observed reductions in ganglioside GM1 they were left with a question - could replacing these important fats help with HD?

GM1 replacement

To address this question, Sipione and her team turned to mice carrying a mutant copy of the human HD gene. These mice develop symptoms, particularly movement problems, that might be similar to symptoms in HD patients. Like HD patients, these mice also have reduced levels of ganglioside GM1.

The simplest possible way to replace something that's missing is to just inject it, and that's just what this team of scientists did. To focus on the role for gangliosides in the brain, Sipione's team used tiny pumps to deliver GM1 directly into the brains of mice for 4 weeks. They were able to measure the levels of GM1 in the brain and determine that this approach was successful - levels of GM1 increased to normal after infusion.

The mice got better

So, did this replacement therapy work? Yes - and surprisingly well, judging by the observed improvements in the behavior of the mice. The mice were injected with GM1 at 5 months of age - while young for a human, this is about middle age for a mouse. By this stage, the mice already had problems with coordination, and infusion with GM1 led to a total reversal of these problems. The team used several different tests to understand how the behavior of the mice has improved, and the treated mice aced all the tests.

This is exciting stuff - many treatments in HD mouse models are begun at an early age, before any symptoms start. This would be much harder to do for humans because ethical and safety concerns make it very difficult to imagine treating HD mutation carriers from birth. Treating animals after they already have symptoms of disease is much more relevant for understanding what might happen if we tried this in humans, but surprisingly most animal trials are not run this way.

Mice treated with GM1 showed much better coordination when tested on a 'rotarod' apparatus

How did it work?

Because we don't fully understand all the jobs performed by gangliosides in the brain, it's hard to say precisely why GM1 injections were so beneficial. But Sipione and her team were curious to know if there were any changes to things that we do understand that might explain the observed benefits.

The huntingtin protein, mutated in HD patients, is modified in cells after it is made. One of the ways it's modified is tagging the protein with small chemical labels that can change where the protein goes within the cell, as well as other, less well understood, effects.

To help understand the GM1 results, Sipione turned to Ray Truant, an expert on these types of modification of the huntingtin protein at McMaster university. The two teams looked at two specific 'addresses' within the huntingtin protein, called S13 and S16. We know that adding 'phosphate' tags at these spots makes the mutant huntingtin protein much less toxic.

In agreement with the idea that more phosphoryation at these two sites is good news, Sipione's team found more phosphorylation in mice treated with GM1. This gives some pointers to scientists as they try to understand the mechanism that GM1 uses to protect cells.

Human potential

The result from Sipione and her team is very exciting, but could it lead to trials in humans? Generally, it's very difficult to project how well these kinds of studies will 'translate' from animals to humans, but in this case there are some good signs.

First, GM1 has been used in humans in clinical trials with a good safety record. Simple safety is a huge hurdle for many drugs. Furthermore, in a small trial of 5 patients GM1 has actually been infused into the brains of Alzheimer's Disease patients for 1 year with no major adverse events. This type of brain delivery is tricky, so it's good news that GM1 seems well tolerated after this kind of direct infusion.

These are very early days for GM1 as a therapy for HD - many steps remain if it is to be tested in human patients. But the level of improvement of the mice is striking, and we should look forward to future studies on the potential role of GM1 as a therapy in HD.

Dr Ray Truant, mentioned in the text, is the external scientific advisor of HDBuzz. Dr Truant had no input into the writing or editing of this article. For more information about our disclosure policy see our FAQ...

GLOSSARY

huntingtin protein The protein produced by the HD gene.

Ganglioside a type of fat with important roles in the brain, decreased in HD patient brains