CHDI Report: Day 2

Day 2 of CHDI's HD therapeutics conference: figuring out energy problems in HD

By Dr Ed Wild | **February 09, 2011** | **Edited by Dr Jeff Carroll**

Our second daily report from CHDI's annual HD therapies meeting in Palm Springs, devoted to problems with energy generation and chemical pathways … and ways we might be able to fix them

Bio-ener…whatnow?

Wednesday 9th February at the CHDI Therapeutics Meeting was all about 'bioenergetics' and 'metabolism'. That's science-speak for how the body uses the nutrients from food to produce energy and stay alive, enabling its organs (like the brain) and cells (like neurons) to carry out their special functions.

Leticia Toledo-Sherman of CHDI outlined the Foundation's strategy for developing drugs to aimed at improving metabolism in HD

Image credit: Gene Veritas

Bioenergetics and metabolism are important topics in HD because we know that they start to be abnormal in people with the HD gene from quite early on in the disease, and there's a relationship with the length of a person's CAG repeat and the energy level in cells - whether they have an abnormal HD gene or not.

There's one more bit of jargon we need to explain before we dive in, and that's ' mitochondria'. Mitochondria are tiny machines that sit inside our cells, processing fuel into energy to enable the cells to do stuff. Because they're so important for bioenergetics, mitochondria featured in all today's talks.

The bioenergetics lowdown

The first presentation, by **Timothy Greenamyre** from the University of Pittsburgh was a comprehensive overview of what we know about mitochondria and HD. He pointed out that the brain uses way more than its fair share of the body's total energy, and that deliberately poisoning the mitochondria of mice can make them look a lot like mice with the HD mutation. Greenamyre described his team's findings looking at calcium (famous for being good for healthy bones and teeth) and mitochondria in HD. Healthy mitochondria can store lots of calcium but in HD, mitochondria can't store as much calcium and they don't hold their electrical charge as well either. Greenamyre's pretty sure the abnormal huntingtin protein is to blame for the mitochondrial problems in HD, but it's not totally clear which abnormalities are dangerous and which are the body's way of coping with the problems the HD mutation causes. Finding drugs that return the mitochondria to normal is likely to help answer these questions.

> **"**We're pretty sure the abnormal huntingtin protein is to blame for the mitochondrial problems in HD "

Next, **Hoby Hetherington** of Yale University introduced a new way of using magnetic resonance imaging scanners to look at metabolism and energy in the brain. The technique is called MRSI, which stands for magnetic resonance spectroscopic imaging. The scanner has a magnet so powerful it can cause atoms to vibrate, and it then detects those vibrations to produce a map of what chemicals are found in hundreds of different parts of the brain. Hetherington's research so far has been in epilepsy, where subtle chemical changes can signal that a part of the brain may be responsible for seizures. But the technique, if used in HD, could be really useful for figuring out the energy problems in people with the HD genetic mutation and, importantly, finding out whether metabolism-altering drugs are having the effect we want.

Mitochondria don't just sit inside cells churning out energy - they are surprisingly active, splitting in half, joining up with other mitochondria and moving around the brain within neurons. **Sarah Berman** from the University of Pittsburgh presented her study of mitochondrial behavior in another neurodegenerative disease, Parkinson's. Berman has developed a system for studying mitchondria in neurons. First she alters all the mitochondria so that they shine red, then makes individual mitochondria glow green by firing a laser them. Using this technique, she can tell whether they're joining up, splitting or just passing each other. She's found that drugs that interfere with the energy producing functions of mitochondria also alter their movement, joining and splitting. She's now studying the proteins that are sometimes abnormal in Parkinson's disease, to see where they fit into the picture, and her techniques could prove very helpful for explaining the mitochondrial and energy problems in HD.

Given all these problems with energy and the mitochondria in HD, is there anything we can do about it? **Leticia Toledo-Sherman**, a chemist with CHDI, explained the organization's efforts to making drugs to alter energy metabolism in HD. Her team is making drugs that block a protein called 'pyruvate dehydrogenase complex kinase' or 'PDHK'. PDHK changes how the mitochondria

inside cells are fed by nutrients from the rest of the cell. She showed evidence that cells with the HD mutation are less efficient at feeding their mitochondria fuel to turn into energy. The PDHK protein regulates this process, and her team thinks that if there were a way to block what it's doing, it might make HD symptoms better. They're well on the way to developing an effective drug to block PDHK that works in the brain. Once they've done this, they'll test it in HD mice to see if it helps their HD symptoms. They hope to do this by the second half of 2011.

Featured speaker

CHDI's therapies meeting brings together HD researchers from round the world

Image credit: Lev Blumenstein

The final talk of the evening was by the eminent neuroscientist **Sol Snyder**, from Johns Hopkins university in Baltimore. In a series of papers over decades from the 1960's to the present, Dr. Snyder has unraveled a number of the basic ways that neurons work, including the discovery of how nitrous oxide, which is actually a gas, changes how neurons fire. Sol has recently been interested in HD, especially after his lab discovered a protein called 'Rhes'. Rhes sticks to the huntingtin protein, and it sticks more strongly when huntingtin is mutated. What's interesting is that this Rhes protein is mostly found in the parts of the brain that are most vulnerable to dying in HD. The question of why different brain regions are selectively vulnerable in HD is still a big mystery - it's the "800lb gorilla in the room", as Snyder explained. He believes that Rhes might be a crucial part of the puzzle.

Sunset Conclusions

Energy and metabolism are important issues in HD and today's sessions highlighted how teams of scientists can share their experiences in HD, and other diseases, to improve our understanding of the problems in HD, and come up with imaginative ways to overcome them. That spirit of working together towards a common goal is what gives the global research community a fighting chance of finding effective treatments for HD.

Dr Carroll and Dr Wild have conducted scientific HD research sponsored by CHDI but have received no honoraria outside that scientific funding. Their attendance at the CHDI conference is supported by the European HD Network, an independent network of HD professionals, from funds entirely independent of CHDI. For more information about our disclosure policy see our FAQ...

GLOSSARY

Parkinson's Disease A neurodegenerative disease that, like HD, involves motor coordination problems

magnetic resonance A technique using powerful magnetic fields to produce detailed images of the brain in living humans and animals

huntingtin protein The protein produced by the HD gene.

neurodegenerative A disease caused by progressive malfunctioning and death of brain cells (neurons)

therapeutics treatments

mitochondria tiny machines inside our cells that process fuel into energy, enabling cells to function

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.

neuron Brain cells that store and transmit information

kinase A protein whose job it is to add a specific kind of chemical tag to other proteins. Kind of like a stapler.

Rhes a protein found in the brain regions damaged early in Huntington's disease.
