HDBuzz

Huntington's disease research news. In plain language. Written by scientists. For the global HD community.

Sheep leading the flock: metabolism and biomarkers in HD

Sheep can help us to identify HD biomarkers and recognize metabolic changes that occur before symptoms develop.

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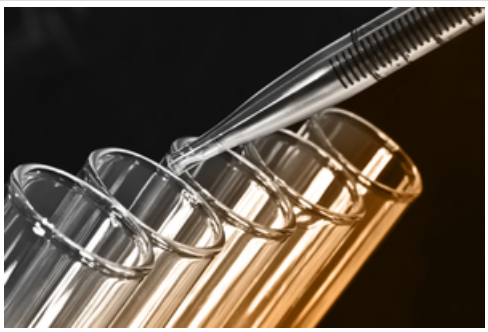
Beyond affecting movement, mood, and thinking, HD involves a complex set of changes to the body that can be difficult to predict in different individuals. Recently, researchers were able to identify consistent early changes in metabolism by studying a group of HD sheep. This large animal model is helping scientists to track altered substances in the blood that could predict HD progression and response to treatment.

Disrupted metabolism in HD

People with Huntington's disease often experience extreme weight loss, also known as cachexia. Alongside excessive movements, cachexia is one of the best-recognized signs of HD, but it has historically been a challenge to explain. Initially it was believed that the constant repetitive motions of chorea burned excess energy, or that increasing difficulty eating and swallowing led to weight loss. However, detailed chemical analysis of tissue and blood samples from patients and model organisms has led to newer theories about weight loss in HD. In fact, cachexia involves a complex set of changes to cellular metabolism, meaning that HD affects the body's ability to transform food into energy.



Tracking a group of key metabolites in the blood over a 24-hour period could predict a sheep's disease status.

Tracking metabolic changes in HD is an important pursuit, in part because it may help us to combat weight loss. Furthermore, studying the effects of HD outside the brain could reveal novel biomarkers, measurements that can be used to predict HD progression. Biomarkers can make diagnostics and drug testing easier and more reliable, especially when detectable in the blood. They can also help us understand how HD impacts many facets of life, including energy, appetite, and sleep. Recently, researchers in the UK and Australia analyzed the blood of a remarkable animal model: Huntington's disease sheep. Their findings revealed surprising differences in normal and HD sheep that add to our understanding of altered metabolism in HD, and contribute to the ongoing hunt for HD biomarkers.

Measuring metabolites to track HD

As cells break down the sugars, proteins, and fats in food, nutrients are converted into fuel. This process generates thousands of individual substances, known as *metabolites*. Because many metabolites circulate in the blood or the fluid that bathes the brain, measuring their levels is a common way to study metabolic changes. Researchers can perform a *metabolomics* study in which they simultaneously measure hundreds or thousands of metabolites in blood, cerebrospinal fluid (CSF), or tissue. By comparing samples from healthy individuals and HD patients, we can better understand which types of changes are associated with disease.

From these studies, we have learned that many metabolites are disrupted in HD, but unfortunately, the experimental data are often inconsistent. Metabolites can vary greatly between individuals and even within the same person. Levels can change based on the time of day, how recently the person ate or slept, their stress levels, and the contents of their last meal. In people, these factors are extremely difficult to control. Unless participants were to live round-the-clock at a study center for months on end, eat exactly the same diet, and sleep on precisely the same schedule, it would be difficult to determine which metabolic changes were caused by HD, and which by other factors.

As with many biological questions, scientists usually overcome this challenge by studying laboratory mice, which can be fed and housed in an extremely controlled way. The down side is that rodents process food and energy quite differently from humans. For example, they have some dissimilar metabolites, their metabolic rate is much higher, and – fun fact – they can't vomit to get rid of toxins. This certainly doesn't exclude mice from metabolic research, but in the search for biomarkers, HD researchers wanted to make use of a bigger and potentially more relevant model.

HD sheep

It's been a while since we reported on the sheep model of Huntington's Disease. Professor Jenny Morton at the University of Cambridge helped to champion the use of genetically modified sheep to study HD. Morton also headed the recent study on their metabolites, along with researchers in the UK, Australia, and the Netherlands. If you're wondering "why sheep?" the answer is multifaceted. First, a sheep's brain and body is much closer to the size of a human's, and its chemical makeup is similar. Sheep are capable of learning complex behavioral tasks, and they are not expensive to maintain if you have the space (hello, Australia). Most importantly, during a metabolic study, a sheep's food, housing, exercise, and sleep schedules can be very carefully controlled. Each sheep can be fitted for special equipment to collect blood samples over a whole day and night without disturbing them too much.

The HD sheep studied in this experiment were 5 years old. The lifetime of a sheep can vary a lot depending on surroundings, diet, and care, but Morton estimates that 5 years is roughly one third of a natural lifespan. Since the model was created nearly a decade ago, she and her team have thoroughly tested many aspects of their biology, brain activity, and behavior. So far, the sheep are considered to be presymptomatic: they haven't shown signs of developing HD, with the exception of disrupted sleep cycles and very minor changes to the brain.

Early metabolic changes in HD sheep

To examine differences in metabolism between HD and normal sheep, researchers collected blood samples frequently for 24 hours, then checked the levels of 130 metabolites. Surprisingly, even though the HD sheep have not shown other signs of illness, the levels of many metabolites were abnormal.

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In particular, the findings suggested problematic changes to an important metabolic process known as the urea cycle. The urea cycle removes a toxin called ammonia that is normally produced when proteins are broken down for energy. In a series of steps, cells must convert toxic ammonia into the less toxic urea, which can leave the body in the form of urine. To see whether the urea cycle is functioning properly, researchers can measure levels of urea and other metabolites formed during the intermediate steps. Two examples are citrulline and arginine, protein building blocks known as amino acids. Morton and colleagues found that citrulline, arginine, and urea were increased in the blood of the 5-year-old HD sheep compared to normal sheep. This suggests that the urea cycle is disrupted in presymptomatic HD.

Arginine and citrulline are also tightly connected to the production of nitric oxide, a molecule that plays a role in cell-to-cell messaging and blood circulation. The researchers were not able to measure nitric oxide directly in this study, but it will be an important step in the future. Interestingly, nitric oxide and urea cycle disruptions have recently been identified in HD mouse models. There is also evidence that mutant huntingtin might contribute to impaired breakdown of amino acids. Another set of dysregulated metabolites were sphingolipids, fatty substances that help to form the protective barrier surrounding nerve cells. HD sheep had lower levels of sphingolipids in the blood, which could be an early indication of brain degeneration or dysfunction.

Using metabolites as biomarkers

So could one of these dysregulated metabolites be used as a biomarker in people? Not exactly. Measuring a single blood metabolite is unlikely to be a useful way to track disease progression or recovery. However, tracking a group of key metabolites over a 24-hour period could predict a sheep’s disease status, Morton and colleagues discovered. They used complex math to identify a set of 8 substances in the blood that could be monitored together to distinguish between the normal and HD sheep. Based on levels of all 8 metabolites, they could correctly predict 80% of the time whether a sheep had the HD gene. In short, with careful and controlled monitoring, the researchers found a group of sheep metabolites that change consistently in presymptomatic disease.

This is approaching the first of three main goals of research on biomarkers: (1) to find a change that reliably occurs in the body during HD, (2) to see if the change becomes more drastic over time, and (3) to determine whether a medication can correct the change or slow it down. With further improvement and validation in people, this method of combining multiple blood metabolites could be useful in the future to understand whether a treatment might be slowing progression of HD.

Where do we go from here?

This study contributes to a growing body of knowledge about the specific metabolic processes that might go awry in HD, like the urea cycle, nitric oxide messaging, and the cushioning around brain cells. It also suggests a potential method for using a group of metabolites to reflect an overall state of disease. However, it's important to remember that levels of metabolites in the blood (or even in spinal fluid) don't necessarily correspond directly with the health of the brain. Nevertheless, studying the presymptomatic HD sheep continues to provide clues to the origins of metabolic symptoms like cachexia. Currently, Morton and colleagues are studying how age and gender affect levels of metabolites, and whether the changes persist over time. As the sheep move towards middle age, they may also begin to reveal valuable information about HD brain pathology and behavior.

As with all animal research, one major caveat is that the results need to be confirmed in people. In the case of metabolic research, that means finding ways to collect samples and examine metabolites under controlled conditions. It's difficult to account for the many ways people eat, sleep, and spend their days, but there are still concrete ways to decrease the variability of human data. For example, there are ongoing initiatives to help ensure that individual samples of blood, spinal fluid, or tissue are collected from HD patients in standard ways all over the world. In parallel, large animal models like sheep can help us to explore potential biomarkers and develop the methods to use them when new treatments arise.

Professor Jennifer Morton has previously contributed articles to HDBuzz. She was not involved in the decision to write this story, its drafting or editing. For more information about our disclosure policy see our FAQ...

Glossary

CSF A clear fluid produced by the brain, which surrounds and supports the brain and spinal cord.

Metabolomics the simultaneous measurement of many metabolites in a sample

amino acid the building blocks that proteins are made from

Metabolite a chemical produced by cells as they break down fuels for energy

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

biomarker a test of any kind - including blood tests, thinking tests and brain scans - that can measure or predict the progression of a disease like HD. Biomarkers may make clinical trials

of new drugs quicker and more reliable.

chorea Involuntary, irregular ‘fidgety’ movements that are common in HD