A faulty filter? Blood vessel changes in Huntington's disease

New research reveals blood vessel changes that could contribute to problem in HD

By Melissa Christianson | May 13, 2015 | Edited by Professor Ed Wild

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Because brain cell death drives symptoms in Huntington's disease, these cells steal the spotlight in disease-related research. But new research on the brain's blood supply has uncovered changes in HD that could be making it harder for the brain cells to cope with the disease.

Driven by What's Inside

Huntington's disease is caused by a small change in the Huntingtin gene, just one of the 25,000 genes that make up human DNA. This small change makes the gene extra-long, which causes a lot of problems for cells of the body – especially brain cells. Brain cells are so delicate that even this single change makes them get sick and die, thereby causing the symptoms of Huntington's disease.

The brain is like an engine controlling a car: it is critical for making the car run, but it actually can't do much without the rest of the car.

Image credit: Freelmages

Because brain cell death drives the development of Huntington's symptoms, it makes sense that most research on the disease – and how we might fight it – focuses on these cells. However, it is important to remember that **brain cells do not exist in isolation**. Not only are they surrounded by helper cells that keep them healthy, they also interact closely with many systems of the body. For example, all brain cells rely heavily on the body's blood supply or 'vascular' system to provide them with nutrients like sugar and oxygen and to take

away their waste products.

Instead of considering the brain as an isolated organ in the body, therefore, it is more accurate to think of the brain like an engine that controls a car. The engine is critical for making the car run, but it actually can't do much if it's isolated on its own. Instead, it requires help from other car systems, like the fuel lines or the electrical system, to make just about anything happen. In exactly the same way, the brain requires the help of the body's internal systems to function properly and keep things running smoothly.

Thus, although brain changes are an important part of Huntington's disease, understanding them without the context of the rest of the body probably won't provide the complete picture we need to identify effective disease treatments.

Built to Protect

Because brain cells are so delicate, interacting with the rest of the body's systems is actually quite dangerous for them. This poses a problem for the way the brain and blood interact. Although brain cells desperately need the nutrients provided by the blood, that blood is chock full of hazards like chemical toxins, immune system cells, and other dangerous contaminants that could easily damage and kill brain cells.

So what's the brain to do?

It has solved this problem by developing a special, aptly-named shield known as the**blood-brain barrier**. The blood-brain barrier protects the delicate cells in the brain from hazards in the blood and the rest of the body.

You can think of the blood-brain barrier like the fuel filter in a car. Just like the fuel filter lets through gasoline but keeps out contaminants that would damage the engine, the blood-brain barrier lets through nutrients but not hazards that would damage the brain.

So, the blood-brain barrier and the blood supply it allows into the brain are really important for keeping brain cells healthy. They consequently have a lot of power to influence brain cell survival. Surprisingly though, little is known about whether – and how – they change in Huntington's disease.

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Start Your (Research) Engines

To fill in this knowledge gap, scientists at Université Laval in Quebec designed a series of experiments to examine what happens to the vascular system and blood brain barrier in Huntington's disease.

To do so, they carefully studied these two systems in both humans with Huntington's disease and a mouse model of the disease in which the normal Huntington's gene was replaced with an extra-long copy. This sort of dual-armed, species-bridging approach is powerful, because it allows scientists to ask very thorough questions about the things they're testing.

Like humans with Huntington's disease, the Huntington's mice develop decreased body weight as well as progressive movement and thinking problems as they age. These mice provide a pretty good model of the vascular system and blood-brain barrier. Using them in this study therefore provides a handy way to ask and answer questions that would be difficult or unethical to ask in humans.

Break Through: What Did They Find?

Using this dual-armed approach, the scientists discovered three striking pieces of information.

First, they found clumps of the Huntington's protein stuck together inside cells that make up the blood vessels and blood-brain barrier. These clumps are exactly the same type of clumps that occur in – and poison – brain cells in HD. This suggests that, just like brain cells, the brain's primary fuel line is threatened by the genetic change causing Huntington's disease.

Second, the scientists found that organization of the blood vessels that supply the brain are altered in Huntington's. In both humans with Huntington's and mice modeling the disease, there were many more blood vessels than normal, but these blood vessels were small.

Given that the little three-pound lump of brain sitting in the average human skull uses 20% of all the oxygen and 25% of all the sugar carried by the blood, even small changes in blood supply lines could affect how the brain functions.

The brain's shield, known as the blood brain barrier, begins to leak in Huntington's disease - so it no longer protects the brain as effectively.

Image credit: FreeImages

Finally, and perhaps most importantly, the scientists found that the blood-brain barrier in Huntington's disease was altered enough to make it leaky. Leaks are never a good thing – just ask a politician. A leaky blood-brain barrier is a huge problem, because it won't effectively protect the brain from hazards in the blood. Just like a leaky fuel filter allows gasoline contaminants in to damage the engine, a leaky blood brain barrier could let blood hazards in to damage the brain.

Shift(ing) Expectations: What Does it All Mean?

Together, these three new pieces of information reveal a consistent pattern of changes in the vascular system and blood-brain barrier – important pieces of kit that fuel and protect the brain. These changes happen as a consequence of the disease, not just because brain cells are already dying, so they could influence brain cell survival very early in the disease.

Although scientists don't yet know specifically how these changes affect brain cell survival in Huntington's disease, they suspect that the effects are not good. Similar changes in the vascular system and blood-brain barrier occur in other diseases associated with brain cell death, like Alzheimer's and Parkinson's disease, and so it is likely that blood flow or blood-brain barrier changes put brain cells at risk of dying.

Put together, the new findings provide solid evidence that the brain changes driving symptoms of Huntington's disease are not happening in isolation – and are in fact accompanied by important changes outside of the brain.

Moving Forward: What Does It Mean for Us?

Although the research described here does not directly develop drugs or therapies for Huntington's, it is valuable because it poses answerable questions that help us understand what happens in the disease. Every bit more we understand about the disease improves the search for better and more effective therapies.

What's more, this work provides an important reminder that Huntington's disease affects more than just the brain. For Huntington's treatments to be maximally effective, therefore, we may need therapies that protect not only brain cells but also cells in other parts of the body.

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

GLOSSARY

blood-brain barrier A natural barrier, made from reinforcements to blood vessels, that prevents many chemicals from getting into the brain from the bloodstream

Vascular system the vessels and/or tissue that carry fluids like blood throughout the body

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