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Protecting the brain from a deadly genetic disease

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Huntington's disease (HD) is a cruel, hereditary condition that leads to severe physical and mental deterioration, psychiatric problems and eventually, death. Currently, there are no treatments to slow down or stop it. HD sufferers are born with the disease although they do not show symptoms until late in life. In a new study published in The *Journal of Neuroscience*, Stephen Ferguson and Fabiola Ribeiro of Robarts Research Institute at The University of Western Ontario identified a protective pathway in the brain that may explain why HD symptoms take so long to appear. The findings could also lead to new treatments for HD.

The symptoms of Huntington's disease are caused by cell death in specific regions of the brain. Patients who have HD are born with a mutated version of the protein huntingtin (Htt), which is thought to cause these toxic effects. While researchers know HD results from this single, mutated protein, no one seems to know exactly what it does, why it does not cause symptoms until later in life, or why it kills a specific set of brain cells, even though Htt is found in every single cell in the human body.

Ferguson and Ribeiro used a genetically-modified mouse model of HD to look at the effects of mutated Htt on the brain. "We found there was some kind of compensation going on early in the life of these mice that was helping to protect them from the development of the disease," says Ferguson, director of the Molecular Brain Research Group at Robarts, and a professor in the Department of Physiology & Pharmacology at

Western's Schulich School of Medicine and Dentistry. "As they age, they lose this compensation and the associated protective effects, which could explain the late onset of the disease."

Ferguson adds that metabotropic glutamate receptors (mGluRs), which are responsible for communication between brain cells, play an important role in these protective effects. By interacting with the mutant Htt protein, mGluRs change the way the brain signals in the early stages of HD in an attempt to offset the disease, and save the brain from cell death. As a result, mGluRs could offer a drug target for HD treatment.

Because HD is a dominant genetic disease, every child with an affected parent has a 50 per cent chance of inheriting the fatal condition. This research, funded by the Canadian Institutes of Health Research, sheds light on the onset of HD and the potential role of a mutant protein in patients, paving the way for the development of new drug therapies.

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