Sentry enzyme blocks two paths to Parkinson's disease

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The degeneration of brain cells that occurs in Parkinson's disease may be caused by either externally provoked cell death or internally initiated suicide when the molecule that normally prevents these fatal alternatives is missing, according to studies in mouse models by investigators at St. Jude Children's Research Hospital.

Parkinson's disease is a disease in which nerve cells in part of the brain called the substantia nigra die, resulting in the loss of dopamine, a nerve-signaling molecule that helps control muscle movement. The absence of dopamine from these cells, called dopaminergic neurons, causes a loss of muscle control, trembling and lack of coordination.

The molecule that prevents damage to the substantia nigra is an enzyme called GST pi ("pie"). This molecule stands like a sentry at the crossroads of several biochemical pathways, any one of which can lead to Parkinson's disease, the researchers reported in an article in the Feb. 1 early online edition of *Proceedings of the National Academy of Sciences*.

The job of the antioxidant GST pi is to protect the cell from death caused by either environmental toxins (externally evoked cell death), such as herbicides and pesticides, or a self-destruction process called apoptosis (cell suicide), triggered by certain stressful conditions in the cell. If GST pi levels are reduced or this enzyme is overwhelmed by toxins, these nerves are at increased risk of death. Previous research has shown that the ability of GST pi to protect cells against toxic molecules is directly linked to the ability of cancer cells with excessive amounts of

this enzyme to reduce the effectiveness of chemotherapy.

The finding that GST pi plays a key role in preventing Parkinson's disease suggests that measuring levels of this enzyme might be an effective way to determine individuals at risk for developing this disease, according to Richard Smeyne, Ph.D., an associate member of the Department of Developmental Neurobiology at St. Jude. "In the future, treatments that increase GST pi levels in the substantia nigra might help to prevent or delay the onset of Parkinson's disease or reduce its severity," said Smeyne, the report's senior author.

GST pi is one of a family of similar enzymes that eliminate free radicals generated by pesticides and other chemicals. Two members of this family are present in the brain, but only one of them, GST pi, is found in the dopaminergic neurons of the substantia nigra. Free radicals are highly unstable molecules that readily interact with other molecules, causing cell damage.

The study sheds light on the cause of most cases of Parkinson's disease, which currently are unexplained. "The majority of these cases of Parkinson's disease appear to arise because individuals who have a genetic susceptibility to the disease are exposed to environmental toxins such as pesticides and herbicides, which trigger the formation of free radicals that kill dopaminergic neurons in the substantia nigra," Smeyne said. "We also know that GST pi blocks the process of cell suicide triggered by stresses that the cell can't overcome, such as an increase in the presence of free radicals or a loss of the cell's ability to produce energy.".

Smeyne's team showed that of the two known types of GST in the brain, only GST pi was present in the dopaminergic neurons that are lost in Parkinson's disease. The scientists then treated two different populations of mice with MPTP, a chemical that causes loss of these cells, in order

to determine if levels of GST pi changed. In mice known to be sensitive to MPTP, there was a complete but transient loss of GST pi in the dopaminergic neurons of the substantia nigra, while the same area of the brain in MPTP-resistant mice never completely lost GST pi and recovered their original levels within 12 hours.

In addition, the team showed that when MPTP-resistant mice were treated with this drug, the presence of GST pi in the dopaminergic neurons prevented activation of cJUN, a molecule that triggers apoptosis. These findings are evidence that GST pi prevents apoptosis in dopaminergic neurons of the substantia nigra, Smeyne said.

The investigators also showed in cell culture studies that blocking production of GST pi in substantia nigra cells left them vulnerable to MPTP, causing a significant death rate among these cells. In addition, when the investigators blocked GST pi production in the dopaminergic neurons of the substantia nigra, about one-quarter of them died, even though they were not treated with MPTP. "This suggests that even in the absence of MPTP the enzyme GST pi plays a critical role in preventing cell death that may occur with the natural buildup of free radicals," Smeyne said.

Finally, the investigators studied the effect of MPTP on the substantia nigra of normal, "wild-type" mice and mice that lacked one (+/-) or both (-/-) genes for GST pi. Wild-type and GST pi (+/-) mice showed similar resistance to MPTP, but GST pi (-/-) mice lost slightly less than half of their dopaminergic neurons following treatment with MPTP. Six hours after MPTP treatment, the formation of free radicals increased 300 percent in the substantia nigra of GST pi (-/-) mice compared with the substantia nigra of GST pi (+/+) mice. These results are additional evidence that GST pi may play an important role in preventing Parkinson's disease," Smeyne said.

Results of the St. Jude study showing the importance of GST pi could help to explain previous work by other researchers linking loss of this enzyme to destruction of dopaminergic neurons. For example, there is some evidence that alterations in the gene for GSP pi are linked to increased risk of Parkinson's disease after pesticide exposure. Also, although most Parkinson's disease cases have no known cause, experts believe that they are caused by the interaction of genetic susceptibility to Parkinson's disease with exposure to a variety of environmental factors, such as pesticides and herbicides.

"Therefore, the new findings bring researchers a step closer to understanding why Parkinson's disease occurs and potentially how to develop more effective treatments for it," Smeyne said.

Source: St. Jude Children's Research Hospital