UT SOUTHWESTERN MEDICAL CENTER NEWS

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Pre-clinical study finds Parkinson's cell death blocked by stopping inflammatory factor

DALLAS – Sept. 12, 2006 – Blocking one of the body's natural inflammatory factors gives substantial protection against cell death in the brain associated with Parkinson's disease, researchers at UT Southwestern Medical Center have found in a study on rats.

By using a drug against an inflammatory molecule called tumor necrosis factor or TNF, the researchers saw a 50 percent drop in dopamine neuron death in the brains of rats injected with compounds that cause Parkinson's-like cell death.

"Our findings suggest that TNF-dependent inflammation may be part of the progressive features of Parkinson's disease, and this gives us an opportunity with anti-TNF therapy to slow down or prevent the progression of the disease," said Dr. Malú Tansey, assistant professor of physiology at UT Southwestern and senior author of the study. "Our prediction is that independent of the environmental toxin or trigger that induces its production in the midbrain, TNF is likely to be a common mediator of dopamine neuron death."

The research will appear online and in the Sept. 13 issue of the *Journal of Neuroscience.*

Tumor necrosis factor is necessary for a functioning immune system. Its effects include the local inflammation and redness around wounds, and the painful swelling around joints in rheumatoid arthritis. TNF also activates other cells – including cells in the brain called microglia – that eat bacteria and other pathogens.

While the results point in a direction for treating neurodegenerative diseases with anti-inflammatories, a few problems will need to be addressed before anti-TNF therapies could come into widespread use to fight neurodegeneration, Dr. Tansey said. For instance, commercially available anti-TNF drugs as well as the new drug used in this study are too large to independently cross from the bloodstream into brain tissue.

Parkinson's disease affects 5 percent of people over 65, and is the second most common neurodegenerative disease after Alzheimer's. Parkinson's disease comes about because of the death of a certain class of nerve cells in an area of the brain called the substantia nigra. By the time serious

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symptoms appear, more than 80 percent of the dopamine-producing nerve cells are already dead, and the damage is irreversible.

In addition to its beneficial role, TNF has been a suspected player in Parkinson's because elevated levels of it are found in post-mortem brains and cerebrospinal fluid of people with the disease. A previous study by other researchers found that non-steroidal anti-inflammatory drugs that block production of TNF and related molecules can reduce the risk of developing Parkinson's by 46 percent.

In the current study, UT Southwestern researchers injected two different substances into the rats' brains to cause cell death in the substantia nigra – low-dose infusion of LPS, a toxin from bacteria often used to mimic chronic inflammation of the central nervous system, and 6-hydroxydopamine, which kills cells by creating an overwhelming amount of reactive oxygen and nitrogen molecules. Cell death was measured by counting neurons in stained brain slices.

When an experimental TNF inhibitor called XENP345, designed specifically to block soluble TNF, was also introduced into the brain, dopamine neuron death was reduced by about half.

The same effect was found on cultured dopamine neurons exposed to either toxin.

The researchers are now looking into why TNF inhibition did not fully protect against cell death. For example, the drug may not have been able to fully diffuse throughout the tissue, it might take longer to work than the weeks allowed in the experiment, or dopamine neuron loss might also involve processes independent of TNF.

"If an intervention could still reduce the extent or rate of cell death by 50 percent, it could make a huge difference in the life of a Parkinson's disease patient," Dr. Tansey said.

Other UT Southwestern researchers involved in the study were graduate students Melissa McCoy and Terina Martinez; Kelly Ruhn, research assistant in physiology; Christine Smith, research assistant at the Mobility Foundation Center; Dr. Barry Botterman, associate professor of cell biology; and Dr. Keith Tansey, assistant professor of neurology. A researcher at Xencor, Inc., which manufactures the experimental TNF inhibitory compound XENP345, also contributed.

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