Parkinson's: Neurons destroyed by 3 simultaneous strikes

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In a study that reveals the clearest picture to date of neuron death in Parkinson's disease, researchers at Columbia University Medical Center have found that a trio of culprits acting in concert is responsible for killing the brain cells.

The study, published in the April 30 issue of *Neuron*, showed that three molecules - the neurotransmitter dopamine, a calcium channel, and a protein called alpha-synuclein - act together to kill the neurons.

The discovery gives researchers a new understanding of how to save the neurons, say the study's authors, Eugene Mosharov, Ph.D., associate research scientist, and David Sulzer, Ph.D., professor of neurology & psychiatry at Columbia University Medical Center.

"Though the interactions among the three molecules are complex, the flip side is that we now see that there are many options available to rescue the cells," says Dr. Mosharov.

The symptoms of Parkinson's - including uncontrollable tremors and difficulty in moving arms and legs - are blamed on the loss of neurons from the substantia nigra region of the brain.

Researchers had previously suspected dopamine, alpha-synuclein and calcium channels were involved in killing the neurons, but could not pin the deaths on any single molecule.

The new paper, along with previous studies with Dr. Ana Maria Cuervo at Albert Einstein College of Medicine, shows that it is the combination of all three factors that kills the neurons.

The studies found that neurons die because calcium channels lead to an increase of dopamine inside the cell; excess dopamine then reacts with alpha-synuclein to form inactive complexes; and then the complexes gum up the cell's ability to dispose of toxic waste that builds up in the cell over time. The waste eventually kills the cell.

The neurons will survive if just one of the three factors is missing, Drs. Sulzer and Mosharov also found. "It may be possible to save neurons and stop Parkinson's disease by interfering with just one of the three factors," Dr. Mosharov says.

That means that one drug already in clinical trials - which blocks the culprit calcium channel - may work to slow or stop the progression of the disease, an achievement none of the current treatments for Parkinson's disease can accomplish.

Good Dopamine; Bad Dopamine

The idea that dopamine contributes to the death of neurons may seem paradoxical, since most
Parkinson's patients take L-DOPA to increase the amount of dopamine inside the cells.

The new study shows that it's the location of the dopamine inside the neurons that determines its toxicity.

Most of dopamine inside the neurons is packaged into compartments that are shipped to the edge of the cell where the dopamine is released. The motor symptoms of Parkinson's arise when the amount of dopamine

released by the cells declines. L-DOPA improves symptoms by boosting the amount of dopamine released by the cells. As long as dopamine is confined inside the compartments before it is released, it is safe.

Outside the compartments in the cell's cytoplasm, however, Drs. Sulzer and Mosharov found that dopamine - in concert with calcium and alpha-synuclein - is toxic.

New Idea for Treatment

A better treatment, the researchers say, may be to push more dopamine into the compartments where it has no toxic effect on the cell.

"That would be a magic treatment," Dr. Mosharov says. "Not only would it stop cells from dying and the disease from progressing, it would improve the patient's symptoms at the same time by giving their neurons more dopamine to release."

Drs. Sulzer and Mosharov are currently working on genetic therapies that could accomplish this feat, but caution that it will be years before any such treatment is ready for clinical trials, if ever.

Source: Columbia University Medical Center (news : web)