



Caryl Sortwell, PhD



George Mandybur, MD

September 2, 2008
FOR IMMEDIATE RELEASE

CONTACT: Tom Rosenberger, APR
Communications Department
(513) 569-5260

CONTACT: Cindy Starr, MSJ
Communications Department
(513) 569-5321
cstarr@MayfieldClinic.com

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Surgery for Parkinson's disease protects dopamine cells by boosting trophic factor, Gardner Center researchers find

Novel study may alter surgical timetable for treatment often deemed a last resort

CINCINNATI – Deep brain stimulation, a surgical technique often viewed as a last resort for people with Parkinson's disease, halts the progression of dopamine-cell loss in animal models, according to preliminary research by scientists at the James J. and Joan A. Gardner Family Center for Parkinson's Disease and Movement Disorders, a center of excellence at The Neuroscience Institute at the University of Cincinnati (UC) and University Hospital.

The scientists also discovered clues to why the technique works. The act of stimulating neurons with electrodes boosted the amount of an important protein in animals' brains. The protein, a trophic factor known as BDNF (brain-derived neurotrophic factor), is a nurturing, growth-promoting chemical.

Parkinson's disease is a degenerative neurological disorder involving the death of dopamine-producing brain cells, or neurons.

"Demonstrating that deep brain stimulation halts the progression of dopamine-cell loss was basically a confirmation and extension of previous findings," says Caryl Sortwell, Ph.D., Associate Professor of Neurology at UC and the study's lead investigator. "But finding the mechanism is a novel discovery that is even more critical. We now know not only that it works, we also are beginning to understand how it is working."

Dr. Sortwell recently announced her team's results at a professional conference held by the Cleveland Clinic and the National Institute of Neurological Disorders and Stroke.

The research holds important implications for patients with Parkinson's disease and could alter the current recommended timetable for surgical intervention.

In a typical treatment scenario, a patient has lost about 50 percent of his or her dopamine-producing neurons when symptoms first appear and a diagnosis is made. The typical patient then waits an average of 14 additional years before undergoing deep brain stimulation surgery. During that 14-year span, medications can offer symptomatic relief, but cell loss continues unabated. There is at present no cure for the disease.

Dr. Sortwell's research was a response to an observation by physicians, including co-investigator George Mandybur, M.D., a neurosurgeon with the Mayfield Clinic and the Neuroscience Institute, who have long been able to neutralize, in certain patients, some of the most debilitating symptoms of Parkinson's disease, including tremor, stiffness, and slowness, by stimulating an area deep within the brain.

"The surgery for Parkinson's disease has been available for over 10 years, and in that time we have noticed that in some patients the disease does not seem to progress as rapidly after surgery as it did before the surgery," Dr. Mandybur says. As a result, he and others theorized that DBS not only alleviated symptoms, but also provided neuroprotection.

The UC study, Dr. Mandybur says, "helps us to understand why this is going on and what may be happening in the brain. It also gives some evidence to support performing the surgery earlier to slow the overall progression of Parkinson's disease."

The study, which is continuing, is supported by a \$120,000 grant from the Sunflower Revolution fundraiser, a partnership of the University Hospital Foundation and the Davis Phinney Foundation. The 2008 Sunflower Revolution, scheduled for Sept. 5-7, includes a gala, a free educational symposium for patients, families, and caregivers, and bike rides of 20, 40, and 100 kilometers. (See www.sunflowerrev.org.)

During the DBS study, researchers implanted high-frequency stimulating electrodes in the subthalamic nucleus, an area of the brain associated with movement, in rats and then induced dopamine neuron loss. When the rats had experienced a 50 percent loss of dopamine neurons, the researchers initiated brain stimulation in half of the group. Measurements of surviving, functioning dopamine neurons in rats implanted with active stimulators were then compared to a control group implanted with inactive stimulators. While the control group's loss of dopamine neurons increased to 75 percent after two weeks, the rats implanted with active stimulators experienced no further loss of cells during that time.

Subsequent tissue analysis revealed that in rats implanted with active stimulators the trophic factor BDNF had tripled in the striatum, a part of the brain that houses dopamine terminals and "receives" the dopamine neurotransmitters that are produced in the substantia nigra.

The study has brought together investigators from four academic disciplines: Dr. Sortwell, Timothy Collier, Ph.D., and doctoral student Anne Spieles-Engemann, from UC's Department of Neurology; Michael Behbehani, Ph.D., from the Department of Physiology; Jack Lipton, Ph.D., from the Department of Psychiatry; and Dr. Mandybur, from the Department of Neurosurgery. Dr. Behbehani, Professor of Molecular and Cellular Physiology and Anesthesia, established the method for implanting the electrodes in the rat's tiny subthalamic nucleus.

The initial study platform was funded by UC's Millennium Fund and subsequently by The Neuroscience Institute.

The Davis Phinney Foundation, named for the former Tour de France cyclist Davis Phinney and based in Boulder, Colo., is dedicated to supporting research aimed at understanding, preventing, and treating Parkinson's disease, which affects an estimated 1.5 million Americans. In 2006 the foundation named The Neuroscience Institute and Stanford University its first Davis Phinney Research Centers.

The Neuroscience Institute, a regional center of excellence at UC and University Hospital, is dedicated to patient care, research, education, and the development of new treatments for stroke, brain and spinal tumors, epilepsy, traumatic brain and spinal injury, multiple sclerosis, Alzheimer's disease, Parkinson's disease, disorders of the senses (swallowing, voice, hearing, pain, taste, and smell), and psychiatric conditions (bipolar disorder, schizophrenia, and depression).