Novel Parkinson's treatment strategy involves cell transplantation

March 25 2010

UCSF scientists have used a novel cell-based strategy to treat motor symptoms in rats with a disease designed to mimic Parkinson's disease.

The strategy suggests a promising approach, the scientists say, for treating symptoms of Parkinson's disease and other neurodegenerative diseases and disorders, including epilepsy.

The scientists transplanted embryonic neurons from fetal rats into an area of the adult rat brain known as the striatum, which integrates excitatory and inhibitory neurotransmitter signals to control movement. In Parkinson's disease, cells that produce the neurotransmitter dopamine are damaged, and thus unable to project their communication wires, or axons, to the region. As a result, the balance of excitation and inhibition in the striatum is lost, causing the motor deficits that are a primary symptom of the disease.

In the study, the transplanted embryonic neurons migrated and integrated into the correct neural circuitry of the striatum, matured into so-called GABAergic inhibitory interneurons, and dampened the over-excitation in the region. The rats had improved motor function, as seen in their balance, speed, and length of stride during walking. Moreover, the healthy "control" rats in which the cells had been transplanted took longer strides and ran faster on a runway test.

The results, the scientists say, demonstrate that the transplanted cells, known as embryonic medial ganglionic eminence (MGE) cells, can very

precisely modify the balance of excitation and inhibition in neural circuits to influence behavior. As overactive neural circuits are associated with other neurodegenerative diseases - a result of nonfunctioning or missing cells or abnormal synaptic transmission -- the finding may have broad implications.

"This strategy represents a whole new approach to treating nervous system disorders," says neurologist Arnold Kriegstein, MD, PhD, the senior author of the study and director of the Eli and Edythe Broad Center of Regeneration Medicine and Stem Cell Research at UCSF.

The study, featured on the cover of the journal *Cell Stem Cell* (vol. 6, issue 3, 2010), was led by Verónica Martínez-Cerdeño, PhD, at the time a postdoctoral fellow in the Kriegstein lab, and was a collaboration involving Arturo Alvarez-Buylla, PhD, UCSF Heather and Melanie Muss Professor of Neurological Surgery and Krys Bankiewicz, MD, PhD, UCSF professor of neurological surgery.

The approach used by the team differs from another cell-based strategy for Parkinson's disease currently being explored by other research teams. This traditional transplantation strategy involves attempting to replace the dopamine-producing cells that are lost in the disease, by grafting precursors for these cells directly in the striatum. The loss of these cells is thought to account for most of the disease's symptoms -- motor deficits, cognitive and autonomic dysfunction and disturbances in mood.

This traditional strategy has shown severe drawbacks, including that the grafted dopaminergic cells show little, if any, dispersion when grafted into the striatum, and that patients have developed disabling spontaneous movements in preliminary trials, prompting early suspension of the trials.

The ability to modify the neural circuitry of the striatum, part of a larger

region known as the basal ganglia, is a function only cells can perform, says Kriegstein. The nervous system is a complex system of neural networks composed of highly individualized cells that relay electrochemical signals between regions of the brain and spinal cord at millisecond speeds, accounting for every behavior, emotion, and thought. "Each cell has its own role to play based on the circuits in which it is embedded," he says. "It has to carry out its role at exactly the right time, with exactly the right partners, and the activity pattern changes moment by moment.

"Once MGE cells were integrated into striatal neural circuitry, they would be able to modify circuit activity, in a way no other therapies can."

Current treatment approaches - drugs, surgery and electrical stimulation -- are relatively blunt instruments, he says. Drugs, for instance, generally act indiscriminately, affecting whole areas of the nervous system, so there often are multiple side effects.

The new study findings complement two other recent UCSF studies using MGE cells to modify neural circuits. In a collaborative study among the laboratories of Scott Baraban, PhD, professor of neurological surgery; John Rubenstein, MD, PhD, professor of psychiatry, and Alvarez-Buylla, the cells were grafted into the neocortex of juvenile rodents, where they reduced the intensity and frequency of epileptic seizures. (*Proceedings of the National Academy of Sciences*, vol. 106, no. 36, 2009). Other teams are exploring this tactic, as well.

In the other study (*Science*, Vol. 327. no. 5969, 2010), UCSF scientists reported the first use of MGEs to broaden the period of plasticity, or capacity to change, in the mouse visual cortex. The finding, reported by the labs of Alvarez-Buylla and Michael Stryker, PhD, professor of physiology, might some day be used, they say, to create a new period of

plasticity of limited duration for repairing damaged brains.

Looking ahead, the team studying MGE cells in the rat model of Parkinson's disease plans to target a more specific sub region of the striatum, with the goal of getting a more precise effect. They also want to see if the cells could be genetically modified to produce dopamine, thus more directly addressing the biochemical changes of Parkinson's disease, and they plan to attempt to prompt human embryonic stem cells to differentiate, or specialize, into MGE cells in the lab, with the goal of establishing a mechanism for creating a sufficient supply of the cells for clinical use.

Provided by University of California - San Francisco