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Scientists construct 'off switch' for Parkinson therapy

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A common antibiotic can function as an "off switch" for a gene therapy being developed for Parkinson's disease, according to University of Florida researchers writing online in advance of September's *Molecular Therapy*.

The discovery in rats answers an important question — how can new, therapeutic genes that have been irrevocably delivered to the human brain to treat Parkinson's be controlled if the genes unexpectedly start causing problems?

Meanwhile, in a review of Parkinson treatments, the researchers say that prior experimental attempts using growth factors — naturally occurring substances that cause cells to grow and divide — to rescue dying brain cells may have failed because they occurred too late in the course of the disease.

Together, the findings suggest that gene therapy to enable the brain to retain its ability to produce dopamine, a neurotransmitter that falls in critically short supply in Parkinson's patients, could be safely attempted during earlier stages of the disease with an added likelihood of success.

Parkinson's disease affects more than 1 million Americans, causing patients to gradually develop movement problems, including tremors, stiffness and slowness. It is caused by degeneration and death of nerve connections that produce dopamine, a substance necessary for communication between cells that coordinate movement.

"We have worked every day for 10 years to design a construct to the gene delivery vector that enhances the safety profile of gene transfer for Parkinson's disease," said Ronald Mandel, a professor of neuroscience at UF's McKnight Brain Institute and the Powell Gene Therapy Center. "With that added measure of safety, we believe we can intervene with gene transfer in patients at earlier stages of the disease. We strongly believe that trials to save dopamine-producing connections in patients with Parkinson's disease have failed because the therapy went into patients who were in the late stages of the disease and who had too few remaining dopamine-producing connections."

Often patients are given prescriptions for levodopa, or L-dopa, which is converted into dopamine by enzymes in the brain. But the treatment loses its effectiveness over time and does nothing to slow the disease's progression.

Meanwhile, trials in the United States to treat Parkinson's involving direct infusion of growth factors or the transplantation of genes that produce growth factors have had limited success, with some side effects.

Mandel's research group has concentrated on using an adeno-associated virus to engineer brain cells in animal models with genes that can protect dopamine-producing cells, which then do the vital work of producing GDNF, short for glial cell line-derived neurotrophic factor. The naturally occurring protein is important for the survival of dopamine-producing neurons during brain development, and a survival factor when given to adults.

In this case, scientists engineered the virus with two genes that must act in concert to produce the protein. But this precise interaction can be inhibited with dietary doxycycline, an antibiotic that is often prescribed in low doses to treat bacterial growth related to acne.

Depending on the amount of the antibiotic, protein production can be reduced or stopped, which would for the first time give medical investigators the ability to regulate gene therapy after the treatment was delivered.

"With this technique, you could adjust the therapy in the patient," said Fredric P. Manfredsson, a postdoctoral associate in UF's department of neuroscience. "That would be extremely helpful because no one is really certain yet what dosage is required for a protective effect in humans. The process is also much more sensitive than we had imagined it would be. GDNF production can be shut down completely with a dose of doxycycline that is much smaller than what is commonly prescribed."

Mandel said that adding the safety construct to the gene vector and proving its effectiveness were arduous tasks in which Manfredsson played an essential role.

A variety of methods were used to gauge GDNF production, but one was uncommon and involved the novel observation of the rats' weight. In prior research, the scientists had found delivering the protein to certain regions of the brain would hinder weight gain in younger rats and can cause weight loss in older rats. In the recent experiments, scientists found they could control the rate of weight gain in the rats with dietary doxycycline, which essentially verified they were controlling the GDNF therapy.

"The ability to control gene regulation is important for the future development of gene therapy, and optimizing its safe application to humans," said Dr. Mark Tuszynski, a professor of neurosciences and director of the Center for Neural Repair at the University of California, San Diego, who did not participate in the research. "The work of Dr. Mandel and colleagues brings us an important step closer to this goal."

Source: University of Florida (news : web)