Experimental Parkinson's therapy may have robust weight-loss effect

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A growth factor used in clinical experiments to rescue dying brain cells in Parkinson patients may cause unwanted weight loss if delivered to specific areas of the brain, according to University of Florida researchers in the March online edition of *Molecular Therapy*.

The discovery is a cautionary warning for experimental treatments to treat Parkinson's disease that use GDNF, short for glial cell line-derived neurotrophic factor.

In addition, the finding broadens understanding of the brain's role in the regulation of metabolism and body weight, suggesting that gene therapy techniques in the brain potentially could control obesity.

"People shouldn't interpret our result to mean this is a terrible side effect that precludes ability to do GDNF gene therapy for Parkinson's disease, but it does show that it is extremely important to place the therapy in the correct brain region," said Ron Mandel, a professor of neuroscience at UF's McKnight Brain Institute and the Powell Gene Therapy Center. "The good news for Parkinson's patients is that the finding doesn't discredit the current target."

Parkinson's disease affects between 500,000 and 1.5 million Americans, causing patients to gradually develop movement problems, including tremors, stiffness and slowness of movement.

Current treatments only address symptoms and do nothing to slow the

disease's progression, which is caused by degeneration and death of nerve cells that produce dopamine, a substance necessary for communication between cells that coordinate movement.

GDNF rescues the dopamine-producing cells in cell cultures and animal models of Parkinson's disease.

But Parkinson patients were disappointed in September 2004 when the biotechnology company Amgen discontinued a clinical trial using GDNF because of concerns about safety and effectiveness. The therapy was delivered through surgically implanted catheters to a region called the putamen, and several patients said their physical conditions and quality of life improved.

A different approach in a more recent trial by the biopharmaceutical company Ceregene involved gene therapy, in which the gene to produce neurturin, a sister protein to GDNF, was transferred into the putamen region of Parkinson patients. But it showed no marked effectiveness.

In a clinical trial where GDNF was delivered to the fluid-filled spaces of the brain, a common side effect was weight loss beyond what could be attributed to surgery, diet changes and energy expenditure.

Based on these results UF researchers looked for areas in the brain that might be responsible for weight loss. The UF researchers noticed that GDNF delivery to the area of the brain known to control weight and general metabolism reduced weight gain in younger rats and caused significant weight loss in older ones.

In the current study, UF scientists compared weight loss in obese rats when two distinct brain targets received therapy using an adeno-associated virus to deliver the GDNF gene.

When GDNF flooded a bundle of nerves known as the nigrostriatal tract, a potential target for Parkinson therapy, the obese rats lost a great deal of weight — about 80 grams. But when GDNF protein was overexpressed in a different therapeutic target, the hypothalamus, weight loss was only about half as much. In both locations, there was a steady decrease in body weight throughout the experiment that could only partially be explained by food intake.

"These are interesting findings that enhance our understanding of how the dopamine system interacts with obesity," said Dr. Ole Isacson, a professor of neurology at Harvard Medical School and director of the Center for Neuroregeneration Research at McLean Hospital who did not participate in the study. "An interesting corollary is that overexpression of GDNF may act on satiation or appetite reduction — clearly this is a unique angle for using GDNF, which has only been applied for neuroprotection for Parkinson's disease or motor neuron disease."

The discovery also suggests that direct injections of GDNF therapy to certain brain regions are not advisable because patients could lose unhealthy amounts of weight.

"It is a fascinating discovery as a future potential treatment for weight loss, and for Parkinson's treatment, it means it is important to watch patients' weight and metabolism carefully," said Dr. Pedro Lowenstein, director of the Gene Therapeutics Research Institute at Cedars-Sinai Medical Center who was not involved in the research. "It is also interesting because there is a propensity for Parkinson patients to get depressed, and it is not very clear why. This study found a link between GDNF and CRH neurons — cells that are involved in mood regulation. That is very intriguing."

Meanwhile, researchers studying potential obesity therapies that work by influencing how the brain regulates energy use and food intake now have

much more to consider.

"The results show for the first time that GDNF overexpression in an anatomical area in the brain known as the nigrostriatal tract is involved in metabolism," Mandel said. "For people who study metabolism in the brain, this sheds some new light on the playing field. But it shows the playing field is more complicated that anyone dreamed."

Source: University of Florida (news : web)