

JUNE 22, 2001

## Gene Therapy Restores Feeding Behavior to Starving Mice

Researchers have used gene therapy to rejuvenate feeding behavior in starving mice. The genetically engineered mice avoided eating because their brains contained a low level of dopamine.

The scientists' experiments, which were reported in the June 2001 issue of the journal *Neuron*, provide new information about a region of the brain that helps integrate internal hunger signals and external sensory information about food to trigger feeding behavior.

---

"I was quite impressed by the fact that we could inject the virus once and rescue feeding behavior for the life of the animal."

— Mark S. Szczypka

---

A research team led by Richard D. Palmiter, a Howard Hughes Medical Institute investigator at the University of Washington, demonstrated that gene therapy restored dopamine production in specific areas of the brains of mutant mice. The mice, which were developed by Qun-Yong Zhou in Palmiter's laboratory in the mid-1990s, lack tyrosine hydroxylase, an enzyme that is required to produce L-DOPA, a chemical precursor that is converted into the neurotransmitter dopamine. These mice lack the motivation to feed, and die of starvation a few weeks after birth, unless they are hand-fed or injected daily with L-DOPA. The gene therapy restored feeding behavior in the mice.

"These dopamine-deficient mice have many other behavioral deficits," said Palmiter. "In addition to not eating adequately, they show no preference for sweets, they fail to build nests and they lack curiosity in novel environments. They are generally hypoactive, they are also slow to initiate movements and they have difficulty with coordination — a syndrome that resembles parkinsonism."

According to Palmiter, researchers did not know which region of the brain was responsible for the impaired feeding behavior and other deficits noted in the mice. Palmiter and his colleagues suspected that dopamine-producing neurons in the mid-brain that send their axon processes to the striatum played

a key role in integrating brain signals to produce specific behaviors. But they did not know which part of the striatum would be involved. The striatum is divided into two segments — the caudate putamen and the nucleus accumbens.

Mark S. Szczyпка, a postdoctoral fellow in Palmiter's laboratory, attempted to restore dopamine production in the caudate putamen and nucleus accumbens, by injecting harmless adeno-associated viruses carrying the genes for tyrosine hydroxylase and GTP cyclohydrolase I. The viruses were supplied by co-author Brian A. Donahue of Cell Genesys, Inc., of Foster City, California.

Surprisingly, viral injections restored feeding behavior only when the injections targeted the caudate putamen. Targeting the caudate putamen also revived the animals' preference for palatable, high-fat foods and sugar water. "I would speculate that hunger signals are produced because these animals are starving most of the time," said Palmiter. "Those signals are probably reaching the caudate putamen, where they would interact with sensory signals reflecting the sight and smell of food. Our guess, however, is that in the absence of dopamine, the caudate putamen can't put those signals together to elicit food-seeking behavior."

Injections into the nucleus accumbens did not improve feeding on normal rodent chow, but they did improve exploratory behavior and a preference for more palatable foods. However, the mice did not eat the palatable food long enough or in sufficient quantity to maintain weight. "Considerable research on drug addiction and the reward mechanisms in the brain had implicated the nucleus accumbens in processing reward-like behaviors," said Szczyпка. "We assumed that eating food was a rewarding behavior, so we were surprised that treatment of the nucleus accumbens did not work."

Restoration of dopamine production in the caudate putamen also rejuvenated nest-building behavior. "Mice readily build nests when given nesting material," said Palmiter. "But in the absence of dopamine, the mice never built nests. Since the treated mice resumed nest-building, we suspect that other motivated behaviors may also be rescued by treatment."

Dopamine has many functions outside the caudate putamen, said Michelle Brot, a co-investigator on the study. Brot points out that "restoration of feeding by viral treatment of the caudate putamen provides a unique model for investigating the role of dopamine in other brain regions, such as its functions in the nucleus accumbens in mediating reward, and its role in the hippocampus in learning and memory."

The motor coordination of the mice treated in either brain region did not appear to improve very much following gene therapy. The treated mice were still slow to initiate movement and had poor coordination. This indicated that other brain regions remained dopamine-deficient, said Palmiter.

Future studies will seek to define mechanisms by which dopamine facilitates feeding. In addition, the scientists will attempt to pinpoint the region that

restores feeding and possibly dissociate it from nest-building behavior. They also plan to restore dopamine production to dopamine-producing neurons in the substantia nigra and the ventral tegmental area. They predict that this treatment will correct the motor deficits in these mice.

The rescue of feeding behavior in mice may offer insight into nutritional problems in Parkinson's disease patients, said Palmiter. "It's known that people with Parkinson's have eating difficulties, which have been ascribed to difficulties in manipulating utensils, chewing and swallowing, as well as depression," Palmiter said. "Our mouse studies suggest that there is an underlying motivational deficit in Parkinson's disease, as well."

Szczyпка noted that viral gene therapy can be a very effective means of treating neurological and other genetic disorders. "I was quite impressed by the fact that we could inject the virus once and rescue feeding behavior for the life of the animal," he said. "Admittedly, a mouse's life is short relative to a person's life, but still it's an efficacious treatment with a great deal of potential."