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Got brain? Neural mechanisms play role in healthy bone growth

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Scientists searching for a gene therapy to control obesity have unexpectedly discovered a way that the brain regulates bone growth, a finding that shines new light on osteoporosis and other bone-robbing diseases.

Researchers from the University of Florida's McKnight Brain Institute transferred the gene to produce leptin — a hormone that has been linked with appetite control, obesity and diabetes — into the brains of mice that, because of a genetic defect, are leptin-deficient and obese.

The gene transfer not only helped the mice lower their body weight, it unexpectedly increased bone growth and normalized their bone volume, adding or reducing it as needed, according to UF and Oregon State University researchers.

The findings, to be published this week in the journal *Peptides*, advance efforts to use gene therapy to treat human obesity while underscoring the importance of the brain in matters more often associated with nutrition. This is the first study to show that without leptin in the brain, bones do not grow properly.

"Everyone naturally thinks about calcium and the foods that we eat in regard to strong bones, and while that is very important, it seems ultimately the brain plays an integral role in the development and growth of bones," said Satya P. Kalra, a distinguished professor of neuroscience in the UF College of Medicine. "It appears that you can use gene therapy

to provide leptin continuously in the brain to promote bone growth. We still have to do more experiments, but I was surprised that the effects thus far would be so robust."

The findings provide a new outlook on diseases such as osteoporosis, which is estimated to contribute to 2 million bone fractures annually in the United States. Discovering ways to enhance bone accumulation during early growth is important for preventing osteoporosis later in life, the researchers said.

"On the basis of previously published research, we expected the gene therapy to result in bone loss — we thought that osteoporosis would be a potential negative side effect of the treatment," said Urszula T. Iwaniec, an assistant professor of nutrition and exercise sciences at Oregon State University and the lead author of the research. "But when we increased leptin in the brain, we saw increased bone growth and normalization of bone mass. Bone that was abnormally low or abnormally high became normal and the skeletons of these mice no longer differed from normal healthy mice. This indicates that leptin is essential for normal bone health."

The researchers concentrated on restoring the leptin in the hypothalamus in the brain, not leptin produced by fat cells and readily circulated in the bloodstream.

Researchers injected a virus carrying the leptin gene into the brains of leptin-deficient young mice. Inability to produce leptin causes extreme obesity, shorter-than-normal leg bones and excess volume in the spongy bone of the vertebrae.

The virus "infected" the brain cells with the ability to produce the hormone, resulting in mice that weighed half what the leptin-deficient mice usually weigh. In addition, their bone growth resembled that of

normal mice.

“The question of whether the brain regulates bone growth has been highly debated, so this is an important contribution because the researchers normalized bone growth by targeting the brain,” said Mark Hamrick, an associate professor of cellular biology and anatomy at the Medical College of Georgia who was not involved in the research. “They’ve also taken a very novel approach, using a virus to increase expression of leptin in the hypothalamus.”

Source: University of Florida