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Bone Finding May Point to Hope for Osteoporosis

By GINA KOLATA November 27, 2008

Bone formation appears to be controlled by serotonin, a chemical previously known mainly for its entirely separate role in the brain, researchers are reporting.

The discovery could have enormous implications, osteoporosis experts say, because there is an urgent need for osteoporosis treatments that actually build bone.

Osteoporosis affects 10 million Americans over age 50. It results in bone loss, and its hallmark is fragile bones that break easily. With one exception, current treatments only slow further bone loss rather than increase bone formation. And the exception, parathyroid hormone, given by injection, is recommended only for short-term use and costs about $6,700 a year.

But in a paper published online Wednesday in the journal Cell, a team led by Dr. Gerard Karsenty, chairman of the department of genetics and development at the Columbia University College of Physicians and Surgeons, reports the discovery of an unexpected system that appears to control bone formation.

At its heart is serotonin made by the gut rather than the brain, whose role outside the brain had been a mystery. Ninety-five percent of the body's serotonin is made by the gut, but gut serotonin cannot enter the brain because it is barred by a membrane, the so-called blood-brain barrier.

Dr. Karsenty reports, though, that gut serotonin can directly control bone formation. It is released into the blood, and the more serotonin that reaches bone, the more bone is lost. Conversely, the less serotonin, the denser and stronger bones become. Dr. Karsenty was even able to prevent menopause-induced osteoporosis in mice by slowing serotonin production.

Osteoporosis researchers were dumbfounded by the report.

"I am very excited by this paper," said Dr. J. Christopher Gallagher, an osteoporosis specialist and professor of medicine at Creighton University. "It is a groundbreaking paper. One is completely surprised."

Dr. Ronald N. Margolis, senior adviser for molecular endocrinology at the National Institute of Diabetes and Digestive and Kidney Diseases, said: "I was astonished. My jaw was dropping."

Dr. Clifford J. Rosen, a senior scientist at the Maine Medical Center Research Institute, was no less impressed. "This is amazing science," Dr. Rosen said. "Amazing. The science is spectacular."

Dr. Ethel S. Siris, who directs the Toni Stabile Osteoporosis Center at Columbia, cautioned that the work was not with humans but instead involved mice that were engineered to have human genes. "This stuff is really exciting basic — underscore basic — research," Dr. Siris said.

The story of the serotonin-bone connection began with reports of a rare inherited condition causing fragile bones and blindness. Children with the condition had bones so weak that they needed wheelchairs or devices to assist them in walking.

The problem turned out to be a mutation that inactivated a gene called LRP5.

A few years later, another mutation was found in LRP5 that produced the opposite effect: extremely dense bones and resistance to osteoporosis. In this case, LRP5 was overactive. People with this gene mutation, Dr. Karsenty said, had jawbones so dense that it was difficult to extract their teeth.

Osteoporosis researchers jumped on those findings, realizing that LRP5 could hold clues to the disease. But most assumed that LRP5's role was in bone itself.

With Dr. Karsenty's work, said Dr. Bjorn R. Olsen, a bone growth researcher at Harvard Medical School, "that has now been proven completely wrong."

Instead, Dr. Karsenty discovered that LRP5 acts on serotonin-producing cells in the gut. It blocks an enzyme that converts the amino acid tryptophan to serotonin. The more LRP5, the more the enzyme is blocked, and the less serotonin is made. The gene has no effect, apparently, on brain cells that make serotonin.

After the gut releases serotonin into blood, serotonin travels to bone-forming cells and inhibits their growth.

"We made mice with the inactivated gene," Dr. Karsenty said, in which "the bone-forming cells are on strike." The cells simply would not grow, and the mice developed severe osteoporosis.

But the bone cells themselves were fine. When Dr. Karsenty grew them in the lab, where they were not exposed to serotonin, they developed normally.

That told him that the problem was not in the bone cells but in some molecule in the mice's circulation. And that, Dr. Karsenty says, led him to serotonin. The mice had four to five times more serotonin in their blood than mice without the mutation.

He tested the idea by adding serotonin to normal mouse bone cells in the laboratory. The cells stopped growing.

He could even control bone formation in the mice with the mutated gene by giving them a diet deficient in tryptophan, the precursor of serotonin. Without much tryptophan, the mice could not make much serotonin. And their bones grew denser. (But animals with a normal version of the gene did not grow denser bones when they ate a tryptophan-deficient diet.)

Dr. Karsenty and his colleagues also did the reverse experiment, making mice with the mutation that causes superdense bones in humans. Those animals, he said, had "amazing bones" that were hard to break, and they did not develop osteoporosis.

When Dr. Karsenty looked at patients with the dense-bones mutation, they had low levels of serotonin in their blood.

Osteoporosis patients, though, tend to have normal serotonin levels, Dr. Karsenty said. Their disease involves not impaired bone formation but accelerated bone loss.

Bone is constantly being formed and absorbed, but when the balance shifts toward loss more than formation, the result can be osteoporosis. Dr. Karsenty's hope is to find a drug that depresses the gut's serotonin synthesis and stimulates bone growth in these patients.

Dr. T. John Martin, an emeritus professor of medicine at the University of Melbourne in Australia, cautions that all this will take years. He is enthusiastic, though.

"This will really change thinking in the field," Dr. Martin said. "It will have a big impact. I'm certain of that."

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