Inhibiting serotonin in gut could cure osteoporosis

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An investigational drug that inhibits serotonin synthesis in the gut, administered orally once daily, effectively cured osteoporosis in mice and rats reports an international team led by researchers from Columbia University Medical Center, in the Feb. 7 issue of *Nature Medicine*. Serotonin in the gut has been shown in recent research to stall bone formation. The finding could lead to new therapies that build new bone; most current drugs for osteoporosis can only prevent the breakdown of old bone.

"New therapies that inhibit the production of serotonin in the gut have the potential to become a novel class of drugs to be added to the therapeutic arsenal against osteoporosis," said Gerard Karsenty, M.D., Ph.D., chair of the Department of Genetics and Development at Columbia University College of Physicians and Surgeons, lead author of the paper. "With tens of millions of people worldwide affected by this devastating and debilitating bone loss, there is an urgent need for new treatments that not only stop bone loss, but also build new bone. Using these findings, we are working hard to develop this type of treatment for human patients."

The Nature Medicine paper follows on a major discovery, also made by Dr. Gerard Karsenty's group (published in the Nov. 26, 2008 issue of *Cell*), that serotonin released by the gut inhibits bone formation, and that regulating the production of serotonin within the gut affects the formation of bone. Prior to this discovery, serotonin was primarily known as a neurotransmitter acting in the brain. Yet, 95 percent of the

body's serotonin is found in the gut, where its major function is to inhibit bone formation (the remaining five percent is in the brain, where it regulates mood, among other critical functions). By turning off the intestine's release of serotonin, the team was able, in this new study, to cure osteoporosis in mice that had undergone menopause.

Based on their findings reported in the *Cell* paper, Dr. Karsenty and his team postulated that an inhibitor of serotonin synthesis should be an effective treatment for osteoporosis. Shortly thereafter, they read about an investigational drug, known as LP533401, which is able to inhibit serotonin in the gut. "When we learned of this compound, we thought that it was important to test it as proof of principle that there could be novel ways to treat osteoporosis with therapies that can be taken orally and regulate the formation of serotonin," said Dr. Karsenty.

Dr. Karsenty and his team developed a research protocol to test their theory, where they administered the compound orally, once daily, at a small dose, for up to six weeks to rodents experiencing post-menopausal osteoporosis. Results demonstrated that osteoporosis was prevented from developing, or when already present, could be fully cured. Of critical importance, levels of serotonin were normal in the brain, which indicated that the compound did not enter the general circulation and was unable to cross the blood-brain barrier, thereby avoiding many potential side effects.

Implications for the Treatment of Osteoporosis

Most osteoporosis drugs, including those currently under clinical investigation, do not generate new bone but rather, prevent the breakdown of old bone. Only one drug currently on the market can generate new bone - but it must be taken by injection once a day, and because it may increase the risk of bone cancer, at least in rats, its use is restricted for short-term use in women with severe osteoporosis.

"There is an urgent need to identify new, safe therapies that can increase bone formation on a long term basis and to such an extent that they compensate for the increase in bone resorption caused by menopause," said Dr. Karsenty. "Furthermore, it is important to note that since this study was conducted in rodents, it will need further confirmation in human subjects."

Osteoporosis: A Disease of Bone Mass Decline

Osteoporosis is a growing public health concern, with the aging population and the incidence of post-menopausal osteoporosis on the rise. It is a disease of low bone mass, most often caused by an increase in bone resorption not compensated by a similar increase in bone formation.

Far from being inert, bone constantly undergoes renovation, with some cells responsible for removing old material and other cells responsible for creating new bone. In humans, after age 20, the balance between bone formation and breakdown tips toward breakdown, and bone mass starts to decline. In women, the rate of decline increases after menopause, when estrogen levels drop and cells that tear down old bone become overactive. Osteoporosis is a disease in which bones become fragile and porous, increasing the risk of breaks. It is diagnosed when bone mass drops below a certain level.

Provided by Columbia University Medical Center