Newly discovered road map of leptin explains its regulation of bone and appetite

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New research from Columbia University Medical Center has illuminated a previously unknown leptin-serotonin pathway in the brain that simultaneously promotes appetite and bone mass accrual. The research, which explains how leptin - well-known appetite-suppressing hormone - acts in the brain, is published in the Sept. 4 issue of *Cell*.

When the leptin-serotonin pathway is turned on in mice, the researchers found, appetite increases, the animals eat more, gain weight, and their bone mass increases. When the pathway is turned off, mice eat less, lose weight, and their bones weaken. Furthermore, leptin was found to not act in the hypothalamus as previously thought, but in the brain stem acting on serotonin, a hormone that in the brain acts to control appetite, mood and anger.

The identification of this pathway helps explain why, as doctors have long known, obese people tend to have a significantly lower prevalence of osteoporosis, says the study's senior author, Gerard Karsenty, M.D., Ph.D., chair of the Department of Genetics & Development at Columbia University's College of Physician and Surgeons. Though obese people produce high levels of leptin, they are resistant, or unresponsive, to its signals - instead, they operate in a false state of leptin deficiency, which increases serotonin - and thereby, appetite and bone mass. Dr. Karsenty points out that these current findings may have more influence on developing a new way to reduce appetite and obesity than preventing osteoporosis.

"It will be difficult to turn on the pathway to strengthen bone without increasing appetite at the same time," Dr. Karsenty said. "But this finding shows that it is feasible to alter parts of the leptin-serotonin pathway to decrease appetite without weakening bone."

HORMONE LEPTIN SUPRESSES BONE FORMATION BY SHUTTING OFF SEROTONIN

Dr. Karsenty and his colleagues discovered this pathway after first noticing the powerful effect of leptin - known for suppressing appetite - on bone mass accrual. Dr. Karsenty previously discovered that leptin is the most powerful inhibitor of bone formation in the body. This new study reveals that high levels of leptin suppress bone formation by shutting off the synthesis of serotonin in certain neurons in the brainstem.

Dr. Karsenty and his colleagues were surprised to observe that increased serotonin in the brainstem also increased appetite in mice. "We previously thought that leptin's modes of action on appetite and bone mass accrual were distinct," Dr. Karsenty said. "But we found instead that they behave more like twins - taking the same pathway through the brainstem. This correlates strikingly with the fact that leptin appears during evolution of bone cells when bone is first formed in the body."

Dr. Karsenty's team found that the appetite and bone pathways diverge once serotonin is released: one set of serotonin receptors turns on appetite, while a second increases bone mass accrual.

The findings may open the door for weight loss drugs that have no side effects on bone density.

"Theoretically, one can imagine that a drug that blocks only the appetite

receptors, but not the bone receptors, could help people lose weight without losing bone mass," Dr. Karsenty said.

Dr. Karsenty explained the surprising link between appetite and the skeleton by noting that the pathway monitors the amount of energy available to maintain bone.

"Our bones are constantly broken down and rebuilt during our lifetimes, and those renovations require an enormous and daily supply of energy," he said.

DISCOVERY CLARIFIES PREVIOUS RESEARCH; ADDS TO WORK ON BONE

In November 2008, Dr. Karsenty published a paper in Cell, which describes how serotonin released from the gut controls bone formation. Unlike the brain's serotonin, an increase in gut serotonin impairs bone formation. (see: www.physorg.com/news146922394.html)

Dr. Karsenty's new research shows that while both derivations of serotonin influence bone mass, the brain's serotonin dominates the effect of serotonin from the gut.

LEPTIN-SEROTONIN PATHWAY MAY ALSO EXPLAIN OSTEOPOROSIS/ANTI-DEPRESSANT LINK

In some studies, selective serotonin reuptake inhibitors (SSRIs), which are commonly used to treat depression, have been associated with osteoporosis in some patients.

SSRIs enhance the action of serotonin, and depending on the person, that

may lead to weakened, or strengthened bones, says study co-author J. John Mann, M.D., Ph.D., professor of translational neuroscience (in psychiatry and in radiology) and vice chair for Research in the Department of Psychiatry at Columbia University Medical Center and the New York State Psychiatric Institute.

"SSRIs work in the brain and in the gut, but in some people they may work more strongly in the gut," Dr. Mann said. "In that case, SSRIs could lead to a decrease in bone growth and osteoporosis."

The hope is that these research findings will help explain this phenomena and lead to potential treatment for this side effect.

Source: Columbia University Medical Center (news : web)