Serotonin could play a large role in bone loss

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Scientists have long known that calcium leaches from the bones both during lactation and in certain types of cancer. The driver behind these phenomena is a molecule called parathyroid hormone related protein (PTHrP), which is secreted by the mammary glands. The signal that regulates the secretion of PTHrP, and where this other unknown molecule exerts its influence, has remained a mystery. Now, in a new study using cells and tissues from mice, cows, and people, a team of researchers at the University of Cincinnati have identified this mystery molecule as serotonin, a neurotransmitter most often recognized for its role in happiness and well-being. The scientists also identified the specific receptor that serotonin acts on in mammary tissue. Understanding these two findings more deeply could lead to better ways to combat bone loss, potentially by using drugs that affect serotonin signaling.

The study is entitled "Mammary Gland Serotonin Regulates Parathyroid Hormone-Related Protein and Other Bone-Related Signals". It appears in the Articles in PresS section of the American Journal of Physiology – *Endocrinology and Metabolism*, published by the American Physiological Society (APS).

The researchers first examined lactating mice with a genetic mutation that prevented them from making serotonin efficiently and compared the amount of PTHrP in these animals to that in lactating normal, healthy mice. Next, they treated mouse and cow mammary cells with serotonin to see if it could induce secretion of PTHrP. They then treated human breast cancer lines with serotonin to see if the neurotransmitter could

change expression of PTHrP and a gene called Runx2, which is known to be involved in metastatic breast cancer and bone loss. Finally, they examined mice genetically modified to be missing a particular type of serotonin receptor, as well as mouse mammary cells, to determine which serotonin receptor might be responsible for influencing PTHrP secretion .

The researchers found that lactating mice genetically modified to prevent them from making serotonin efficiently (tryptophan hydoxylase 1 mutation) had significantly less PTHrP in their mammary glands compared to lactating normal, healthy mice, suggesting that serotonin is pivotally important for producing PTHrP. Supporting these findings, mouse and cow mammary cells treated with serotonin increased their expression of the gene responsible for PTHrP production by 8- and 20-fold, respectively. Treating three human breast cancer cell lines with serotonin increased expression of the PTHrP gene by 20-fold, and also increased expression of Runx2 as well. Though previous studies have shown that a serotonin receptor known as 5-HT7 is important for some mammary gland functions, this current study suggests that a different receptor, known as 5-HT2, is the target responsible for stimulating PTHrP levels.

These findings suggest that serotonin is a molecule that regulates PTHrP production, which in turn affects how calcium leaches from the bones during lactation and soft tissue cancer metastases. The authors suggest that this finding isn't completely surprising, since many antidepressants that act on serotonin have bone loss as a side effect. Understanding the action of serotonin better could help researchers develop better ways to preserve bone, they say, potentially through the action of drugs that act on the serotonin system.

"The complexity of 5-HT (serotonin) signaling demands cautious interpretations and the testing of new hypotheses and additional model

systems. With improved knowledge, serotonergic drugs may provide novel opportunities for therapeutic interventions," the authors say.

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