Serotonin Rising — The Bone, Brain, Bowel Connection

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In a recent article, Yadav et al.[1] elucidated the regulation of gut-produced serotonin by low-density lipoprotein receptor–related protein 5 (Lrp5) and the deleterious effect of serotonin on bone mass. This discovery reflects the rapid advances taking place in bone biology and lends support to three newly understood facts about skeletal physiology.

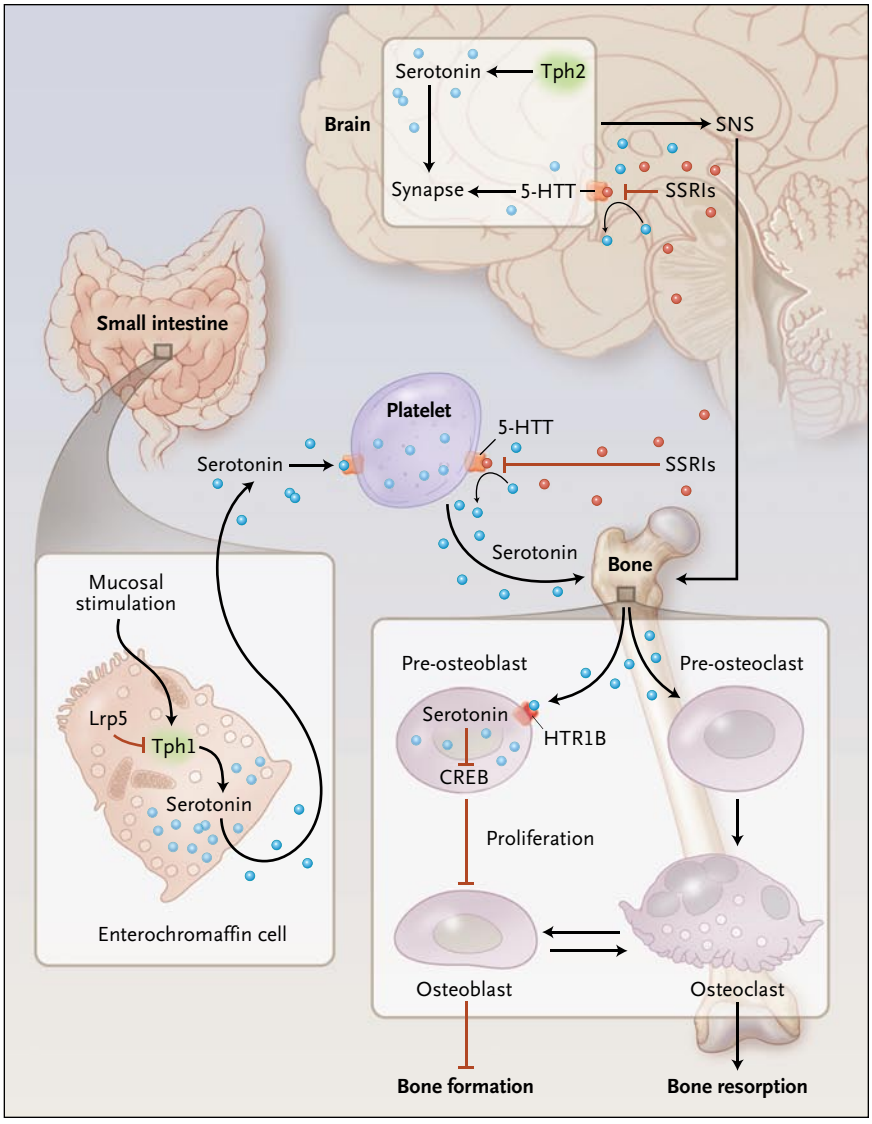
The first fact relates to the preeminence, in skeletal acquisition and maintenance, of a signaling pathway consisting of the mammalian homologue of wingless in drosophila (Wnt), Lrp5 or Lrp 6, and β-catenin. This pathway's importance was firmly established through clinical observations from gain-of-function and loss-of-function mutations in the *LRP5* gene, genetically engineered mouse models of Wnt–Lrp components, and in vitro studies of this signaling network in osteoblasts. The second fact is the importance of adipose tissue in modulating bone turnover. Studies in mice have established that leptin, an adipokine secreted from peripheral fat depots, plays a prominent role in bone formation by activating sympathetic signals through a hypothalamic relay, rather than through endocrine or paracrine pathways in the skeleton. The third and most provocative new concept is that the brain can have an important influence on the process of skeletal remodeling.

Although not all the mechanisms operative in the bone–brain connection have been defined, clinical observations suggest that this link may be very important. For example, after traumatic brain injury, the rate of new bone formation can suddenly and rapidly increase. Conversely, several studies have suggested that clinical depression may be associated with low bone mass. And most recently, two large cohort studies revealed that the use of selective serotonin-reuptake inhibitors (SSRIs), the class of drugs most frequently prescribed for depression, is associated with twice the annual rate of bone loss that occurs with older tricyclic antidepressants.[2]

How does the brain influence osteoblastic activity and regulate bone remodeling? Three mechanisms are plausible. First, in experimental states of bone formation, neural stem cells are early and critical components in the process of angiogenesis and osteoblastic recruitment. Second, there is strong evidence that there are β-adrenergic receptors on osteoblasts and that enhanced sympathetic activity can trigger these receptors to suppress bone formation and cause bone loss. Third, several groups have demonstrated the presence of neurotransmitter receptors on osteoblasts. These include the cannabinoid receptor type 1 and the family of neuropeptide Y (NPY) receptors (Y1 through Y5). In a recent study, Tam et al. demonstrated that the increased bone formation seen after traumatic brain injury was mediated by the cannabinoid receptor on osteoblasts.[3] Another neurotransmitter is NPY, which is an important hypothalamic mediator of appetite. NPY fibers have also been found in the bone marrow and periosteum, and several studies suggest that Y1 receptors in the osteoblast mediate the effects of NPY on bone remodeling.[4] Serotonin (5-hydroxytryptophan, or 5-HT) is another neurotransmitter with abundant receptors in bone and brain; recent efforts have focused on delineating its importance for skeletal acquisition and maintenance.

The physiological actions of serotonin are unique because of serotonin's ubiquitous nature as a neurotransmitter and its potent effects on target tissues. Most circulating serotonin arises from synthesis in the duodenum by specialized neuroendocrine enterochromaffin cells. The life cycle of serotonin begins with meal-induced mucosal stimulation of the gut, which increases the enzymatic activity of tryptophan hydroxylase (Tph) 1, leading to serotonin synthesis (see diagram). Serotonin is then released locally to stimulate intestinal peristalsis, as well as to enter the circulation, where it is taken up by platelets by means of the specialized 5-HT membrane transporter 5-HTT. Platelets can either store serotonin or release it during the clotting process to enhance vascular constriction and platelet aggregation.

In the central nervous system, serotonin synthesis is catalyzed by Tph2 (see diagram). It is released at neural synapses, and its reuptake is controlled by 5-HTT. Circulating serotonin does not cross the blood–brain barrier, so all its activity in the brain is mediated by synthesis, reuptake, and binding to a 5-HT receptor (Htr), of which there are several, within the central nervous system. Heritable or acquired variations in the molec-



Physiological Actions of Serotonin — Synthesis, Transport, Reuptake, and Receptor Activation — in the Mouse.

Yadav et al.[1] demonstrated that serotonin in the gut inhibited bone formation by means of the circulation, completely independently of serotonin activity in the brain. The term 5-HTT denotes the 5-hydroxytryptamine (5-HT) membrane transporter, CREB cyclic AMP response element-binding protein, Htr1b 5-HT receptor 1b, Lrp5 low-density lipoprotein receptor–related protein 5, SNS sympathetic nervous system, SSRI selective serotonin-reuptake inhibitor, and Tph tryptophan hydroxylase (1 and 2).

ular structure or function of Tph2, members of the Htr family, or 5-HTT lead to changes in serotonin levels in the central nervous system, which are thought to be responsible for depressive and affective disorders. Pharmacologic inhibition of 5-HTT by SSRIs enhances serotonin activity, and these agents have become extremely popular for treating several psychiatric disorders, including depression.

Previous efforts to study the effects of serotonin on bone cells had mixed results. The experiments centered on modifying 5-HTT or an Htr, primarily because experimental evidence had identified these proteins in osteoblasts and osteoclasts. In some studies in animals, pharmacologic impairment of 5-HTT activity or deletion of the gene encoding the Htr2b receptor resulted in high bone mass, whereas in other studies, deletion of the 5-HTT gene deletion was associated with very low bone mass that was independent of estrogen deficiency.[5] The latter findings were consistent with those from prospective cohort studies, in which both male and female patients who took SSRIs lost bone mass.[2]

Yadav et al. approached this experimental paradox in a different manner, focusing their efforts on the relationship of β-catenin, the intracellular signaling molecule for Lrp5, to serotonin metabolism.[1] It had previously been established that deletion of the *Lrp5* gene led to a profound reduction in histomorphometric markers of bone formation. What was perplexing to investigators was that if β-catenin, the canonical signaling node for Lrp5, was deleted only in osteoblasts, there was no effect on bone formation. This surprising finding caused Yadav et al. to look beyond bone for a site where Lrp5 was modulated and for a mechanism for that regulation. They found it in the most unlikely of places — the duodenum.

In severely osteoporotic $Lrp5^{-/-}$ mice, very high levels of Tph1 expression were found in the enterochromaffin cells, and when this gene was deleted only in the intestine, the bone mass of these $Lrp5^{-/-}$ mice was fully restored. Yadav et al. then demonstrated that circulating levels of seroto-

nin suppressed osteoblast proliferation by binding to the Htr1b serotonin receptor in bone. Most intriguingly, several patients with the rare genetic disorder osteoporosis pseudoglioma, a severe osteoporotic syndrome in children that results from a loss-of-function mutation in *Lrp5*, had high levels of circulating serotonin.

These data provide new perspectives and new opportunities for researchers and clinicians. Certainly they have caused us to rethink the skeleton as a tissue and its integration with the brain and gut. Second, studies are now under way to measure circulating levels of serotonin in individual patients and large cohorts of subjects who have postmenopausal osteoporosis to determine whether serotonin could be a marker of disease status. Third, the study by Yadav et al. has pushed SSRIs back into the spotlight and will probably energize investigators to examine the mechanism of bone loss from these agents and the potential for pharmacologically manipulating the 5-HTT system so that the primary effect of the SSRIs will be limited to the central nervous system. Finally, there may be an opportunity to design or modify existing drugs that inhibit Tph1 activity in the duodenum in the hope of enhancing bone mass. These outcomes and others raise the profile of serotonin and reinforce the thesis that there is a connection among bone, brain, and bowel.

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CABG vs. Stenting: Clinical Implications of the SYNTAX Trial

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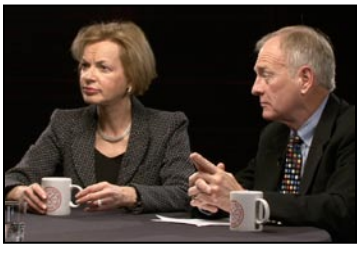

A video is available at NEJM.org

The SYNTAX trial compared coronary-artery bypass grafting (CABG) with percutaneous coronary intervention involving drug-eluting stents for patients with advanced coronary artery disease (results available at NEJM.org). On January 30, 2009, the *Journal* hosted a debate about the clinical implications of the study's findings that the need for repeat revascularization was significantly lower with CABG, but the risk of stroke was significantly higher. What should the new standard of care be? Watch the video and read the community's responses at NEJM.org.