METABOLIC BONE DISEASES

Targeting gut-derived serotonin promotes bone formation

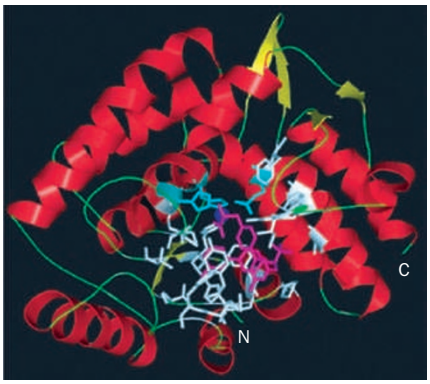
The development of a novel anabolic agent for the treatment of osteoporosis is a step closer to reality, following new research by Yadav *et al.* showing that an inhibitor of tryptophan hydroxylase 1 (Tph1) not only prevents but also reverses bone loss in ovariectomized rodents. This orally available agent, LP533401, blocks the synthesis of serotonin in the gut, which has been shown to be a crucial endocrine regulator of bone metabolism.

Previous research from the same group showed that gut-derived serotonin inhibits osteoblast proliferation and bone formation, but does not affect bone resorption. With this proof-of-concept study, they have now demonstrated that inhibition of Tph1, the enzyme that generates serotonin in the duodenum, can stimulate bone formation and increase bone mass, as well as protect against ovariectomy-induced bone loss. "The role of serotonin as a regulator of bone formation is a recent finding and this work is the first to show that manipulating this pathway could be used therapeutically to treat postmenopausal osteoporosis," says Patricia Ducy, one of the study's investigators.

In the study, once-daily oral administration of LP533401 immediately after ovariectomy prevented the development of osteoporosis in mice, with favorable affects on parameters of bone formation such as osteoblast numbers, bone formation rate and serum concentration of osteocalcin. Notably, administration of LP533401 also reversed osteopenia in mice when administered after bone mass loss had already occurred. "This last point was very important," says Ducy, "because osteoporosis is a 'silent disease' which is most often diagnosed once the bone loss is already serious. If one wants to have a relevant therapy it thus has to work in a curative manner."

The authors also demonstrated that LP533401 treatment fully rescued severe osteopenia in ovariectomized rats, the best-available rodent model of postmenopausal osteoporosis. μCT showed that LP533401 increased bone mass increase in a dose-dependent manner, but also that the rescue effect was observed even with the lowest dose of LP533401 administered (25 mg/kg per day). Biomechanical studies confirmed that these effects were beneficial to bone strength.

In rats, treatment with LP533401 compared favorably with subcutaneously administered parathyroid hormone (PTH). "The effects [of LP533401] on building bone mass are at least as good as those of PTH, which is the only anabolic drug currently approved," says Cliff Rosen, Senior Scientist at Maine Medical Center's Research Institute. Furthermore, Yadav *et al.* suggest that the two agents might act through different anabolic mechanisms, given that LP533401 was more efficient than high-dose PTH in the vertebrae but not in the long bones.



Importantly, the authors demonstrated that although LP533401 treatment decreased concentrations of circulating serotonin in a dose-dependent manner, the drug's effect on brain serotonin levels was negligible. In both rodent models, relatively modest reductions in circulating serotonin (~30%) were associated with profound increases in bone density.

Whereas antiresorptive therapies such as bisphosphonates can slow bone loss they do not rebuild bone mass. The results of the study by Yada *et al.* could represent an important step forward in the development of a new class of agents to treat osteoporosis. The provocative therapeutic message, says Rosen, is that "there are now nonskeletal targets to enhance bone mass."

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Original article Yadav, V. K. *et al.* Pharmacological inhibition of gut-derived serotonin synthesis is a potential bone anabolic treatment for osteoporosis. *Nat. Med.* **16**, 308–312 (2010)