Minireview: A Skeleton in Serotonin's Closet?

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The serotonin molecule plays a multifunctional role in mammalian homeostasis serving as a neurotransmitter in the central nervous system, a gut-derived mediator of peristalsis, and a circulating hormone that regulates appetite, cardiovascular function, and hemostasis. Recent evidence from the clinic and the bench highlight an unexpected target for serotonin action, the skeleton. Clinically, two classes of drugs, the second generation antipsychotic drugs (SGAs) and selective serotonin reuptake inhibitors (SSRIs), which modulate central and peripheral serotonin signaling, have been shown to alter bone remodeling although the mechanism is not clear. In contrast, genetically engineered mouse models have demonstrated a bimodal control system whereby gut-derived serotonin under the control of the Wnt/Lrp/β-catenin system acts systemically to suppress bone formation, whereas CNS serotonin activated by leptin modulates sympathetic outflow to the skeleton. In this brief review, we will summarize recent findings linking serotonin to the skeleton and discuss future directions for this new but challenging aspect of this multidimensional molecule. **(*Endocrinology* 151: 4103–4108, 2010)**

Serotonin (5-hydroxytryptamine, 5-HT) has confounded physiologists and endocrinologists for decades. It has defied our attempts to classify it as a hormone, in part because it is a gut-derived paracrine factor, a modulator of gastrointestinal motility, a neurotransmitter, an appetite mediator, a regulator of circadian rhythmicity, a determinant of platelet contraction and hemostasis, an integrator of energy modulation, and a molecule that when altered in central nervous system (CNS) synapses is related to depression (1–3). Indeed, serotonin defies a single classification; rather it is a simple, but evolutionarily conserved molecule with pleiotropic effects on multiple target tissues. And, remarkably, investigators have recently found another target for serotonin, the skeleton.

Bone remodeling is necessary to maintain skeletal mass but requires the tight coupling of bone formation to resorption. In certain physiological states as well as in several pathologic situations, the remodeling sequence can become imbalanced by alterations in energy status (4). For example, during chronic calorie deprivation such as anorexia nervosa, the skeleton adapts to profound deficiencies in nutrient status by switching to a catabolic state with increased bone resorption and suppression of bone formation (4). However, that switch is complex and demands hypothalamic integration from both peripheral energy depots and central neuronal input (5). Leptin, an adipokine secreted in response to expansion of triglyceride storage in the adipocyte, is the principal afferent signal to those higher centers in the hypothalamus; its actions are to regulate appetite and energy expenditure principally through activation of the sympathetic nervous system as an efferent modulator of energy depots (6). Importantly, but not surprisingly, the skeleton is also targeted by hypothalamic output. The Karsenty laboratory has been out front in efforts to demonstrate that control of skeletal mass relative to energy status occurs through the leptin-hypothalamic-sympathetic nervous system, although other neurotransmitters such as neuropeptide Y have also been implicated in both central and peripheral regulation of bone mass (7–9).

Serotonin is found in high concentrations in certain portions of the CNS acting as a neurotransmitter to regulate metabolic rate and appetite in hypothalamic nuclei, thus making it another potential modulator of energy status (3). Serotonin also influences cognitive and psychological function in higher centers of the brain (1, 3). Drugs that target serotonin receptors or transporters have been

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Abbreviations: 5-HT, 5-Hydroxytryptamine; 5-HTP, 5-hydroxy-L-tryptophan; 5-HTT, 5-hydroxytrophan transporter; CNS, central nervous system; SGA, second generation antipsychotic agent; SSRI, elective serotonin reuptake inhibitor; Tph, tryptophan hydroxylase.

developed to treat a wide range of psychiatric disorders from depression to schizophrenia to the autism complex. Two classes of drugs that have effects on CNS serotonin are the second generation antipsychotic agents (SGAs) and the selective serotonin reuptake inhibitors (SSRIs). Use of these agents has increased recently, and with wider utilization has come recognition of significant adverse metabolic and skeletal events. Dramatic weight gain, often associated with the metabolic syndrome, bone loss, and greater fracture prevalence have startled clinicians and provided an impetus for studying the serotonin-metabolic-CNS-skeletal connection.

Serotonin's peripheral effects occur through local synthesis in the enterochromaffin cells of the gut. Its principal function is to regulate intestinal peristalsis, and its secretion is triggered by food in the gut. The enzyme responsible for serotonin synthesis in the gut is Tph1, and an inhibitor of this enzyme is currently in phase II trials for the treatment of irritable bowel syndrome. The surprising discovery that *Tph1* expression was one of the most markedly up-regulated genes in a *Lrp5*-deficient mouse with low bone mass led to a series of studies demonstrating serotonin signaling in the regulation of bone mass. In this brief review we will summarize recent findings both from human and mouse models regarding the central regulation of bone remodeling and discuss the limitations of current studies as well as the immense potential for targeting serotonin either centrally or peripherally for the treatment of osteoporosis.

Serotonin Physiology

Serotonin (5-Hydroxytryptamine; 5-HT) is a neurotransmitter and governs a wide range of physiological functions from complex behavioral activities to gastrointestinal peristalsis depending on its site of synthesis (10–12). Serotonin is generated from L-tryptophan, which is hydroxylated to 5-hydroxy-L-tryptophan (5-HTP). This reaction is catalyzed by the rate-limiting enzyme, tryptophan hydroxylase (Tph). 5-HTP is then converted into serotonin (13). Circulating serotonin is produced in the enterochromaffin cells of the duodenum by Tph1 and is released into the circulation, to be taken up principally by platelets through the 5-hydroxytrophan transporter (5-HTT) (13). Gut-derived serotonin accounts for 95% of total serotonin in the body, but it does not cross the blood-brain barrier (11). Platelet serotonin is an important regulator of cellular contraction and serves as a modulator of hemostasis once the clotting system is activated (3). In the CNS, serotonergic neurons mainly reside in the dorsal, median, and caudal raphe nuclei of the brainstem (2, 3). These project to almost of all parts of the brain including the hypothalamus (2, 3). In contrast to Tph1, Tph2 is responsible for the production of local production of serotonin in the CNS (14). Serotonin receptors consist of at least seven major families and at lease 14 subtypes, and these have been found in many tissues both centrally and in the periphery (2). Serotonin in the brain is involved in the regulation of food intake as evidenced by mouse models lacking 5-HT_{1A}R, 5-HT_{1B}R, or 5-HT_{2c}R, all of which have been shown to exhibit increased food intake (1). With respect to the role of serotonin in the regulation of skeletal mass, there is consistent evidence that 5-HT and 5-HTT are expressed in osteoblasts as are the serotonin receptors (15–17). In addition, 5-HTT is also expressed in RANKL-induced osteoclasts *in vitro* (18). Genetic models that induce functional changes in the receptors or transporters have been shown to affect peak bone mass in mice (19–21). In humans, at least one study has shown that serum serotonin is weakly but inversely correlated with total body and spine areal bone mineral density and with femur neck total and trabecular volumetric bone mineral density (22). These skeletal phenotypic differences were associated with alterations in trabecular number, and trabecular thickness at the radius assessed by high-resolution peripheral quantitative CT. Although body weight is a confounder in these regression analyses, several key parameters were still significantly different following the adjustment for body mass index (22).

Serotonin regulation of skeleton: indirect implications from clinical observations

SGAs such as risperidone have been widely used for the treatment of behavioral problems in autism spectrum disorders and acute psychotic symptoms because of their effectiveness and low adverse event rates compared with earlier first generational antipsychotic drugs (23). However, accumulating evidence suggests there may be serious long-term adverse metabolic effects from these drugs, including weight gain, nighttime eating, and the metabolic syndrome (24). With respect to the skeleton, bone loss has been associated with schizophrenic individuals taking psychotropic medication (25). Howard *et al.* (26) reported a higher risk of hip fractures among individuals using antipsychotic medications. Because the SGAs act as a potent blocker for the 5-HT_{2A} receptor and are a weaker inhibitor of the dopamine D2 receptor (27), these data suggest that blockade of serotonin signaling through 5-HT receptor could have a negative effect on skeletal accrual. However, the SGAs also cause various degrees of hyperprolactinemia, which can accelerate bone resorption by suppressing gonadotropin secretion (28). Prolactin is produced by lactotrophs in the anterior pituitary and is negatively regulated by dopamine signaling from tuberoinfundibulum neurons in

arcuate nuclei in the hypothalamus through dopamine D2 receptors (23, 28). The SGAs also inhibit dopamine D2 receptors as well as the 5-HT_{2A} receptors (27), so it is conceivable that the SGAs cause hyperprolactinemia through inhibition of dopamine signaling. Nevertheless, it is still unclear whether the inhibition of 5-HT_{2A} receptor by SGAs, which is operative within the CNS, has any role in the pathogenesis of bone loss. Interestingly, we recently observed that pubertal male C57BL/6J mice treated with risperidone had significant trabecular bone loss due to increased bone resorption (29). Surprisingly, these mice did not gain weight but rather showed an adipose redistribution phenotype with enhanced marrow adiposity and significant hepatic lipid deposition. Thus it is likely that the bone loss with these agents is multifactorial and relates to both central and peripheral alterations in serotonin, prolactin, and the gonadotropins.

Selective serotonin reuptake inhibitors in human and mouse models

SSRIs, which have been widely used for depression, have recently been associated with bone loss and an increased risk for fracture (30–37). In support of this finding, 5-HTT knockout mice exhibit reduced bone mass (19). In line with this, treatment of SSRIs has been reported to reduce bone mass, although the effect of SSRIs on bone mass in experimental models is not clear (38, 39 and see Table 1). SSRIs are inhibitors of 5-HTT and increase the local concentration of serotonin at the pericellular space, although its chronic use reduces serotonin content in the platelets by 80–95% (40). Therefore, one has to be cautious in interpreting these clinical findings because SSRIs are likely to inhibit 5-HTT function at multiple levels including the CNS, platelets, and the skeletal microenvironment. In that respect, as noted, osteoblasts and osteoclasts express serotonin receptors and 5-HTT (13, 15–18), making it likely that serotonin plays some role in lineage allocation and/or osteoblast and osteoclast function/differentiation. It is conceivable that the SSRIs increase the skeletal micro-concentration of serotonin through inhibition of uptake by osteoblasts thereby prolonging serotonin exposure, although even in platelets it is still controversial how a reduction of serotonin content or alterations in reuptake in platelets directly affects their function. In addition, there are certain to be other mechanisms. Peripheral serotonin synthesis is catalyzed by Tph1 in the gut, and circulating serotonin can have a direct negative effect on skeletal mass through activation of osteoblastic serotonin receptors, although these findings need to be confirmed independently (21). Thus the SSRIs may decrease bone mass by enhancing the local concentration of serotonin.

However serotonin pharmacology is not simple. The SSRIs cross the blood brain barrier and block reuptake of serotonin in the CNS, thus increasing local serotonin concentrations. Serotonin may activate its receptors in the ventromedial hypothalamus, which in turn could modulate sympathetic outflow and increase bone mass (19). The discrepancy between patients treated with SSRIs and mouse models may come from the site and context specific nature of expression profiles for 5-HTT. 5-HTT expression is limited to serotonergic neurons in the raphe nuclei of adults, but broader expression profiles of 5-HTT are observed in the fetal brain of rodents (41, 42). Thus, use of SSRIs in adults may have a distinctly different effect on central serotonergic regulation of bone mass from those observed in genetically engineered mouse models. Furthermore, an appreciation of an increasing level of complexity and redundancy in the serotonin system continues to confound our understanding of the role of SSRIs in modulating bone mass. For example, Yadav and colleagues (21) demonstrated that inhibition of *Tph1* in the gut (it is not expressed in the brain) resulted in high skeletal mass and this enzyme was under the control of Lrp5, a

TABLE 1. Genetically engineered mouse models for analyzing skeletal action of serotonin

Mouse		Skeletal phenotype	Reference
5-HTT$^{-/-}$	Global knock out of serotonin transporter	Low bone mass, low bone formation	20
Tph1$^{-/-}_{gut}$	Gut-specific *Tph1* knock out under *villin* promoter	Reduced serotonin levels in the gut High bone mass, increased bone formation	21
Tph1$^{-/-}_{do}$	Osteoblasts specific *Tph1* knock out under *al(I)Col* promoter	Minimal increase in bone mass	21
Htr1b$^{-/-}$	Global knock out of *Htr1b. Htr1b* is the most abundantly expressed serotonin receptor in osteoblasts	High bone mass, increased bone formation	21
Tph2$^{-/-}$	Global knock out of *Tph2*	No detectable serotonin in the CNS Low bone mass, low bone formation, increased bone resorption	19
Htr2c$^{-/-}$	Global knock out of *Htr2c. Htr2c* is most abundantly expressed in the hypothalamus	Low bone mass, low bone formation, increased bone resorption High sympathetic activity	19

5-HTT, 5-HT(5-hydroxytryptamine) transporter; Tph, tryptophan hydroxylase; Htr, 5-HT receptor.

coreceptor for Wnt signaling. Conditional deletion of *Tph1* in the gut confirmed there was increased bone formation and high bone mass, with very low circulating serotonin, suggesting a peripheral effect of endocrine secreted serotonin on bone mass (21). Notwithstanding these findings, it is still difficult to extrapolate from mouse models to define precisely how the SSRIs mediate their effects on bone mass.

Regulation of skeletal mass by serotonin in the brain

To further understand the role of serotonin in the CNS and its interaction with skeletal acquisition independent of the gut, Yadav *et al.* (19) took a genetic approach. They analyzed $Tph2^{-/-}$ mice because Tph2 is the rate-limiting enzyme for the production of serotonin in the CNS. $Tph2^{-/-}$ mice showed almost complete absence of serotonin in the brain despite normal blood serotonin levels. Skeletal phenotyping revealed low bone mass both in long bones and vertebrae accompanied by impaired bone formation and increased bone resorption, implying that serotonin in the CNS has a significant positive role in the regulation of skeletal accrual. Based on their observation that the skeletal phenotype in $Tph2^{-/-}$ mice is the mirror image of the phenotype observed in β-adrenergic receptor ($Adr\beta2$) knockout mice (8) the authors hypothesized that the low bone mass phenotype in $Tph2^{-/-}$ mice was caused by increased sympathetic tone. To test this hypothesis, Yadav *et al.* (19) generated $Tph2^{-/-}$;$Adr\beta2^{+/-}$ mice and found the low bone mass phenotype in $Tph2^{-/-}$ mice was rescued in the absence of one allele of $Adr\beta2$. These data suggest that serotonin in the CNS regulates skeletal acquisition through suppression of sympathetic tone, thereby implicating the hypothalamus as a principal target for serotonin.

This same group next investigated the central mechanism by which serotonin affected bone mass. Because VMH neurons are critical integrators of energy metabolism through modulation of sympathetic tone, the authors used genetically engineered mouse models to demonstrate that serotonergic neurons targeted the VMH thereby affecting sympathetic output. First they identified that neurons in the brain stem projected to the VMH area in the hypothalamus. Second, deletion of *Htr2c*, which is the most abundantly expressed serotonin receptor in the hypothalamus, caused low bone mass accompanied by increased sympathetic activity. The double $Tph2^{+/-}$; $Htr2c^{+/-}$ mice exhibited a low bone mass phenotype with high sympathetic tone despite normal skeletal mass and sympathetic tone in $Tph2^{+/-}$ and $Htr2c^{+/-}$ mice. Third, rescuing the *Htr2c* expression in the VMH neurons on the $Htr2c^{-/-}$ background reversed the low bone mass phenotype of $Htr2c^{-/-}$ mice. These findings were provocative but left a more important question: where did leptin fit in this homeostatic scheme?

Leptin regulation of brain serotonin synthesis and bone mass

Leptin is produced by adipocytes and regulates a wide range of physiological functions including energy homeostasis, appetite, reproductive capacity, and bone accrual (6). The complexity of leptin's actions on skeletal accrual lies in the difference between the direct effects of leptin on bone and its indirect actions through hypothalamus (43). It is now well established that leptin decreases vertebrae trabecular bone mass through indirect activation of the sympathetic nervous system via VMH neurons (7, 9). Takeda *et al.* (9) reported that chemical lesioning of VMH neurons by gold thioglucose increased bone mass, thereby recapitulating the skeletal phenotype observed in *ob*/*ob* mice. But intriguingly, conditional knockouts of the leptin receptor in VMH neurons using the SF-1 promoter did not show a skeletal phenotype (44). These data pointed to an important role for leptin mediation of sympathetic activity but paradoxically not directly through VMH neurons. This conclusion, however, was counter to

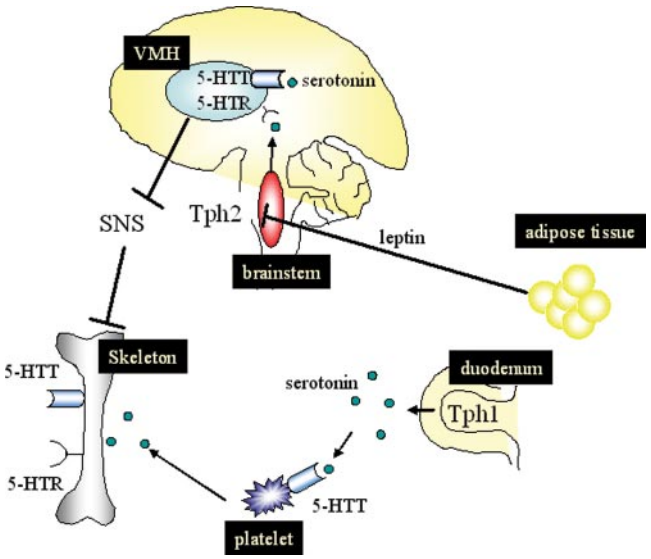

FIG. 1. Schematic model of serotonin action on skeleton. Adipose tissue-derived adipokine, leptin, suppresses *Tph2* expression in the brain stem, resulting in the decreased amount of serotonin in the brain. Brain-derived serotonin, catalyzed by Tph2, binds to serotonin receptor (5-HTR) in the ventral medial hypothalamic (VMH), inactivates tone from the sympathetic nervous system (SNS), and enhances skeletal acquisition. Thus, leptin induces bone loss by suppressing serotonin signaling in the VMH. Gut-derived serotonin, catalyzed by Tph1, is up-taken by platelet through 5-HTT and has been shown to suppress skeletal accrual. Osteoblasts and osteoclasts express 5-HTR and serotonin transporter (5-HTT), and serotonin network is likely to be operative at the skeletal environment. Expression of 5-HTT in the brain is developmental stage-dependent,, and the hypothalamic expression of 5-HTT needs to be determined. Tph, Tryptophan hydroxylase; 5-HTR, 5-HT(5-hydroxytryptamine) receptor; 5-HTT, 5-HT transporter.

previous evidence suggesting that leptin after crossing the blood-brain barrier directly targets the hypothalamus. Yadav *et al.* (19) suggested that the VMH was the ultimate target for leptin but that there was an intermediate step in the CNS process. These authors found that *Tph2* expression was increased in *ob*/*ob* mice and leptin ICV infusion decreased *Tph2* expression. Leptin strongly suppressed the activity of serotonergic neurons in wild-type mouse, but not in mice lacking the leptin receptor in serotonergic neurons. Moreover, these mice showed a high bone mass phenotype. These lines of evidence together with the studies showing a pro-osteogenic activity of serotonin in the CNS through its receptor in VMH nuclei suggest that effect of leptin on skeletal accrual is mediated through its receptor expressed in serotonergic neurons residing in the brain stem. It appears from these studies that CNS serotonin mediates leptin's effect by binding to its receptors in VMH neurons, completing a feedback loop for afferent signaling through the brain stem.

Summary: More Questions than Answers

The likelihood that serotonin regulates bone mass through both central and peripheral mechanisms pose as many questions as answers (Fig. 1). It also provides tremendous research opportunities. Although there are convincing data in conditional mouse models, there are still inconsistencies between animal models and clinical observations. For example, the osteoporotic phenotype has not been reported in patients with serotonin producing cartinoids despite high concentrations of free and platelet serotonin (45, 46). Future studies will be needed to fully define this complex regulatory system in humans; for example: how is the balance maintained between the pro-osteogenic effects of central control *vs.* the negative effects of circulating gut-derived serotonin? Is there a threshold effect so that at a critical circulating serotonin level an increase in bone formation occurs? If so, why is this necessary for skeletal maintenance? And furthermore, what do circulating serotonin concentrations really mean, particularly because 90% or more is taken up by platelets. If leptin's central effects are mediated through the serotoninergic system originating in the brain stem, how close is this connection to the VMH centers for appetite and energy metabolism? How does the suprachiastmatic nucleus, which modulates light-dark signals from the retina and energy intake, relate to serotonin production and modulation of bone mass? Can we develop anabolic skeletal agents that selectively block serotonin production in the periphery or enhance it in the brain to stimulate bone formation? How closely do the mouse models of conditional deletions in the serotonergic regulatory system recapitulate human metabolism and skeletal turnover? These and other questions provide fertile ground for determining whether there is a skeleton in serotonin's closet and, if so, how this system can be modulated therapeutically to treat osteoporosis.

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