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PERSPECTIVES

Depression, Selective Serotonin Re-Uptake Inhibitors and the Regulation of Bone Mass

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Abstract

An increasing number of studies suggests that low bone mineral density (BMD) is disproportionately prevalent among patients with depressive disorders. However, authorities such as the National Institutes of Health, the National Osteoporosis Foundation, the National Osteoporosis Society (UK) and Osteoporosis Canada, have not yet officially acknowledged depression as a risk factor for osteoporosis. This could be because the causal relationship between depression and low bone mass has not been fully elucidated. In a recent study using a mouse model for depression we have demonstrated a causal relationship between depressive-like behavior and bone loss, which could be prevented by an antidepressant. The depression-induced bone loss was associated with increases in skeletal norepinephrine and serum corticosterone levels. Bone loss, but not the depressive behavior, could be blocked by a β-blocker, portraying an important role for adrenergic signaling in communicating depressive signals to the skeleton. For an unknown reason, selective serotonin re-uptake inhibitors (SSRIs), which have emerged as first-line agents in the treatment of depressive disorders, appear to have deleterious skeletal effects in both humans and experimental animals. The antidepressant effect of SSRIs is attributed to increased serotonin levels. Hence, their negative skeletal effect has to be evaluated not only in view of the causal relationship between depression and bone loss, but also vis-à-vis the presence of a skeletal serotonergic system, the stimulation of bone formation and bone density by exogenously administered serotonin and the paradoxical negative regulation of bone formation and bone mass by serum, gut-derived serotonin. Physicians should be aware of the unfavorable consequences of SSRIs on BMD and fracture risk. *IBMS BoneKEy*. 2009 January;6(1):8-15.

Keywords: Adrenergic signaling; Antidepressant; Bone loss; Bone mass; Bone remodeling; Depression; Fracture; Glucocorticoids; Major depressive disorder; Norepinephrine; Osteoporosis; Selective serotonin re-uptake inhibitors; Serotonin; Serotonin receptors; Sympathetic nervous system.

Introduction

In the last decade and a half, the possible association between depression and osteoporosis has been the subject of a growing body of research implicating major depressive disorder (MDD) as a risk factor for bone loss and osteoporosis (reviewed in (1)). Like osteoporosis, MDD is a prevalent disease, considered the second leading global cause of years of life lived with disability (2). Both depression and osteoporosis are approximately 3-fold more common in women than in men (3;4).

In spite of the high prevalence of both diseases, most official publications emanating from authorities such as the National Institutes of Health, the National Osteoporosis Foundation, the National Osteoporosis Society (UK) and Osteoporosis Canada, do not fully acknowledge depression as a risk factor for bone loss and osteoporosis, apparently because the literature on the relationship between these conditions is inconclusive. Some studies report that MDD patients suffer from up to 15% bone loss, while others, particularly large-scale population-based studies, show a weak or no relationship between the two conditions.

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Causal Relationship Between Depression and Bone Loss

That the association between depression and osteoporosis has not been officially acknowledged could also be because the causal relationship between MDD and osteoporosis has not been fully elucidated. In the early 1980s, osteoporosis researchers suggested that depression is one of the major negative consequences of bone loss and osteoporotic fractures. These researchers believed that osteoporosis occurred first, leading to a reactive depression. A similar, but distinct psychiatry literature reported that low bone mineral density (BMD) appears to be an undesirable consequence of MDD (reviewed in (5)). The perspective that osteoporosis causes depression argues that MDD results from the pain and discomfort associated with osteoporotic fractures. The other approach, that depression is the causal process, claims that most studies demonstrate an association of depression with low BMD rather than with an increased fracture rate. That depression is the causal attribute has been further proposed based on the well-established depression-induced increases in glucocorticoids and norepinephrine (6), agents also known to suppress bone formation and bone mass (7;8).

In support of the latter concept, we have recently demonstrated loss of bone mass and architecture in mice with chronic mild stress (CMS), an established rodent model for depression (Fig. 1). The bone loss in this

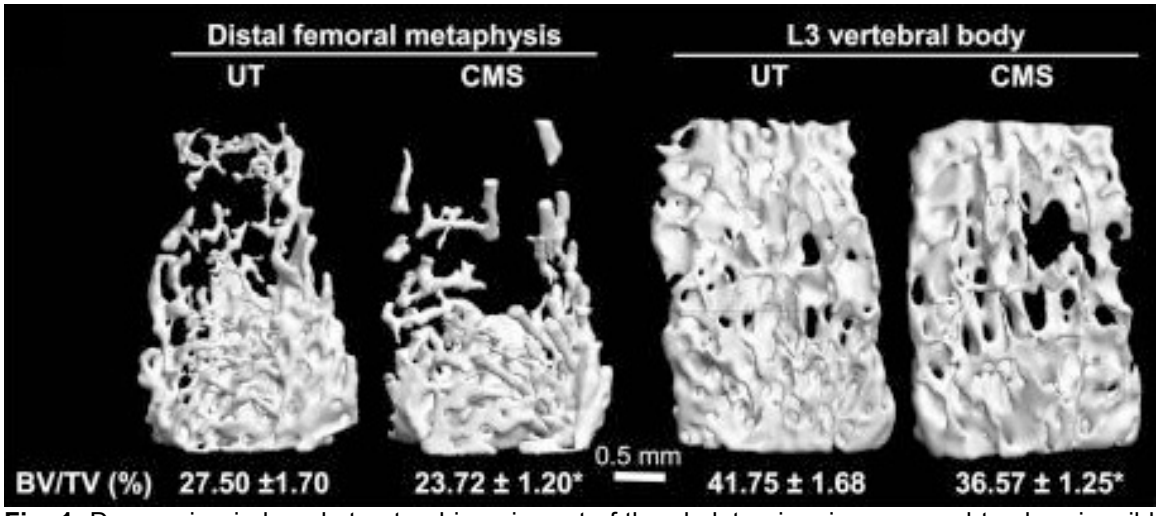

Fig. 1. Depression-induced structural impairment of the skeleton in mice exposed to chronic mild stress (CMS) for 4 weeks or left untreated (UT); μCT analysis. Copyright (2006) National Academy of Sciences, USA (9).

model results mainly from decreased bone formation. The reduced bone formation, the trabecular bone loss, measured by micro-computed tomography (μCT) in the distal femoral metaphysis and lumbar vertebral bodies, as well as the depressive symptoms (reduced sucrose preference and social exploration) could be prevented by the antidepressant drug imipramine (9). As expected, the depressive-like state was associated with increased norepinephrine levels in bone and elevated serum corticosterone. Furthermore, the CMS-induced bone loss, but not the depressive-like state, could be prevented using the β-adrenergic antagonist, propranolol, portraying bone sympathetic innervation as a brain-to-bone pathway communicating depressive signals to the skeleton. Although serum corticosterone is also elevated in mice subjected to CMS, the role of the hypothalamic-pituitary-adrenal (HPA) axis in depression-induced bone loss remains to be unraveled, since it is unclear whether the elevation of serum corticosterone induced by CMS is sufficient to cause a negative

bone remodeling balance and bone loss. Interestingly, although leptin has been implicated in both depression and the regulation of bone remodeling (10;11), no relationship could be established between serum leptin levels and the CMS-induced bone loss.

The adrenergic system and HPA-axis are the most studied pathways mediating depressive signals from the central nervous system (CNS) to the periphery. However, several other systems implicated in both depression and osteoporosis could be involved in this process, such as the endocannabinoid system (12;13) and inflammatory cytokines like interleukin (IL)-1 (14;15), IL-6 (16;17) and tumor necrosis factor α (18;19). In addition, dietary and behavioral patterns commonly observed in psychiatric patients may also contribute to the pathogenesis of osteoporosis.

Cigarette smoking is more common in psychiatric populations (20). It increases the risk for the onset of MDD (21;22) and has repeatedly been shown to negatively influence bone mass in cross-sectional studies of both men and women (23;24). Likewise, depression and excessive alcohol consumption are common co-morbidities and alcohol abuse is a recognized risk factor for osteoporosis (25;26). Finally, although with a less well-defined cause-effect relationship, changes in food consumption are typically associated with depression and certain nutrients reported to be deficient in patients with MDD are required for the maintenance of good bone health (27).

The Skeletal Serotonergic System

Biogenic amine transporters are important regulators, controlling the synaptic and extracellular concentrations of these amines in the CNS by their high-affinity re-uptake from the extracellular to the intracellular milieu. They are also major targets for many antidepressant drugs that inhibit their activity, thereby potentiating the effect of the biogenic amines. The skeletal role of these drugs, in particular that of the selective serotonin re-uptake inhibitors (SSRIs), which are targeted to the serotonin transporter, has recently attracted substantial interest because of the drugs' potential impact on osteoporosis and resultant fractures.

Serotonin (5-hydroxytryptamine, 5-HT) is a monoamine neurotransmitter best known for its role in the CNS, gastrointestinal (GI) tract and cardiovascular (CV) system. In the CNS, it is produced by pre-synaptic neurons, and is released into the synaptic gap. This results in activation of pre- and post-synaptic 5-HT receptors, thus influencing a handful of behavioral, physiological and cognitive functions (28; 29). In the GI tract, 5-HT is synthesized and secreted by enterochromaffin cells and diffuses to enteric nerve endings to stimulate peristalsis (30;31). In both the CNS and GI tract, the duration and intensity of serotonergic activity is enhanced by the sodium chloride-dependent 5-HT transporter (5-HTT) (32;33). In the CV system, 5-HT is taken up primarily by platelets via 5-HTT and stored in dense granules (34). It is released by activated platelets and induces blood vessel constriction or dilation (35), and smooth muscle cell hypertrophy and hyperplasia (36).

Osteoblasts, osteocytes and osteoclasts express functional 5-HT receptors and 5-HTT (reviewed in (37)). In osteoblasts, 5-HT receptor agonists influence cell proliferation, potentiate the parathyroid hormone-induced increase in AP-1 activity and modulate the cellular response to mechanical stimulation. In osteocytes, 5-HT increases whole-cell cAMP and PGE_2 levels, which are also involved in the transduction of mechanical stimuli (38). In osteoclasts, 5-HT and 5-HTT have been shown to affect differentiation, but not activity (37).

What is the source of 5-HT in bone tissue? The CNS does not appear to be a likely source of 5-HT available to bone cells, as the blood-brain barrier is impermeable to 5-HT and serotonergic innervation has not yet been demonstrated in the skeleton. As in the case of other neurotransmitters, such as endocannabinoids (12), 5-HT could be synthesized and released by bone cells and act in an autocrine/paracrine manner. Indeed, mRNA transcripts for tryptophan

hydroxylase-1 (Tph1), a rate-limiting enzyme in 5-HT synthesis, have been detected in osteoblast and osteocyte cell lines (39). Most of the organism's 5-HT is produced in the GI tract and stored in dense granules in platelets. Because 5-HT from this source is released only upon platelet activation (34), it is an unlikely activator of bone cell 5-HT receptors. However, a small fraction of the GI-derived 5-HT remains in the serum (40). A recent study suggests that serum 5-HT is a negative regulator of osteoblast proliferation, bone formation and bone mass (41). In view of the expression of Tph1 in osteoblasts, the local production of 5-HT should now be followed directly in bone tissue from wild type and Tph1/Tph2 knockout mice (42) and in the bone of mice deficient in other genes known to regulate Tph activity (41).

What is the physiologic role of the skeletal serotonergic system? The diversity of actions of 5-HT results from the occurrence of multiple 5-HTRs, which are divided into seven classes based on their signaling pathways (43). Of these, only 5-HT_{1A}R, 5-HT_{2A}R, 5-HT_{1B}R and 5-HT_{2B}R are expressed in osteoblasts and only the expression of 5-HT_{2B}R is increased during osteoblast differentiation. Mice deficient in 5-HT_{2B}R have accelerated age-related, low turnover bone loss, secondary to impaired osteoblast recruitment and proliferation (44). In line with these findings, rats treated with 5-HT have increased BMD (45). In contrast, mice deficient in osteoblastic 5-HT_{1B}R have a high bone mass phenotype, secondary to increases in osteoblast number and bone formation (41). Disruption of the 5-HTT gene or pharmacological inhibition of 5-HTT by SSRIs leads to a low bone mass phenotype in growing mice (37). These findings suggest that 5-HT has different age-dependent effects: it inhibits peak bone mass accrual in the growing skeleton and maintains bone remodeling and bone mass at balance in the adult skeleton. However, this explanation is challenged by the finding of deleterious effects of SSRIs, both on trabecular and cortical bone, in adult mice (46). Obviously, these apparently paradoxical data indicate that further studies are required to elucidate issues such as the differential activity of the various 5-HTRs, the possible interaction between 5-HTRs and 5-HTT and possible dose-dependent effects of 5-HT. In addition, systemic, indirect effects of SSRIs need to be ruled out using conditional gene deletion in the osteoblastic and osteoclastic cell lineages.

SSRIs and Bone Health

In humans, SSRIs have emerged as first-line agents in the treatment of depressive disorders. Most clinical studies report that antidepressants in general, but mainly SSRIs, are associated with low BMD and a dose-dependent increase in the risk of fractures and low bone mass in children (reviewed in (47)). The reason for these deleterious effects is not known but may be linked to direct and indirect 5-HT effects on bone cells and the risk of falls, which is increased in SSRI users, especially after prolonged administration (48). Hence, physicians treating growing children and elderly depressive patients should be aware of the unfavorable short- and long-term consequences of SSRIs on BMD and fracture risk.

Finally, depression is a complex process, and is likely to involve numerous different disorders of CNS signaling. In view of the number of so-called neurotransmitters/neuropeptides and their receptors expressed in bone (*e.g.*, endocannabinoids, neuropeptide Y, substance P, opioids (49-52)), it should be emphasized that the serotonergic system and SSRI drugs are probably only one example of the manifestation of this crossover of signaling defects and drug effects.

Conflict of Interest: None reported.

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