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# The therapeutic potential of descending regulatory pathways from brain to bone in osteoporosis: focusing on the brain-bone axis

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Osteoporosis (OP) is a growing global health concern, characterized by reduced bone mass, deterioration of bone microarchitecture, and consequently increased bone fragility. The brain-bone axis, a complex regulatory network encompassing the nervous, endocrine, and immune systems, elucidates the central role of the brain in regulating bone homeostasis. Consequently, this axis has become a major focus of interdisciplinary research into the pathogenesis of OP. However, the current understanding of the descending regulatory pathways from the brain to the bone remains incomplete. Therefore, this paper preliminarily explores the mechanisms and experimental evidence of different descending regulatory pathways from a new perspective. It integrates multiple descending regulatory pathways, discusses some of their interrelationships, and reveals the complex network nature of central bone metabolism regulation. Our objective is to elucidate the role of the central nervous system (CNS) in OP pathogenesis, thereby offering new insights and directions for future research on its prevention and treatment.

## KEYWORDS

bone fragility, brain-bone axis, interrelationship, neuroendocrine, osteoporosis

## 1 Introduction

Osteoporosis (OP) is a systemic metabolic bone disease characterized by reduced bone mass, impaired bone microarchitecture, and increased bone fragility (1). The fundamental mechanism involves an imbalance between osteoblast-mediated bone formation and osteoclast-mediated bone resorption. This imbalance, characterized by a relative predominance of resorption over formation, ultimately leads to bone loss. Postmenopausal osteoporosis (PMOP), a major subtype of primary OP, is primarily driven by the rapid decline in estrogen levels during menopause. The most significant bone loss typically occurs within the first 2–3 years following the onset of menopause. The global burden of OP is escalating in tandem with population aging. In China, the direct medical costs attributable to osteoporotic fractures are projected to reach \$18.9 billion by 2035, with this figure likely rising by approximately 34% when it comes to 2050 (2). OP

poses a substantial societal burden and profoundly compromises the quality of life, especially in women. Consequently, the identification of novel therapeutic targets is of paramount importance. In this context, emerging evidence of a close relationship between the central nervous system (CNS) and bone metabolism offers promising new directions and insights for the OP prevention and treatment (3).

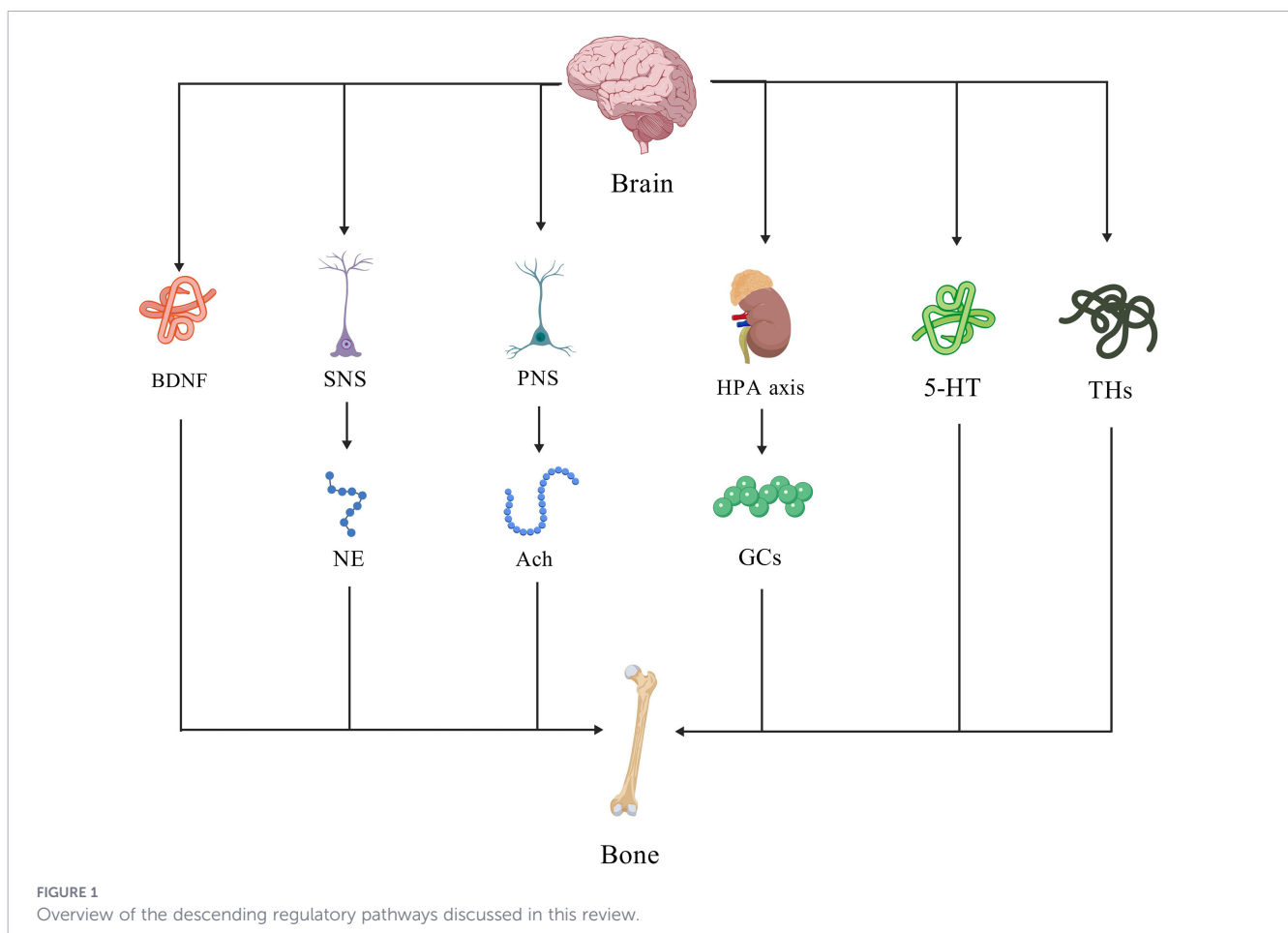
The brain-bone axis is an emerging research paradigm that describes a complex bidirectional regulatory network connecting the CNS and the bone. This axis integrates components ranging from specific brain structures [e.g., the cerebral cortex, hypothalamus, and autonomic nervous system (ANS)] to a multitude of signaling molecules, including neuroendocrine factors and hormones. Ultimately, it functions as the principal pathway through which the nervous system centrally regulates the balance between osteoblast-mediated bone formation and osteoclast-mediated bone resorption, thereby maintaining skeletal homeostasis (3, 4). The concept of the brain-bone axis underscores the critical role of the CNS in OP, presenting promising new avenues for identifying therapeutic targets and developing innovative prevention strategies.

Based on recent literature, this review summarizes the current understanding of the brain-bone axis, centering on three key aspects: the mechanisms underlying key signaling molecules, and the direct regulation of several bone via neural pathways, (Figure 1). All Figure ures in this review were created using [BioGDP.com](https://www.biogdp.com) (5).

## 2 Downstream regulation from the CNS to the bone

### 2.1 Brain-derived neurotrophic factor

Brain-derived neurotrophic factor (BDNF) is the most abundant, widely distributed, and extensively characterized neurotrophic factor in the mammalian CNS. In rodents, its expression is predominantly localized to regions such as the hippocampus and entorhinal cortex. The complexity of BDNF expression is underscored by its transcriptome, which is driven by at least nine distinct promoters that generate over 20 transcript variants. Notably, all these splice variants encode an identical precursor protein, known as pre-proBDNF (6). Functioning as an autocrine and paracrine factor, BDNF exerts its effects by binding primarily to its high-affinity receptor, tropomyosin receptor kinase B (TrkB), on pre- and postsynaptic membranes. Through this signaling pathway, BDNF is critical for regulating neuronal survival, differentiation, growth, and the maintenance of synaptic plasticity and normal neuronal function (7). Recent studies have provided evidence that serum BDNF levels are positively correlated with bone mineral density (BMD) in female athletes (8). In elderly women, a daily step count exceeding 5,000 has been associated with elevated levels of oxidative stress markers (e.g., GSH and MDA) and significant alterations in bone turnover markers (e.g., osteocalcin and CTX-1) in blood samples. Notably, this



level of physical activity is also linked to a marked increase in circulating BDNF levels (9). Collectively, these findings suggest that BDNF levels may serve as a potential indicator of skeletal health and point to a possible causal role of BDNF in bone metabolism.

To address these questions, 7,8-dihydroxyflavone (7,8-DHF), a small-molecule BDNF mimetic, has been widely utilized in basic research. 7,8-DHF specifically binds to the extracellular domain of the TrkB receptor with high affinity, crosses the blood-brain barrier (BBB), and activates downstream signaling pathways such as MAPK and Akt, thereby mimicking the neurotrophic effects of BDNF (10, 11). In the ovariectomized (OVX) rat model, it was found that 7,8-DHF significantly improved bone microstructure and biomechanical properties while reducing urinary calcium levels, without exhibiting any uterotrophic activity. (12). At the cellular level, 7,8-DHF promotes bone formation by enhancing the differentiation and mineralization capacity of osteoblast precursor cells (e.g., MC3T3-E1) and stimulating the secretion of osteoprotegerin (OPG). Concurrently, it inhibits osteoclastogenesis by suppressing RANKL-induced osteoclast differentiation in precursor cells (e.g., RAW264.7) and downregulating RANKL mRNA expression. This dual action on both anabolic and catabolic pathways effectively modulates bone remodeling balance (Figure 2). The pro-osteogenic effects are potentially mediated through the activation of key signaling pathways, including cAMP-response element binding protein (CREB) and Wnt/ $\beta$ -catenin (12, 13).

## 2.2 Sympathetic nervous system pathways and norepinephrine

The sympathetic nervous system (SNS), one of the two primary divisions of the ANS, originates from the intermediolateral nucleus of the spinal cord's gray matter in the thoracic and upper lumbar

(T1-L2) regions. The peripheral ganglia of the SNS comprise the paravertebral chain ganglia, which flank the vertebral column, and the prevertebral ganglia, located anterior to the aorta in the abdomen. Cholinergic preganglionic neurons connect the CNS to these ganglia. Noradrenergic postganglionic neurons then project from the ganglia to innervate various target tissues, including the heart, digestive system, and reproductive organs. It is noteworthy that bone tissue receives direct sympathetic innervation, primarily via the periarterial plexuses (14, 15). Anatomical tracing studies published over two decades ago have demonstrated that sensory nerves from the femur project to the dorsal root ganglia (DRG) at corresponding lumbar spinal levels. Furthermore, these neural pathways were shown to extend to higher brain centers, including the anterior cingulate cortex, motor cortex, paraventricular nucleus (PVN) of the hypothalamus, and specific nuclei within the brainstem (16, 17). The SNS mediates its effects primarily via the release of norepinephrine (NE), which activates adrenergic receptors (ARs) on target cells. Consequently, circulating NE levels are widely used as a key biomarker of overall sympathetic tone (18). Studies have demonstrated that tibial NE levels are significantly elevated in ovariectomized (OVX) mice compared to sham-operated controls. *In vitro*, treatment with exogenous NE induces phosphorylation of the transcription factor CREB in osteoclasts. This, in turn, promotes the secretion of extracellular vesicles (EVs) by osteoclasts, ultimately enhancing bone resorptive activity (19). These findings suggest that  $\beta$ -ARs on bone cells represent a critical signaling intermediary for sympathetic regulation of bone metabolism, operating alongside direct neural innervation.

$\beta$ -ARs belong to the G-protein-coupled receptor (GPCR) superfamily. Upon binding NE, the primary sympathetic

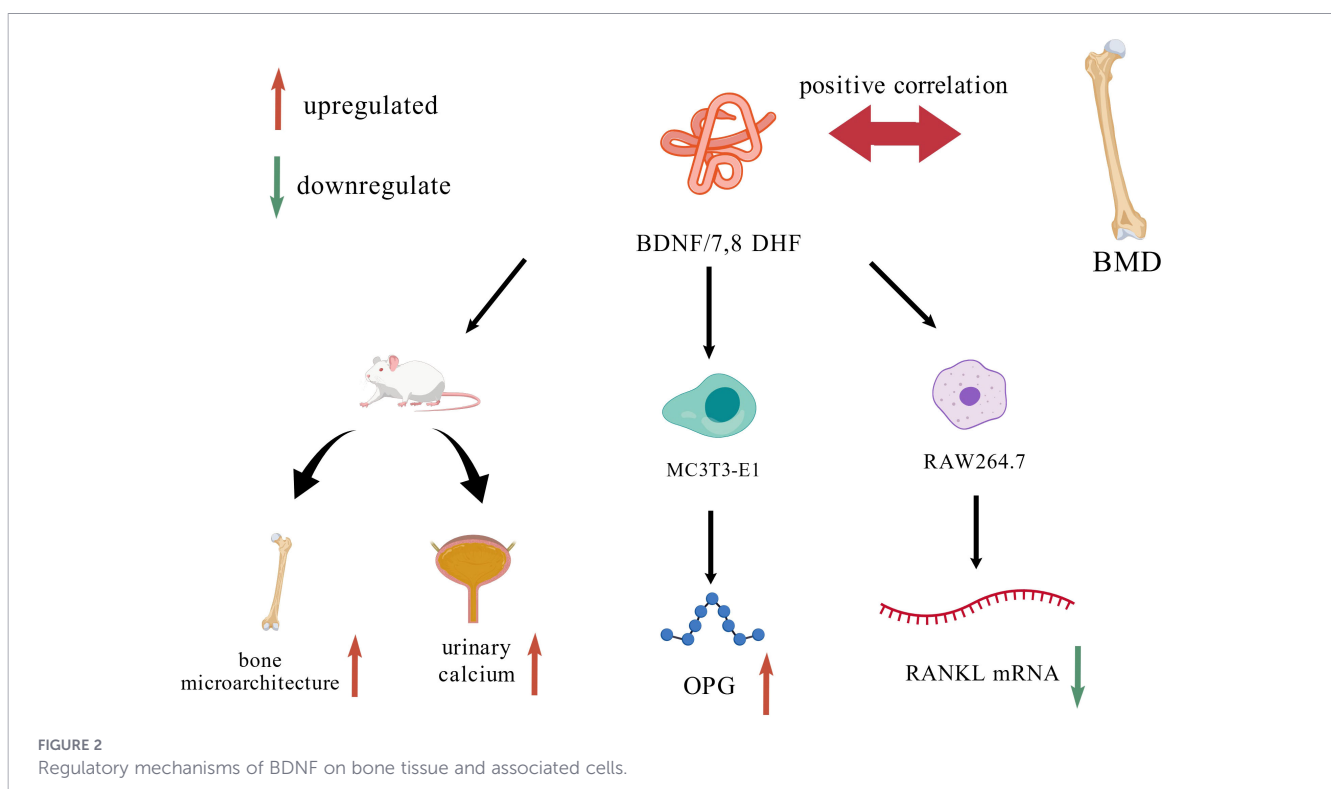


FIGURE 2  
Regulatory mechanisms of BDNF on bone tissue and associated cells.

neurotransmitter,  $\beta$ -ARs activate stimulatory G (Gs) proteins. This, in turn, triggers adenylate cyclase activity, leading to intracellular accumulation of cyclic AMP (cAMP) and propagation of the signal from the membrane to the cytoplasm (20). Pharmacological blockade of  $\beta$ -ARs has been shown to significantly improve tibial trabecular bone microarchitecture in ovariectomized mice and to accelerate the process of fracture healing (21, 22). Consistent with these *in vivo* observations, *in vitro* experiments revealed that  $\beta$ -AR activation inhibits osteogenic differentiation of bone marrow-derived mesenchymal stem cells (BMSCs) and simultaneously promotes osteoclastogenesis from bone marrow macrophages (BMMs). This demonstrates that the NE- $\beta$ -AR signaling pathway directly regulates bone remodeling by dually suppressing bone formation and enhancing bone resorption at the cellular level (22). Intriguingly, differentiated mature osteoblasts, but not osteoclasts, express the NE transporter (NET), which functions to clear extracellular NE and terminate its signaling. Corroborating this functional role, pharmacological inhibition of NET in wild-type mice results in a low bone mass phenotype, likely due to impaired NE clearance and subsequent overactivation of  $\beta$ -adrenergic signaling (23).

In summary, SNS regulates bone remodeling through two principal pathways: direct neural innervation and systemic NE signaling. Accumulated evidence indicates that sympathetic tone generally exerts a catabolic effect on the skeleton, suppressing bone formation and potentiating bone resorption.

### 2.3 The parasympathetic nervous system and acetylcholine

The parasympathetic nervous system (PNS) constitutes the other major division of the ANS, with the vagus nerve (cranial nerve X) representing its most prominent and widely distributed component. Originating in the medulla oblongata, the vagus nerve projects extensively to innervate numerous thoracic and abdominal organs, including the heart, lungs, liver, and gastrointestinal tract. It plays a critical role in the regulation of essential physiological functions such as heart rate, respiration, and immune responses (24). As a major cholinergic nerve, the vagus nerve mediates critical functions—including trophic, anti-inflammatory, and analgesic effects—primarily through the release of its principal neurotransmitter, acetylcholine (ACh). Growing evidence underscores its significant role in the pathophysiology of various musculoskeletal disorders, such as rheumatoid arthritis, osteoarthritis, and spondyloarthritis (25). Notably, intraoperative vagus nerve stimulation (VNS) has been shown to significantly increase lumbar spine bone mineral density (BMD) in patients. This finding reveals the therapeutic potential of modulating parasympathetic activity and opens new avenues for developing innovative diagnostic and treatment strategies for skeletal disorders, especially OP (26).

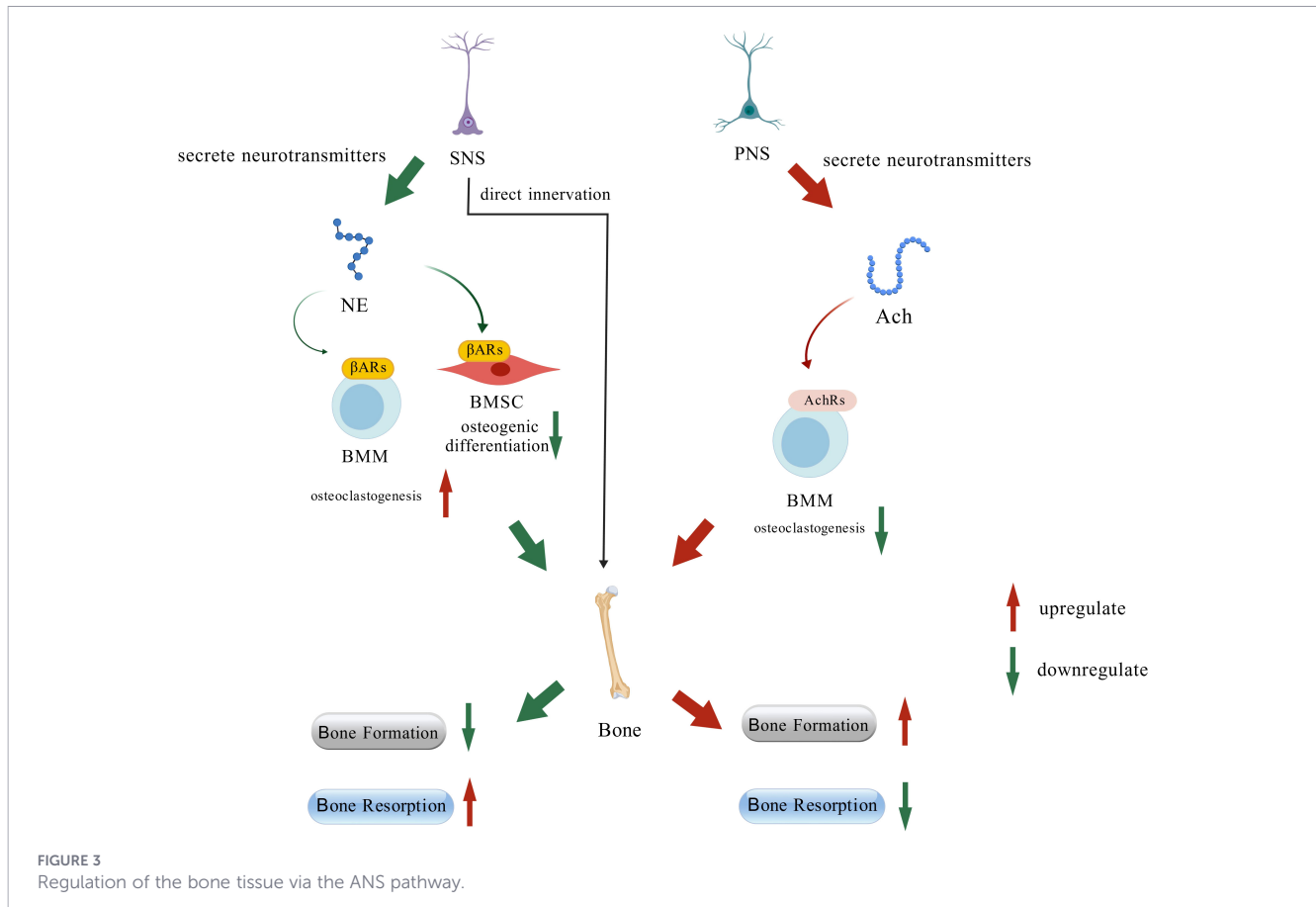
Similar to the relationship between SNS and NE, PNS's primary neurotransmitter, acetylcholine (ACh) also plays a crucial role in regulating bone remodeling (27). ACh is a principal neurotransmitter in vertebrates and the key signaling molecule in PNS postganglionic nerve fibers. It is synthesized within nerve terminals through a

reaction between acetyl-CoA and choline, catalyzed by the enzyme choline acetyltransferase (28). The primary classes of acetylcholine receptors are nicotinic (nAChRs) and muscarinic (mAChRs). The abundant expression of mAChRs in bone tissue implies a significant role for the PNS in regulating bone remodeling. mAChRs consist of five subtypes: the excitatory M1, M3, and M5, and the inhibitory M2 and M4. Their distribution patterns within the skeleton are both species- and site-specific (28, 29). Female mice with M3 receptor knockdown displayed significantly lower femoral bone density, impaired biomechanical properties, and markedly suppressed bone formation compared to wild-type controls (30). Furthermore, brain-derived ACh positively regulates the maintenance of peak bone mass in mice, with the effect exhibiting sexual dimorphism. This observed dimorphism may be attributable to the subtype-specific distribution of mAChRs within skeletal tissue (31). nAChRs also play a critical role in bone remodeling. These receptors function as pentameric ligand-gated ion channels composed of various combinations of subunits, such as  $\alpha$ 1- $\alpha$ 10,  $\beta$ 1- $\beta$ 4, and others (32). Early studies reported that stimulation of mouse BMMs with nAChR agonists—both non-selective and  $\alpha$ 7-subtype-specific—produces a bidirectional, dose-dependent effect on osteoclastogenesis: inhibition at higher concentrations but potentiation at lower doses. *In vitro* experiments further confirmed that nAChR ligands can inhibit the differentiation of osteoclast precursors (33). Genetic deletion of the nAChR  $\alpha$ 9 subunit in mice results in significant deterioration of bone strength, microarchitecture, and trabecular morphology (34). Interestingly, some reports indicate that  $\alpha$ 7 knockout mice exhibit no significant differences in bone volume fraction or trabecular morphological parameters compared to wild-type mice. At 6 weeks of age, mRNA expression of  $\alpha$ 1,  $\alpha$ 4,  $\alpha$ 5, and  $\alpha$ 9 in tibial tissue was significantly higher than in 3-week-old mice, suggesting that  $\alpha$ 9 may play a primary role in promoting bone formation (35, 36). Additionally, the activation of the anti-inflammatory pathway mediated by  $\alpha$ 7 nAChRs and the upregulation of estrogen receptor (ERs) expression may play important roles in regulating bone mass. Rats treated with the  $\alpha$ 7-nAChRs agonist PNU-282987 exhibited a significant increase in ERs expression and bone mineral density, along with a blockade of NF- $\kappa$ B nuclear translocation and a marked suppression in the synthesis and release of multiple pro-inflammatory cytokines, including TNF- $\alpha$ , IL-1 $\beta$ , and IL-6. Notably, TNF- $\alpha$  and IL-6 are crucial stimulatory factors for osteoclastogenesis, directly impacting the proliferation and differentiation of osteoclasts (37–40).

Similar to the SNS, the PNS modulates bone remodeling via neurohumoral signaling. A key distinction, however, PNS exerts a more positive effect on osteogenesis by modulating ERs and the anti-inflammatory pathway in contrast to the catabolic influence of the SNS (Figure 3).

### 2.4 The hypothalamic-pituitary-adrenal axis and glucocorticoids

Glucocorticoids (GCs) are a major class of steroid hormones that play critical roles in a wide range of physiological processes, such as metabolism, immune and inflammatory responses, development, and reproduction (41). The production of GCs depends on the



hypothalamic-pituitary-adrenal (HPA) axis. This system includes the paraventricular nucleus of the hypothalamus, the pituitary gland, and the adrenal cortex, connecting the CNS to peripheral organs. When the HPA axis is activated, the hypothalamus releases corticotropin-releasing hormone (CRH), which stimulates the pituitary gland to secrete adrenocorticotropic hormone (ACTH). ACTH then promotes the synthesis and release of GCs from the adrenal glands. Finally, GCs enter the circulation to regulate the function of various organs and tissues, including feedback effects on the brain (42, 43).

The link between GCs and bone loss is sufficiently strong that a major category of secondary OP is termed glucocorticoid-induced osteoporosis (GIO). This condition is characterized by a profound imbalance in bone remodeling, typically manifesting as a rapid increase in bone resorption coupled with a suppression of bone formation in patients undergoing exogenous GC therapy (44, 45). Whether endogenous or exogenous GCs, a substantial body of research has demonstrated their effects on various bone cells, including osteoblasts, osteoclasts, and osteocytes (46–48). Firstly, Treatment with GCs in both human osteoblast culture medium and Wnt3a-conditioned medium derived from human osteoblasts resulted in decreased T-cell factor (Tcf)/lymphoid enhancer factor (Lef) transcriptional activity, along with reduced intracellular accumulation and nuclear translocation of  $\beta$ -catenin. The canonical Wnt inhibitor DKK1 was able to recapitulate these effects. This similarity strongly suggests that the inhibition of osteogenesis and upregulation of intracellular RANKL by GCs are mediated through suppression of the Wnt signaling pathway (49,

50). Furthermore, GCs induce a dose-dependent reduction in Wnt16 expression in both MC3T3-E1 cells and mouse BMSCs. Consistent with this cellular effect, GC administration also leads to a decrease in BMD in mice (51). Additionally, GCs promote bone resorption through multiple mechanisms. They enhance the collagenase-mediated degradation of type I collagen by osteoblasts in the extracellular matrix. Furthermore, GCs can induce osteoblast autophagy and apoptosis, which also contributes to the net loss of bone (52–54). Tracing back based on the above clues, it can be found that in both human and mouse bone tissues,  $11\beta$ -hydroxysteroid dehydrogenase type 1 ( $11\beta$ -HSD1) plays a critical role in the regulation of GCs and osteoblasts.

$11\beta$ -HSD1 is an enzyme heavily involved in prereceptor GCs metabolism. Its expression in bone increases with age, and it catalyzes the reduction of inactive GCs to their active state for receptor binding. Its function is likely closely associated with metabolic syndromes such as type II diabetes and central obesity (55). In mouse-derived cells, it has been observed that  $11\beta$ -HSD1 can inhibit osteogenic differentiation, and this effect can be reversed by the  $11\beta$ -HSD1 inhibitor KR-67500 (56). Furthermore, it was observed that in bone marrow-derived human mesenchymal progenitor cells (hMSCs) overexpressing  $11\beta$ -HSD1, adipogenic differentiation was significantly increased, while osteogenic differentiation was inhibited (57). This mechanism was also demonstrated in the clinical trial by Abbas et al.: PMOP patients who orally took the  $11\beta$ -HSD1 inhibitor AZD4017 showed lower serum  $11\beta$ -HSD1 levels and relatively increased osteocalcin levels

compared to the placebo group. However, it could not fully reverse the bone loss caused by estrogen deficiency (58).

Studies in model organisms such as zebrafish confirm the evolutionarily conserved effects of GCs. In zebrafish, GC treatment reduces the activity of the osteoblast metabolic enzyme alkaline phosphatase (ALP) and downregulates key osteogenic marker genes, including RUNX2 and SP7 (59). Collectively, the evidence demonstrates that GCs suppress osteogenesis through a multitude of conserved mechanisms across multiple species.

Through their action on osteoblasts, GCs increase the RANKL/OPG ratio, thereby indirectly promoting osteoclast differentiation and maturation. However, the direct effects of GCs on osteoclasts themselves are more complex and not purely stimulatory (47). Early research indicated that GCs inhibit the proliferation of osteoclast precursors (BMMs) without impairing their differentiation into mature osteoclasts. Furthermore, GCs were found to suppress the bone-resorbing activity of mature osteoclasts while simultaneously prolonging their survival by inhibiting apoptosis (60). Simultaneously, GCs upregulate calcitonin receptor (CTR) mRNA expression in mouse osteoclast-like cells (OCLs), further inhibiting bone resorption (61). However, contemporaneous studies also revealed that GCs can promote osteoclastogenesis by significantly downregulating the endogenous production of interferon- $\beta$  (IFN- $\beta$ ). As IFN- $\beta$  is a known inhibitor of RANKL signaling, its reduction removes a key endogenous brake on osteoclast differentiation (62). Recent studies reveal a species-specific dual role for GCs. In mice, GCs promote the proliferation of classical monocytes and their differentiation into osteoclasts. Conversely, in bluefin tuna, GCs inhibit bone repair by preventing the accumulation of both osteoclasts and osteoblasts at fracture sites (63, 64). Crucially, in genetically modified mice lacking the glucocorticoid receptor (GR) specifically in osteoclasts, the inhibitory effect of GCs on bone formation was significantly attenuated. This finding provides direct genetic evidence that osteoclasts are essential cellular mediators of GC-induced suppression of osteogenesis (60). The evidence summarized above indicates that the effects of GCs on osteoclasts are complex and bidirectional. The precise mechanisms underlying these context-dependent effects remain an important area for future investigation.

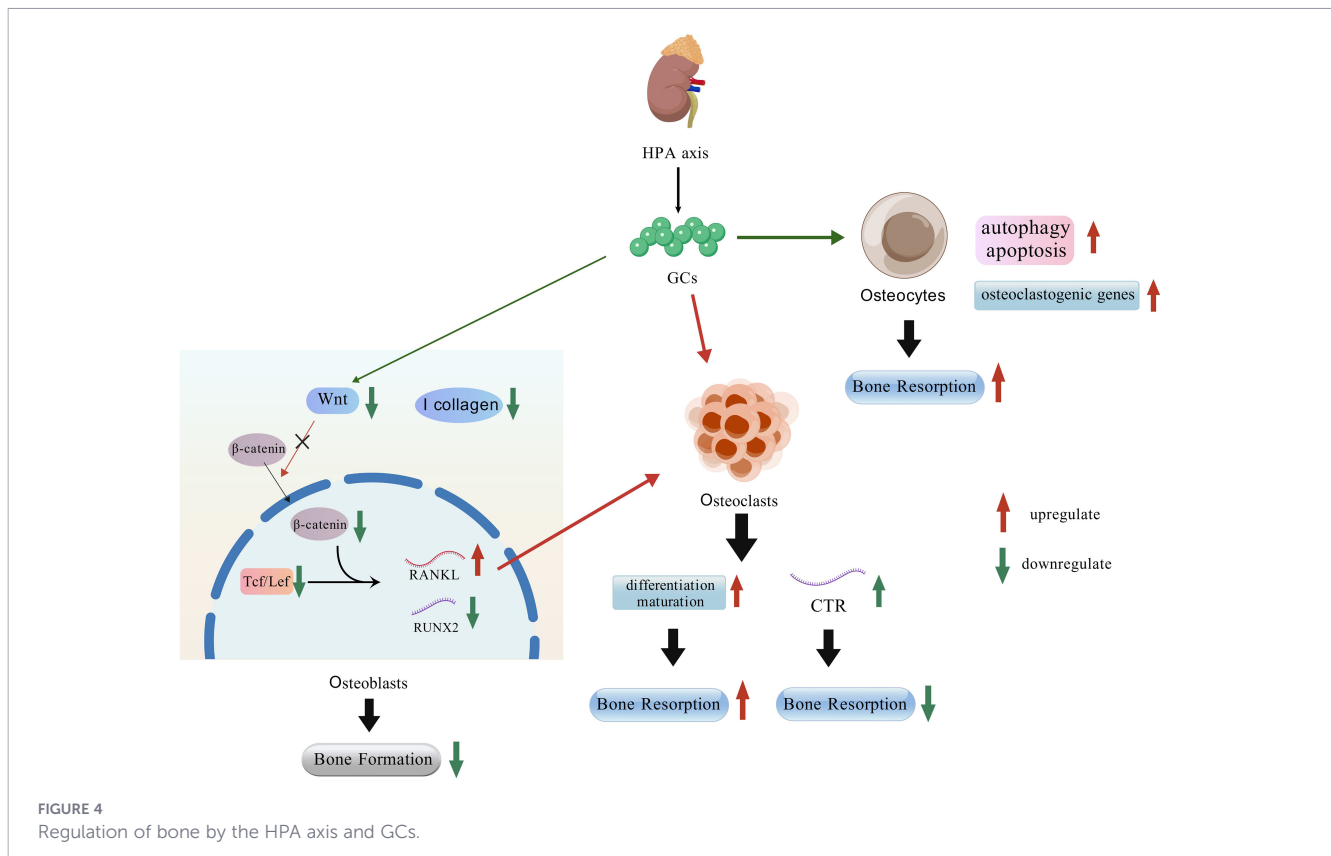
Another critical aspect of GCs' skeletal effects centers on osteocytes. As the terminal differentiation stage of osteoblasts, osteocytes represent over 90% of all bone cells and play a central role in regulating bone aging and maintaining skeletal homeostasis (65). Preliminary histological studies revealed enlarged osteocyte lacunae specifically in the lumbar vertebrae of GC-treated mice. This specific morphological change was not observed in mice with estrogen deficiency alone, suggesting it may be a distinct pathological feature of GC-induced bone deterioration (66). *In vitro* experiments demonstrated that GC treatment of mouse osteocytes significantly reduced cell viability, increased autophagy markers, and promoted autophagosome accumulation. These findings were corroborated by *in vivo* studies, collectively indicating that GCs induce osteocyte autophagy and apoptosis (67, 68). The regulation of autophagy and apoptosis by GCs is

not mutually exclusive but exhibits a dose-dependent relationship. For instance, in the MLO-Y4 osteocyte cell line, low-dose exogenous GCs primarily induce autophagy, whereas high doses trigger apoptosis (69). At the molecular level, GCs upregulate the expression of key osteoclastogenic genes—such as Acp5 (TRAP), Mmp13, Atp6v0d2, and Ctsk—in osteocytes. This transcriptional reprogramming of osteocytes contributes to the promotion of cortical bone resorption (70). Although research on the effects of GCs on osteocytes remains limited, the existing body of evidence consistently points toward a net catabolic effect, primarily driven by enhanced bone resorption (Figure 4).

## 2.5 Serotonin

Serotonin, or 5-hydroxytryptamine (5-HT), is a major monoamine neurotransmitter derived from tryptophan. It is widely distributed in the CNS and the gastrointestinal tract, where it regulates critical functions including mood, cognition, pain perception, sleep, memory, and gut motility (71, 72). The pleiotropic effects of serotonin (5-HT) are mediated by its cognate receptors (5-HTRs). These receptors are categorized into seven families based on their distinct signaling pathways. As members of the G protein-coupled receptor (GPCR) superfamily, 5-HTRs share a characteristic structure consisting of seven transmembrane-spanning helices, with an extracellular N-terminus and an intracellular C-terminus (73). Ligand binding to GPCRs induces a conformational change in the transmembrane domain, initiating intracellular signal transduction. This process involves the activation of heterotrimeric G proteins and G protein-coupled receptor kinases (GRKs), which propagate the extracellular signal into the cell and trigger a downstream signaling cascade (74). 5-HT is synthesized directly from the amino acid tryptophan. Although the biosynthetic pathway is similar in the brain and the gut, the maintenance of cerebral 5-HT synthesis—which depends on adequate tryptophan availability—requires normal HPA axis function (75). Both gut-derived and brain-derived 5-HT regulate bone formation, although their specific effects on bone mass can be divergent. Overall, central 5-HT signaling appears to exert a more dominant influence on the regulation of bone mass (76, 77). This review will focus specifically on the role of brain-derived 5-HT in the regulation of bone mass.

The seminal work by Yadav et al. showed that leptin-deficient mice exhibit elevated brain 5-HT levels and high bone mass, phenotypes reversible upon genetic suppression of tryptophan hydroxylase 2 (Tph2). Their research established that brain-derived 5-HT regulates bone mass through the ventromedial hypothalamus (VMH) by attenuating SNS tone. Mechanistically, 5-HT signaling in the VMH enhances the expression and phosphorylation of the transcription factor CREB, which modulates the transcription of key genes controlling sympathetic outflow. The net effect of this central regulatory circuit is a reduction in sympathetic tone, leading to increased bone formation and bone mass (77, 78). Collectively, these findings establish 5-HT as a central regulator of bone metabolism. Its

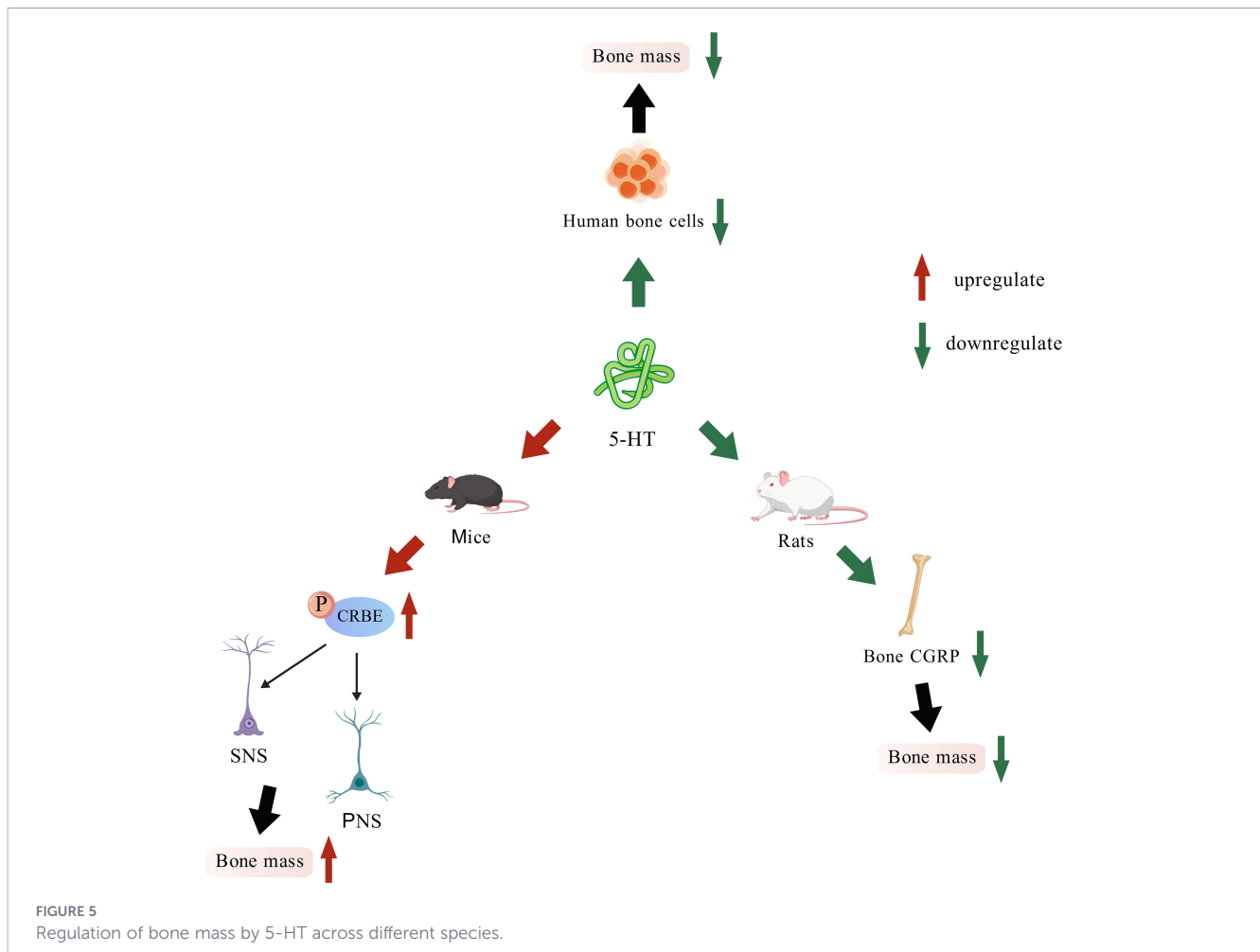


effects are mediated downstream through the ANS and NE signaling pathways. Notably, these pathways exhibit partial synergy and crosstalk with BDNF-mediated signaling. The clinical relevance of this mechanism is supported by the observation that patients with neuropsychiatric disorders characterized by central 5-HT deficiency frequently present with comorbid OP and an elevated risk of fragility fractures (79, 80).

In ovariectomized (OVX) rats, levels of 5-HT and its mRNA are significantly elevated in the spinal cord. This elevation may be linked to pain-induced release of calcitonin gene-related peptide (CGRP) in the spinal dorsal horn of OVX rats. It has been proposed that spinal CGRP promotes 5-HT release, which in turn downregulates CGRP expression within bone tissue. This paradoxical feedback loop may ultimately contribute to accelerated bone loss (81). Studies by Lam et al. reported a related phenomenon: in a rat model of depression treated solely with selective 5-HT reuptake inhibitors (SSRIs), no significant bone loss was observed. In contrast, *in vitro* evidence demonstrates that SSRIs can directly induce apoptosis and suppress function in both human osteoblasts and osteoclasts (82, 83) (Figure 5). These seemingly paradoxical phenomena can be attributed to the functional antagonism between brain-derived and gut-derived serotonin. Since 5-HT cannot cross the blood-brain barrier, there are notable differences in both the production and function of brain-derived and gut-derived 5-HT. Gut-derived 5-HT, primarily secreted by enterochromaffin cells, acts on the 5-HT<sub>1B</sub> receptors of osteoblasts, inhibiting their proliferation and function. Interestingly, the effector molecule in the intermediate cascade of reactions remains CREB (84).

## 2.6 Thyroid hormone

Thyroid hormones (THs), secreted by thyroid follicular cells, are critical regulators of metabolism, growth, and development. Their biosynthesis is governed by the hypothalamic-pituitary-thyroid (HPT) axis and depends on the availability of inorganic iodide. The enzyme thyroid peroxidase (TPO) catalyzes two key steps: the iodination of tyrosine residues on thyroglobulin (TG) and the coupling of iodotyrosines to form thyroxine (T4) and triiodothyronine (T3). The entire process is under negative feedback control, primarily by thyroid hormones themselves, which suppress the release of thyrotropin-releasing hormone (TRH) from the hypothalamus and thyroid-stimulating hormone (TSH) from the pituitary, maintaining systemic homeostasis (85). The biological actions of THs are primarily mediated by thyroid hormone receptors (THRs), which are encoded by two distinct genes: THRA (TR $\alpha$ ) and THRB (TR $\beta$ ) (86). The primary thyroid hormone secreted into the circulation is thyroxine (T4), which functions as a prohormone. T4 is activated by outer-ring deiodination to form the biologically active hormone T3. T3 then binds to nuclear THRs to modulate the transcription of target genes (87). The expression of THRs and specific transporters in chondrocytes, osteoblasts, and osteoclasts provides the cellular basis for T3 action on the skeleton. Mechanistically, T3 exerts its anabolic effects primarily by activating the IGF-1 and Wnt/ $\beta$ -catenin signaling pathways (88–90). Beyond these core pathways, THs employ additional mechanisms to regulate bone homeostasis in a cell- and tissue-specific manner.



Genetic disruption of TH signaling in mice results in severe impairment of endochondral ossification. Conversely, exogenous TH administration rescues this phenotype, as evidenced by the restoration of normal chondrocyte differentiation and the expression of key markers including collagen II, collagen X, and osteocalcin (91). This phenomenon is also widely observed in humans. For example, children with hypothyroidism, which leads to decreased levels of THs, typically present with severe defects in endochondral ossification, resulting in bone dysplasia (88). In adults, THs have been shown to significantly increase serum ALP activity and maintain normal osteoblast function. However, both excessively high and low levels of THs can lead to bone loss through different mechanisms, which may be related to the inhibitory effects of THs on osteoclast activity and osteoblast proliferation (92, 93). Furthermore, in an experiment using chondrocytes derived from fertilized eggs, it was observed that THs promote the upregulation of intracellular bone morphogenetic protein 4 (BMP-4) expression and elevate collagen X mRNA levels (94). Perhaps the regulatory mechanisms of THs on bones also exhibit certain species specificity.

Additionally, in TH-specific transporter monocarboxylate transporter 10 (MCT10) knockout mice, a reduction in femoral trabecular bone volume accompanied by decreased osteoblast numbers was observed at 12 weeks, confirming that THs also exert regulatory effects on osteoblasts (95). T3 regulates osteoblast

differentiation and mineralization primarily through the IGF-1 and Wnt/ $\beta$ -catenin signaling pathways. However, its overall effects are highly context-dependent, exhibiting significant species specificity as well as variable outcomes—ranging from promotion to inhibition to no effect—on the proliferation of different osteoblast cell lines depending on their origin and passage number (88). For example, T3 inhibits the growth of osteoblasts derived from mouse skull bone but promotes the proliferation of human osteoblast-like cells (96, 97).

However, reports indicate that excessive levels of THs may lead to bone loss by increasing the activity and number of osteoclasts (98, 99). But recent *in vitro* studies show that THs inhibit osteoclast differentiation from mouse macrophage precursors by activating the AMPK pathway, thereby helping preserve bone mass. Knocking out THRs reverses this effect (100). Although THs modulate the Wnt/ $\beta$ -catenin pathway in osteoclasts, research confirms that the effects of T3 on these cells are independent of the downstream RANKL signaling cascade (98). Therefore, the direct effect of THs on bone resorption remains unclear at present.

In summary, the regulation of bone cells by THs is complex and may even be bidirectional or antagonistic. Based on existing research, potential confounding factors likely include cell lines, passage numbers, cell types, species, and the developmental stage of primary cells.

### 3 Discussion

Bone is not an isolated organ. Therefore, a comprehensive understanding of OP pathogenesis and the development of effective treatments requires moving beyond a narrow focus on bone cells alone. Compelling evidence now establishes the brain as a critical regulator in the initiation and progression of this disease. This review synthesizes current evidence for the brain's descending regulation of the skeleton, establishing bone as a target organ of the CNS. Major pathways identified include BDNF, the ANS (comprising the SNS and PNS), the HPA axis, 5-HT, and THs. The BDNF and PNS pathways generally promote osteogenesis, whereas the SNS and HPA axis pathways exert inhibitory effects. Other pathways discussed exhibit more complex context-dependent or functional antagonism.

Critically, these pathways do not operate in isolation but form an integrated regulatory network. A prime example is the HPA axis and the ANS, which function as core components of the stress response system to coordinate adaptation to daily challenges. Their coordinated function is exemplified by the concurrent regulation of heart rate and the dynamic control of stress-induced cortisol secretion and recovery (101). When the stress response system becomes dysregulated, the resulting allostatic load inflicts cumulative damage on the brain and body, manifesting as hippocampal atrophy and bone loss. Estrogen appears to confer neuroprotective benefits that mitigate this damage. This pathophysiology underscores the integral role of the HPA axis and ANS dysregulation in the pathogenesis of OP. Specifically, this is manifested as the HPA axis and the ANS working synergistically in daily life to maintain stress balance, while under the influence of estrogen, they inhibit bone loss caused by allostatic load. (102). The ANS is modulated by cardiovascular reflexes—such as the baroreceptor and chemoreceptor reflexes—with the nucleus tractus solitarius (NTS) acting as the central integration site for these afferent signals. Experimental evidence confirms that 5-HT, by acting on receptors within the NTS, participates in regulating both the sympathetic and parasympathetic branches of the ANS. This mechanism reveals an indirect pathway through which central 5-HT signaling can modulate skeletal muscle function, complementing its potential direct effects (103, 104). Further evidence indicates that THs may influence bone, in part, through downstream ANS pathways. For example, the bone loss induced by TH excess in mice is attenuated by genetic deletion of  $\alpha$ ARs. Additionally, T3 has been shown to interact with 5-HT receptors to modulate hippocampal BDNF expression, suggesting potential crosstalk between endocrine and monoaminergic systems in the central regulation of bone (97, 105). The above evidence preliminarily suggests the existence of a complex regulatory network. That is, beyond the direct impact of each pathway on bone, both THs and 5-HT can transmit neural signals to the ANS by binding to receptors at different sites, thereby achieving indirect regulation of bone.

The preceding discussion outlined how BDNF, by activating the Wnt pathway in bone tissue, upregulates downstream effectors such as RUNX2 and OPG to promote bone formation. Notably, RUNX2—a central transcription factor in this osteogenic pathway—also functions as a key signaling molecule in the upstream bone-to-brain communication axis. RUNX2 is a master transcription factor governing skeletal development. Its functions include inducing

chondrocyte proliferation, promoting the commitment of bone progenitor cells to the osteoblast lineage, and driving the subsequent maturation of pre-osteoblasts into functional osteoblasts (106). RUNX2 promoter activity is detected in the mouse brain, with particularly high levels in the hippocampus and no significant activity in the cerebellum. Genetic knockdown of RUNX2 significantly attenuates brain injury and edema following middle cerebral artery occlusion (107–109). This appears to suggest the existence of additional descending regulatory pathways with RUNX2 as the central hub molecule.

Clinical evidence confirms the link between CNS disorders (e.g., Alzheimer's disease, anorexia nervosa) and OP. Key mechanisms include HPA axis hyperactivity and excessive SNS activation, which drive bone loss. Additionally, long-term use of exogenous GCs and TH is a common cause of iatrogenic OP (110, 111). The findings reviewed in this paper highlight the therapeutic potential of non-pharmacological interventions—such as physical exercise—for skeletal disorders. These benefits are mediated through multiple pathways: by improving emotional state and stress resilience to normalize ANS and HPA axis activity, by elevating central BDNF levels, and by inhibiting bone loss through downregulation of resorptive signaling networks.

This review has several limitations. First, the exploration of the downstream brain-to-bone regulatory network remains preliminary, with mechanistic insights into individual pathways requiring further depth. Second, the upstream bone-to-brain regulatory axis is not discussed in detail. Finally, the reliance on multi-species literature may introduce bias in interpreting the relative importance and conserved function of the various pathways described. In summary, the evidence presented delineates a brain-bone axis that functions as a highly integrated network engaging the nervous, endocrine, and immune systems. This framework provides a novel, multidisciplinary foundation for developing future strategies to prevent and treat skeletal metabolic disorders such as OP.

### Author contributions

YR: Methodology, Validation, Writing – original draft. LZ: Methodology, Supervision, Writing – original draft. MX: Methodology, Writing – original draft. YC: Investigation, Writing – original draft. XW: Investigation, Project administration, Writing – original draft. SL: Funding acquisition, Writing – review & editing. GY: Funding acquisition, Writing – review & editing. GC: Funding acquisition, Writing – review & editing.

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## Conflict of interest

The author(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Generative AI statement

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## References

- Lane JM, Russell L, Khan SN. Osteoporosis. *Clin Orthop.* (2000) 372:139–50. doi: 10.1097/00003086-200003000-00016
- Yang L, Dong Z, Yuan B, Lei J, Zhang J, Zhang X, et al. Top comorbidities in osteoporotic fracture patients in a northeast population in China. *BMC Public Health.* (2025) 25:1640. doi: 10.1186/s12889-025-22331-0
- Shi H, Chen M. The brain-bone axis: unraveling the complex interplay between the central nervous system and skeletal metabolism. *Eur J Med Res.* (2024) 29:317. doi: 10.1186/s40001-024-01918-0
- Dimitri P, Rosen C. The central nervous system and bone metabolism: an evolving story. *Calcif Tissue Int.* (2017) 100:476–85. doi: 10.1007/s00223-016-0179-6
- Jiang S, Li H, Zhang L, Mu W, Zhang Y, Chen T, et al. Generic diagramming platform (GDP): a comprehensive database of high-quality biomedical graphics. *Nucleic Acids Res.* (2025) 53:D1670–6. doi: 10.1093/nar/gkae973
- Sullivan BJ, Kadam SD. Brain-derived neurotrophic factor in neonatal seizures. *Pediatr Neurol.* (2021) 118:35–9. doi: 10.1016/j.pediatrneurol.2021.01.011
- Colucci-D'Amato L, Speranza L, Volpicelli F. Neurotrophic factor BDNF, physiological functions and therapeutic potential in depression, neurodegeneration and brain cancer. *Int J Mol Sci.* (2020) 21:7777. doi: 10.3390/ijms21207777
- Nose S, Yoshino O, Nomoto K, Harada M, Dohi M, Kawahara T, et al. Serum brain-derived neurotrophic factor levels mirror bone mineral density in amenorrheic and eumenorrheic athletes. *Int J Sports Med.* (2019) 40:276–82. doi: 10.1055/a-0835-6119
- Śadowska-Krepa E, Rzetecki A, Zajac-Gawlak I, Nawrat-Szoltysik A, Rozpara M, Mikuláková W, et al. Comparison of selected prooxidant-antioxidant balance and bone metabolism indicators and BDNF levels between older women with different levels of physical activity. *BMC Geriatr.* (2023) 23:489. doi: 10.1186/s12877-023-04205-5
- Liu X, Chan C-B, Jiang S-W, Pradoldej S, Huang J, He K, et al. A synthetic 7,8-dihydroxyflavone derivative promotes neurogenesis and exhibits potent antidepressant effect. *J Med Chem.* (2010) 53:8274–86. doi: 10.1021/jm101206p
- Liu C, Chan CB, Ye K. 7,8-dihydroxyflavone, a small molecular TrkB agonist, is useful for treating various BDNF-implicated human disorders. *Transl Neurodegener.* (2016) 5:2. doi: 10.1186/s40035-015-0048-7
- Xue F, Zhao Z, Gu Y, Han J, Ye K, Zhang Y. 7,8-Dihydroxyflavone modulates bone formation and resorption and ameliorates ovariectomy-induced osteoporosis. *Elife.* (2021) 10:e64872. doi: 10.7554/eLife.64872
- Xiong J, Liao J, Liu X, Zhang Z, Adams J, Pacifici R, et al. A TrkB agonist prodrug prevents bone loss via inhibiting asparagine endopeptidase and increasing osteoprotegerin. *Nat Commun.* (2022) 13:4820. doi: 10.1038/s41467-022-32435-5
- Elefteriou F, Campbell P, Ma Y. Control of bone remodeling by the peripheral sympathetic nervous system. *Calcif Tissue Int.* (2014) 94:140–51. doi: 10.1007/s00223-013-9752-4
- Scott-Solomon E, Boehm E, Kuruvilla R. The sympathetic nervous system in development and disease. *Nat Rev Neurosci.* (2021) 22:685–702. doi: 10.1038/s41583-021-00523-y
- Dénes A, Boldogkoi Z, Uherezky G, Hornyák A, Rusvai M, Palkovits M, et al. Central autonomic control of the bone marrow: multisynaptic tract tracing by recombinant pseudorabies virus. *Neuroscience.* (2005) 134:947–63. doi: 10.1016/j.neuroscience.2005.03.060
- Edoff K, Grenegård M, Hildebrand C. Retrograde tracing and neuropeptide immunohistochemistry of sensory neurons projecting to the cartilaginous distal femoral epiphysis of young rats. *Cell Tissue Res.* (2000) 299:193–200. doi: 10.1007/s004419900142
- Elefteriou F. Impact of the autonomic nervous system on the skeleton. *Physiol Rev.* (2018) 98:1083–112. doi: 10.1152/physrev.00014.2017
- Guo Q, Chen N, Qian C, Qi C, Noller K, Wan M, et al. Sympathetic innervation regulates osteocyte-mediated cortical bone resorption during lactation. *Adv Sci (Weinh).* (2023) 10:e2207602. doi: 10.1002/advs.202207602
- Naga Prasad SV, Nienaber J, Rockman HA. Beta-adrenergic axis and heart disease. *Trends Genet.* (2001) 17:S44–49. doi: 10.1016/s0168-9525(01)02487-8
- Fontaine RL, Brooks DJ, Barlow D, Neilson RJ, Lary CW, Houseknecht KL, et al. Atenolol, alone or in combination with PTH, has a modest effect on bone in female C57BL/6j mice. *J Bone Miner Res.* (2025) 9:zia087. doi: 10.1093/jbmrpl/ziaf087
- Huang J, Wu T, Jiang Y-R, Zheng X-Q, Wang H, Liu H, et al.  $\beta$ -Receptor blocker enhances the anabolic effect of PTH after osteoporotic fracture. *Bone Res.* (2024) 12:18. doi: 10.1038/s41413-024-00321-z
- Ma Y, Krueger JJ, Redmon SN, Uppuganti S, Nyman JS, Hahn MK, et al. Extracellular norepinephrine clearance by the norepinephrine transporter is required for skeletal homeostasis. *J Biol Chem.* (2013) 288:30105–13. doi: 10.1074/jbc.M113.481309
- Ma L, Wang H-B, Hashimoto K. The vagus nerve: An old but new player in brain-body communication. *Brain Behav Immun.* (2025) 124:28–39. doi: 10.1016/j.bbi.2024.11.023
- Courties A, Berenbaum F, Sellam J. Vagus nerve stimulation in musculoskeletal diseases. *Joint Bone Spine.* (2021) 88:105149. doi: 10.1016/j.jbspin.2021.105149
- Tamimi A, Tamimi F, Juweid M, Al-Qudah AA, Al Masri A, Dahbour S, et al. Could vagus nerve stimulation influence bone remodeling? *J Musculoskelet Neuronal Interact.* (2021) 21:255–62.
- Spieker J, Frieß JL, Sperling L, Thangaraj G, Vogel-Höpker A, Layer PG. Cholinergic control of bone development and beyond. *Int Immunopharmacol.* (2020) 83:106405. doi: 10.1016/j.intimp.2020.106405
- Świt P, Pollap A, Orzel J. Spectroscopic determination of acetylcholine (ACh): A representative review. *Top Curr Chem (Cham).* (2023) 381:16. doi: 10.1007/s41061-023-00426-9
- Liu P-S, Chen Y-Y, Feng C-K, Lin Y-H, Yu T-C. Muscarinic acetylcholine receptors present in human osteoblast and bone tissue. *Eur J Pharmacol.* (2011) 650:34–40. doi: 10.1016/j.ejphar.2010.09.031
- Lips KS, Kneffel M, Willscheid F, Mathies FM, Kampschulte M, Hartmann S, et al. Altered ultrastructure, density and cathepsin K expression in bone of female muscarinic acetylcholine receptor M3 knockout mice. *Int Immunopharmacol.* (2015) 29:201–7. doi: 10.1016/j.intimp.2015.05.012
- Ma Y, Elefteriou F. Brain-derived acetylcholine maintains peak bone mass in adult female mice. *J Bone Miner Res.* (2020) 35:1562–71. doi: 10.1002/jbmr.4024
- Stokes C, Treinin M, Papke RL. Looking below the surface of nicotinic acetylcholine receptors. *Trends Pharmacol Sci.* (2015) 36:514–23. doi: 10.1016/j.tips.2015.05.002

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33. Mandl P, Hayer S, Karonitsch T, Scholze P, Györi D, Sykourti D, et al. Nicotinic acetylcholine receptors modulate osteoclastogenesis. *Arthritis Res Ther.* (2016) 18:63. doi: 10.1186/s13075-016-0961-x
34. Baumann L, Kauschke V, Vikman A, Dürselen L, Krasteva-Christ G, Kampschulte M, et al. Deletion of nicotinic acetylcholine receptor alpha9 in mice resulted in altered bone structure. *Bone.* (2019) 120:285–96. doi: 10.1016/j.bone.2018.11.003
35. Kliemann K, Kneffel M, Bergen I, Kampschulte M, Langheinrich AC, Dürselen L, et al. Quantitative analyses of bone composition in acetylcholine receptor M3R and alpha7 knockout mice. *Life Sci.* (2012) 91:997–1002. doi: 10.1016/j.lfs.2012.07.024
36. Ma Y, Li X, Fu J, Li Y, Gao L, Yang L, et al. Acetylcholine affects osteocytic MLO-Y4 cells via acetylcholine receptors. *Mol Cell Endocrinol.* (2014) 384:155–64. doi: 10.1016/j.mce.2014.01.021
37. Mazurov A, Hauser T, Miller CH. Selective alpha7 nicotinic acetylcholine receptor ligands. *Curr Med Chem.* (2006) 13:1567–84. doi: 10.2174/092986706777442011
38. Ma F, Gong F, Lv J, Gao J, Ma J. Effects of a7nAChR agonist on the tissue estrogen receptor expression of castrated rats. *Int J Clin Exp Path.* (2015) 8:13421–5.
39. Wang H, Yu M, Ochani M, Amella CA, Tanovic M, Susarla S, et al. Nicotinic acetylcholine receptor alpha7 subunit is an essential regulator of inflammation. *Nature.* (2003) 421:384–8. doi: 10.1038/nature01339
40. Li G, Zhang C, Li Y, Yang J, Wu J, Shao Y, et al. Optogenetic vagal nerve stimulation attenuates heart failure by limiting the generation of monocyte-derived inflammatory CCRL2+ macrophages. *Immunity.* (2025) 58:1847–1861.e9. doi: 10.1016/j.immuni.2025.06.003
41. Vandewalle J, Luypaert A, De Bosscher K, Libert C. Therapeutic mechanisms of glucocorticoids. *Trends Endocrinol Metab.* (2018) 29:42–54. doi: 10.1016/j.tem.2017.10.010
42. Zhou L, Wang T, Yu Y, Li M, Sun X, Song W, et al. The etiology of poststroke depression: a hypothesis involving HPA axis. *BioMed Pharmacother.* (2022) 151:113146. doi: 10.1016/j.biopha.2022.113146
43. Gulyaeva NV. Biochemical mechanisms and translational relevance of hippocampal vulnerability to distant focal brain injury: the price of stress response. *Biochem (Moscow).* (2019) 84:1306–28. doi: 10.1134/S0006297919110087
44. Compston J. Glucocorticoid-induced osteoporosis: an update. *Endocrine.* (2018) 61:7–16. doi: 10.1007/s12020-018-1588-2
45. Liu X, Chai Y, Liu G, Su W, Guo Q, Lv X, et al. Osteoclasts protect bone blood vessels against senescence through the angiogenin/plexin-B2 axis. *Nat Commun.* (2021) 12:1832. doi: 10.1038/s41467-021-22131-1
46. Chen M, Fu W, Xu H, Liu C-J. Pathogenic mechanisms of glucocorticoid-induced osteoporosis. *Cytokine Growth Factor Rev.* (2023) 70:54–66. doi: 10.1016/j.cytogfr.2023.03.002
47. Chotiarnwong P, McCloskey EV. Pathogenesis of glucocorticoid-induced osteoporosis and options for treatment. *Nat Rev Endocrinol.* (2020) 16:437–47. doi: 10.1038/s41574-020-0341-0
48. Hardy RS, Zhou H, Seibel MJ, Cooper MS. Glucocorticoids and bone: consequences of endogenous and exogenous excess and replacement therapy. *Endocr Rev.* (2018) 39:519–48. doi: 10.1210/er.2018-00097
49. Ohnaka K, Tanabe M, Kawate H, Nawata H, Takayanagi R. Glucocorticoid suppresses the canonical Wnt signal in cultured human osteoblasts. *Biochem Biophys Res Commun.* (2005) 329:177–81. doi: 10.1016/j.bbrc.2005.01.117
50. Kovács B, Vajda E, Nagy EE. Regulatory effects and interactions of the wnt and OPG-RANKL-RANK signaling at the bone-cartilage interface in osteoarthritis. *Int J Mol Sci.* (2019) 20:4653. doi: 10.3390/ijms20184653
51. Hildebrandt S, Baschant U, Thiele S, Tuckermann J, Hofbauer LC, Rauner M. Glucocorticoids suppress Wnt16 expression in osteoblasts *in vitro* and *in vivo*. *Sci Rep.* (2018) 8:8711. doi: 10.1038/s41598-018-26300-z
52. Wang L, Heckmann BL, Yang X, Long H. Osteoblast autophagy in glucocorticoid-induced osteoporosis. *J Cell Physiol.* (2019) 234:3207–15. doi: 10.1002/jcp.27335
53. Delany AM, Jeffrey JJ, Rydziel S, Canalis E. Cortisol increases interstitial collagenase expression in osteoblasts by post-transcriptional mechanisms. *J Biol Chem.* (1995) 270:26607–12. doi: 10.1074/jbc.270.44.26607
54. Deng S, Dai G, Chen S, Nie Z, Zhou J, Fang H, et al. Dexamethasone induces osteoblast apoptosis through ROS-PI3K/AKT/GSK3 $\beta$  signaling pathway. *BioMed Pharmacother.* (2019) 110:602–8. doi: 10.1016/j.biopha.2018.11.103
55. Tomlinson JW, Walker EA, Bujalska IJ, Draper N, Lavery GG, Cooper MS, et al. 11beta-hydroxysteroid dehydrogenase type 1: a tissue-specific regulator of glucocorticoid response. *Endocr Rev.* (2004) 25:831–66. doi: 10.1210/er.2003-0031
56. Park JS, Bae SJ, Choi S-W, Son YH, Park SB, Rhee SD, et al. A novel 11 $\beta$ -HSD1 inhibitor improves diabetes and osteoblast differentiation. *J Mol Endocrinol.* (2014) 52:191–202. doi: 10.1530/JME-13-0177
57. Blaschke M, Koepp R, Streit F, Beismann J, Manthey G, Seitz M-T, et al. The rise in expression and activity of 11 $\beta$ -HSD1 in human mesenchymal progenitor cells induces adipogenesis through increased local cortisol synthesis. *J Steroid Biochem Mol Biol.* (2021) 210:105850. doi: 10.1016/j.jsbmb.2021.105850
58. Abbas A, Schini M, Ainsworth G, Brown SR, Oughton J, Crowley RK, et al. Effect of AZD4017, a selective 11 $\beta$ -HSD1 inhibitor, on bone turnover markers in postmenopausal osteopenia. *J Clin Endocrinol Metab.* (2022) 107:2026–35. doi: 10.1210/clinem/dgac100
59. Yu T, Chen M, Wen J, Liu J, Li K, Jin L, et al. The effects of all-trans retinoic acid on prednisolone-induced osteoporosis in zebrafish larvae. *Bone.* (2024) 189:117261. doi: 10.1016/j.bone.2024.117261
60. Kim H-J, Zhao H, Kitaura H, Bhattacharyya S, Brewer JA, Muglia LJ, et al. Glucocorticoids suppress bone formation via the osteoclast. *J Clin Invest.* (2006) 116:2152–60. doi: 10.1172/JCI28084
61. Wada S, Udagawa N, Akatsu T, Nagata N, Martin TJ, Findlay DM. Regulation by calcitonin and glucocorticoids of calcitonin receptor gene expression in mouse osteoclasts. *Endocrinology.* (1997) 138:521–9. doi: 10.1210/endo.138.2.4905
62. Takuma A, Kaneda T, Sato T, Ninomiya S, Kumegawa M, Hakeda Y. Dexamethasone enhances osteoclast formation synergistically with transforming growth factor-beta by stimulating the priming of osteoclast progenitors for differentiation into osteoclasts. *J Biol Chem.* (2003) 278:44667–74. doi: 10.1074/jbc.M300213200
63. Liu P, Gao Y, Luo P, Yu H, Guo S, Liu F, et al. Glucocorticoid-induced expansion of classical monocytes contributes to bone loss. *Exp Mol Med.* (2022) 54:765–76. doi: 10.1038/s12276-022-00764-6
64. Azetsu Y, Chatani M, Dodo Y, Karakawa A, Sakai N, Negishi-Koga T, et al. Treatment with synthetic glucocorticoid impairs bone metabolism, as revealed by *in vivo* imaging of osteoblasts and osteoclasts in medaka fish. *BioMed Pharmacother.* (2019) 118:109101. doi: 10.1016/j.biopha.2019.109101
65. Cui J, Shibata Y, Zhu T, Zhou J, Zhang J. Osteocytes in bone aging: Advances, challenges, and future perspectives. *Ageing Res Rev.* (2022) 77:101608. doi: 10.1016/j.arr.2022.101608
66. Lane NE, Yao W, Balooch M, Nalla RK, Balooch G, Habelitz S, et al. Glucocorticoid-treated mice have localized changes in trabecular bone material properties and osteocyte lacunar size that are not observed in placebo-treated or estrogen-deficient mice. *J Bone Miner Res.* (2006) 21:466–76. doi: 10.1359/JBMR.051103
67. Li C, Yang P, Liu B, Bu J, Liu H, Guo J, et al. Prednisolone induces osteocytes apoptosis by promoting Notum expression and inhibiting PI3K/AKT/GSK3 $\beta$ /catenin pathway. *J Mol Histol.* (2021) 52:1081–95. doi: 10.1007/s10735-021-10006-0
68. Xia X, Kar R, Gluhak-Heinrich J, Yao W, Lane NE, Bonewald LF, et al. Glucocorticoid-induced autophagy in osteocytes. *J Bone Miner Res.* (2010) 25:2479–88. doi: 10.1002/jbmr.160
69. Jia J, Yao W, Guan M, Dai W, Shahnazari M, Kar R, et al. Glucocorticoid dose determines osteocyte cell fate. *FASEB J.* (2011) 25:3366–76. doi: 10.1096/fj.11-182519
70. Yee CS, Meliadi C, Kaya S, Chang W, Alliston T. The osteocytic actions of glucocorticoids on bone mass, mechanical properties, or perilacunar remodeling outcomes are not rescued by PTH(1-34). *Front Endocrinol (Lausanne).* (2024) 15:1342938. doi: 10.3389/fendo.2024.1342938
71. Fouquet G, Coman T, Hermine O, Côté F. Serotonin, hematopoiesis and stem cells. *Pharmacol Res.* (2019) 140:67–74. doi: 10.1016/j.phrs.2018.08.005
72. Andrews PW, Bosyj C, Brenton L, Green L, Gasser PJ, Lowry CA, Pickel VM. All the brain's a stage for serotonin: the forgotten story of serotonin diffusion across cell membranes. *Proc Biol Sci.* (2022) 289. doi: 10.1098/rspb.2022.1565
73. Parajulee A, Kim K. Structural studies of serotonin receptor family. *BMB Rep.* (2023) 56:527–36. doi: 10.5483/BMBRep.2023-0147
74. Stevens RC, Cherezov V, Katritch V, Abagyan R, Kuhn P, Rosen H, et al. The GPCR Network: a large-scale collaboration to determine human GPCR structure and function. *Nat Rev Drug Discov.* (2013) 12:25–34. doi: 10.1038/nrd3859
75. Dell'Osso L, Carmassi C, Mucci F, Marazziti D. Depression, serotonin and tryptophan. *Curr Pharm Des.* (2016) 22:949–54. doi: 10.2174/1381612822666151214104826
76. Ducy P. 5-HT and bone biology. *Curr Opin Pharmacol.* (2011) 11:34–8. doi: 10.1016/j.coph.2011.01.007
77. Yadav VK, Oury F, Suda N, Liu Z-W, Gao X-B, Confavreux C, et al. A serotonin-dependent mechanism explains the leptin regulation of bone mass, appetite, and energy expenditure. *Cell.* (2009) 138:976–89. doi: 10.1016/j.cell.2009.06.051
78. Oury F, Yadav VK, Wang Y, Zhou B, Liu XS, Guo XE, et al. CREB mediates brain serotonin regulation of bone mass through its expression in ventromedial hypothalamic neurons. *Genes Dev.* (2010) 24:2330–42. doi: 10.1101/gad.1977210
79. Brotman AW, Stern TA. Osteoporosis and pathologic fractures in anorexia nervosa. *Am J Psychiatry.* (1985) 142:495–6. doi: 10.1176/ajp.142.4.495
80. Oświecimska J, Ziora K, Pluskiewicz W, Geisler G, Broll-Waśka K, Karasek D, et al. Skeletal status and laboratory investigations in adolescent girls with anorexia nervosa. *Bone.* (2007) 41:103–10. doi: 10.1016/j.bone.2007.03.018
81. Zhang R-H, Zhang X-B, Lu Y-B, Hu Y-C, Chen X-Y, Yu D-C, et al. Calcitonin gene-related peptide and brain-derived serotonin are related to bone loss in ovariectomized rats. *Brain Res Bull.* (2021) 176:85–92. doi: 10.1016/j.brainresbull.2021.08.007

82. Lam RW, Wong H-K, Kumarsing RA, Chua AN, Ho RC, McIntyre RS, et al. Fluoxetine improves bone microarchitecture and mechanical properties in rodents undergoing chronic mild stress - an animal model of depression. *Transl Psychiatry*. (2022) 12:339. doi: 10.1038/s41398-022-02083-w
83. Hodge JM, Wang Y, Berk M, Collier FM, Fernandes TJ, Constable MJ, et al. Selective serotonin reuptake inhibitors inhibit human osteoclast and osteoblast formation and function. *Biol Psychiatry*. (2013) 74:32–9. doi: 10.1016/j.biopsych.2012.11.003
84. Yadav VK, Ryu J-H, Suda N, Tanaka KF, Gingrich JA, Schütz G, et al. Lrp5 controls bone formation by inhibiting serotonin synthesis in the duodenum. *Cell*. (2008) 135:825–37. doi: 10.1016/j.cell.2008.09.059
85. Babić Leko M, Gunjača I, Pleić N, Zemunik T. Environmental factors affecting thyroid-stimulating hormone and thyroid hormone levels. *Int J Mol Sci*. (2021) 22:6521. doi: 10.3390/ijms22126521
86. Ortiga-Carvalho TM, Sidhaye AR, Wondisford FE. Thyroid hormone receptors and resistance to thyroid hormone disorders. *Nat Rev Endocrinol*. (2014) 10:582–91. doi: 10.1038/nrendo.2014.143
87. Tedeschi L, Vassalle C, Iervasi G, Sabatino L. Main factors involved in thyroid hormone action. *Molecules*. (2021) 26:7337. doi: 10.3390/molecules26237337
88. Bassett JHD, Williams GR. Role of thyroid hormones in skeletal development and bone maintenance. *Endocr Rev*. (2016) 37:135–87. doi: 10.1210/er.2015-1106
89. Wang L, Shao YY, Ballock RT. Thyroid hormone interacts with the Wnt/beta-catenin signaling pathway in the terminal differentiation of growth plate chondrocytes. *J Bone Miner Res*. (2007) 22:1988–95. doi: 10.1359/jbmr.070806
90. Wang L, Shao YY, Ballock RT. Thyroid hormone-mediated growth and differentiation of growth plate chondrocytes involves IGF-1 modulation of beta-catenin signaling. *J Bone Miner Res*. (2010) 25:1138–46. doi: 10.1002/jbmr.5
91. Xing W, Cheng S, Wergedal J, Mohan S. Epiphyseal chondrocyte secondary ossification centers require thyroid hormone activation of Indian hedgehog and osterix signaling. *J Bone Miner Res*. (2014) 29:2262–75. doi: 10.1002/jbmr.2256
92. Vergatti A, Abate V, Garofano F, Fiore A, De Filippo G, Strazzullo P, et al. Are dietary habits the missing link between hashimoto's thyroiditis and osteoporosis? *Nutrients*. (2025) 17:2109. doi: 10.3390/nu17132109
93. Delitala AP, Scuteri A, Doria C. Thyroid hormone diseases and osteoporosis. *J Clin Med*. (2020) 9:1034. doi: 10.3390/jcm9041034
94. Lassová L, Niu Z, Golden EB, Cohen AJ, Adams SL. Thyroid hormone treatment of cultured chondrocytes mimics *in vivo* stimulation of collagen X mRNA by increasing BMP 4 expression. *J Cell Physiol*. (2009) 219:595–605. doi: 10.1002/jcp.21704
95. Lademann F, Mayerl S, Tsourdi E, Verrey F, Leitch VD, Williams GR, et al. The thyroid hormone transporter MCT10 is a novel regulator of trabecular bone mass and bone turnover in male mice. *Endocrinology*. (2022) 163:bqab218. doi: 10.1210/endo/bqab218
96. Scarlett A, Parsons MP, Hanson PL, Sidhu KK, Milligan TP, Burrin JM. Thyroid hormone stimulation of extracellular signal-regulated kinase and cell proliferation in human osteoblast-like cells is initiated at integrin alphaVbeta3. *J Endocrinol*. (2008) 196:509–17. doi: 10.1677/JOE-07-0344
97. Fonseca TL, Teixeira MBCG, Miranda-Rodrigues M, Silva MV, Martins GM, Costa CC, et al. Thyroid hormone interacts with the sympathetic nervous system to modulate bone mass and structure in young adult mice. *Am J Physiol Endocrinol Metab*. (2014) 307:E408–418. doi: 10.1152/ajpendo.00643.2013
98. Kanatani M, Sugimoto T, Sowa H, Kobayashi T, Kanzawa M, Chihara K. Thyroid hormone stimulates osteoclast differentiation by a mechanism independent of RANKL-RANK interaction. *J Cell Physiol*. (2004) 201:17–25. doi: 10.1002/jcp.20041
99. Miura M, Tanaka K, Komatsu Y, Suda M, Yasoda A, Sakuma Y, et al. A novel interaction between thyroid hormones and 1,25(OH)(2)D(3) in osteoclast formation. *Biochem Biophys Res Commun*. (2002) 291:987–94. doi: 10.1006/bbrc.2002.6561
100. Zhang W, Chen Y, Wang Y, Zhou Y, Guo H, Xu J. TSH inhibits osteoclast differentiation through AMPK signaling pathway. *Gene*. (2025) 955:149442. doi: 10.1016/j.gene.2025.149442
101. Chubar V, Vaessen T, Noortgate WVD, Lutin E, Bosmans G, Bekaert B, et al. Mild daily stress, in interaction with NR3C1 DNA methylation levels, is linked to alterations in the HPA axis and ANS response to acute stress in early adolescents. *Psychoneuroendocrinology*. (2023) 150:106045. doi: 10.1016/j.psyneuen.2023.106045
102. McEwen BS. Sex, stress and the hippocampus: allostasis, allostatic load and the aging process. *Neurobiol Aging*. (2002) 23:921–39. doi: 10.1016/s0197-4580(02)00027-1
103. Sévoz-Couche C, Brouillard C. Key role of 5-HT3 receptors in the nucleus tractus solitarius in cardiovascular stress reactivity. *Neurosci Biobehav Rev*. (2017) 74:423–32. doi: 10.1016/j.neubiorev.2016.04.014
104. Sévoz-Couche C, Nosjean A, Franc B, Hamon M, Laguzzi R. Dorsal medullary 5-HT3 receptors and sympathetic premotor neurons in the rat. *J Physiol*. (1998) 508:747–62. doi: 10.1111/j.1469-7793.1998.747bp.x
105. Vaidya VA, Castro ME, Pei Q, Sprakes ME, Grahame-Smith DG. Influence of thyroid hormone on 5-HT(1A) and 5-HT(2A) receptor-mediated regulation of hippocampal BDNF mRNA expression. *Neuropharmacology*. (2001) 40:48–56. doi: 10.1016/s0028-3908(00)00094-0
106. Komori T. Molecular mechanism of runx2-dependent bone development. *Mol Cells*. (2020) 43:168–75. doi: 10.14348/molcells.2019.0244
107. Jeong J, Jin J, Kim H, Kang S, Liu JC, Lengner CJ, et al. Expression of Runx2 transcription factor in non-skeletal tissues, sperm and brain. *J Cell Physiol*. (2008) 217:511–7. doi: 10.1002/jcp.21524
108. Wang J, Fang C-L, Noller K, Wei Z, Liu G, Shen K, et al. Bone-derived PDGF-BB drives brain vascular calcification in male mice. *J Clin Invest*. (2023) 133:e168447. doi: 10.1172/JCI168447
109. Ai Z, Huang W, Hu W, An R, Lei G, Gu W, et al. Knockdown of RUNX2 attenuated A1 astrocyte overactivation, brain injury, and cerebral edema during ischemic stroke. *NeuroMol Med*. (2025) 27:48. doi: 10.1007/s12017-025-08868-8
110. Zhang F, Zhang W. Research progress in Alzheimer's disease and bone-brain axis. *Ageing Res Rev*. (2024) 98:102341. doi: 10.1016/j.arr.2024.102341
111. Starr TB, Kreipe RE. Anorexia nervosa and bulimia nervosa: brains, bones and breeding. *Curr Psychiatry Rep*. (2014) 16:441. doi: 10.1007/s11920-014-0441-4