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Brain-Bone Axis: The Bridge Connecting the Central Nervous System and the Skeletal System

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ABSTRACT

The Brain-Bone Axis (BBA) is a bidirectional regulatory network connecting the central nervous system and the skeletal system, challenging the traditional view of their functional independence. In recent years, with the deep integration of neurobiology and bone metabolism research, the complex regulatory mechanisms of the BBA have been gradually revealed. The central nervous system regulates bone remodeling through the sympathetic or parasympathetic nervous systems, neuropeptides, and hormonal signals, while the skeletal system, in turn, modulates brain development and function via the secretion of bone-derived hormones such as osteocalcin (OCN) and fibroblast growth factor 23 (FGF23). This article briefly outlines the core regulatory molecules and pathways of the BBA, its pathophysiological role in bone metabolic diseases and neurodegenerative diseases, and discusses therapeutic strategies targeting the BBA, providing references for mechanistic research and clinical intervention of related diseases.

Abbreviations: BBA: Brain-Bone Axis; OCN: Osteocalcin; FGF23: Fibroblast Growth Factor 23; CNS: Central Nervous System; SNS: Sympathetic Nervous System; PNS: Parasympathetic Nervous System; NE: Norepinephrine; NPY: Neuropeptide Y; DA: Dopamine; RA: Rheumatoid Arthritis; GCs: Glucocorticoids; CGRP: Calcitonin Gene-Related Peptide; PD: Parkinson's Disease; SSRIs: Serotonin Reuptake Inhibitors; BMSCs: Bone Marrow Mesenchymal Stem Cells; PTH: Parathyroid Hormone

Introduction

The skeletal system has long been regarded as a static organ maintaining structural support, hematopoiesis, and calcium-phosphorus homeostasis, while the central nervous system (CNS) was considered the central hub regulating systemic physiological functions. However, research over the past two decades has completely overturned this notion, proposing the novel concept of the "Brain-Bone Axis" – a bidirectional communication network between the brain and bone formed through neural, endocrine, and immune signals, enabling coordinated regulation of multiple physiological processes such as bone remodeling, energy metabolism, and cognitive function. This pathway participates not only in basic physiological processes like skeletal metabolism and neural development but also plays a key role in pathological states such as trauma and neurodegenerative diseases. This review will focus on the bidirectional regulatory mechanisms of the BBA, its disease associations, and therapeutic prospects, integrating core findings from recent literature to provide a systematic perspective for research in this field.

Bidirectional Regulatory Mechanisms of the Brain-Bone Axis

The regulation of the BBA is markedly bidirectional. The brain regulates bone metabolism in a "top-down" manner via neural pathways and molecular signals, while bone influences brain function in a "bottom-up" manner via bone-derived hormones, forming a sophisticated feedback loop.

"Top-Down" Regulation of Bone by the Brain

The brain primarily regulates bone remodeling through the sympathetic nervous system (SNS), parasympathetic nervous system (PNS), and neuropeptide/hormone signaling pathways, with the core being the balance between osteoblast-mediated bone formation and osteoclast-mediated bone resorption.

The Core Regulatory Role of the Sympathetic Nervous System: The sympathetic nerve is the main efferent pathway of the BBA, exerting regulation via the release of norepinephrine (NE). NE inhibits osteoblast differentiation by activating β2-AR and promotes os-

teoclastogenesis by upregulating RANKL expression. Clinical studies confirm that long-term use of β2-AR agonists increases fracture risk, while β-AR antagonists (e.g., propranolol) can promote bone formation.

Coordinated Regulation by Neuropeptides and Hormones: Neuropeptide Y (NPY) is a core regulatory molecule of the BBA, mainly expressed in the hypothalamic arcuate nucleus (ARC), achieving multidimensional regulation through receptors such as Y1, Y2, and Y5. Centrally, NPY inhibits osteoblast activity via Y2 receptors. Peripherally, NPY binds to Y1 receptors on osteoblasts to inhibit osteogenic differentiation. Leptin regulates bone metabolism through both central and peripheral pathways. Centrally, leptin binds to its receptor (ObRb) in the hypothalamic ARC, activating the sympathetic nervous system to inhibit osteoblast proliferation. Peripherally, leptin directly binds to ObRb on osteoblasts and osteoclasts, promoting osteoblast differentiation and inhibiting osteoclast activity. Abnormal leptin levels are associated with various bone metabolic diseases. Leptin resistance in obese patients relieves inhibition on NPY, leading to reduced bone formation; the hypoleptinemic state in anorexia nervosa triggers both bone microstructure damage and an increased fracture risk. Furthermore, dopamine (DA) regulates bone metabolism through specific receptor subtypes. The D1 receptor promotes osteoblast differentiation and ameliorates glucocorticoid-induced bone loss; the D2 receptor inhibits osteoclastogenesis, demonstrating bone-protective effects in rheumatoid arthritis (RA).

Regulatory Roles of the Parasympathetic and Sensory Nerves: The parasympathetic nerve can reduce sympathetic tone, promoting bone mass accrual. Sensory nerves regulate bone mass via secretion of Sema3A. Mice with neuron-specific Sema3A deficiency exhibit increased bone resorption and decreased bone formation due to abnormal sensory nerve development.

"Bottom-Up" Regulation of the Brain by Bone

Bone, as an endocrine organ, inversely regulates brain function by secreting bone-derived hormones, with osteocalcin and FGF23 being the most representative regulatory molecules. Osteocalcin is a non-collagenous protein secreted by osteoblasts. Its carboxylated form participates in bone mineralization, while the undercarboxylated form (ucOC) can cross the blood-brain barrier to exert neuromodulatory effects. In adults, ucOC binds to the GPR158 receptor in brain regions such as the hippocampus and midbrain, improving spatial memory and anxiety-like behaviors. During embryonic development, maternally derived OCN can cross the placental barrier into the fetus, inhibiting neuronal apoptosis in the hippocampal region and regulating lateral ventricle development; maternal OCN deficiency leads to impaired spatial learning ability in offspring. FGF23 is primarily secreted by osteoblasts and osteocytes. Its classical function is regulating calcium-phosphorus homeostasis. Recent studies found it can cross the blood-brain barrier to affect cognitive function. FGF23 knockout mice exhibit reduced hippocampal ATP content and impaired long-term potentiation (LTP), leading to cognitive impairment; the high FGF23 state in chronic kidney disease patients is associated with an increased risk of dementia.

Dysregulation of the Brain-Bone Axis and Disease Associations

Imbalance in the regulatory network of the BBA is a common pathological basis for various diseases, with effects spanning multiple systems, manifesting as coordinated disorders of neural and skeletal functions.

Brain-Bone Axis Dysfunction Associated with Traumatic Brain Injury (TBI)

TBI affects the skeletal system dually. On one hand, TBI disrupts the HPA axis, leading to excessive release of glucocorticoids (GCs) and pro-inflammatory cytokines, inhibiting GH/IGF-1 axis function, and causing long-term bone loss and osteoporosis. On the other hand, TBI can accelerate fracture healing by releasing factors such as calcitonin gene-related peptide (CGRP), and BMP-2, activating osteogenic signaling pathways.

Neurodegenerative Diseases and Abnormal Bone Metabolism

Alzheimer's disease (AD) patients often exhibit decreased bone density. The mechanism is related to inhibition of the cerebral Wnt/β-catenin pathway and neuroinflammation caused by Aβ deposition. Damage to dopaminergic neurons in Parkinson's disease (PD) leads to osteoblast inhibition and osteoclast activation, increasing the risk of osteoporosis and fractures. Furthermore, Nasu-Hakola disease (PLOSL), a typical BBA disorder caused by mutations in the TREM2 or DAP12 genes, simultaneously induces bone cyst formation and early-onset dementia.

Brain-Bone Axis Abnormalities in Metabolic and Psychiatric Diseases

Obesity triggers central leptin resistance via excessive leptin secretion, relieving inhibition on NPY and leading to reduced bone formation. Long-term use of drugs such as selective serotonin reuptake inhibitors (SSRIs) and antiepileptics can also disrupt BBA homeostasis by interfering with neurotransmitter balance, exacerbating bone metabolic abnormalities.

Therapeutic Strategies Based on the Brain-Bone Axis and Research Perspectives

Progress in Drug Therapies Targeting the Brain-Bone Axis

Treatment of Skeletal Diseases: Combining β2-AR antagonists (e.g., propranolol) with parathyroid hormone (PTH) can synergistically promote bone formation and improve osteoporosis; monoclonal

antibodies against RANKL (e.g., denosumab) can simultaneously inhibit bone resorption and neuroinflammation, showing potential value in osteoporosis combined with neurodegenerative diseases.

Treatment of Neurological Diseases: Bone marrow mesenchymal stem cells (BMSCs) and their exosomes have shown neurorestorative potential in TBI animal models, exerting dual protective effects through the release of anti-inflammatory factors and promotion of angiogenesis. Agonist antibodies targeting TREM2 can improve microglial function while modulating bone metabolism, providing new ideas for the treatment of comorbidities like AD and osteoporosis.

Future Research Directions

Future efforts need to focus on core scientific questions regarding BBA regulation, conducting in-depth exploration from multiple dimensions including molecular mechanisms, technological innovation, and clinical translation.

Identifying Key Neural Circuits and Cell-Specific Targets: Utilize technologies like optogenetics and chemogenetics to precisely locate central neural circuits regulating bone metabolism and analyze functional differences of different neuronal subtypes within the BBA; identify specific molecular targets on the surfaces of osteoblasts, osteoclasts, and neural cells to elucidate the molecular mechanisms of direct intercellular crosstalk.

Research on Comorbidity Mechanisms and Precision Diagnosis/Therapy: Conduct multicenter clinical studies targeting the comorbid features of diseases like AD, PD, TBI, and osteoporosis to validate the synergistic therapeutic effects of BBA-targeting drugs; establish risk assessment systems based on BBA molecular biomarkers to achieve early disease warning and stratified treatment.

Promoting Interdisciplinary Technology Integration and Translation: Integrate technologies such as single-cell sequencing, spatial transcriptomics, and artificial intelligence to construct a BBA molecular interaction network database and predict potential regulatory targets; develop novel biomaterials, cell therapies, and gene therapy vectors with both neuroprotective and bone-repair functions to accelerate the translation of basic research findings into clinical applications [1-8].

Summary

As the core regulatory network connecting the central nervous system and bone metabolism, the in-depth analysis of the bidirectional interaction mechanisms of the BBA has brought paradigm shifts to the diagnosis and treatment of cross-system diseases. Current research has clarified the key roles of neural circuits, neurohormones, and bone-derived factors in maintaining organismal homeostasis, yet many scientific gaps remain to be explored. Future research should focus on the specific targets of core regulatory molecules to provide theoretical support for precise intervention. Furthermore, BBA research is not limited to the neural and skeletal systems; its cross-boundary interactions with gut microbiota and immune cells also warrant attention. Future studies could expand to multi-axis networks like “brain-bone-gut” and “brain-bone-immune,” providing a more comprehensive perspective for understanding systemic metabolic homeostasis regulation. With the iteration of research technologies and the deepening of interdisciplinary collaboration, the BBA is expected to become a key breakthrough point for deciphering the comorbidity mechanisms of many chronic diseases, promoting the efficient translation of basic research into clinical applications, and opening new avenues for improving human health.

References

1. Chamouni A, Schreiweis C, Oury F (2015) Bone, brain & beyond. Reviews in Endocrine and Metabolic Disorders 16(2): 99-113.
2. Gao S, Qi L, Li N, Li X, Zhang J, et al. (2025) The role of the brain-bone axis in skeletal degenerative diseases and psychiatric disorders, A genome-wide pleiotropic analysis. Progress in Neuro-Psychopharmacology and Biological Psychiatry 139: 111388.
3. Huang S, Li Z, Liu Y, Gao D, Zhang X, et al. (2018) Neural regulation of bone remodeling: Identifying novel neural molecules and pathways between brain and bone. Journal of Cellular Physiology 234(5): 5466-5477.
4. Liu M, Liu Y, Yu J, Gong J, Zhao C, et al. (2025) Molecular mechanisms and therapeutic implications of the sympathetic nervous system in bone-related disorders: a brain-bone axis perspective. Bone Research 13(1): 98.
5. Massaccesi L, Corsi Romanelli MM, Galliera E (2025) Brain–Bone Axis in Physiological and Pathological Conditions. International Journal of Molecular Sciences 26(19): 9822.
6. Shi H, Chen M (2024) The brain–bone axis: unraveling the complex interplay between the central nervous system and skeletal metabolism. European Journal of Medical Research 29(1): 317.
7. Zhang F, Zhang W (2024) Research progress in Alzheimer’s disease and bone-brain axis. Ageing Research Reviews 98: 102341.
8. Zhang W, Zou J, Zhang L (2025) Bidirectional Interaction Between the Brain and Bone in Traumatic Brain Injury. Advanced Science 12(31): e03149.

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