Systemic Supplementation of Magnesium Attenuates Bone Loss via Acting on Central Nervous System

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INTRODUCTION: Osteoporosis is a prevalent disorder that disrupts bone quality, mainly in aged people, and may result in devastating osteoporotic fractures. Magnesium deficiency is a marked characteristic of osteoporosis, and magnesium level in serum is positively associated with bone mineral density. Magnesium supply can reverse the progression of osteoporosis, but the magnesium content in bone is relatively unaffected, suggesting a distinct mechanism with our previously reported sensory nervous system activated by local implantation of Mg metal [1, 2]. Recent studies report that the central nervous system (CNS) orchestrates bone remodeling via different mechanisms and molecules. The CNS projects sympathetic or parasympathetic nerve endings to bone, while inhibiting sympathetic nerve activity by β-blocker improved bone mass. In the CNS, oral magnesium-L-threonate (MgT) supply improved memory [3]. However, whether magnesium regulates bone metabolism via acting on CNS is still unclear. More importantly, the brain region affected explicitly by magnesium remained unknown.

METHODS: The MgT was injected intraperitoneally (i.p). We selected three different concentrations (25mg/kg/day, 50mg/kg/day and 100mg/kg/day) to test the preventive effect on osteoporosis of MgT. Ovariectomy(OVX) surgery was performed to construct the osteoporotic mice model. Activity labeled neuron and c-Fos staining were used to determine the brain region affected by magnesium i.p injection. Fluorescence labeled retrograde tracing technique by the pseudorabies virus (PRV) was used to identify the brain region connected with bone. Optogenetics and chemogenetics techniques were used to achieve brain region-specific manipulation. Micro-CT and histomorphological staining were used to determine bone quality. Peripheral nerve staining and labeling will be used to determine the change in the peripheral nerve.

RESULTS: MgT injection increased the Mg2+ level in the cerebrospinal fluid. After 1-month, MgT treatment increased BV/TV by 35% and Tb.Th by 15% compared with osteoporotic mice treated with saline ($p < 0.05$, one-way ANOVA) . By activity labeled neurons technique, we found the c-Fos positive neurons in the parabrachial nucleus (PBN) increased by 40% ($p < 0.05$, Student's t-test). We injected PRV into the trabecular bone region of the femur. The PBN region was labeled by GFP, suggesting an anatomical connection between bone and PBN region. PBN hosted most Calca positive neuron subpopulation, and chemogenetic activation of this subpopulation increased the BV/TV of trabecular bone by 40% ($p < 0.05$, Student's t-test). Knocking out magnesium transporter-1 (Magt1) in Calca+ neurons resulted in decreased BV/TV by 30% ($p < 0.05$, Student's t-test). More importantly, Magt1 KO abolished the bone morphology difference between MgT and saline.

DISCUSSION: 1. MgT supply reversed the bone loss in osteoporotic mice. The anti-osteoporotic effect of MgT is stronger than other magnesium forms. 2. Mg2+ acts directly on and activates the PBN region of the CNS and the PBN area sends direct nerve projections to the bone. 3. Activating the Calca+ neurons in the PBN region increased bone mass. 4. MgT's CNS effect on bone homeostasis relies on the magnesium transporter-1 (Magt1) in Calca+ neurons.

SIGNIFICANCE: 1. We identify the magnesium supply by MgT improved bone quality by acting on the CNS. 2. Current results suggest the PBN is a critical brain region in regulating bone remodeling. 3. We apply several advanced technologies in neuroscience to study the functional and anatomical connection between the brain and bone.

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