Osteocyte-Specific Deletion of the α2δ, Auxillary Voltage Sensitive Calcium Channel Subunit

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ABSTRACT

Context: Skeletal unloading due to disease, aging increases bone loss and the risk of skeletal fracture. Conversely, mechanical loading is anabolic to the skeleton, promoting skeletal integrity through increased bone formation. Though osteocytes are the most abundant and mechanosensitive cells within the skeleton, influencing bone formation and resorption, exactly how these forces are transmitted through osteocytes to initiate anabolic responses remains unclear. As calcium influx is the first measurable response of bone cells to mechanical stimuli and voltage sensitive calcium channels (VSCCs) play a critical role in bone formation, given VSCC activity is influenced by its auxiliary α2δ subunit, regulating the gating kinetics of the channel's pore-forming α subunit and forward trafficking of VSCCs to cell membranes, the α2δ subunit may govern anabolic bone responses. Data showing osteopetrosis in global α2δ knockout mice and decreased mechanosensitivity following α2δ knockdown in cultured osteocytes support this notion. Objective: To determine if osteocyte-specific α2δ deletion in a mouse model would affect skeletal development, decrease bone formation and mechanosensitivity. Methods: Generation of an osteocyte-specific α2δ knockout was accomplished by crossing mice (C57BL/6) harboring flanking LoxP sequences flanking Ca2δ2, the gene encoding α2δ, with mice expressing Cre recombinase under the control of the Dmp1 (10Kb) promoter (α2δ-Cre+). To assess skeletal phenotype and mechanosensitivity, longitudinal whole body and site-specific DMP1 in vivo µCT (10wk old), and two weeks of tibial loading (16wks) will be conducted before femurs and forelimbs for mechanical testing, ex vivo µCT, and quantitative histomorphometric analyses. Results: & Conclusion: Preliminary analyses show no differences in whole body or site-specific BMD and BMC values between mice over time, suggesting osteocyte-specific α2δ deletion may not influence skeletal development. However, key differences in mechanosensitivity following tibial loading are expected given the potential role of α2δ in mechanically-induced bone formation.

BACKGROUND

- Osteocytes are the most abundant and mechanosensitive cells within the skeleton, influencing bone formation, key differences in bone formation and resorption. However, key differences in osteocyte-specific α2δ knockout was accomplished by crossing mice (C57BL/6) harboring flanking LoxP sequences flanking Ca2δ2, the gene encoding α2δ, with mice expressing Cre recombinase under the control of the Dmp1 (10Kb) promoter (α2δ-Cre+). To assess skeletal phenotype and mechanosensitivity, longitudinal whole body and site-specific DMP1 in vivo µCT (10wk old), and two weeks of tibial loading (16wks) will be conducted before femurs and forelimbs for mechanical testing, ex vivo µCT, and quantitative histomorphometric analyses. Results & Conclusion: Preliminary analyses show no differences in whole body or site-specific BMD and BMC values between mice over time, suggesting osteocyte-specific α2δ deletion may not influence skeletal development. However, key differences in mechanosensitivity following tibial loading are expected given the potential role of α2δ in mechanically-induced bone formation.

WHOLE BODY COMPOSITION

- Previous data has suggested that α2δ plays a crucial role in proper skeletal development.
- Preliminary analyses show no differences in whole body or site-specific BMD and BMC values between mice over time.
- Data suggests osteocyte-specific α2δ deletion may not influence skeletal development or bone formation.
- Given the role of osteocytes in bone formation, key differences in mechanosensitivity following tibial loading are expected.