BONE

Dual role for cannabinoid receptor in bone metabolism

New research suggests that the type 1 cannabinoid receptor (CB1) pathway has a role not only in regulating peak bone mass but also in protecting against bone loss later in life. Investigations in mice deficient for CB1 (*CR1*$^{-/-}$ mice) have shed light on the mechanisms that direct the differentiation of bone marrow stromal cells (BMSCs) into adipocytes rather than osteoblasts, a phenomenon associated with age-related osteoporosis.

> “Investigations in [*CR1*$^{-/-}$ mice] have shed light on ... the differentiation of bone marrow stromal cells”

CR1$^{-/-}$ mice have an increased peak bone mass at 3 months of age relative to wild-type mice of the same age, but by age 12 months show reduced bone turnover and bone formation, as well as prominent accumulation of adipocytes in the bone marrow compartment. In the study, published in *Cell Metabolism*, histomorphometry and immunoassay of markers of bone turnover were employed to demonstrate that the effects of CB1 deficiency on peak bone mass are attributable to reduced osteoclast differentiation in the context of normal osteoblast activity.

With advancing age, CB1 deficiency seems to predispose mice to osteoporosis through its effects on the differentiation of BMSCs into adipocytes and osteoblasts. Compared with BMSCs from wild-type mice, BMSCs from *CR1*$^{-/-}$ mice showed a reduced capacity to form mineralized bone nodules but preferentially differentiated into adipocytes and expressed higher levels of adipocyte-specific transcription factors. Consistent with this observation, pharmacological blockade of CB1 in wild-type BMSCs inhibited bone module development, stimulated adipocyte differentiation, and increased levels of cyclic AMP in osteoblast and adipocyte precursors, which is known to stimulate adipocyte differentiation and inhibit osteoblast differentiation.

The investigators suggest that alternative signaling pathways maintain normal bone formation when CB1-deficient mice are young, but that these compensatory mechanisms fail as the mice age. The identity and mechanisms of these alternative pathways that affect BMSC differentiation remain to be elucidated.

Together, the results of this study demonstrate the multiple, age-associated effects of cannabinoid receptor signaling on bone metabolism. The authors speculate that CB1 ligands could have therapeutic value through maximizing bone mass accrual and preventing age-related bone loss.

Sarah Price

Original article Idris, A. I. *et al.* Cannabinoid receptor type 1 protects against age-related osteoporosis by regulating osteoblast and adipocyte differentiation in marrow stromal cells. *Cell Metab.* **10**, 139–147 (2009).