Inhibition of sympathetic tone prevents cold-induced bone loss in a mouse model of cold-dwelling humans

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Chronic cold exposure is associated with bone loss in cold-dwelling humans and in animal models, but the mechanisms involved remain unclear. Cold stress upregulates the sympathetic nervous system, which is known to cause bone loss via osteoblast beta-adrenergic receptors. Therefore, we hypothesize that sympathetic activation is a significant cause of cold-induced bone loss, and that such bone loss may be reduced by warming the body through nonshivering thermogenesis (NST) via uncoupling protein-1 (UCP1) in brown adipose tissue.

To test these hypotheses, we used our mouse model of chronic cold exposure to compare skeletal phenotype in untreated mice vs. mice treated with a blocker of beta-adrenergic signaling. Wildtype C57Bl/6J male mice were pair housed at 26°C (thermoneutrality) and 16°C (moderate cold stress) from 3-12 wks of age with food ad libitum. Half of the mice at each temperature were given the beta-adrenergic blocker propranolol in drinking water ad libitum (0.5 mg/ mL) (N=8/group). Results indicate that cold expo- sure decreased bone mineral density, trabecular bone microarchitecture, and cortical bone mass at 16°C vs. 26°C, despite increased core body temperature and higher UCP1 expression. In mice at 16°C, propranolol completely prevented bone loss in both trabecular and cortical compartments, even though UCP1 expression was significantly reduced and body temperature was unchanged. At 26°C, propranolol had no effect on bone mass, body temperature, or UCP1. These data demonstrate that blocking sympathetic tone prevents cold-induced bone loss in mice, implicating sympathetic activation as a significant contributor to cold-induced bone loss in humans.

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