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# GLOBAL CB1 DEFICIENCY EXACERBATES UNLOADING INDUCED BONE LOSS IN A SITE-SPECIFIC AND SEX-DEPENDENT MANNER

**Abstract**

Bone loss during mechanical unloading, or disuse, is a major concern for astronauts during long duration spaceflight and increases fracture risk. The endocannabinoid system (ECS) plays an important role in postnatal bone metabolism. One of its main receptors, cannabinoid receptor 1 (CB1), is predominately found throughout the central nervous system, along with vascular, adipose and skeletal tissue. The ECS has been studied in regards to basic bone metabolism, however little is known on how the ECS affects bone in different mechanical environments. To examine CB1 as a potential therapeutic target, mice with CB1 global deletion (CB1KO) underwent bone disuse by single limb immobilization. Since both male and female CB1KO mice have been shown to have a lower bone mass phenotype compared to wild type mice, we hypothesized that CB1KO mice would be more sensitive to unloading induced bone loss than wild type mice. This is the first study to examine the effects of ECS and CB1 during mechanical unloading of bone, and the first to consider sex as a variable.

All animal procedures were conducted with approval of Virginia Commonwealth University IACUC. Skeletally mature, 20-week-old C57BL/6J WT and global CB1KO male and female mice were placed in casts to immobilize the left hindlimb (n = 5-10 per group). The right hindlimb was used as a contralateral control. After 21 days of immobilization, mice were sacrificed, and femurs and tibia harvested. Skeletal phenotype was assessed using ex vivo micro-CT scans (Bruker Skyscan 1172; 8.9 um). Cortical bone at the diaphysis and cancellous bone at epiphyseal and metaphyseal regions were analyzed by standard micro-CT methodology. Data were compared for the effect of sex, genotype and immobilization using repeated measures 3-way ANOVA (p¡0.05).

All groups displayed significant bone loss due to casting in the femoral epiphyseal and tibial metaphyseal region. Male CB1KO, female WT and CB1KO experienced significant bone loss in the femoral metaphysis, 17.8

This study, for the first time, suggests that CB1 deficiency exacerbates bone loss, particularly in males, during unloading, as well as females being more sensitive than males to bone loss regardless of genotype.