10 ESTROGEN RECEPTOR α (ER α) EXPRESSION IN NEURONAL CELLS AFFECTS BONE MASS

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Background and objective Bone mass is often negatively affected in autoimmune diseases such as rheumatoid arthritis. It has generally been assumed that bone mass is controlled by endocrine mechanisms and/or the local bone environment. Recent findings demonstrate that central pathways are involved in the regulation of bone mass. Estrogen is involved in the regulation of bone mass and the central nervous system is also a target for estrogen actions.

The aim of this study was to investigate in vivo the role of central estrogen receptor- α (ER α) expression for bone mass.

Methods Nestin-Cre mice were crossed with ER α^{lox} mice to generate mice lacking ER α expression specifically in nervous tissue (nestin-ER $\alpha^{-/-}$). Mice homozygous for ER α -loxP, but lacking Cre expression, were used as controls. Phenotyping of the bone was performed using pQCT, μ CT, histomorphometry and three-point bending. Gene expression analyses were performed using real-time PCR and serum analyses with commercial kits.

Results Bone mineral density was increased in both the trabecular and cortical bone compartments in nestin-ER $\alpha^{-/-}$ mice compared to controls. Femoral bone strength was increased in nestin-ER $\alpha^{-/-}$ mice as demonstrated by increased stiffness and maximal load of failure. The high bone mass phenotype in nestin-ER $\alpha^{-/-}$ mice was mainly caused by increased bone formation. Serum leptin levels were elevated as a result of increased leptin expression in white adipose tissue (WAT) and slightly increased amount of WAT in nestin-ER $\alpha^{-/-}$ mice. Leptin receptor mRNA levels were reduced in the hypothalamus but not in bone. Furthermore, nestin-ER $\alpha^{-/-}$ mice displayed disturbed regulation of T cells with reduced proliferation and decreased frequency in bone marrow.

Conclusions In summary, while peripheral ER α activation increases bone mass, the authors here demonstrate that central ER α activation decreases bone mass. Thus, the balance between peripheral stimulatory and central inhibitory ER α actions is important in the regulation of bone mass. The authors propose that the increased bone mass in nestin-ER $\alpha^{-/-}$ mice is mediated via decreased central leptin sensitivity and thereby increased secretion of leptin from WAT which, in turn, results in increased peripheral leptin-induced bone formation. In addition, an altered T cell regulation might contribute to the high bone mass phenotype in the nestin-ER $\alpha^{-/-}$ mice.