Gabapentin Targeting and Bone Mineralization Defects: Proposed mechanism for increased fracture risk in patients taking GBP-class anti-epileptic drugs

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Background and Hypothesis:

Gabapentin (GBP) is an anti-epileptic drug and first-line therapy for neuropathic pain prescribed to 43 million patients in the US. Unfortunately, GBP use is associated with metabolic bone disease, leading to a 2 to 6-fold increased fracture incidence. Until now, the pathophysiology of this drug-induced bone loss was unknown. We hypothesize that the impaired bone mineralization and skeletal defects is a result of downstream effects of GBP targeting of the $\alpha_2\delta_1$ subunit, the only known GBP receptor.

Project Methods:

In vitro: Murine mesenchymal progenitor cells (MPC-2) were treated with GBP doses varying from 0.5mM to 50mM while undergoing osteoblast differentiation for 1 or 2 weeks. Mineralization was assessed by Alizarin red stain. Gene expression was measured by RT-qPCR.
In vivo: The bone phenotype of mice lacking the $\alpha_2\delta_1$ subunit was analyzed by longitudinal DXA analyses and examined histologically.

Results:

In vitro: MPC-2 cells treated with 50mM GBP while differentiating for 1 and 2 weeks had decreased osteoblast mineralization and a 7-fold reduction and 4 fold reduction, respectively, in DMP1.
In vivo: Male and female $\alpha_2\delta_1$ knockout mice showed a significant decrease in whole body longitudinal (6 wk – 18 wk) bone mineral density (BMD) in males ($p<0.001$) and females ($p=0.014$), along with severe osteomalacia, displaying unmineralized osteoid in the trabecular compartment of the distal femoral metaphyses.

Conclusion and Potential Impact:

The impaired mineralization observed following $\alpha_2\delta_1$ deletion, coupled with reduced differentiation of MPC-2 cells treated with GBP suggests that GBP regulates bone quality through a novel mechanism influencing phosphate wasting or 1,25 vitamin D deficiency leading to fracture. With this awareness physicians can monitor these patients for bone mass loss and prescribe drugs to prevent AED-mediated fracture.