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: 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 α2β1 subunit, the only known GBP receptor.

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 α2β1 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 α2β1 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: The impaired mineralization observed following α2β1 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.

Jonathan Wheeler is a third-year medical student.

How did you discover the specialty you are interested in pursuing?
"After two years of learning extensive medical knowledge down in Bloomington, and within the first day of starting my third-year rotations in Methodist Hospital with the Cardiology Consult Service, I knew this was my passion. Being able to take care of the hearts of your patients is such a central factor in their well-being and if I can do this every day of my career I believe I will be impacting every patient I see for the best."

What was your most important takeaway from your research experience?
The research I did with the IMPRS program over the summer between my first and second years was truly transformative for me; it illuminated how basic science research and clinical practice are inextricably linked. Whether it was performing bench work at my molecular genetics lab or shadowing the trauma surgery team at Methodist, that summer showed me how clinical medicine practices could not exist without the discoveries of basic science research and how research is vital to developing the knowledge to progress medical practice and meaningful health outcomes."