Exploring Endogenous Regulators of Megalin Expression and Localization

Miracle Okoli¹, Brian Chapron², Alenka Chapron², Kenneth Thummel²
¹UW GenOM ALVA, ²Department of Pharmaceutics, University of Washington, Seattle, WA

Abstract

Megalin is an important receptor protein that mediates the entry of 25OHD3, the main circulating form of vitamin D3, into the kidney proximal tubules. The kidney proximal tubule epithelial cells (PTECs) convert 25OHD3 into 1a,25(OH)2D3, the active form of vitamin D3. The active form of vitamin D3 is important in the body for maintaining bone mineral homeostasis, inhibiting the growth of cancer cells and protecting against certain immune disorders. In order for vitamin D3 to be kept in homeostasis in the body, it is regulated by different hormones. Hormones such as the parathyroid hormone (PTH) and fibroblast growth factor (FGF23), increase and decrease 1a,25(OH)2D3 levels, to maintain proper vitamin D3 levels. Because of this, it is possible to hypothesize that the same hormones that are important in maintaining proper vitamin D3 levels, may also be important in maintaining megalin in the body as well.

Methods

- Vitamin D3 maintains bone mineral homeostasis, inhibits the growth of cancer cells and acts to protect against some immune disorders
- Megalin is crucial for entry of 25OHD3 into the proximal tubule of the kidney for conversion to 1a,25(OH)2D3
- CYP27B1 is regulated by hormones such as parathyroid hormone (PTH) and fibroblast growth factor (FGF23)
- 1a,25(OH)2D3 regulates itself by a negative feedback loop
- Since megalin is a crucial component for 1a,25(OH)2D3 formation, it is possible that the same hormones vital to regulating vitamin D metabolism are regulating megalin expression and localization as well

Results

- 1a,25(OH)2D3 did suppress megalin gene expression
- Albumin also suppressed megalin, which agreed with previous research
- Results for FGF23 and DBP were so marginal that there may have been no effect; further research is needed to confirm this finding
- PTH had no effect on megalin expression and localization, as well as CYP27B1, our positive control. This unexpected finding may be because the cells were not PTH responsive
- Repeat experiments in PTECs with more donors and statistical analysis

Conclusions and Future Directions

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References