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Molecular Dynamics as Phosphate Sensor in the Intestinal Na^+ Dependent Phosphate Transporter

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Summary

Body phosphate homeostasis is maintained via intestinal absorption and renal excretion and bone metabolism. Hyperphosphatemia is associated with ectopic calcification, cardiovascular disease, and increased mortality in patients with chronic kidney disease (CKD). Fibroblast growth factor 23 (FGF23) is a phosphaturic factor which is produced by the osteocytes. Intestinal inorganic phosphate (Pi) absorption is a key determinant of plasma Pi and FGF23 levels in CKD patients. Dietary Pi is efficiently absorbed (60-70%) through the small intestine by both active and passive Pi transport mechanisms. Active transport of Pi is mediated primarily via the type IIb Na/Pi cotransporter (Slc34a2/NaPi-IIb). Recently, we suggest that intestinal NaPi-IIb functions as Pi sensor in body Pi homeostasis. To investigate the role of NaPi-IIb on Pi sensor in chronic renal failure (CRF) rats, we assessed the NaPi-IIb expression. Adenine-induced CRF rats showed hyperphosphatemia, the elevation of plasma PTH and FGF23 concentrations and the reduction of plasma $1,25(OH)_2D_3$ levels. In the comparison of intestinal NaPi-IIb function in normal and CKD rats, we suggested the disruption of Pi sensing mechanism in CRF rats.

Alterations in function of osteocyte occur in very early stages of chronic renal disease (CKD). FGF23 and DMP1 are made primarily in the osteocytes. These are suggesting that the osteocyte plays the total systemic Pi regulation. We have established “osteocyte-ablated” mice exhibited excessive osteoporosis. To analysis the role of osteocyte in Pi homeostasis, we investigated renal and intestinal Pi handling in the osteocyte-ablate mice. Plasma Pi concentration were not changed in the osteocyte-ablated mice. Plasma FGF23 levels were significantly decreased and plasma PTH levels were not changed in the osteocyte ablated mice. Urinary Pi excretion was markedly increased and renal NaPi-IIa and NaPi-IIc protein levels were significantly decreased in the ablated mice. Intestnal NaPi-IIb protein levels were significant increased and Pi absorption increased. In conclusion, the present study suggested the disruption of Pi sensing mechanism in CRF rats and osteocyte ablated mice.