In vivo effects of renal Npt2a inhibition

Timo Rieg, Linto Thomas, Jianxiang Xue, Jessica Ann Dominguez Rieg

Molecular Pharmacology and Physiology, University of South Florida, Tampa, FL

Introduction: Hyperphosphatemia is common in patients with chronic kidney disease and associated with increased mortality. Oral phosphate binders and dietary phosphate restriction are the current management protocols for patients with hyperphosphatemia; however, their effectiveness is insufficient. In the kidney, the sodium-phosphate cotransporter Npt2a is responsible for bulk uptake of phosphate in the proximal tubule. Recently, an orally bioavailable selective Npt2a inhibitor (Npt2a-I, PF-06869206) has been described to reduce phosphate uptake in HEK cells transfected with mouse or rat Npt2a. So far, its physiological in vivo function has not been tested.

Objective: To describe the in vivo effect of renal Npt2a inhibition in C57BL/6J mice

Material and Methods: Based on in vitro IC 50 concentrations, we chose to study 30 mg/kg (oral gavage, 1% of body weight) in short-term (3 hours) metabolic cage experiments in C57BL/6J mice.

Results: Compared to vehicle (n=14), bolus administration of Npt2a-I (n=12) caused significantly higher (~4-fold) urinary phosphate excretion (104±8 vs 27 ±6 µmol*min⁻¹, P<0.05). Similarly, urinary phosphate/creatinine ratios were also significantly higher (32±2 vs 8±2 mmol*mmol⁻¹, P<0.05). In addition, Npt2a-I caused higher urinary excretion of calcium (9±1 vs 3±1 µmol*min⁻¹, P<0.05), sodium (316±37 vs 113±24 µmol*min⁻¹, P<0.05), and chloride (277±31 vs 91±24 µmol*min⁻¹, P<0.05), as well as their respective creatinine ratios (Ca²⁺ : 2.5±0.2 vs 0.8±0.1; Na⁺ : 92±9 vs 31±6; Cl⁻ : 81±8 vs 25±6 mmol*mmol⁻¹ ; all P<0.05). In contrast, urinary flow rate, urinary potassium excretion, potassium/creatinine ratio, and urinary pH were not significantly different between vehicle and Npt2a-I. In a different set of mice, we studied the effect of Npt2a-I on plasma phosphate and calcium. Under baseline conditions, plasma phosphate and calcium levels were not significantly different between the vehicle and Npt2a-I groups. Oral bolus administration of vehicle did not significantly change plasma phosphate (Δ 0.06±0.08 mmol/L, NS) or calcium (Δ -0.04±0.02 mmol/L, NS) 3 hours after application. In contrast, administration of Npt2a-I caused a significant decrease in
plasma phosphate (Δ -0.5±0.05 mmol/L, P<0.05) without affecting plasma calcium (Δ 0.01±0.03 mmol/L, NS).

Conclusions: In summary, our study demonstrates for the first time that in vivo application of a novel Npt2a inhibitor efficiently increases urinary phosphate excretion leading to a decrease in plasma phosphate levels. Thus, inhibiting Npt2a might be a useful treatment strategy for hyperphosphatemia.

Keywords: Npt2a inhibitor, mice, urinary phosphate excretion, animal model, mice

Funding: TR is supported by the National Institute of Diabetes and Digestive and Kidney Diseases (1R01DK110621). JX was supported by an American Heart Association Predoctoral Fellowship (18PRE33990236) and LT by a Postdoctoral Fellowship (19POST34400026).