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Molecular and Pathophysiological Analyses of Extracellular Calcium-Sensing Receptor in Renal Tubular Acid-Base Transport and Urinary Tract Calcinosi

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Summary

Among the roles and mechanisms of the calcium-sensing receptor (Casr)-mediated phenomena, little is known about the contribution of the Casr to acid-base metabolism in kidneys. Hypercalcemia has been known to induce urine acid secretion. Recent findings strongly suggest that Casr is indeed involved in acid-base metabolism in kidneys.

To test directly whether Casr is involved in medullary thick ascending limbs of Henle's loop (mTALs), on of the major segments for bicarbonate reabsorption, the effects of a potent calcimimetics neomycin (Neo) on pHi were analyzed in the *invitro* miropperfused mouse mTALs.

The mTALs were incubated with 2,7-bis-(2-carboxyethyl)-5(6)-carboxyfluoresceine-acetoxymethylester (BCECF-AM) in HCO₃/CO₂-buffered solution. The baseline pHi in the mTALs was 7.17 ± 0.013 (n = 19). Neo added to basolateral solution caused a significant intracellular alkalinization (pHi -7.28 ± 0.015, n = 19), whereas Neo added to the lumen did not change pHi. The effects of a neomycin (Neo) on pHi were analyzed 1) in ambient Na⁺ free solution with 1 μmol/l bafilomycin adding to the lumen. 2) in K⁺-free solution with apical 3 mmol/l Ba²⁺; with luminal applications 1.5 mmol/l ouabain and 20 μmol/l sch-28080. The effect of Neo on pHi was inhibited either by luminal K⁺ removal or by application of a specific H⁺-K⁺-ATase (HKa) inhibitor Sch-28080 and 1 mmol/l ouabain to the lumen. Ambient Na⁺ removal with addition of 1 μmol/l bafilomycin to lumen did not affect the effect of Neo on pHi.

Our results strongly suggest that H⁺-K⁺-ATase is expressed in the apical membrane of the mouse mTALs, and is activated by stimulation of the Casr in the basolateral membrane. These results imply the possibility of pathogenesis of nephrocalcinosis due to disturbance of acid secretion/base reabsorption via H⁺-K⁺-ATase in the mTALs.