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Altered expression of renal claudins in rats with metabolic acidosis and hypercalciuria

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Objectives: Most of the calcium reabsorption passively occurs through tight junctions in the proximal tubule (PT) and thick ascending limb (TAL) of Henle's loop. This study was undertaken to test whether claudins located in these nephron segments are involved in producing metabolic acidosis-induced hypercalciuria.

Methods: Male Sprague-Dawley rats were randomly divided into controls (n=6) and acid-loaded (n=6). Acid loading was offered by addition of NH₄Cl (7.2 mmol/220 g BW/d) to the food slurry for 7 days. At the end of the animal experiment, kidneys were harvested for immunoblotting, immunofluorescence microscopy and qPCR analysis of claudins. HK-2 and MDCK I cells were also used to examine the effects of acidic pH on the expression of proximal and distal nephron claudins, respectively.

Results: In acid-loaded rats, urine pH was lowered and urinary calcium excretion was elevated. In the kidney, claudin-2 protein and mRNA decreased. Claudin-16 protein and mRNA were also downregulated, and claudin-19 protein and mRNA decreased as well. Consistently, claudin-14 protein and mRNA increased. Furthermore, calcium-sensing receptor protein and mRNA were upregulated. Interestingly, claudin-8 protein and mRNA increased. All these results were confirmed by immunofluorescence microscopy. Cultured HK-2 cells showed that claudin-2 protein expression was decreased by exposure to media with pH 6.0, 6.4, and 6.8 as compared with pH 7.4. Consistent with animal results, cultured MDCK I cells showed that claudin-8 protein expression was increased by exposure to media with pH 6.0, 6.4, and 6.8 as compared with pH 7.4.

Conclusions: In metabolic acidosis, downregulation of claudin-2 in the PT and altered regulatory axis of calcium-sensing receptor-claudin 14-claudin 16/19 in the TAL play roles in producing hypercalciuria.