**Objective**

The Na+/H+ exchanger isoform 3 (NHE3) plays an important role in intestinal and renal Na+ uptake and acid-base regulation.1 While renal-specific NHE3 knockout models have been successfully generated, no intestinal-specific model has been described. Of note, renal-specific NHE3 knockout does not result in altered blood pH or bicarbonate levels2 and conventional intestinal epithelial cell-specific NHE3 knockout mice die shortly after birth.

The objective of this study was to generate and characterize a novel inducible intestinal epithelial-specific NHE3 knockout mouse and determine if lack of intestinal NHE3 leads to acid-base disturbances.

**Methods**

We generated tamoxifen (Tam)-inducible epithelial-specific NHE3 knockout mice (NHE3KO; n=4) by intercrossing NHE3KO (control, Con; n=8) and VillinCreERT2 mice. To induce deletion of NHE3, all mice received Tam (200 mg/kg via oral gavage) for 5 consecutive days. Semi-quantitative fluorescent labeling was used to localize NHE3 in small intestine and colon. Body weight, food and fluid intake were monitored for 32 days. At baseline and 2 weeks after Tam treatment, blood was collected to measure pH, HCO3-, base excess, and Na+ and K+ concentrations. At 32 days mice were euthanized and intestine/colon harvested. Flush pH was determined using a pH electrode (9810BN, Thermo Fisher Scientific). All data represented are mean ± SEM.

At baseline, Con and NHE3KO mice had comparable plasma Na+ and K+ concentrations, blood pH, blood HCO3-, and base excess. Two weeks after Tam treatment, compared to Con mice, NHE3KO mice showed significant metabolic acidosis, decreased blood HCO3-, and negative base excess, while plasma Na+ and K+ remained unaffected. #:P<0.05 vs. baseline, *P<0.05 vs. Con.

**Conclusions**

We successfully generated inducible intestinal epithelial cell-specific NHE3 knockout mice. The mouse model will be useful to study different aspects of NHE3 in the intestine and colon. Our data indicate a prominent role of the intestine for acid-base regulation.

**References**
