LETTER TO THE EDITOR

Reduced NHE3 activity results in congenital diarrhea and can predispose to inflammatory bowel disease

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Submitted 22 December 2016; accepted in final form 8 January 2017

TO THE EDITORS: With great interest we read the review just published in the American Journal of Physiology-Regulatory, Integrative and Comparative Physiology on “Novel developments in differentiating the role of renal and intestinal sodium hydrogen exchanger 3” by Dominguez Rieg and colleagues (2). The authors review recent studies that address the impact of NHE3 loss of function on renal and intestinal pathophysiology.

Coupled operation of Na⁺/H⁺ exchanger 3 (NHE3 encoded by the SLC9A3 gene) and Cl⁻/HCO₃⁻ exchanger downregulated in adenoma (DRA, encoded by the SLC26A3 gene) is the major mechanism for Na⁺, Cl⁻, and fluid absorption in the ileum and colon of the mammalian gastrointestinal tract (4). Renal tubular NHE3 expression has also been documented in several mammalian species. Scl9a3 knockout mice display mild diarrhea and reduced body weight, and up to 70% of these mice die at ages ranging from 3 to 24 wk, most commonly during the week after weaning (1). Moreover, these mice spontaneously develop inflammatory bowel disease (IBD) when housed in a conventional facility and lethal colitis when exposed to low concentrations of dextran sulfate sodium. Colitis symptoms in these mice improve upon housing them in an ultraclean facility. These observations point to an immunomodulatory effect of NHE3 downregulation in IBD. Importantly, both human patients and a number of animal models of IBD have demonstrated impaired NHE3-mediated Na⁺ absorption due to inhibition of NHE3, and diarrhea represents a hallmark of IBD (7).

In contrast, knockout mice of NHE3 in the S1 and S2 segments of the proximal tubule or along the entire tubule/collecting duct do not show any obvious clinical symptoms (3). In their review, Dominguez Rieg and colleagues further state their unpublished observations that conditional noninducible intestinal-specific NHE3 knockout mice die within the first few days of life with only one mouse out of >50 offspring that survived ~2 wk.

We complement the review on novel developments in differentiating the role of renal and intestinal NH3 by pointing to our recent identification of germline mutations in NHE3 (5), as well as to our identification of germline mutations in a regulator of NHE3, guanylate cyclase C (GC-C) (6) in patients with congenital sodium diarrhea (CSD). CSD patients presented with diarrhea of intrauterine onset, with high fecal sodium losses. NHE3 mutations resulted in absent or nonfunctional protein in a subset of patients, and NHE3 was likely inhibited in another subset of CSD patients with constitutively activating and hyper-stimulating mutations in GC-C. Of note, a number of patients with germline GC-C and NHE3 mutations developed IBD, with varying ages of onset implicating reduced NHE3 activity as a predisposition for IBD. NHE3 might be considered to play a role in the composition of the gut microbiota and its deficiency may contribute to dysbiosis observed in patients with IBD. The observation of a spectrum of intestinal symptoms in patients with loss of NHE3 function, and no renal disease in these patients is noteworthy in differentiating the role of renal and intestinal NHE3.

DISCLOSURES
No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

REFERENCES