Intestinal brush-border Na^+/H^+ exchanger NHE3 is required for iron homeostasis in the mouse

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Introduction: Divalent metal-ion transporter-1 (DMT1) is critical for intestinal iron absorption. DMT1 is energized by the H^+ electrochemical potential gradient but the provenance of the H^+ required to drive apical iron uptake is not known.

Aim: To assess the roles of gastric acid and the brush-border acidic microclimate in aiding intestinal iron transport.

Methods: We have examined iron homeostasis and intestinal iron handling in mouse models lacking the α-subunit of the gastric H^+/K^+-ATPase (gHKA) or the brush-border Na^+/H^+ exchangers NHE3 and NHE2.

Results: We found that liver nonheme iron stores (a preferred indicator of chronic iron status) in gHKA-null mice were no different from wildtype mice whether fed normal or low-iron diets (6 weeks) and hematological parameters were unchanged. In NHE2-null mice, liver nonheme iron stores were depleted by 30–80% compared with wildtype mice but no hematological changes were observed. Liver nonheme iron stores were more severely depleted in NHE3-null mice, by 70–90% compared with wildtype mice. In preliminary experiments in which we fed mice ^{59}Fe by oral gavage, lower amounts of ^{59}Fe appeared in blood (30 min – 4 h) and in enterocytes, liver and spleen (harvested at 4 h) of NHE3-null mice compared with their wildtype littermates, suggesting that loss of NHE3 results in defective apical intestinal iron uptake.

Conclusions: Our data indicate that the intestinal Na^+/H^+ exchanger NHE3 (and possibly also NHE2)—but not the gastric H^+/K^+-ATPase—is required to maintain normal iron stores in the mouse, and raise the possibility that the acidic microclimate is critical for DMT1-mediated iron uptake at the intestinal brush border. Experiments are underway to determine whether crossing with the NHE3-null. mouse can rescue the iron-overload phenotype of the Hfe-null mouse model of hereditary hemochromatosis (HHC), an outcome that would establish NHE3 as a therapeutic target for the prevention of iron overload in HHC patients.