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Elucidation of the Intestinal NaCl Absorption Mechanism Using Mini-Guts

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Summary

Intestinal NaCl absorption is thought to be mediated by functional coupling of a Na^+ transporter and a Cl^- transporter. Although the Na^+ transporter has been shown to be Na^+/H^+ exchanger isoform 3 (NHE3) throughout the intestine, the Cl^- transporter is different in each intestinal segment. Namely, slc26a6 plays a major role in Cl^- absorption in the small intestine, and another Cl^- transporter, slc26a3, plays a major role in Cl^- absorption in the large intestine. We have also shown that NHE3 changes coupling partner to H^+-coupled peptide transporter (pepT1) when H^+-coupled peptide absorption is activated. However, the molecular mechanism of each coupling mode remains to be determined. To investigate this, we first determined the involvement of Cl^-/HCO_3^- exchanger in NaCl absorption in each intestinal segment of mice. Chambers were used to measure transepithelial $^{22}Na^+$ and $^{36}Cl^-$ fluxes across the intestinal membrane. The addition of NHE3 specific inhibitor S3226 to the luminal side induced simultaneous inhibition of $^{22}Na^+$ and $^{36}Cl^-$ fluxes in the middle small intestine and middle colon. In addition, the magnitude of functional coupling between NHE3 and Cl^-/HCO_3^- exchanger was approximately equal in the middle small intestine and middle colon. These results suggest that the mode of coupling of NHE3 and each Cl^- transporter is similar along intestinal segments. However, morphological differences between the small intestine and large intestine complicates the interpretation of these results. To overcome this problem, we tried to establish mini-gut monolayers from intestinal stem cells. We assessed the expression of NHE3 and slc26a3 in mini-guts by immunohistochemistry and qPCR. The expression of slc26a3 was not detected in the small intestine mini-guts, but was expressed in the large intestine mini-guts. However, NHE3 was expressed in both type of mini-guts. These results suggest that mini-guts derived from different intestinal segments reflect the segment-specific expression of ion transporters in the intestine.