

SLC26a Family in Gut and Kidney

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SLC26 (human)/Slc26 (mouse) isoforms are members of a large, conserved family of anion exchangers that display highly restricted and distinct tissue distribution. The majority of these isoforms function as anion exchangers with versatility with respect to transported anions. Modes of transport mediated by SLC26/Slc26 members include the exchange of chloride for bicarbonate, hydroxyl, sulfate, formate, iodide, or oxalate, with variable specificity. Several members of the SLC26 family mediate chloride-bicarbonate exchange and are expressed in the gastrointestinal tract and/or kidney, with distinct subcellular (apical or basolateral) localization. These include SLC26A3 (DRA), SLC26A4 (pendrin), SLC26A6 (PAT1 or CFEX), SLC26A7 (PAT2), and SLC26A9 (PAT4). SLC26A7 and SLC26A9 can also function as chloride conductive pathways. SLC26A3 is expressed on the apical membrane of enterocytes in the small and large intestines; whereas, the expression of SLC26A6 (PAT1) is predominantly limited to the apical membrane of the small intestine. SLC26A6 is also expressed on the apical membrane of the kidney proximal tubule. SLC26A4 (Pendrin) is located on the apical membrane of chloride-absorbing/bicarbonate-secreting cells in the collecting duct. SLC26A7 and SLC26A9 are expressed in gastric epithelial cells, with SLC26A7 predominantly detected on the basolateral membrane of parietal cells and SLC26A9 expressed in tubulovesicles in parietal cells and in mucus cells. Slc26a7 expression in the kidney is predominantly limited to the basolateral membrane of acid-secreting cells in the OMCD. Genetically engineered null mice have highlighted the important roles of these isoforms in stomach, intestine, or kidney physiology. Slc26a3 (DRA) deletion in mice recapitulates the phenotype of chloride-losing diarrhea in humans, an autosomal recessive disorder manifested by massive chloride and fluid loss in the stool after birth. Slc26a4 (pendrin) deletion impairs the ability of the kidney to retain salt during salt-deprivation states. Deletion of Slc26a6 (PAT1, CFEX) impairs salt absorption and PGE-2 stimulated bicarbonate secretion in the small intestine. In addition, Slc26a6 deletion increases net oxalate absorption in the small intestine and oxalate excretion in the kidney, consistent with absorptive hyperoxaluria. In the kidney, Slc26a6 plays a major role in apical Cl⁻/oxalate and Cl⁻/OH⁻/HCO₃⁻ exchanges in the proximal tubule. Both DRA and PAT1 are activated by luminal fructose, resulting in enhanced salt absorption in the small intestine. PAT1 deletion blocks fructose-induced hypertension by impairing salt absorption in the small intestine and increasing salt excretion in the kidney. Deletion of Slc26a7 causes a picture consistent with distal renal tubular acidosis, as manifested by metabolic acidosis and inappropriately alkaline urine. Slc26a7 deletion also impairs acid stimulation in the stomach. Slc26a9 deletion completely abrogates acid stimulation in the intact stomach and isolated gastric mucosa in mice as young as 3-4 weeks old. Slc26a9 deletion causes complete loss of tubulovesicles and rearrangement of actin cytoskeleton in parietal cells. In conclusion, Slc26a3, Slc26a4, Slc26a6, Slc26a7, and Slc26a9 play essential roles in the transport of electrolytes in the gastrointestinal tract and kidney tubules, with resulting systemic electrolyte homeostasis, acid base regulation, or gastric acid secretion.
