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Characteristics of rat downregulated in adenoma (rDRA) expressed in HEK 293 cells.

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Abstract

Studies with apical membrane vesicles have shown that two distinct and separate anion exchange processes are present in rat distal colon, 4,4'-diisothiocyanatostilbene-2,2'-disulfonic acid (DIDS)-sensitive $\text{Cl}(-)\text{-HCO}_3(-)$ exchange, and DIDS-resistant $\text{Cl}(-)\text{-OH}(-)$ exchange. These studies proposed that anion exchanger (AE)-1 isoform encodes the former as both apical membrane DIDS-sensitive $\text{Cl}(-)\text{-HCO}_3(-)$ exchange, and AE1 specific mRNA are present only in surface cells and are downregulated in Na-depleted rats, whereas downregulated in adenoma (DRA) encodes the latter as both DIDS-resistant $\text{Cl}(-)\text{-OH}(-)$ exchange, and DRA-specific proteins are present in apical membranes of both surface and crypt cells and are not altered in Na(+)-depleted rats. Studies were, therefore, initiated to identify the function of rat DRA (rDRA) in vitro. rDRA cDNA isolated from rat distal colon encodes a 757-amino-acid protein which has 96 and 81% homology with mDRA and hDRA, respectively. rDRA-specific mRNA expression was detectable only in specific segments of the digestive tract (duodenum, ileum, cecum, proximal colon, and distal colon) but not in the stomach, jejunum, or in the kidney, brain, heart, and lung. HEK 293 cells stably transfected with rDRA exhibited DIDS-insensitive and intracellular acid pH (pH(i) 6.5)-sensitive Cl uptake that: (1) was significantly stimulated by outward Cl(-), HCO₃(-), isobutyrate, and possibly OH(-) gradients; (2) was saturated as a function of increasing extracellular Cl concentrations with an apparent K (m) for Cl of 2.9 +/- 0.3 mM; and (3) was inhibited competitively by extracellular oxalate but not by SO₄(2-). A high rate of DIDS-insensitive Cl influx at pH 6.5 was also present under physiological Cl(-) concentration. Our observations that rDRA mediates DIDS-insensitive, acid pH-dependent Cl(-) uptake are consistent with prior observations that rDRA does not mediate DIDS-sensitive Cl(-)-HCO₃(-) exchange in rat distal colon. We speculate that, in addition to mediating pH-sensitive Cl(-) uptake, rDRA may function as a modifier of other anion transport proteins.

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