Gastric chloride channels as potential drug targets

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We found that the sub-pS Cl^- channels (0.3-0.4 pS) are present abundantly in the basolateral membrane of rabbit and rat gastric parietal cells. The channel activation is linked to cytoprotection against ethanol-induced injury. The channel activity is inhibited by interleukin-1β via Rho/Rho-kinase-dependent production of superoxide anion (O_2^-). This sub-pS Cl^- channel may be a target for therapeutic modulation of gastric cytoprotective function. On the other hand, we found that ClC-5 protein is co-localized with gastric H^+,K^+-ATPase in the parietal cells. Immunoprecipitation using the anti-H^+,K^+-ATPase antibody showed the association between ClC-5 and the H^+,K^+-ATPase in isolated hog gastric vesicles. Furthermore, the tetracycline-regulated stable expression of ClC-5 in the HEK293 cells that stably express H^+,K^+-ATPase α- and β-subunits significantly increased the activity of H^+,K^+-ATPase, $^{86}Rb^+$ transport and phosphorylation level of the H^+,K^+-ATPase. On the contrary, this expression of ClC-5 did not affect the expression level of H^+,K^+-ATPase in the plasma membrane. These results suggest that ClC-5 acts as an up-regulator of gastric H^+,K^+-ATPase. We suggest that ClC-5 may be a potential target for therapeutic modulation of gastric acid secretion.