

Choosing sides in the battle against gastric acid

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Commentary

The duodenum is the first segment of the small intestine, just distal to the gastric pylorus. This positions the epithelial lining of the duodenum directly in the path of destructive gastric acid leaving the stomach. Because pancreatic bicarbonate secretions only enter the gut lumen farther down the gastrointestinal tract, the early duodenum must defend itself, unaided, from this acidic stress. The duodenal defenses can be conveniently grouped as pre-epithelial (e.g., neutralization of acid in the lumen), epithelial (e.g., tight junctions, membrane impermeability to acid, secretion of alkali and mucus), and subepithelial (e.g., afferent and efferent neural mechanisms, blood flow). Each of these contributions to mucosal defense is potentially important to human health because acid damage is a crucial aggravating factor in formation and persistence of duodenal ulcers (1). In terms of duodenal defense, strong interest has centered on the avid bicarbonate secretion mediated by duodenal epithelial cells. This is unequivocally the first line of defense, as the bicarbonate reaching the gut lumen will act to neutralize intraluminal acid (producing CO₂ and water) before it ever reaches the cells. Elegant and rigorous experiments have shown that, as a consequence of this neutralization, the spaces directly adjacent to the epithelium have close to a neutral pH (2, 3). This juxtamucosal alkaline layer also contributes to mucosal defense by directly shielding duodenal epithelial [...]

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The duodenum is the first segment of the small intestine, just distal to the gastric pylorus. This positions the epithelial lining of the duodenum directly in the path of destructive gastric acid leaving the stomach. Because pancreatic bicarbonate secretions only enter the gut lumen farther down the gastrointestinal tract, the early duodenum must defend itself, unaided, from this acidic stress. The duodenal defenses can be conveniently grouped as pre-epithelial (e.g., neutralization of acid in the lumen), epithelial (e.g., tight junctions, membrane impermeability to acid, secretion of alkali and mucus), and subepithelial (e.g., afferent and efferent neural mechanisms, blood flow). Each of these contributions to mucosal defense is potentially important to human health because acid damage is a crucial aggravating factor in formation and persistence of duodenal ulcers (1).

In terms of duodenal defense, strong interest has centered on the avid bicarbonate secretion mediated by duodenal epithelial cells. This is unequivocally the first line of defense, as the bicarbonate reaching the gut lumen will act to neutralize intraluminal acid (producing CO₂ and water) before it ever reaches the cells. Elegant and rigorous experiments have shown that, as a consequence of this neutralization, the spaces directly adjacent to the epithelium have close to a neutral pH (2, 3). This juxtamucosal alkaline layer also contributes to mucosal defense by directly shielding duodenal epithelial cells from luminal acid. The article by Akiba et al. in this issue of the *JCI* (4) is interesting and important because it raises a new possibility: that bicarbonate secretory mechanisms may have an even greater role in acid defense through their effects on intracellular pH of duodenal epithelial cells.

The central observation reported by Akiba et al. is that two anion transport inhibitors (DIDS and NPPB) both block bicarbonate secretion into the lumen but that these agents have opposite effects on cellular damage in response to luminal acid (4). Most strikingly, NPPB actually reduces the damage in response to luminal acid. These results are not readily compatible with conventional models of extracellular defense, since inhibition of bicarbonate secretion will compromise both luminal neutralization of acid and the juxtamucosal alkaline layer. Despite uncertainty about the molecular specificity of the drugs, these new *in vivo* results clearly demonstrate a dissociation between bicarbonate secretion and cytoprotection.

Is intracellular pH more important than extracellular pH?

The authors extend their findings by measuring cytosolic pH in duodenal epithelial cells and showing that DIDS causes cellular acidification, whereas NPPB causes cellular alkalization (4). They hypothesize that, at least in their specific condition, cytoprotection is mediated by bicarbonate transport, creating a relatively alkaline pH on the inside rather than the outside of the epithelial cell. If this hypothesis is correct, a corollary is that such effects on intracellular pH would be the dominant protective effect compared with extracellular pH changes. Neither hypothesis can be proven yet, because the mechanisms of DIDS and NPPB action remain speculative, and it is unknown whether changes in extracellular pH occurred as predicted in these experiments. The authors speculate that NPPB inhibits bicarbonate efflux from the cell via the apical cystic fibrosis transmembrane conductance regulator (CFTR) anion channel, leading to

an accumulation of intracellular bicarbonate and consequent alkalization (4). In contrast, DIDS might inhibit basolateral bicarbonate uptake via NBC1-mediated Na⁺/HCO₃⁻ cotransport, causing cellular acidification in the absence of adequate alkali uptake. The ideas are readily compatible with current evidence about bicarbonate transport routes, although molecular mechanisms of duodenal bicarbonate secretion remain controversial (5).

The putative site of NPPB action is particularly intriguing, since CFTR has been commanding attention as an essential component of duodenal bicarbonate secretion. Duodenal bicarbonate secretion is absent in CFTR knockout mice lacking functional CFTR (6–8). The simplest interpretation is that CFTR acts as a bicarbonate-conducting anion channel, although it could also be an essential regulator of another bicarbonate efflux route (9, 10). With respect to this scenario, Akiba et al. (4) highlight the potential relevance of the cytoprotective effect of NPPB by citing published clinical observations that cystic fibrosis (CF) patients (also lacking a functional CFTR protein) have fewer peptic ulcers than do normal individuals. This is especially intriguing since CF patients have normal gastric acid secretion, but they lack both duodenal and pancreatic alkali secretion. While a very attractive parallelism, the depth of the comparison remains to be proven. The basal cytosolic pH levels of isolated (unpolarized) duodenal enterocytes from normal and CF patients have been similar, although their pH regulatory mechanisms do differ (11). Further, there is significantly more peptic ulcer disease in African-American CF patients than in Caucasian CF patients, suggesting that genotype/phenotype correlations

may need to be examined (12). However, Akiba et al. (4) should be credited with giving the first evidence to suggest a potential (and testable) mechanism for a puzzling clinical observation.

Where in the duodenum is bicarbonate secreted?

One controversial feature of the paper is that the experiments are designed to study pH_i and damage at the villus tip. Conventional wisdom holds that bicarbonate secretion is a function of Brunner's glands, duodenal crypt glands distant from villi. Hence, the cells physiologically mediating bicarbonate secretion may not be the same as those examined to assess cytoprotection. However, there is no compelling evidence that bicarbonate secretion is restricted (or even localized) to Brunner's glands, structures that may play a greater role in secretion of mucin and bioactive peptides (13). Most relevant to this study, initial *in situ* hybridization studies localized CFTR mRNA exclusively to crypts in human duodenum (14). However, CFTR protein has been observed all along the villus/crypt axis in human and mouse duodenum, albeit with greater staining in crypts (15–17). In rats, evidence suggests the presence of an infrequent, highly CFTR-expressing cell interspersed among villus cells (18). Ultimately, where bicarbonate is secreted may not matter as much as where it provides protection. The work

of Akiba et al. (4) makes a compelling case that blocking bicarbonate secretion *in vivo* can increase or decrease acid damage to cells at the villus tip.

Overall, the article by Akiba et al. (4) shifts attention about benefits of bicarbonate secretion from the outside of the cell to the inside of the cell. There are now some fascinating and pressing questions about the response of duodenal cells in CFTR knockout mice to acidic stress. In that model system, there will also be a unique opportunity to evaluate whether NPPB is having cytoprotective effects other than via direct effects on CFTR. Thus, while Akiba et al. (4) successfully drive a wedge between the long-standing correlations of enhanced bicarbonate secretion and enhanced mucosal protection, it remains to be seen whether that wedge can be driven deeper.

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