Gastroduodenal Mucus and Bicarbonate: The Defensive Zone

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The surface mucosa of the stomach and duodenum is frequently exposed to a potentially corrosive mixture of hydrochloric acid and pepsin and intraluminal pH is often between 1 and 2. Such acidity would be injurious to ordinary epithelia so that it is clear that mechanisms exist to protect the stomach and duodenum under normal circumstances. The notion that gastric mucus and non-parietal gastric alkali secretion may be able to provide such protection is not new, having been proposed by Heatley as long ago as 1959 [1], but only recently have experimental techniques allowed this hypothesis to be tested.

Gastric mucus consists of a glycoprotein tetramer whose structure determines its physical properties of adherence, elasticity and flow [2]. The polymeric structure of high molecular weight causes individual molecules to overlap in surface mucus resulting in gel formation [3] and the resultant layer can substantially reduce the rate of flow of hydrogen ions across it [4]. The sulphide bonds which bind the subunits are broken down by luminal pepsin [5] resulting in glycoprotein monomer or soluble mucus without the ability to form a gel. The adherent mucus gel layer is therefore in an equilibrium with fresh secretion from goblet cells continually replenishing that eroded from the surface. The thickness of this dynamic layer has now been measured both in experimental animals [6] and in man [7] using fresh unfixed specimens since ethanol used to fix specimens causes degradation and shrinkage of the gel layer. It is clear from such observations that the layer is continuous in vivo but has a variable thickness of 5–200 μm in man [7]. Mucus gel is therefore clearly a potentially protective layer, and the mechanism by which this may occur has become clearer since the discovery of bicarbonate secretion from both gastric and proximal duodenal mucosa [8]. For many years such secretion had been inferred from the electrolyte content of gastric juice [9] but only since the advent of powerful inhibitors of the quantitively much greater acid secretion has bicarbonate secretion been convincingly demonstrated. We now know that the surface epithelium of both stomach and duodenum of experimental animals and man secretes endogenous alkali by an active process [10]. In the stomach bicarbonate is secreted at a basal rate amounting to 5–10 per cent maximal acid output [11], whilst duodenal mucosa secretes alkali at twice the rate of basal gastric bicarbonate production [12]. The gastric fundus appears to transport bicarbonate by a purely metabolically dependant process but in both antrum and duodenum around 30 per cent alkalinization is due to passive transfer [13]. Cellular mechanisms of secretion also appear to differ between gastric and duodenal mucosa, being chiefly electroneutral Cl/HCO₃ exchange in the stomach but electrogenic HCO₃ transport in the duodenum [10]. Control mechanisms of gastroduodenal
bicarbonate secretion have also been studied extensively. Secretory rate varies under the influence of enteric neurones [14] and the vagus nerves [15]. Hormonal factors which may play a role in modulating bicarbonate secretion include cholecystokinin, pancreatic glucagon and gastric inhibitory polypeptide in the stomach and gastric inhibitory polypeptide and neurotensin in the duodenum [16]. Gastrin, secretin and histamine have no effect on bicarbonate secretory rate of gastric or duodenal mucosa. Local paracrine agents, especially prostaglandins are potent stimulants of both gastric and duodenal bicarbonate secretion [17], which is particularly interesting in view of the known cytoprotective properties of this group of compounds. Bicarbonate secretion may also be altered by luminal influences via local control mechanisms and increase in intraluminal acidity particularly has been shown to accelerate markedly the rate of alkali secretion by the stomach [18] and duodenum [19] in man, an effect which clearly may be of importance in 'autoregulation' of bicarbonate secretion. Other luminal influences on bicarbonate secretion are bile acids which have been shown to inhibit gastric bicarbonate secretion [20].

The importance of the dual secretion of both mucus and bicarbonate by the gastroduodenal mucosa is that the mucus gel layer may be able to create a relatively stable low turbulence mixing zone adjacent to the epithelium. Thus, although the small bicarbonate secretion alone could not provide protection against acid, if confined to the juxtaepithelial layer then a standing pH gradient may be produced due to the steady secretion of mucus and bicarbonate and the slowed diffusion of hydrogen ions into the layer approaching the epithelium. It has now become possible to measure pH changes across such small distances using microelectrodes and a pH gradient does indeed exist across both gastric and duodenal mucus gel in experimental animals [21] and in man [22]. Thus a 'mucus–bicarbonate' barrier has been shown to be present and may contribute to protection against damaging luminal acid. To what extent can this layer explain observations of gastric damage and protection observed clinically and in the laboratory?

At first sight this attractive hypothesis has much circumstantial evidence to support its importance. Many agents known to be injurious to the gastroduodenal mucosa inhibit bicarbonate secretion including NSAIDs [17], bile salts [20] and ethanol [10]. Moreover these damaging agents have also been shown to reduce mucus gel thickness which would further impair the function of the barrier layer [21]. In experimental animals stress can inhibit bicarbonate secretion and may predispose to ulceration if acid secretion is also high [23]. Conversely, agents known to protect the mucosa against injury such as prostaglandins, sucrafate, aluminium and bismuth compounds [24] also appear to be stimulants of gastroduodenal bicarbonate secretion and prostaglandins also markedly increase mucus gel release and thickness [6]. This evidence therefore appears to fit the hypothesis that the mucus–bicarbonate barrier may form a credible defensive layer. It is pertinent therefore to ask whether or not defects within such a layer may contribute to human disease such as peptic ulcer.

Impairment of prostaglandin production in patients with peptic ulcer has been suggested by a number of studies [25–27] and this could give rise to functional disabling of the mucus–bicarbonate barrier. Furthermore, in peptic ulcer patients there is some evidence that the composition of surface mucus is altered with increased proportion of monomeric (non-gel forming) glycoprotein [28]. Bicarbonate secretion in gastric ulcer patients has not been studied but duodenal bicarbonate production is impaired in duodenal ulcer patients both in the basal state and in response to luminal acid [29]. Furthermore, using an endoscopic pH probe it has been demonstrated that juxtamucosal pH in the duodenal cap of ulcer patients was significantly lower than that in normal subjects at luminal pH values below 3 [30]. Unfortunately it cannot be proved whether or not these defects are the cause of peptic ulcer or the effects of previous ulceration but they may at least contribute to the recurrent nature of the disorder.

Factors other than mucus and bicarbonate secretion however must also be important in
overall mucosal defences and, persuasive though it is, the mucus–bicarbonate barrier is unlikely to explain all the facets of epithelial protection adequately. First of all the gradient may not be sustainable under all circumstances and is very susceptible to changes in secretory rate and mucus thickness. Some evidence indicates that the pH gradient may be overwhelmed by a luminal pH of less than 1.5 [21] and this occurs frequently in vivo. Furthermore, the same gradient could not be maintained where the mucus layer is very thin although this may be in part offset by recruitment of the adjacent unstirred fluid which can also contribute to the extent of the gradient [31]. The mucus–bicarbonate barrier cannot protect the cells lining the gastric glands which remain undamaged despite the presence of 150 mM HCl. The protective effect of the prostaglandins is not confined to acid-induced damage. Prostaglandins can protect gastroduodenal mucosa against a wide variety of noxious agents including ethanol and strong alkali solutions [32], against which the mucosal HCO₃⁻ layer could have no effect. Other mechanisms must also be important. Hydrophobic phospholipids have been found to line the gastric mucosa and contribute to defences [33]. Additionally the ability of the cells of the epithelium to migrate rapidly to cover areas of damage may also be important in overcoming day-to-day injury [34]. Mucosal blood flow also appears to be crucial to epithelial integrity and impairment of flow decreases the ability of the mucosa to withstand injury [35].

Gastroduodenal mucosal protection may thus be considered to be a process of several tiers with perhaps each process either contributing independently or forming a safety net against failure of the others. The mucus–bicarbonate barrier is perhaps best seen as a first-line defence against luminal acid. Further work on its possible relevance to human disease processes such as gastritis, gastric erosion, stress ulcer and peptic ulcer is awaited with much interest.

REFERENCES