The enhanced mucolytic activity of human pepsin 1 compared with pepsin 3: implications in peptic ulceration

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Gastric juice of patients with chronic gastric or duodenal ulceration contains increased amounts of pepsin 1 (Walker & Taylor, 1980a). Pepsin 1 is secreted by the fundic but not by the pyloric glands of the stomach (Etherington & Taylor, 1967). It has been shown to have a potent collagenolytic action, being 5 times more active than the principle pepsin, pepsin 3 (Etherington et al., 1980). When the gastric juice of such patients enters the existing ulcer-crater this action on native collagen will frustrate healing by collagen deposition, thus potentiating ulceration and possibly explaining the chronic reaction seen histologically. The gastric and duodenal glands are supported by a network of collagen fibres and increased secretion of pepsin 1 could conceivably initiate gastric ulceration intramucosally by lysing collagen. However, this explanation cannot apply to pyloric or duodenal ulcers; penetration from the lumen of the normally protective mucus barrier must precede any enhanced proteolytic activity of pepsin 1 on the underlying mucosa.

The mucolytic activity of pepsin 1 and 3 isolated by the method of Roberts & Taylor (1978) was, therefore, determined by measuring the percentage fall in specific viscosity of a solution of pig gastric mucus. Porcine gastric mucus was solubilized by homogenization of the surface gel and purified by Sepharose 4B gel-filtration followed by CsCl equilibrium density centrifugation. Pig gastric mucus glycoprotein has a polymeric structure similar to that of human gastric mucus, consisting of a tetramer ($M_r$, $2 \times 10^6$) of subunits ($5 \times 10^5$) joined together by disulphide bridges. These disulphide bridges are located in regions of the molecule susceptible to proteolysis (Pearson et al., 1980; Allen, 1981). Viscosity is therefore a very sensitive measurement of proteolytic activity on mucus glycoprotein because the undegraded (human or pig) glycoprotein tetramer has a high viscosity, which falls rapidly when it is split into subunits by digestion (Pearson et al., 1979).

Fig. 1 shows that in the same mass concentration (based on assay using haemoglobin digestion at pH 1.9), pepsin 1 digests porcine mucus glycoprotein more readily than does pepsin 3 over the whole pH range measured. The differences are particularly striking above pH 3.8. Pepsin 3 has minimal activity above pH 3.8, whereas pepsin 1 exerts considerable mucolytic activity up to and at the highest pH value studied so far (pH 5.1). In fact, at pH 4 pepsin 1 has 6 times the mucolytic activity of pepsin 3.

The differences between these enzyme profiles was not a result of rate-limiting substrate concentrations as this only happened at enzyme concentrations greater than 1.5% (w/w) (enzyme-mucus glycoprotein), 3 times the actual concentrations used here.

These results demonstrate that pepsin 1 has the properties needed to breach the mucus barrier, and further implicates pepsins as having a major role in the pathogenesis of peptic ulcer. In the normal subject the rate of mucolysis by pepsin (by pepsin 3, for there is little or no pepsin 1 present) is in a dynamic balance with mucus-gel secretion. Therefore in these normal conditions no penetration or reduction in thickness of the mucus layer will occur. In peptic ulcer, the proportion of pepsin 1 is increased (Walker & Taylor, 1980a; Roberts et al., 1981). Therefore the gastric juice of peptic ulcer patients will have an enhanced ability to degrade mucus, thus destroying the balance between secretion and erosion. Evidence for enhanced mucolytic activity in duodenal and gastric ulcer patients comes from studies on mucus gel removed at gastrectomy (Younan et al., 1982), which shows that the gel from duodenal and gastric ulcer patients contains more degraded (low ($M_r$) glycoprotein than normal.

Furthermore, the demonstration that pepsin 1 is active at pH 5.1 and possibly above, allows it to be implicated in duodenal ulcer development. This would particularly be the case when an increased secretion of pepsin 1 is accompanied by reduced bicarbonate, as occurs in smokers (Walker & Taylor, 1980b).