ANTIULCER ACTIVITY OF AN ACTIVATION PEPTIDE OF PEPSINOGEN

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Pepsinogen, encapsulated and proteolytically inactive in the gastric chief cell is, upon secretion, activated at pH4 or less, spontaneously changing to pepsin with 327 amino acid residues. The remaining 44 amino acids at the NH_2-terminus of pepsinogen which contain most of the basic residues of pepsinogen give rise to a variety of peptides depending on the activation conditions which precede isolation (Dykes & Kay 1976; Christensen, Pedersen & Foltmann 1977; Dunn and others 1978). One such peptide comprising the first 16 of these amino acids, P1-16 (Anderson & Harthill 1973) contains the highly basic sequence -arg-lys-lys- and can act as a partial non-competitive inhibitor of the acidic pepsin; at a pepsin:peptide mole ratio of 1:5, 50% inhibition of peptic digestion of azocoll at pH5 can be demonstrated (Anderson & Harthill, unpublished). Based on the belief that pepsin is ulcerogenic for an unhealthy mucosa exposed to acid, a protective role for such peptides requires consideration.

Adult male guinea-pigs (fasted 24h; water ad lib.) were anaesthetised with sodium pentobarbitone (30 mg kg^{-1}) followed by high duodenal ligation; each received 6mg kg^{-1} histamine acid phosphate subcutaneously. Treated (12) animals also received 10mg kg^{-1} P1-16; 12 control animals received 1ml.kg^{-1} saline, both intraperitoneally. Experiments with 6 animals (3 treated, 3 control) were carried out on separate days and the results considered as two groups (treated, control). Gastric lesions visible at 1h were scored on a 4-plus scale which ranged from one or two isolated erosions to numerous erosions with ulceration. Perforation occurred in one control animal. One treated and two control animals died during the experiment. Mean overall scores were 2.6 (10 controls) and 1.4 (11 treated animals) for which the Wilcoxon rank sum test gave significance of difference at $p < 0.05$. Such numerical significance, suggesting the animals treated with P1-16 enjoyed some protection from histamine ulceration, is considered adequate only to suggest further study of the systemic effect of gastrointestinal peptides associated with pepsinogen activation. Gastric secretion collected at 1h showed lower acidity (titrated to pH7.4) in the treated animals:1.135, 0.715 ml 0.1M HCl per ml secretion for controls, treated respectively ($p = 0.02$-0.05); significant differences for luminal peptic activity and volume of secretion were not observed.

The rate of development of the acute lesions in this experiment, including the possibility of progression to perforation could be associated with peptic digestion of mucosal tissue at least as a contributory causal factor. Whether protection of the treated animals was due to peptic inhibition at mucosal cellular level is not known but inhibition of pepsin by P1-16 can be demonstrated at pH5, which although high for pepsin with its optimum for proteolysis around 2, could conceivably occur at mucosal cellular level, particularly in cells with altered permeability. The basic character of the peptide with 5 basic amino acids (2 arg, 3 lys) in a total of 16 would facilitate association with the acidic pepsin. Such an action would not necessarily be reflected in peptic activity of the accumulated gastric secretion.

The range of effects now known for naturally occurring, including gastrointestinal, peptides suggests that restriction of activity of systemic P1-16 to pepsin inhibition is probably unlikely. The decrease in acidity of secretion in the present experiment supports that view.

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