

Leading articles

Mucus, pepsin, and peptic ulcer

In spite of a vast amount of research we still do not know the cause of chronic peptic ulceration. It is generally agreed that the disease must be because of a breakdown in the balance between 'aggressive' and 'defence' factors, but how this occurs has remained elusive.

Most studies have concentrated on the role of hydrochloric acid in upsetting this balance. This work has been reinforced by the finding that medical and surgical treatments which decrease acid secretion are effective in healing chronic peptic ulceration. Unfortunately this emphasis on acid secretion has tended to obscure the facts that acid has never on its own been shown to induce an ulcer,^{1 2} that none of these treatments can be said to cure the ulcer diathesis permanently, and that factors which inhibit acid secretion usually also affect intragastric peptic activity either directly or indirectly.

Recognition of these facts have led some groups to concentrate on the other aspect – that of mucosal defence.³ These latter studies have yielded important information on how the gastric mucosa defends itself against aggression, but have not as yet explained why peptic ulcer disease occurs in some individuals, and not in others. A possible answer to this question is provided by the paper by Pearson *et al* in this issue of *Gut*. These authors have shown an important relationship between pepsin secretion and the breakdown of gastric mucus. Their findings could be important in explaining the recognised genetic basis of peptic ulcer disease in many individuals.⁴⁻⁶ In order to interpret their paper it is necessary to examine what is already known about secretion of pepsin and mucus secretion.

Pepsin secretion

Interest in the role of pepsin in peptic ulcer disease has always taken second place to that of acid. Whilst total peptic activity is often measured at the same time as acid secretion, the results are seldom given much prominence and there is a tendency to assume that whatever happens to acid secretion must also happen to pepsin secretion. Yet this is clearly untrue as there are now many examples where acid and pepsin secretion have become dissociated, most notably during administration of secretin, when acid is inhibited and pepsin is stimulated.

The role of secretion of pepsin in ulcer disease has received intermittent attention over the years. As long ago as 1932 Vanzant *et al*⁷ concluded that there was a relationship between the severity of ulcer disease and pepsin secretion, a view subsequently supported by Borg and Bergstrom⁸ in an extremely detailed study of this topic. Since then others have shown a role for pepsin secretion in peptic ulceration⁹⁻¹¹ and a relationship between total serum pepsinogen and ulcer disease.¹²⁻¹⁴

A further aspect of this relationship came to light when it was recognised that pepsin and its precursor pepsinogen existed in more than one form and that variations in the proportions of these molecular species might occur in different individuals. Unfortunately progress in this area has been frustrated by confusion over the terminology used to distinguish one enzyme from another.¹⁷⁻²³ This is partly explained by the different methods used to separate these enzymes and partly because the various pepsinogens do not necessarily give rise to a single pepsin. Foltmann²⁴ has recently tried to produce some order out of this confusion and his article is well worth reading for anyone interested in this aspect.

The serum pepsinogens (Pg) have received most attention, because radioimmunoassay techniques for their measurement²⁵⁻²⁸ have overcome the time consuming isolation procedures needed previously.¹⁵ Serum pepsinogens have been divided into three major groups labelled pepsinogen I (Pgl), pepsinogen II (PgII) and 'slow-migrating-protease' (SMP): the Pgl group has been most studied in relationship to peptic ulceration. These enzyme precursors are found in the chief and mucous neck cells of the mucosa of the gastric fundus and body, but not in the antral mucosa.²⁹ Serum Pgl is raised above the normal range (50-175 ng PGI/ml)²⁸ in between one half and two-thirds of all duodenal ulcer patients. It is higher in those with the more severe forms of ulcer disease^{30 31} and has been shown to correlate with the acid secretory capacity of the stomach³² and to be inherited as an autosomal dominant trait. Measurements of Pgl can therefore be used as a marker for the ulcer diathesis in some families.³³

Whilst these studies are useful in identifying a group of patients at risk of peptic ulcer disease they do not tell us how they are responsible for the disease process. Pepsinogen I actually contains at least five electrophoretically discrete bands which on acid activation convert into four enzyme species, pepsins 1 to 4.³⁴ It is this variation between the pepsinogens and pepsins which has, and still does, lead to considerable confusion.

So far there have been fewer studies of the pepsins secreted in gastric juice. This is because accurate quantitative methods have not been available. One of the first methods described for separating the pepsins present in gastric juice was that of Turner *et al*³⁵ which relied on the observation that their pepsin I was relatively resistant to alkaline inactivation at pH 7.25 when compared with all the other pepsins present.³⁶ An adaptation of this method was used to investigate whether there was a relationship between the concentration of pepsin I in gastric juice and the activity of duodenal ulceration³⁷ and the effects of truncal vagotomy.³⁸

An alternative approach has been that adopted by Etherington and Taylor.^{39 40} They used agar gel electrophoresis at acid pH to separate the pepsins present in gastric juice and described seven distinct pepsins which they numbered 1 to 7 on the basis of their decreasing mobility to the anode. In subsequent studies the same group found that duodenal and gastric ulcer patients appeared to produce more pepsin 1 than did healthy controls.^{41 42} A major criticism has been that the work relied on visual comparisons of the size of a spot on an electrophoretic plate for the measurement of the amount of each pepsin enzyme present. This technique can therefore only be regarded as semiquantitative.

Their data do, however, point to the possibility that peptic ulcer is associated with the secretion of an increased amount of pepsin 1, which has been shown to be a constituent of the pepsins produced when pepsinogen I is activated.³⁴

Gastric mucus

Mucus exists in the stomach as an insoluble gel layer adherent to the mucosal surface and as a soluble mucus mixed with the luminal juices. It is the former that is regarded as important in mucosal protection.

Hollander⁴³ proposed a two-component system for mucosal protection consisting of an alkaline mucus cover overlying a rapidly regenerating epithelial cell layer. This concept was further developed by Heatley,⁴⁴ who proposed that, because mucus was easily permeable to hydrogen ions, it must act as an unstirred layer, where acid diffusing in from the lumen could be neutralised by an alkaline mucosal bicarbonate secretion. Recent studies have confirmed that this is indeed true and that there is a pH gradient demonstrable from a low pH on the luminal surface of the mucus to a near neutral pH on its mucosal surface.⁴⁵⁻⁴⁷

Whilst the mucus layer is permeable to small ions and solutes it is impermeable to pepsins (MW 35,000). Therefore as long as there is a continuous layer of mucus covering the surface of the mucosa, there is no way in which pepsin can damage the surface epithelial layers. Mucosal defence can be compromised, however, because pepsin can break down the mucus. There must therefore be a balance between the secretion of new mucus and its erosion on the luminal surface.^{48 49}

Another aspect is the structure of the glycoprotein constituent of gastric mucus. The gastric mucus glycoprotein is a polymer of on average approximately four equal sized subunits joined by disulphide bonds.^{50 51} Each subunit consists of a glycosylated part (consisting of a protein core surrounded by carbohydrate side chains – ‘bottle-brush’) and a non-glycosylated part. It is the latter that is attacked by proteolytic enzymes, breaking the molecule down into its subunits.^{51 52}

The importance of this lies in the change that occurs in the physical properties of the glycoprotein during the breakdown.⁵³ In its native polymeric form the glycoprotein forms a water insoluble elastic gel of high viscosity. As a gel it has important physical properties, including high adhesiveness which makes it adhere closely to the underlying mucosal surface, resistance to shear, ability to selfanneal (reform when cut) and capacity to flow over a surface to form a continuous layer. These properties, characteristic of the native glycoprotein, are greatly affected by breakdown of the glycoprotein into subunits. When broken down entirely to subunits the glycoprotein is no longer able to form a gel, is soluble in water and behaves as a viscous fluid.

In patients with peptic ulcer disease the mucus covering the antral mucosa contains less ‘native’ glycoprotein,⁵⁴ the greatest change being found in patients with gastric ulceration. This would suggest that the mucus is less effective as a gel covering of the mucosa, more liable to breakdown and may be less able to resist the passage of large molecules through its interstices.

Mucus and pepsin

It now can be seen that there is an important relationship between pepsin and mucus in the stomach, mucus acting as a barrier to the entry of pepsin into the epithelial cells, whilst being continuously eroded on its surface by luminal pepsin.

The importance of the observations of Pearson and colleagues lies in the finding that different molecular species of pepsin behave in fundamentally different ways when their ability to breakdown mucus glycoprotein is assessed. Their observation that the rate of breakdown by pepsin 1 is substantially faster than that by pepsin 3 and occurs over a wider pH range, is very interesting. To date the pH range of peptic activity has usually been assessed using a pure protein as substrate, when peptic activity occurs between pH 1.0 and 3.5, with only minimal activity up to pH 5.0. It comes as a considerable surprise therefore, that when measured against gastric glycoprotein pepsin 1 has a pH range extending up to 5.0, whilst pepsin 3 (the major constituent of normal gastric juice) shows little or no mucolytic activity above pH 3.5.

As it has been claimed that pepsin 1 is increased in peptic ulceration⁴⁰ and Pearson *et al* have shown that the juice of duodenal ulcer patients has a mucolytic pH profile more like that of pepsin 1, one is led to the conclusion that a cause of peptic ulceration may lie in the secretion of an abnormal amount of pepsin 1. As pepsin 1 is one of the pepsins produced from pepsinogen I, the role of hereditary factors in the aetiology of peptic ulceration begins to fall into place. Clearly what is now needed is a detailed examination of the control of pepsin 1 secretion within the stomach. The amount produced by an individual needs to be related to whether he or she has a peptic ulcer and of what type. At present such studies are not easily undertaken, as there is no simple quantitative assay technique for pepsin 1 that can be used in large numbers of samples. The availability of such a method would open a new area of research into the cause of this mysterious disease.

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