Gastric surfactant and the hydrophobic mucosal barrier

The old wives tale of an ‘inside lining’ protecting the stomach wall against acid retains a certain intuitive appeal, which has found refuge in the concept of a gastric mucosal barrier to the back-diffusion of hydrogen ions. Preference for a physical barrier arose from the many fundamental physiological studies of Horace Davenport and coworkers in the 1950–1970s1,2 and offered many theoretical advantages over alternative mechanisms proposed for mucosal protection.3 Davenport envisaged the gastric mucosal barrier as distinct from the mucus layer – or mucus/bicarbonate blanket4 – which, arguably, offers inadequate protection because refined mucus is too permeable to hydrogen ions while mucus is absent from the extremely corrosive environment of the oxyntic duct and sparse, if not absent,5 from considerable areas of the lumen of the stomach, especially in certain monogastric mammals such as the dog.

Hydrophobicity
A striking property of the stomach wall is its hydrophobicity as witnessed when the present writer placed a droplet of water on the luminal surface of canine mucosa rinsed free of gastric contents to find that it ‘beaded up’, as though placed on Polythene, rather than spontaneously wetting the surface as anticipated on a hydrophilic mucoid layer. It was even more interesting to find that this hydrophobicity, as quantified by the contact-angle (θ) made by the droplet on the surface, was largely eliminated by the major ‘breaker breakers’ – that is, bile salts, ethanol, and aspirin.6 Northfield and his group have subsequently used θ as a quantifiable clinical index of active gastritis and one still viable even if the barrier breaker is Helicobacter pylori.7

Surfactant adsorption
This raises the question of what substance might be transforming the hydrophilic mucoid layer into a surface so hydrophobic that the contact angle in many normal stomachs can exceed 90° – that is, approaching that of Polythene (93°) or Teflon (108°). In the physical sciences such transformations are routinely effected by the adsorption (binding) of synthetic surfactants (see Figure A) when many of their adsorbed layers are much exploited commercially for the protection that they afford the surface against corrosion.8 For instance, the ‘underseal’ protecting a motorcar against rusting is provided by a hydrophobic monomolecular layer (monolayer) of a synthetic surfactant, the visible coating being applied simply to protect that monolayer from abrasion by sand and stones.

It was the realisation9 that many of the synthetic surfactants used as ‘corrosion inhibitors’ had similar chemical structures to dipalmityl phosphatidylcholine (DPPC) – that is, the surface active component of lung surfactant – which led this writer to perform the hydrophobicity test described above. About that time phospholipid had been discovered in a predominantly saturated form (including DPPC) in gastric juice and in ‘light scrapings’ from the stomach wall,10 later confirming its composition11 and surface activity.6

Morphology
If surface active phospholipid (SAPL) provides the outermost layer of the gastric mucosa it is not surprising that electronmicroscopy failed to demonstrate a gastric mucosal barrier when using conventional aldehyde fixatives as these, and glutaraldehyde in particular, destroy hydrophobic surfaces.12 Substituting tannic acid, it was possible to demonstrate an oligolamellar layer of SAPL on the luminal surface, displaying its characteristic interlaminar spacing of about 45 Å13 while Lichtenberger’s group demonstrated SAPL in similar locations using iodo-3-iodoplatinate fixation.14 They also demonstrated almost the same hydrophobicity however much they rinsed the mucosal surface,15 indicating the ability of the hydrophobic lining to coalesce and reform.

The most exciting finding to this writer was the many10–14 layers of SAPL coating the epithelial surface of oxyntic ducts15 as these surfaces are mucus free yet exposed to a particularly corrosive environment in which pepsinogen has been secreted from chief cells to mix with HCl at a pH of 1. The source of the SAPL seems to be lamellar bodies found in parietal cells and mucus neck cells16 with some reported in chief cells.16 Lamellar bodies are unequivocally the form in which SAPL is produced in the lung.17

Surface mucus is interesting because the many classic studies of the Slomianys have established the cytoprotective effect of phospholipid and the reduced permeability to hydrogen ions that it can impart to mucus.18–20 Our studies would agree with that finding but, with such a very low solubility of DPPC in the aqueous environment, amounting to a critical micelle concentration of only 5×10−10 molar,21 it is this writer’s contention that the SAPL is present largely as the intergranular matrix.
material of unsecreted mucus, which, in any case, provides the major resistance to hydrogen ions diffusing from the lumen of the stomach to the vital organelles of surface mucus cells. Just a monolayer of SAPL adsorbed to a filter paper decreases its permeability to hydrogen ions by an order of magnitude. Thus unsecreted mucus is effectively a number of mini-barriers of SAPL in series, which explains why the pH gradient seems to be effectively continuous and why mucus offers less resistance to acid and becomes less viscous the more it is 'refined', refinement removing the insoluble intergranular matrix of SAPL.

In interpreting electronmicrographs it is always prudent to be aware of possible artefacts. Although the formation of oligolamellar layers of SAPL is not one of those normally listed, there must be much SAPL present for these lamellations to form even if they are artefact; although epifluorescence microscopy would tend to confirm their reality.

**Helicobacter pylori**

These ultrastructural studies have been extended to the parasites that can survive in the highly corrosive environment of the stomach. Thus it was interesting to find some evidence of oligolamellar SAPL on the cuticle of the Barber's Pole worm, which thrives in the abomasum of Australian sheep, and essentially the same coating on *H pylori*. It is similar to SAPL found on the cuticles of many creatures, including the cockroach, which is difficult to kill because droplets of any aqueous insecticide simply 'bounce off' those hydrophobic creatures unless a wetting agent is incorporated. Gastric mucus is also a wetting agent and this could stabilise the surfactant layer on the gastric mucosa by reducing the surface energy of what is otherwise (Figure C) a high energy interface with aqueous gastric contents.

**Basic physiology**

Physiologically, a gastric mucosal barrier of SAPL is not only compatible with the many studies of Davenport, for example, it has the same pK value (buffering capability) as phosphate and is more permeable to lipids than aqueous solutes, but such layers are also good electrical insulators. This is exploited in vivo by SAPL in the form of myelin and can explain changes in the electrical characteristics of the gastric mucosa and the desired shift in pH gradients induced by fortifying the barrier with exogenous SAPL. Another interesting aspect is the role of prostaglandins where the administration of PGE₂ not only protects against ulcers but promotes the secretion of SAPL and enhances hydrophobicity in doing so.

**Barrier breakers**

Of more direct clinical relevance, stress ulcers are associated with a change in the lipid profile of the gastric mucosa, while each of the barrier breakers displays some affinity for SAPL. Bile salts form a chemical complex with SAPL and ethanol is a solvent for SAPL, while nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit the production of prostaglandins controlling SAPL synthesis as reviewed elsewhere. Hence it is easy to envisage the synergisms that occur between them as they all erode the same barrier, eventually permitting the back diffusion of sufficient acid to produce a gastric ulcer. An interesting exception is *H pylori*, which might be expected to function as a barrier breaker by secreting phospholipase A₂, which is found in abundance in these bacteria and is very effective in digesting SAPL. The aggressive capability of lysates of *H pylori* on SAPL layers has been demonstrated recently. Thus *H pylori* might ingest SAPL, but would refrain from secreting phospholipase for fear of compromising their own defence against acid as outlined above, possibly explaining why so few gastric ulcers are associated with these bacteria. Another fascinating aspect of *H pylori* is why these bacteria are not found in the duodenum where they do cause ulcers. Upon entering the duodenum they would encounter bile which, as a very effective barrier breaker, would remove their protective coating of SAPL, causing them to disintegrate and deposit their 'package' of potent enzymes. It is also interesting that no synergism between *H pylori* and other barrier breakers seems to have been reported and this may indicate a compromise between the synergism expected and the capability of other barrier breakers to remove their defence against acid, thus destroying them. This argument is consistent with the reduced prevalence of these bacteria in patients using NSAIDs.

**Lubrication**

If the gastric mucosal barrier is provided by surfactant, then the same basic metabolic deficiency that predisposes the subject to gastritis could also compromise the same oligolamellar structure of ubiquitous SAPL elsewhere in the body, whether its functions are barrier-like or lubrication. Thus it is interesting that patients with peptic ulcer displayed impaired pulmonary function. SAPL displays excellent high load bearing lubrication and is now one of the leading contenders as the lubricant in the joints and at other sliding surfaces in vivo, for example, facilitating gastric motility both from within the gastrointestinal tract and from within the peritoneal cavity. In animal joints it is interesting that the induction of arthritis sensitises them to peptic ulcer; while NSAIDs have been shown to have an adverse effect upon articular cartilage in animal studies. If NSAIDs are 'barrier breakers' not only to the gastric mucosal barrier but also to the structure providing lubrication, possibly compromising other desirable physiological functions, it raises a serious clinical problem concerning their widespread prescription for the relief of pain in the rheumatic diseases.

**Exogenous surfactant**

If the gastric mucosal barrier is a physical reality composed of SAPL, then it should be possible to protect against peptic ulcer by administering exogenous SAPL, or promoting its secretion. In the second case PGE₂ analogues such as misoprostol are successful as discussed above, while moderate protection has been reported using ambroxol, which, in the lung, at least, is known to promote the secretion of SAPL. Many animal studies have now been reported in which mucosal protection has been derived from exogenous surfactant administered in various forms, including a commercial grade of lecithin and others using a variety of challenges. One of the more interesting avenues is dietary SAPL because this could be useful clinically for preventing ulcers, especially in NSAID patients. Dietary SAPL is available to some degree in milk, which has a modest protection rate, while claims have been made for plantain bananas boiled and eaten as vegetables in India. We sought a source of lamellar bodies as SAPL 'packaged' in a much more potentially surface active physical state, and found them in ripe bananas, which were very effective in rats, especially when dispersed in milk or a fat reduced dairy product. If a little egg yolk is added to boost the SAPL content and the puree spray dried, a powder of all natural ingredients is produced for...
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Molecular models for surface protection (A) by adsorption of a cationic surfactant, the most effective industrial corrosion inhibitors having a terminal guanidylated ammonium (QA) ion and strong (saturated) alkyl chains, ideally C22h; adsorption can but cohesion may not be. (B) by the time honoured process of ‘phosphating’, in which highly charged mobile cations ‘pull’ negatively charged phosphate ions into a cohesive barrier – as in ‘Pink Primer’ – but adhesion to the surface can fail; (C) by the system envisaged in vivo where the Celestial Committee designing the stomach have effectively combined (A) and (B), ensuring cohesion by placing mobile cations between the phosphate groups whose central location does not interfere with strong adsorption of the terminal guanylation ammonium ions of the SAPL molecules enhanced by neutralisation of the phosphates. The cathodic side of the stomach surfactant into a close packed hydrocarbon structure resembling a very thin polyethylene layer – a popular substance for fabricating acid containers and one of comparable hydrophobicity to the stomach. Redrawn from Hills.1

which protection rates have reached 80–90%, leading to clinical trials that are now in progress.

An alternative approach in enhancing a gastric mucosal barrier is to bind the indigenous (or exogenous) SAPL more effectively, improving phosphate to phosphate ionic bonds by interspersing highly charged cations – see Figure (C). Tighter binding of phosphate groups – as in ‘phosphating’ (Figure (B)) – ‘pulls’ the outwardly orientated fatty acid chains together and, since these are straight (saturated), they will pack tightly into a very cohesive hydrocarbon barrier to water (Figure (C) D), hence the hydrogen ion.23 54 In any aqueous environment these are never H+ (a proton) but H2O4−.25 This compact barrier structure would be dislodged if the surfactant molecules were to lose one alkyl chain, explaining why lysolecithin is such an effective barrier breaker.19 Cohesion imparted by phosphate to phosphate bonding by cations may be one reason why aluminium hydride is more effective than other antacids and why surfactate is effective as the aluminium salt,21 Al2O3 ions reducing the area per molecule of a monolayer of SAPL by about 30%.57 Incidentally, surfactate is moderately surface active.54 The same ionic mechanism could apply to the ‘gold plated stomach’,38 where gold salts administered intravenously or intramuscularly for rheumatoid arthritis have been found to reduce the ulceration caused by NSAIDs co-administered to these patients. Binding to SAPL could also be one of the reasons why gold and aluminium are not taken up in the circulation – which is fortunate in view of their neurotoxic effects when delivered intravenously. A similar role for bismuth is possible.

Thus the concept of a gastric mucosal barrier of tightly packed hydrocarbon chains provided by surfactant molecules bound to the surface by their polar ends offers a simple physical model for an ‘inside lining’ based on principles well accepted in the physical sciences,21 together with an explanation for the hydrophobic nature of the normal gastric mucosa and many aspects of mucosal protection.

2 Davenport HW. The gastric mucosal barrier – a soon term. Ann Arbor: University of Michigan,
26 Hills BA. Gastric mucosal barrier: evidence for Helicobacter pylori ingesting surfactant and deriving protection from it. Gut 1993; 34: 588–93.