RELATIONSHIP BETWEEN LESION FORMATION AND PERMEABILITY OF RAT GASTRIC MUCOSA TO $H^+$ AND OTHER CATIONS

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The relationship between lesion formation and ionic permeability has been investigated in rat gastric mucosa in vivo. Changes in these parameters were measured in the mucosa treated topically with prostaglandins E₂ and A₂ and/or aspirin. Particular attention was paid to the net flux of $H^+$ ions across the gastric mucosa.

1. The effect of aspirin concentrations of 5 mM, 20 mM and '40 mM' (the latter, a suspension in a saturated solution) was investigated. Aspirin concentrations of 20 mM and '40 mM' produced a marked increase in lesion formation and increased the net mucosal to serosal flux of $H^+$ ions. Aspirin 5 mM produced a significant increase in lesion formation but did not cause a significant change in net $H^+$ ion flux. This result suggests that aspirin can have a direct irritant effect on the gastric mucosa and that the back diffusion of $H^+$ ions is not a pre-requisite for the development of overt mucosal ulceration.

2. The effect of aspirin-induced gastric mucosal damage was investigated. Concentrations of PGE₂ of $10^{-5}$ M and $10^{-4}$ M ameliorated aspirin-induced damage, but these changes were not necessarily accompanied by a significant reduction in net $H^+$ ion flux. Again, this result is not consistent with a direct relationship between lesion formation and mucosal permeability to $H^+$ ions.

3. Since PGA₂ did not ameliorate aspirin-induced mucosal damage, the protective effect of PGE₂ could not be attributed to its conversion to PGA₂ in the acidic environment of the gastric lumen.

4. Changes in gastric mucosal potential difference (p.d.) and net fluxes of Na⁺ and K⁺ ions may occur without a concomitant change in the permeability of the gastric mucosa to acid back-diffusion. Thus, the assumption cannot be made that a change in the permeability of the gastric mucosa to one particular ion reflects a general increase in ionic permeability.

Introduction

The formation of gastric mucosal lesions following topical acetylsalicylic acid (aspirin) is dependent on the presence of luminal acid (Cooke, 1973; Fromm, 1978). However, the precise role of acid in the development of these lesions is unclear. It is well established that an acidic environment is required to maintain aspirin (pKₐ 3.5) in its non-ionized form, thus increasing the lipid solubility of the molecule and the rate of absorption across the mucosal membrane (Cooke, 1973; Fromm, 1978). Following absorption, it is possible that aspirin causes gastric mucosal damage through a direct irritant effect (Rainsford, 1977), perhaps involving such mechanisms as the inhibition of active ion transport (Fromm, 1978) and the inhibition of oxidative metabolism (Rainsford & Whitehouse, 1980).

Davenport (1967) has proposed that aspirin per se does not cause gastric ulceration, but that the compound initially disrupts the gastric mucosal 'barrier' which allows the back-diffusion of $H^+$ ions down a steep concentration gradient; an effect which causes mucosal damage and haemorrhage.

Further evidence, albeit circumstantial, that acid back-diffusion may be important in the development of gastric ulceration is derived from experiments using the stable analogue of prostaglandin E₂, 16,16-dimethyl PGE₂. The latter compound reduces both gastric lesion formation and the back-diffusion of $H^+$ ions induced by aspirin in rats (Bommelaer & Guth, 1979) and dogs (Miller & Tepperman, 1979).

In the present experiments the effects of prostaglandins E₂ and A₂ and/or aspirin on lesion formation and several indices of gastric mucosal permeability have been studied in anaesthetized rats. Particular attention has been paid to the relationships between lesion formation and mucosal permeability to $H^+$.
ions since this might provide some insight into the importance of acid back-diffusion in the development of aspirin-induced mucosal damage.

Methods

Female Wistar rats (170–210 g) were deprived of food overnight, but allowed water ad libitum. The rats were anaesthetized with urethane (1.25 g/kg s.c.), the trachea intubated and a jugular vein cannulated. The abdomen was opened by a midline incision and the stomach exposed. An incision was made in the duodenum about 1 cm from the pyloric sphincter, and the gastric lumen was rinsed thoroughly with isotonic mannitol solution. A polythene tube was tied into the stomach via the duodenal incision, exteriorized through a stab-wound in the right flank and connected to a 3-way tap. This tube was used to instil solutions into and drain solutions from the stomach.

Gastric mucosal potential difference (p.d.) was measured using polythene catheters filled with 1% w/v agarose in 4 M KCl. One catheter was passed through the mouth and down the oesophagus and positioned in the stomach with a tie at the gastrooesophageal junction. A reference electrode was placed in a subcutaneous saline-filled bleb in a hind-foot. The agarose-KCl bridges were connected to a high input impedance d.c. amplifier via calomel electrodes placed in separate beakers of saturated KCl solution. The amplifier was connected to a Devices chart recorder calibrated on a 0–100 mV scale.

Each experiment was divided into five 30 min periods. During each of the first two periods 4 ml of a control solution was placed in the stomach. This solution contained HCl 100 mM, NaCl 10 mM, mannitol 80 mM and [14C]-polyethylene glycol-4000 ([14C]-PEG, 5 g/litre and 1 μCi/litre) as a volume marker. The osmolarity of the solution was 300–302 mosm/kg as measured by depression of freezing point (Advanced 3W II Osmometer). Preliminary experiments showed that 97.9 ± 1.5% (n = 6) of the [14C]-PEG could be recovered from the stomach, this result indicating that the compound was suitable for use as a volume marker in these experiments.

During the third period of the experiment a 'test' solution (4 ml) was placed in the stomach. In most experiments this solution was similar to the 'control' solution except that mannitol was replaced with acetylsalicylic acid, such that osmolarity remained constant. The concentrations of aspirin used were 5 mM, 20 mM and '40 mM'. This latter solution contained the quantity of aspirin theoretically required to achieve a 40 mM concentration, but it was not possible to dissolve all the aspirin and consequently a suspension of aspirin in a saturated solution was obtained. In some experiments a buffered aspirin solution was used. This was prepared by dissolving sufficient aspirin for a 20 mM solution with an equimolar amount of NaOH. The osmolarity of the solution was made up to 300 mosm/kg by the addition of mannitol, and the pH was 4.5; at this pH, 91% of the drug is ionized (Cooke, 1973).

During periods 4 and 5 the 'control' solution was again placed in the stomach. At 10 min intervals during each period, adequate mixing of the gastric contents was ensured by gently withdrawing the solution from the stomach into a syringe and injecting the sample back into the stomach.

Between each period the stomach was rinsed out thoroughly with three 4 ml aliquots of isotonic mannitol solution. Preliminary experiments showed that the third wash of mannitol contained a mean of 1.2% of the radioactivity initially instilled into the stomach. This result indicated that any contamination of solutions between periods was minimal.

Prostaglandins were applied topically to the gastric mucosa. The rats were preloaded with these compounds during the second period of the experiment, and also treated during the period of aspirin damage (period 3). The prostaglandins were initially dissolved in ethanol at a concentration of 10 mg/ml. Further dilutions were then made in 0.01% (v/v) Tween 80 (Sigma). For the addition of PGE_2 or PGA_2 to the acidic solutions not more than 0.5 ml of the Tween 80 preparation was added to a 15 ml sample.

The concentration of H⁺ ions in the gastric aspirate was measured by titration against 0.1 N NaOH using a Radiometer-TTT60 autotitrator. This measurement was not made during period 3 of the experiment since the titration value would reflect both unabsorbed aspirin and HCl. The concentrations of Na⁺ and K⁺ ions were measured with a Radiometer FLM3 flame photometer. The activity of [14C]-PEG in the solutions was determined by liquid scintillation spectrometry and the total volume of the final solution in the stomach was calculated using the formula:–

\[ V_o = \frac{V_i \times PEG_i}{PEG_o} \]

where \( V_o \) = volume of gastric aspirate, \( V_i \) = volume of instilled solution (4 ml), \( PEG_o = \text{[14C]}\text{-PEG activity of gastric aspirate}, \( \text{PEG_i} = \text{[14C]}\text{-PEG activity of instilled solution.} \)

The total amounts of H⁺, Na⁺ and K⁺ in the solutions were calculated from the product of volume and concentration. The net ion flux was then calculated as the difference between the initial and final amounts in μEq/30 min.

At the end of each experiment the stomach was removed and opened along the greater curvature.
The extent of lesion formation in the glandular region of the stomach was estimated using a grid system, and expressed as a percentage of the total surface area of the glandular mucosa.

**Materials**

Acetylsalicylic acid (aspirin) and polyethylene glycol-4000 (BDH Ltd), [14C]-polyethylene glycol-4000 (Radiochemical Centre, Amersham), mannitol (Sigma), prostaglandins E2 and A2 (PGE2 and PGA2, Cambrian) were used. All solutions were pre-warmed for 5 min at 37°C before instillation into the stomach.

**Analysis of results**

In analysing the data, allowance has been made for inter-preparation variability and any time-dependent changes that might occur during the course of a 2.5 h experiment. For this purpose the effect of aspirin on the measured parameters, recorded during periods 4 and 5, has been expressed as the change (Δ) from the corresponding control periods; the measurements for period 3 are not shown since they were affected by changes in the composition of the instillate. Thus, the total flux of each ion during the hour following aspirin treatment (periods 4 and 5 combined), was compared with the total flux during the hour prior to aspirin (periods 1 and 2 combined), and the appropriate Δ values calculated. For p.d., each Δ value was calculated as the difference between the control value at the end of period 2 and the test value at the end of period 5.

Results have been expressed as mean ± s.e.mean. The difference between two samples was examined statistically using the Mann Whitney U test as described by Siegel (1956). A two-tailed test was used and P values of less than 0.05 were considered to be significant.

**Table 1**  Control experiments: lesion formation, transepithelial potential difference (p.d.) and net ion fluxes in rat gastric mucosa during five consecutive 30 min periods

<table>
<thead>
<tr>
<th>30 min periods</th>
<th><strong>p.d.</strong> (mV)</th>
<th><strong>net m–s</strong> flux H+ (μEq/30 min)</th>
<th><strong>net s–m</strong> flux Na+ (μEq/30 min)</th>
<th><strong>s–m</strong> flux K+ (μEq/30 min)</th>
<th>% lesion formation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>52.8 ± 1.7</td>
<td>42.8 ± 4.5</td>
<td>20.5 ± 1.9</td>
<td>2.9 ± 0.5</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>53.2 ± 1.2</td>
<td>56.3 ± 6.9</td>
<td>17.8 ± 1.8</td>
<td>2.0 ± 0.1</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>52.7 ± 0.9</td>
<td>50.4 ± 9.0</td>
<td>18.8 ± 1.6</td>
<td>1.8 ± 0.1</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>52.5 ± 1.0</td>
<td>50.6 ± 8.9</td>
<td>21.5 ± 1.0</td>
<td>1.6 ± 0.2</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>50.0 ± 2.4</td>
<td>50.1 ± 4.9</td>
<td>20.0 ± 1.0</td>
<td>1.4 ± 0.2</td>
<td>7.7 ± 0.8</td>
</tr>
</tbody>
</table>

*The polarity of the p.d. was such that the mucosal surface was negative with respect to the reference electrode.

**m–s** indicates that the net ion flux was in the direction of mucosa to serosa. **s–m** indicates that the net ion flux was in the direction of serosa to mucosa.

Each value is the mean of six observations.

**Results**

**Control experiments**

As shown in Table 1, when control conditions were maintained throughout all five 30 min experimental periods, transepithelial p.d., net mucosal to serosal (m–s) flux of H+ and net serosal to mucosal (s–m) flux of Na+ remained relatively constant. However, the net serosal to mucosal (s–m) flux of K+ fell during the course of the experiment, the change being particularly marked between periods 1 and 2. In addition, a small degree of lesion formation occurred even in the absence of topical aspirin.

**Comparison of buffered and unbuffered aspirin**

Since the main purpose of the present study was to investigate the possible role of acid in the damage induced by aspirin in the gastric mucosa, it was important to establish the absolute necessity of acid in lesion formation in the present experimental situation. Therefore experiments were carried out to compare the effects of 20 mM aspirin, both in buffered and unbuffered solutions, on gastric mucosal permeability and lesion formation.

The results are shown in Figure 1. Unbuffered 20 mM aspirin produced significant changes in p.d. and ion flux compared with the corresponding control values and caused marked lesion formation. However, when buffered, the same concentration of aspirin failed to produce any significant changes in these parameters.

**The effect of increasing concentrations of unbuffered aspirin**

Having established the dependence of the damaging effects of topical aspirin on the presence of acid, the relationship between gastric mucosal permeability,
aspirin to the gastric mucosa caused a significant increase in gastric mucosal lesion formation without a concomitant increase in the rate of back-diffusion of H\(^+\) ions. Indeed, measurement of net s-m flux of Na\(^+\) and K\(^+\) ions also failed to reveal any change in the ionic permeability of the gastric mucosa, and there was no significant change in transepithelial p.d.

The higher concentrations of unbuffered aspirin of 20 mm and ‘40 mm’ produced significant increases in lesion formation, p.d. and the rate of flux of H\(^+\), Na\(^+\) and K\(^+\) ions, indicating a definite increase in mucosal permeability.

**Effect of prostaglandin E\(_2\) on the gastric mucosa**

As a prerequisite for studying the effect of PGE\(_2\) on the aspirin-induced changes, it was necessary to determine the effect of PGE\(_2\) alone. Lesion formation, p.d. and ion flux values are recorded in Table 2 and compared with the corresponding control values given in Table 1. At the high concentration of 10\(^{-4}\) M, PGE\(_2\) had no significant effect on mucosal p.d., lesion formation or net flux of H\(^+\) or K\(^+\) ions. A small but significant increase in net s-m flux of Na\(^+\) ions did occur during period 5 of the experiment. However, since the change in Na\(^+\) ion flux was not consistent (it did not occur during periods 3 and 4) and no change in mucosal permeability was revealed by the other parameters measured, it was considered that this would not interfere with subsequent interpretation of the effect of PGE\(_2\) on the aspirin-induced changes.

**The effect of topical prostaglandin E\(_2\) on aspirin-treated gastric mucosa**

As topical ‘40 mm’ aspirin caused the most marked and distinct changes in all of the parameters measured, this dose of aspirin was used in experiments on PGE\(_2\). The results are shown in Figure 2. The series of ‘40 mm’ aspirin controls was repeated, and there

![Figure 1](image.png)

**Figure 1** The effect of aspirin on lesion formation, transepithelial potential difference (p.d.) and net ion fluxes in rat gastric mucosa. The control Δ values are calculated from the original data recorded in Table 1. The sign given to the Δ values (ordinate axes) refers to the direction in which the changes occurred: + indicates a mean increase; − indicates a mean decrease. Statistical comparisons are made with the appropriate control data; *P < 0.05, **P < 0.01. n as indicated.

especially to H\(^+\) ions, and lesion formation was investigated using three concentrations of aspirin viz., 5 mm, 20 mm and ‘40 mm’. The results are recorded in Figure 1.

The most significant observation in this series of experiments was that the topical application of 5 mm

<table>
<thead>
<tr>
<th>30 min periods</th>
<th>p.d. (mV)</th>
<th>net m-s flux H(^+) ((\mu)Eq/30 min)</th>
<th>net s-m flux Na(^+) ((\mu)Eq/30 min)</th>
<th>net s-m flux K(^+) ((\mu)Eq/30 min)</th>
<th>% lesion formation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>55.4±1.1</td>
<td>32.5±6.7</td>
<td>22.6±1.9</td>
<td>2.9±0.2</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>54.0±2.8</td>
<td>44.2±3.2</td>
<td>21.0±1.5</td>
<td>1.8±0.1</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>52.4±3.0</td>
<td>44.9±2.9</td>
<td>26.0±2.7</td>
<td>1.7±0.2</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>52.0±1.8</td>
<td>48.1±6.0</td>
<td>24.2±2.4</td>
<td>1.5±0.2</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>50.6±2.8</td>
<td>43.0±4.2</td>
<td>26.3±1.7*</td>
<td>1.4±0.2</td>
<td>6.0±1.4</td>
</tr>
</tbody>
</table>

PGE\(_2\) (10\(^{-4}\) M) was applied topically to the gastric mucosa during periods 2 and 3. Each value is the mean of 5 observations.

Statistical comparison of p.d., ion fluxes and lesion formation was made with the corresponding control values in Table 1. *P < 0.05.
were p.d. or 1 response induced by related manner. aspirin-induced lesion reduced lesion formation concentrations of increase tenfold 2 3.0 10^4 formation. lesion reduced the ly lesion formation, poor index of formation without significant inhibition produc tion Na+ net flux values for (Asp)-induced effect (PGA2) (Asp)-induced gastric formation, particularly stud ied. Besides measuring net m–s flux of H+ ions, mucosal permeability was assessed by measuring transepithelial p.d. and net s–m flux of Na+ and K+ ions (Ivey, 1971). However, it should be pointed out that these latter parameters, particularly p.d. and net K+ ion flux, should be interpreted with some caution (Thjodleifsson & Wormsley, 1977; Fromm, 1979). For example, the transepithelial p.d. may be affected not only by mucosal permeability (resistance), but also by active ion transport (Tarnawski & Ivey, 1980). In addition, an increase in net s–m K+ ion flux may be the result of both a change in mucosal permeability and the exfoliation of cells into the gastric lumen (Davenport, 1965). Nevertheless, it was considered that measurement of p.d. and net fluxes of H+ , Na+ and K+ ions would provide more information about mucosal permeability than measurement of H+ ion flux alone.

In this study a low incidence of gastric lesion formation was observed in the absence of topical aspirin. This effect might be caused by the insertion of polythene catheters into the stomach, or by the prolonged exposure to exogenous HCl. However, the effect of aspirin or PGE2 was always compared with the low level of lesion formation observed in the control experiments.

The data with buffered and unbuffered 20 mM aspirin confirm previous observations (several authors cited by Cooke, 1973) that the presence of acid in the gastric lumen is an absolute requirement for the ulcerogenic effect of topical aspirin. This result is

In addition, the results show that PGE2, at concentrations of 10^{-6} M and 10^{-5} M, produced respectively small and large (significant) inhibitions of lesion formation without any significant changes in the aspirin-induced m–s flux of H+ ions. At a concentration of 10^{-5} M, PGE2 significantly reduced both lesion formation and the net m–s H+ ion flux.

**The effect of topical prostaglandin A2 on aspirin-treated gastric mucosa**

Since PGE2 is converted to PGA2 in the presence of acid (Bindra & Bindra, 1977), the possibility existed that PGE2 was converted to PGA2 in the gastric lumen and that the inhibition of lesion formation was due to the activity of the latter compound. However, the results given in Figure 2 show that this is unlikely because 10^{-5} M PGA2 failed to inhibit significantly aspirin-induced lesion formation.

**Discussion**

In the present experiments the relationship between gastric lesion formation and ionic permeability of the gastric mucosa, particularly to H+ ions, has been studied. Besides measuring net m–s flux of H+ ions, mucosal permeability was assessed by measuring transepithelial p.d. and net s–m flux of Na+ and K+ ions (Ivey, 1971). However, it should be pointed out that these latter parameters, particularly p.d. and net K+ ion flux, should be interpreted with some caution (Thjodleifsson & Wormsley, 1977; Fromm, 1979). For example, the transepithelial p.d. may be affected not only by mucosal permeability (resistance), but also by active ion transport (Tarnawski & Ivey, 1980). In addition, an increase in net s–m K+ ion flux may be the result of both a change in mucosal permeability and the exfoliation of cells into the gastric lumen (Davenport, 1965). Nevertheless, it was considered that measurement of p.d. and net fluxes of H+ , Na+ and K+ ions would provide more information about mucosal permeability than measurement of H+ ion flux alone.

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The data with buffered and unbuffered 20 mM aspirin confirm previous observations (several authors cited by Cooke, 1973) that the presence of acid in the gastric lumen is an absolute requirement for the ulcerogenic effect of topical aspirin. This result is
predictable since the pKₐ value for aspirin is 3.5, and at higher pH values the lipid solubility and rate of absorption of the compound are diminished (Cooke, 1973). The role of acid back-diffusion in the aetiology of aspirin-induced gastric mucosal damage is a more contentious subject. Topical application of 5 mM aspirin to the gastric mucosal surface produced a significant increase in the level of lesion formation without changing the rate of acid back-diffusion. This result suggests that under these conditions aspirin damages the gastric mucosa through a direct irritant effect, and not via an increase in the rate of flux of H⁺ ions into the mucosal tissue. Raising the concentrations of aspirin to 20 mM and ‘40 mM’ increased both the degree of lesion formation and the rate of acid back-diffusion in a dose-related manner. A possible interpretation of these observations is that relatively low concentrations of topically applied aspirin damage the gastric mucosa through a direct irritant action, but that this is not severe enough to allow a detectable increase in the net m-s flux of H⁺ ions across the mucosa. In the presence of higher concentrations of aspirin the damage to the gastric mucosa was sufficient to allow a measurable flux of H⁺ ions down their concentration gradient. It is possible that this flux of acid into the mucosal tissue then exacerbates the direct damaging effect of aspirin.

The topical application of PGE₂ alone to the gastric mucosa had little effect on the parameters measured, although it did cause a small, inconsistent increase in net s-m Na⁺ ion flux. It is reported that topical 16,16-dimethyl PGE₂ stimulates the secretion of HCO₃⁻ in vivo (Kauffman, Reeve & Grossman, 1980), and it is probable that this secretion is coupled to Na⁺ co-ion (Allen & Garner, 1980). However it is unlikely that the increase of flux of Na⁺ ions into the gastric lumen, observed in the present work, is due to stimulation of NaHCO₃ secretion by PGE₂ since no apparent increase in net m-s flux of H⁺ ions occurred. Bolton & Cohen (1979) found that topical 16,16-dimethyl PGE₂ stimulated the net s-m fluxes of both Na⁺ and Cl⁻ ions. A similar effect of PGE₂ in the present study would explain the small secretion of Na⁺ ions, although such a mechanism could not be confirmed since Cl⁻ ion flux was not measured.

Concentrations of PGE₂ of 10⁻⁵ M and 10⁻⁴ M ameliorated the gastric mucosal damage induced by ‘40 mM’ aspirin. Although this effect of 10⁻⁴ M PGE₂ was accompanied by a significant reduction in the aspirin-induced net m-s H⁺ ion flux, the effect of the lower concentration of PGE₂ was not. Thus in the present work the inhibition of lesion formation was not necessarily accompanied by a significant reduction in the rate of acid back-diffusion. The maximal inhibition of aspirin-induced lesion formation by PGE₂ was only 56%, and it is possible that treatment of the gastric mucosa with PGE₂ in the presence of a lower concentration of aspirin (i.e. 20 mM) might have revealed a different relationship between lesion formation and H⁺ ion permeability. At the present time there is no consensus of opinion about the effect of E prostaglandins on mucosal H⁺ ion permeability in the rat. Bommelaer & Guth (1979) reported that 16,16-dimethyl PGE₂ reduced both aspirin-induced gastric damage and acid back-diffusion, whereas Puurunen (1980) found that PGE₂ ameliorated ethanol-induced mucosal damage without diminishing the back-diffusion of H⁺ ions. Whether these results reveal a genuine difference between PGE₂ and its methylated derivative is not known, but certainly there is no firm evidence at present to support the view that PGE₂ itself affects mucosal permeability to H⁺ ions.

Direct application of 10⁻⁵ M PGA₂ had no effect on aspirin-induced changes in lesion formation, p.d., H⁺ and K⁺ ion fluxes. This result provides no evidence that a significant proportion of the activity of PGE₂ can be attributed to the formation of PGA₂ which may occur in the acid environment of the gastric lumen.

The mechanism through which exogenous PGE₂ ameliorates gastric mucosal damage is obscure although it may involve the replacement of endogenous PGE₂, the amount of which is diminished by aspirin treatment (Konturek, Piastucki, Brzozowski, Radecki, Dembinska-Kiec, Zmuda & Gryglewski, 1981). One possibility is that PGE₂ increases gastric mucosal blood flow and thus prevents excessive accumulation of acid within the mucosal tissue (Whittle, 1980). Indeed, topical administration of 16,16-dimethyl PGE₂ to resting canine gastric mucosa does cause vasodilatation (Cheung, 1980). Another possibility is that PGE₂ averts mucosal damage through the stimulation of mucus and/or bicarbonate secretion (Allen & Garner, 1980). Topical application of PGE₂ to the rat gastric mucosa does stimulate mucus production (Bolton, Palmer & Cohen, 1978), but as discussed above, there was no evidence in the present study that topical PGE₂ caused luminal alkalinization.

Several mechanisms have been implicated in the gastric damage induced by aspirin (Rainsford, 1977; Rainsford & Whitehouse, 1980; Whittle, 1980) including an increased permeability of the mucosa to H⁺ ions (Davenport, 1967). However, considering all of the data presented in the present investigation, it is possible that lesion formation in rat gastric mucosa is not primarily determined by the permeability of the epithelium to H⁺ ions. This conclusion is based on the observations that under certain circumstances aspirin may damage the mucosa without an increase in acid back-diffusion, and similarly PGE₂ may inhibit aspirin-induced damage without effect-
ing mucosal permeability to the H\(^+\) ions. Nevertheless, as discussed by Bugat, Thompson, Aures & Grossman (1976), it is still possible that under conditions where a gross change in H\(^+\) ion permeability was not observed, a small localized back-diffusion of H\(^+\) occurred which escaped detection.

The value of measuring changes in p.d. and fluxes of Na\(^+\) and K\(^+\) ions as indices of mucosal permeability must also be considered. The data obtained using aspirin alone do suggest that significant changes in

net m\(-\)s H\(^+\) ion flux are accompanied by concomitant changes in the other parameters. However, the experiments using both aspirin and PGE\(_2\) (10\(^{-6}\)M and 10\(^{-3}\)M) showed that changes in p.d. and net flux of K\(^+\) ions may occur without a concomitant change in the rate of acid back-diffusion. Thus, the assumption cannot be made that a change in the permeability of the mucosa to one particular ion indicates a general increase in ionic permeability.

References


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