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# The effects of the stable thromboxane $A_2$-mimetic, U46619, on gastric mucosal damage and gastric non-parietal secretion in the rat

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**1** The effects of the thromboxane $A_2$-mimetic, U46619, and the thromboxane receptor antagonist, AH23848, on ethanol-induced gastric mucosal damage and gastric non-parietal secretion have been examined in the rat.

**2** Oral dosing with U46619 or AH23848 produced a dose-related inhibition of ethanol-induced gastric mucosal damage in the conscious rat, and these effects were partially blocked by indomethacin treatment.

**3** Intragastric application of U46619 or AH23848 to the stomach of the anaesthetized rat stimulated the gastric secretion of a juice which consisted principally of $Na^+$ and $Cl^-$ ions. These secretagogue effects of both compounds were blocked by indomethacin treatment.

**4** These results show that U46619 and AH23848 induce secretory and protective effects in the stomach of the rat, although these responses probably do not involve thromboxane receptors and are mediated, at least in part, by endogenous prostaglandins.

**5** The results are discussed in relation to the role of endogenous thromboxane $A_2$ in gastric mucosal protection, and of the possible protective function of non-parietal secretion in the stomach.

## Introduction

Some discrepant results exist in the literature about the role of thromboxane $A_2$ ($TXA_2$) in gastric mucosal ulceration. It has been shown that the stable $TXA_2$-mimetic, U46619 (11α, 9α,-epoxymethano-prostaglandin $H_2$; Coleman *et al.*, 1981), is a powerful vasoconstrictor in the stomach of the rat (Whittle *et al.*, 1985) and dog (Kauffman & Whittle, 1982; Whittle & Moncada, 1983), and because of the importance of blood flow in maintaining gastric mucosal integrity (Guth, 1984), Whittle *et al.* (1981) have suggested that endogenous $TXA_2$ may be implicated in the pathogenesis of gastric ulceration. This latter interpretation has been further strengthened by the observation that both the thromboxane synthesis inhibitors, dazmegrel (Hawkey *et al.*, 1985) and 1-benzylimidazole (Whittle, 1984), and a thromboxane receptor antagonist, SK&F88046 (Price *et al.*, 1985), ameliorated ethanol-induced gastric mucosal damage in the rat.

In contrast with the above findings Tao & Wilson (1984) found that treatment with U46619 protected the gastric mucosa from ethanol-induced damage in the rat. They also showed that this compound stimulated the secretion of gastric non-parietal juice.

In the present experiments the effects of U46619 and the thromboxane receptor antagonist, AH23848 (Brittain *et al.*, 1985) on ethanol-induced gastric mucosal damage and gastric non-parietal secretion have been investigated in the rat, and the effect of indomethacin treatment on these responses examined. A preliminary account of these results has been presented to the British Pharmacological Society (Bunce & Clayton, 1985).

## Methods

Female rats weighing approximately 120 g were used. The rats were starved for 48 h before use, but allowed water *ad libitum*.

### *Ethanol-induced lesion formation*

These experiments were carried out following the method of Robert *et al.* (1979). Rats were dosed subcutaneously (s.c.) with indomethacin, 5 mg $kg^{-1}$, or 1% $NaHCO_3$ solution as control. After 75 min the

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rats were dosed orally with the test prostaglandin or vehicle control; the dose volume was 5 ml $kg^{-1}$. After a further 30 min the rats were dosed orally with 1 ml of absolute ethanol and 60 min later were killed. The stomachs were excised, opened along the greater curvature, pinned out on a flat surface with the mucosal surface uppermost and the mucosa rinsed thoroughly. The extent of macroscopically visible lesion formation was then assessed by planimetry.

*Gastric non-parietal secretion*

The rats were injected with indomethacin, 5 mg $kg^{-1}$ s.c., or vehicle control and then anaesthetized with pentobarbitone, 50 mg $kg^{-1}$ i.p. The trachea was intubated to facilitate breathing. A jugular vein was cannulated and atropine, 3 μmol $kg^{-1}$ i.v., injected to inhibit gastric acid secretion. The abdomen was opened by midline incision and the pylorus and oesophagus were ligated close to the stomach. An incision was made in the rumen of the stomach and the gastric lumen rinsed thoroughly with 300 mM mannitol solution. A small polythene fistula was then inserted and tied into the ruminal incision and the abdomen closed with the distal end of the gastric fistula exteriorized. At this stage a maintenance infusion of pentobarbitone, 100 μg $kg^{-1}$ $min^{-1}$ i.v., was commenced.

Following a 10 min 'stabilization period', gastric non-parietal secretion was stimulated by intragastric administration of a prostanoid via the gastric fistula; the dose volume was 0.25 ml 100 $g^{-1}$ body wt. and the control vehicle was 275 mM mannitol/25 mM theophylline. Preliminary experiments showed that prostanoids stimulated more consistent secretory responses in the presence of 25 mM theophylline; 275 mM mannitol was added to provide an isotonic solution. Gastric secretion was collected over a 1 h period and at the end of this time the stomach was removed taking care not to damage the oesophageal and pyloric ligatures. The intragastric contents were then expressed into a suitable container via the gastric fistula and the volume measured. The gastric samples were centrifuged and the supernatant fluid used for the assays.

Sodium and potassium outputs were measured by flame photometry. Chloride output was measured by coulometric titration. The outputs of acid or bicarbonate were measured by back-titration as follows. To 0.1 ml of gastric aspirate were added 0.1 ml of 50 mM $H_2SO_4$ and 1 ml of distilled water, and the samples were heated at 100°C for 15 min to expel residual $CO_2$. The total acid in these samples was then determined by automatic titration to pH 7 using 0.1 N NaOH, from which the output of acid or bicarbonate was calculated.

*Expression of results*

The effect of a prostanoid on gastric mucosal lesion formation was expressed as percentage inhibition compared with the appropriate control. The $ED_{50}$ value for a compound in this test was calculated as the dose required to inhibit lesion formation by 50%; these values were calculated with 95% confidence limits.

Secretory volumes were calculated as the volume of juice collected from the stomach less the volume of intragastric vehicle injected at the beginning of the 1 h secretory period.

Results are expressed as mean ± s.e.mean. Statis-

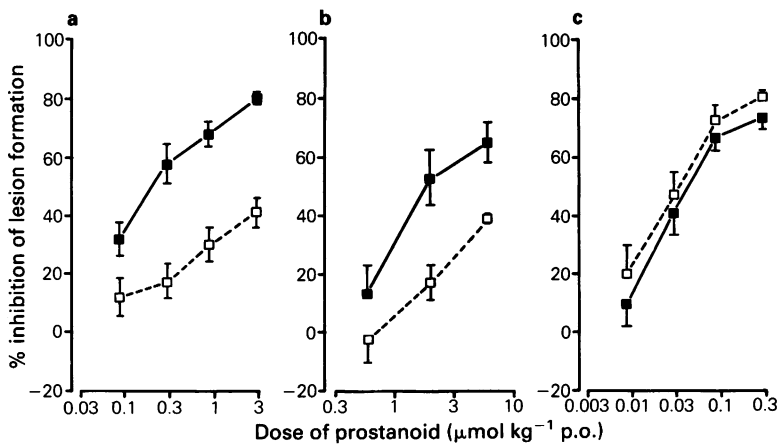


**Figure 1** The effects of (a) U46619, (b) AH23848 and (c) prostaglandin $E_2$ on ethanol-induced gastric mucosal lesion formation in the conscious rat in the absence (■) and presence (□) of indomethacin, 5 mg $kg^{-1}$ s.c. Each point is the mean of 5–10 observations. Vertical lines show s.e.mean.

**Table 1** The protective effect of prostanoids against ethanol-induced gastric mucosal lesion formation

| | $ED_{50}$ value ($\mu$mol kg$^{-1}$ p.o.) (95% confidence limits) *Without indomethacin* **With indomethacin* | |
|---|---|---|
| U46619 | 0.24 (0.14–0.39) | >2.8 |
| AH23848 | 2.5 (1.5–4.8) | >6.0 |
| Prostaglandin $E_2$ | 0.06 (0.04–0.08) | 0.04 (0.02–0.06) |

* Indomethacin did not affect gastric ulceration. Ethanol caused 67.5 ± 4.3% ($n = 20$) and 63.9 ± 3.8% (n = 19) of the mucosal surface to be damaged in the absence and presence of indomethacin, 5 mg kg$^{-1}$ s.c., respectively ($P > 0.05$). Indomethacin alone did not induce mucosal damage as measured by macroscopic examination.

tical comparisons were made by means of Student's $t$ test for unpaired data, a $P$ value of less than 0.05 was considered to be significant.

*Materials*

Indomethacin (Sigma) was dissolved at 10 mg ml$^{-1}$ in 10% $NaHCO_3$ solution, further dilutions were then made with isotonic saline. Mannitol (Sigma) and theophylline (BDH) were dissolved in distilled water to give an isotonic solution for intragastric instillation. Prostaglandin $E_2$ ($PGE_2$) was purchased in stock solution (Prostin E, Upjohn). U46619 and AH23848 ([1α(z),2β,5α]-(±)-7-[5[[(1,1'-biphenyl)-4-yl]methoxy]-2-(4-morpholinyl)-3-oxocyclobentyl]-4-heptenoic acid) were synthesized in our own laboratories; these compounds were dissolved at 20 mg ml$^{-1}$ in 60% aqueous ethanol and stored at −20°C. All compounds were then diluted with the appropriate vehicle for administration; a solution containing 25 mM theophylline/275 mM mannitol was used for the secretion experiments and 0.01% w/v Tween 80 for the lesion experiments.

## Results

*Ethanol-induced lesion formation*

The effects of prostanoids on ethanol-induced gastric mucosal lesion formation are shown in Figure 1. Without indomethacin treatment the $TXA_2$-mimetic, U46619, the thromboxane receptor antagonist, AH23848, and $PGE_2$ inhibited lesion formation. Treatment of rats with indomethacin (5 mg kg$^{-1}$ s.c.) markedly diminished the protective action of U46619 and AH23848, but did not significantly change the protective effect of $PGE_2$. The $ED_{50}$ values calculated from these experiments are summarized in Table 1.

*Gastric non-parietal secretion*

In the first instance experiments were carried out in the absence of indomethacin treatment. The effect of U46619 on gastric non-parietal secretion is shown in Figure 2; in this series of experiments under control conditions the stomach secreted at a rate of 0.42 ± 0.08 ml h$^{-1}$ and doses of U46619 of 0.3 and 3 $\mu$mol kg$^{-1}$ intragastrically stimulated a dose-related increase in the output of this non-parietal juice. Under both control and stimulated (with U46619) conditions the principal cation in the juice was $Na^+$ and the

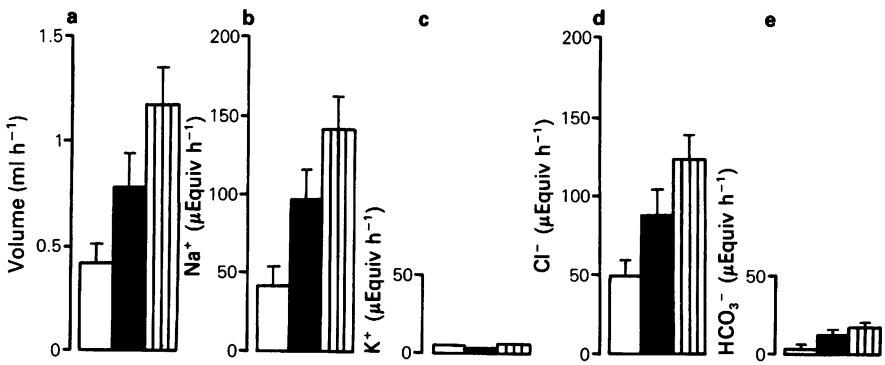


**Figure 2** The effect of U46619 on gastric non-parietal secretion in the anaesthetized rat. Open columns represent control secretion; solid columns, secretion in the presence of U46619 0.3 $\mu$mol kg$^{-1}$ (intragastrically); hatched columns, secretion in the presence of U46619 3 $\mu$mol kg$^{-1}$ (intragastrically). The outputs of (a) fluid, (b) $Na^+$, (c) $K^+$, (d) $Cl^-$ and (e) $HCO_3^-$ were measured over a 1 h period. Each mean value is taken from 6–7 observations. Vertical lines show s.e.mean.

**Table 2** The effect of prostanoids and indomethacin on ion fluxes in rat gastric mucosa

| *Treatment* | n | *[1]Volume* | *[2]$Na^+$* | *[2]$K^+$* | *[2]$Cl^-$* | *[2,3]$H^+/HCO_3^-$* | *[2,4]Total cations* | *[2,4]Total anions* |
|---|---|---|---|---|---|---|---|---|
| Control | 5 | 0.46 | 59.4 | 1.6 | 51.6 | (−)6.6 | 61.1 | 58.2 |
| | | ± 0.02 | ± 3.8 | ± 0.09 | ± 4.5 | ± 2.4 | ± 3.8 | ± 3.2 |
| $PGE_2$ (0.3 μmol $kg^{-1}$ topically) | 6 | 1.13 | 152.1 | 3.5 | 126.2 | (−)19.4 | 155.6 | 145.6 |
| | | ± 0.08 | ± 10.4 | ± 0.6 | ± 8.7 | ± 4.5 | ± 10.8 | ± 9.5 |
| U46619 (3 μmol $kg^{-1}$ topically) | 6 | 1.18 | 141.1 | 6.0 | 122.5 | (−)16.7 | 147.1 | 139.2 |
| | | ± 0.17 | ± 21.1 | ± 0.8 | ± 16.1 | ± 3.1 | ± 21.8 | ± 19.0 |
| AH23848 (30 μmol $kg^{-1}$ topically) | 6 | 0.87 | 109.3 | 3.3 | 98.4 | (−)9.3 | 112.6 | 107.7 |
| | | ± 0.06 | ± 7.2 | ± 0.4 | ± 6.0 | ± 2.0 | ± 7.5 | ± 6.6 |
| Indomethacin (5 mg $kg^{-1}$ s.c.) | 6 | 0.22 | 27.4 | 1.1 | 32.3 | (+)5.8 | 34.3 | 32.3 |
| | | ± 0.06 | ± 6.1 | ± 0.3 | ± 7.5 | ± 1.8 | ± 7.7 | ± 7.5 |

Results are expressed as mean ± s.e.mean.
[1] Values show net secretion of fluid in ml $h^{-1}$.
[2] Values show net secretion of ions in μEquiv $h^{-1}$.
[3] For $H^+/HCO_3^-$; (+) indicates net $H^+$ secretion, (−) indicates net $HCO_3^-$ secretion
[4] In each test there was no significant difference ($P > 0.05$) between the total outputs of cations and anions.

principal anion $Cl^-$; the juice also contained smaller amounts of $K^+$ and $HCO_3^-$. In Table 2 a comparison is made of the composition of the gastric juice stimulated by each of the prostanoids studied; the response to the largest dose of each compound is recorded. These results show that, like U46619, $PGE_2$ and AH23848 stimulated the secretion of a juice rich in $Na^+$ and $Cl^-$ ions with lesser amounts of $K^+$ and $HCO_3^-$. The data in Table 2 also reveal that under control conditions and with each prostanoid there was no significant difference between the outputs of total cations and total anions; this result indicates that no major ionic component of the gastric juice was omitted from analysis.

Since $Na^+$ is a major component of non-parietal juice, but only a minor component of parietal juice (Makhlouf, 1981), this ion was used as the index of non-parietal secretion in the subsequent investigation. A comparison of the effect of the prostanoids on non-parietal secretion is shown in Figure 3; like U46619, $PGE_2$ and AH23848 stimulated a dose-related increase in $Na^+$ output and, as in the lesion experiments (Figure 1) the rank order of potency was $PGE_2 > U46619 > AH23848$.

The changes in gastric non-parietal secretion induced by indomethacin were next investigated. The effect of indomethacin (5 mg $kg^{-1}$ s.c.) on gastric non-parietal secretion under basal conditions is included in Table 2; the compound significantly ($P < 0.05$) inhibited the secretory volume and the outputs of the major ionic constituents, $Na^+$ and $Cl^-$. It is interesting to note that in the presence of indomethacin a net $H^+$ secretion was observed; it is likely that the inhibition of non-parietal secretion by indomethacin, as indicated by the fluxes of fluid, $Na^+$ and $Cl^-$, resulted in a reduction of $HCO_3^-$ output which then revealed an ongoing $H^+$ secretion. Because of this effect of indomethacin, and because the secretory responses to the prostanoids were superimposed on the basal secretion, when assessing the effect of indomethacin treatment on prostanoid-stimulated secretion it was necessary to consider the output of $Na^+$ above the appropriate mean basal level, i.e. the $Na^+$ output above the corresponding control value. Calculated in this way (i.e.change in $Na^+$ output above control), the effects of indomethacin treatment on the secretory response to U46619, AH23848 and $PGE_2$ are shown in Figure 4. Indomethacin treatment significantly reduced the secretagogue effects of U46619 and AH23848, but had no effect on the $Na^+$ output stimulated by $PGE_2$.

Some experiments were carried out (in the absence of indomethacin treatment) to determine the effect of AH23848 on U46619-induced secretion. $Na^+$ output in the presence of U46619 (0.3 μmol $kg^{-1}$) was 101.5 ± 14.0 μEquiv $h^{-1}$ ($n = 5$), and AH23848 (3 μmol $kg^{-1}$; a dose which itself had little effect, Figure 4) did not significantly change this response (104.3 ± 8.1 μEquiv $h^{-1}$, $n = 5$).

## Discussion

The present study confirms the results of Tao & Wilson (1984) that the $TXA_2$-mimetic, U46619, ameliorates ethanol-induced gastric mucosal damage. The observation that this effect of U46619 was diminished by indomethacin treatment is novel, and suggests that the protective response was not direct but mediated by endogenous prostaglandins. This effect of indomethacin is unlikely to be a non-specific action since the compound did not influence the protective

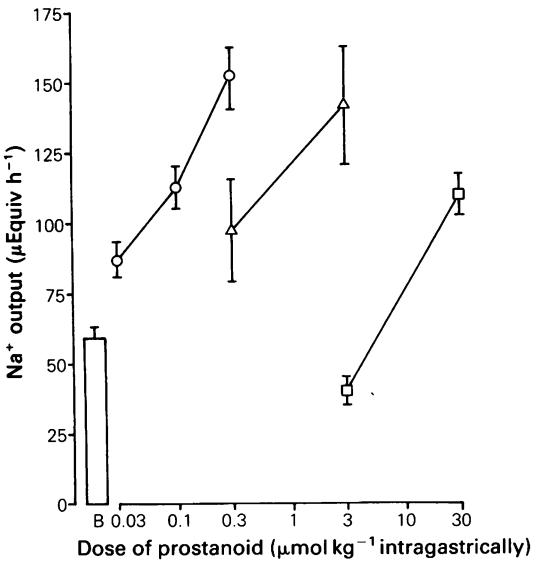


**Figure 3** The effects of prostaglandin $E_2$ (O), U46619 (Δ) and AH23848 (□) on gastric $Na^+$ output in the anaesthetized rat. Experiments were carried out in the absence of indomethacin treatment. The histogram shows the basal level (B) of $Na^+$ output. Each point is the mean of 5–8 observations. Vertical lines show s.e.mean.

action of $PGE_2$. On this basis therefore, as defined by Robert *et al.* (1983), intraluminal U46619 may be regarded as a mild irritant to the gastric mucosa. In contrast with the above findings Whittle & Moncada (1983) have demonstrated that close-arterial infusion of U46619 to the canine stomach, by reducing gastric mucosal blood flow, increases the propensity for the mucosa to ulcerate. In view of these findings it is interesting to speculate on whether endogenous $TXA_2$ could possibly exert a protective effect in the gastric mucosa, as implicated by the results of the present study. Certainly the gastric mucosa of the rat does synthesize $TXA_2$ (as measured by $TXB_2$ production: Robert *et al.*, 1983; Wallace & Whittle, 1985), although this rate of synthesis does not change in tissue damaged by ethanol ingestion (Wallace & Whittle, 1985). Thus it is likely that even in damaged tissue we must consider the protective role of a basal level of $TXA_2$ turnover. Because of the potent vasoconstrictor activity of $TXA_2$ (Whittle *et al.*, 1981), to exert a protective effect this prostanoid would probably have to be synthesized by the cells of the gastric mucosa rather than by the intravascular platelets, and indeed there is evidence that such a locus of synthesis does exist (Chan *et al.*, 1986). However, if endogenous $TXA_2$ exerts a protective role then inhibitors of $TXA_2$ synthesis or thromboxane receptor antagonists might be expected to exacerbate drug-induced mucosal damage. Such an observation has never been made; these compounds (thromboxane synthetase inhibitors

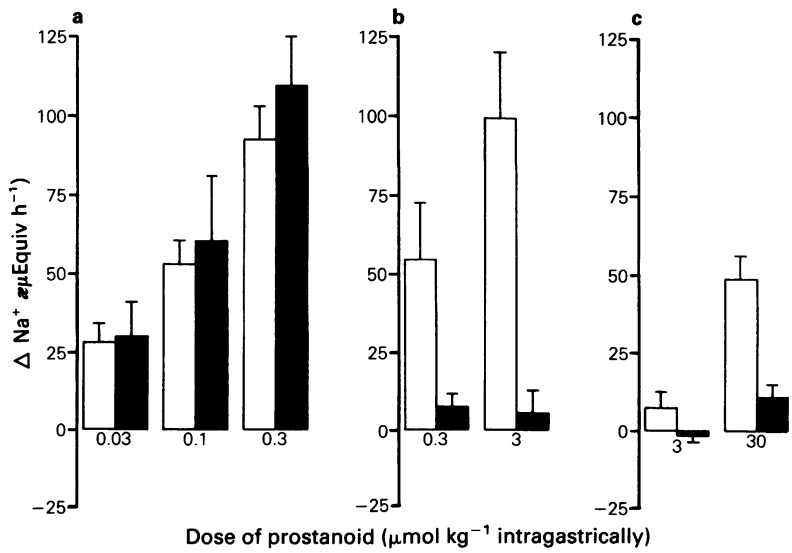


**Figure 4** The effect of indomethacin on (a) prostaglandin $E_2$, (b) U46619 and (c) AH23848 stimulated gastric non-parietal secretion in the anaesthetized rat. Open columns represent secretion in the absence of indomethacin and solid columns represent secretion in the presence of indomethacin, 5 mg $kg^{-1}$ s.c. $Na^+$ output (μEquiv $h^{-1}$) was calculated as the increase stimulated by the prostanoid above the corresponding mean basal level. Each mean value is taken from 5–8 observations. Vertical lines show s.e.mean.

(Hawkey *et al.*, 1985; Whittle, 1984) and thromboxane receptor antagonists (Price *et al.*, 1985; this study)) ameliorate ethanol-induced gastric damage in the rat. It must, therefore, be concluded that the protective action of U46619 seen in the present study is a pharmacological effect and does not necessarily relate to the actions of endogenous $TXA_2$.

It would have been instructive to obtain direct evidence about the role of thromboxane receptors in the protective response to U46619 by co-administration of a thromboxane receptor antagonist. However, AH23848 itself induced a protective response and it was therefore considered that any result from such a combination of U46619 and AH23848 would be impossible to interpret clearly. Nevertheless, the observation that both an agonist and an antagonist produced mucosal protection is not consistent with the involvement of thromboxane receptors. As with U46619, the protective effect of AH23848 was sensitive to indomethacin treatment indicating an involvement of endogenous prostaglandins. Other workers (Price *et al.*, 1985) have also shown that a thromboxane receptor antagonist, SK&F88046, protected gastric mucosa against ethanol-induced damage in the rat. However, it would be necessary to ascertain the effect of indomethacin treatment in such experiments before any conclusions were reached about the role of endogenous $TXA_2$ in gastric mucosal damage.

The present study also confirms the observation of Tao & Wilson (1984) that intragastric U46619 stimulates gastric non-parietal secretion in the rat and additionally shows that, as with stimulation by E and F prostaglandins (Bunce, 1985), this secretion consists principally of $Na^+$ and $Cl^-$ ions with smaller amounts of $K^+$ and $HCO_3^-$. This secretagogue effect of U46619, like that of AH23848, was sensitive to indomethacin treatment indicating that these responses were mediated by endogenous prostaglandins. These latter results, together with the resistance of the U46619-induced secretory response to antagonism by AH23848, corroborates the previous assertion that both U46619 and AH23848 were acting as mild irritants in the stomach to release endogenous prostaglandins and that such an effect was not mediated by thromboxane receptors.

Since both the protective and secretory effects of both U46619 and AH23848 in the rat stomach were sensitive to indomethacin treatment it is interesting to speculate whether the gastric secretion of non-parietal juice itself mediates the protective response. First, the doses of U46619 used in the mucosal protection and secretory experiments were of the same order; a result which is compatible with a functional association of these effects. In contrast with this, AH23848 $3\,\mu mol\,kg^{-1}$ p.o. induced a protective effect, but when applied intragastrically failed to stimulate non-parietal secretion; the latter response was not obtained until the dose was increased to $30\,\mu mol\,kg^{-1}$. However, it must be pointed out that these experiments on mucosal protection and non-parietal secretion were carried out in different groups of animals under different experimental conditions, e.g. in conscious and anaesthetized animals using different routes of drug administration. Thus, more stringent experimental criteria would have to be applied before any putative relationship between mucosal protection and non-parietal secretion could be clearly identified.

The dose of indomethacin used in this study, which has previously been shown to inhibit gastric mucosal cyclo-oxygenase activity in the rat by approximately 90% (Whittle & Salmon, 1983), produced an almost complete block of the gastric secretory responses to U46619 and AH23848, but only partially inhibited the protective responses to these compounds. These results may suggest that in the present experiments the dose of indomethacin used failed to achieve a sufficient reduction in the level of prostaglandin synthesis to inhibit completely a response mediated via endogenous prostaglandins. Other possible interpretations are that U46619 and AH23848 are in part exerting a direct effect which is probably unrelated to activity at thromboxane receptors, or that the compounds are producing an indirect effect involving non-prostaglandin mediator(s) yet to be identified.

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