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CONTRACTILE AND RELAXANT ACTIONS OF PROSTAGLANDINS ON GUINEA-PIG ISOLATED TRACHEA

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1 The effects of 12 prostaglandins on guinea-pig isolated trachea have been examined in the presence of indomethacin. Two series of experiments were carried out, the first on preparations without tone ('zero tone'), and the second on preparations with tone induced with acetylcholine ('high tone').

2 The compounds tested fell into two groups. The first, comprising prostaglandins $F_{1\alpha}$, $F_{2\alpha}$, $F_{2\alpha}$ acetal, I_2 and Wy 17186, contracted both zero and high tone preparations. The second, comprising prostaglandins A_1, A_2, B_1, B_2, E_1, E_2 and $F_{2\beta}$, contracted zero, but relaxed high tone preparations. Responses to the second group of compounds are probably the resultant of their contractile and relaxant actions.

3 The order of potency for contracting zero tone preparations was prostaglandin E (PGE) > F = I = Wy 17186 > B > A, 2-series compounds being 5 to 18 times more potent than 1-series compounds.

4 The order of potency for relaxing high tone preparations was PGE > F_β > B > A > Wy 17186 > F_α = I = 0. There was little difference between the potency of 1- and 2-series compounds.

5 The possible relevance of these results to the interpretation of the effects of prostaglandins on human airways is discussed.

Introduction

Guinea-pig isolated trachea is generally considered to resemble human airway smooth muscle in its responses to drugs (Foster, 1974). Since bronchoconstrictor prostaglandins may contribute to the pathogenesis of asthma, and bronchodilator prostaglandins may be of value in its treatment (Mathé, Hedqvist, Strandberg & Leslie, 1977), the actions of these compounds on guinea-pig trachea are of interest.

Prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) which is a bronchoconstrictor in experimental animals and in man (Rosenthale, 1975), contracts guinea-pig isolated trachea (Puglisi, 1973; Farmer, Farrar & Wilson, 1974) as do PGG_2, PGH_2 (Hamberg, Hedqvist, Strandberg, Svensson & Samuelsson, 1975) and PGD_2 (Dawson, Lewis, McMahon & Sweatman, 1974, Hamberg *et al.*, 1975). Prostaglandins of the E series are generally considered to be bronchodilators in experimental animals and in man (Rosenthale, 1975) and have been shown to relax guinea-pig isolated trachea (Puglisi, 1973). However, E series prostaglandins also have contractile actions on this preparation; guinea-pig isolated trachea has spontaneous tone and whilst PGE_1 and PGE_2 cause relaxation when tone is present, they cause contraction when it is absent (Puglisi, 1973; Lambley & Smith, 1975). In view of the importance of the level of tone in determining the response to E series prostaglandins, we considered it necessary to examine the effects of a range of prostaglandins on the trachea under conditions of controlled tone. The spontaneous tone was abolished by treatment with indomethacin (Farmer *et al.*, 1974). Two series of experiments were carried out, the first on preparations without tone (described hereafter as 'zero tone' preparations) and the second on preparations in which tone was induced with acetylcholine (described hereafter as 'high tone' preparations). We have carried out a quantitative comparison of the effects of twelve prostaglandins of diverse chemical structure and biological activity on these preparations.

Methods

Strips of trachealis muscle taken from guinea-pigs of either sex, weighing 300 to 400 g, were prepared by the method of Coburn & Tomita (1973). The strips were suspended in 2 ml organ baths containing modified Krebs solution maintained at 37°C and gassed with a 95% O_2 and 5% CO_2 mixture. A resting ten-

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sion of 1 g was applied. Tension was measured by means of a Statham Microscale Accessory (Model UL5) attached to a Statham Universal Transducing cell (Model UC3). All agonist concentration-effect curves were obtained cumulatively and all experiments were carried out in the presence of indomethacin (1 μg/ml). In experiments with high tone preparations, acetylcholine (ACh, 10 μg/ml) was added to the Krebs solution. This concentration of ACh causes a contraction approximately 80% of the maximum obtainable.

Potency determinations

On zero tone preparations, concentration-effect curves were obtained for contractile responses to $PGF_{2\alpha}$ at 30 min intervals until sensitivity was constant. A further concentration-effect curve was obtained 30 min later for one of the other prostaglandins. All responses were expressed as a percentage of the maximum response to $PGF_{2\alpha}$. On high tone preparations, concentration-effect curves for relaxant responses to PGE_1 were obtained at 30 min intervals and repeated until sensitivity was constant. A further concentration-effect curve for relaxant responses was obtained 30 min later for one of the other prostaglandins. Responses to PGE_1 were expressed as percentage reduction of acetylcholine-induced tone; responses to all other prostaglandins were expressed as a percentage of the maximum response to PGE_1.

Expression of potency

Potencies were expressed as equipotent concentrations, $PGF_{2\alpha} = 1$ for zero tone preparations and $PGE_1 = 1$ for high tone preparations. On zero tone preparations, equipotent concentration was obtained by dividing the EC_{50} for the test prostaglandin by the EC_{50} for $PGF_{2\alpha}$ on each preparation. The maximum response achieved was not the same for all compounds, therefore EC_{50} for each compound was defined as the concentration producing 50% of its own maximum response. On high tone preparations, it was not possible to obtain a clearly defined maximum response with all compounds, furthermore, in some cases, the largest responses obtained were less than 50% of the maximum response to PGE_1. Therefore, equipotent concentrations were obtained by comparing the EC_{30} for each prostaglandin with that for PGE_1, EC_{30} being defined as that concentration required to cause a response equivalent to 30% of the maximum response to PGE_1.

All equipotent concentrations, EC_{50} and EC_{30} values quoted are geometric means with 95% confidence limits in parentheses. The maximum responses quoted are arithmetic means with 95% confidence limits in parentheses.

Drugs and solutions

The composition of the modified Krebs solution (g/l) was as follows: NaCl 6.9, KCl 0.35, K_2HPO_4 0.16, $MgSO_4.7H_2O$ 0.29, glucose 2.0, $NaHCO_3$ 2.1 and $CaCl_2.6H_2O$ 0.28.

The following drugs were used: acetylcholine chloride (BDH), indomethacin (Merck, Sharp and Dohme), (−)-noradrenaline bitartrate (Winthrop), prostaglandins A_1, A_2, B_1, B_2, E_1, E_2, $F_{1\alpha}$, $F_{2\alpha}$ (Cambrian), prostaglandin $F_{2\beta}$ (Wyeth), prostaglandin I_2 (synthesized by Dr A. H. Wadsworth, Glaxo-Group Research) 11-deoxy-15-methyl-15 R,S-prostaglandin E_2 (Wy 17186, Wyeth), prostaglandin Fα acetal (University of Minnesota).

Acetylcholine was dissolved in 0.9% w/v NaCl solution (saline), indomethacin and all prostaglandins with the exception of PGI_2 were dissolved in 1% $NaHCO_3$ in saline. PGI_2 was dissolved in Tris/HCl buffer pH 9.0 on the day of the experiment and dilutions made with Tris/HCl buffer pH 8.0 immediately before use. All prostaglandins were kept on ice.

Results

Zero tone preparations

The results of these experiments are summarized in Table 1. $PGF_{2\alpha}$ (0.03 to 3 μg/ml) and all of the other prostaglandins caused concentration-related contractions of the tracheal strip. PGE_2 was the most potent, being 22 times more potent than $PGF_{2\alpha}$. Prostaglandins E_1, $F_{2\beta}$, I_2, $F_{2\alpha}$ acetal and Wy 17186 were of similar potency to $PGF_{2\alpha}$ and prostaglandins A_1, A_2, B_1, B_2 and $F_{1\alpha}$ were less potent. The order of potency of the different classes of prostaglandins was E > F = I = Wy 17186 > B > A, and, where comparison was possible, 2-series compounds were 5 to 18 times more potent than 1-series compounds.

The maximum responses obtained with prostaglandins $F_{1\alpha}$, I_2, $F_{2\alpha}$ acetal and Wy 17186 were similar to that obtained with $PGF_{2\alpha}$. However, all of the other compounds gave maximum response which were clearly smaller than that to $PGF_{2\alpha}$. In the case of the more potent compounds, prostaglandins E_1 and E_2, the concentration-effect curves were bell-shaped in that increasing the concentration above that giving maximum contraction caused relaxation (see Figure 1). In the cases of prostaglandins A_1, A_2, B_1, B_2 and $F_{2\beta}$, their lower potency and limited solubility meant that concentrations higher than those required for maximum contraction could not be achieved. Hence it could not be determined if their concentration-effect curves were also bell-shaped.

High tone preparations

The results are summarized in Table 2. PGE_1 (0.1 to 30 μg/ml) caused concentration-related relaxations of the tracheal strip contracted by acetylcholine. In 48 experiments, the maximum inhibition of ACh-induced tone caused by PGE_1 was 71.3 ± 2.1%. Prostaglandins A_1, A_2, B_1, B_2, E_2 and $F_{2\beta}$ also relaxed the trachea. The maximum relaxation achieved with PGE_2 was similar to that to PGE_1 but a clearly defined maximum response was not obtained with any of the other prostaglandins in concentrations up to 30 μg/ml. In no case was the response obtained at 30 μg/ml consistently greater than the maximum response to PGE_1. Like PGE_1, PGA_1 caused only relaxation of high tone preparations, but prostaglandins E_2, A_2, B_1 and B_2, at low concentration, caused small contractions of the trachea. Typical results with prostaglandins E_1 and E_2 are shown in Figure 2. The remaining compounds, prostaglandins $F_{1\alpha}$, $F_{2\alpha}$, I_2 and Wy 17186 (up to 30 μg/ml) and $PGF_{2\alpha}$ acetal (up to 3 μg/ml), contracted the trachea, although at 30 μg/ml, Wy 17186 caused small (less than 30% of the PGE_1 maximum) relaxations.

The most potent compound was PGE_1. PGE_2 was about half as potent as PGE_1 and all of the other compounds were 20 or more times less potent than PGE_1. One of these, PGA_1, gave highly variable results (see Table 2). Although there was some variation, overall there was little difference between the potency of 1 and 2-series compounds. The order of potency of the different classes of prostaglandin was $E > F_\beta > B > A >$ Wy 17186 $= F_\alpha = I = 0$.

Discussion

The prostaglandins we have tested fall into two groups. The first, comprising prostaglandins $F_{1\alpha}$, $F_{2\alpha}$, $F_{2\alpha}$ acetal and Wy 17186, contracted both zero tone and high tone preparations. Any relaxant activity that these compounds may have is too weak to manifest itself. The second group of compounds, comprising prostaglandins A_1, A_2, B_1, B_2, E_1, E_2 and $F_{2\beta}$, contracted zero tone preparations and relaxed high tone preparations. This dual action probably accounts for the findings, that on zero tone preparations, these compounds all gave lower maximum contractions than did those of the first group, and that the concentration-effect curves obtained with prostaglandins E_1 and E_2 were bell-shaped. Similarly, the inability of any prostaglandin to cause complete relaxation of high tone preparations could also be a consequence of this dual action. These results demonstrate the importance of the level of tone in determining the response of guinea-pig isolated trachea to prostaglandins and consequently the value of controlling this tone when examining the actions of compounds of this type.

An interesting and unexpected finding was that E-series prostaglandins not only contract zero tone preparations, but are more potent than F_α-series compounds. The spontaneous tone of guinea-pig isolated trachea is caused by endogenous prostaglandin formation (Farmer *et al.*, 1974), and Gryglewski, Dembinska-Kiec, Grodzinska & Panczenko (1976) have reported that guinea-pig isolated trachea synthesizes E-series rather and F_α-series prostaglandins or thromboxanes. This, taken together with our results,

Table 1 Contractile actions of prostaglandins on guinea-pig isolated tracheal strips without tone

Prostaglandin	*EC_{50} μg/ml** (95% c.l.)	*Equipotent concentration* (95% c.l.) [$PGF_{2\alpha}$ = 1]	*Maximum response* (95% c.l.) [$PGF_{2\alpha}$ = 100%]	n
A_1	6.5 (5.0–8.3)	41.1 (32.3–52.3)	42 (25–59)	6
A_2	0.34 (0.14–0.84)	2.6 (1.5–4.7)	45 (33–57)	4
B_1	2.5 (2.0–3.1)	16.3 (10.7–24.9)	33 (28–39)	5
B_2	0.40 (0.20–1.0)	3.2 (1.9–5.4)	42 (32–52)	7
E_1	0.05 (0.03–0.07)	0.57 (0.38–0.85)	28 (19–37)	9
E_2	0.004 (0.002–0.008)	0.05 (0.03–0.08)	42 (33–51)	12
$F_{1\alpha}$	1.1 (0.38–2.9)	17.9 (11.2–28.7)	88 (81–95)	10
$F_{2\alpha}$	0.085 (0.072–0.10)	1	100	85
$F_{2\beta}$	0.13 (0.10–0.17)	1.4 (1.0–1.8)	61 (50–72)	12
I_2	0.33 (0.06–1.72)	1.6 (0.7–3.6)	78 (51–105)	4
$F_{2\alpha}$ acetal	0.18 (0.08–0.41)	1.2 (0.4–3.4)	95 (85–105)	10
Wy 17186	0.31 (0.19–0.52)	1.6 (0.9–2.9)	116 (108–124)	6

* The concentration of each compound giving a response 50% of its own maximum response.

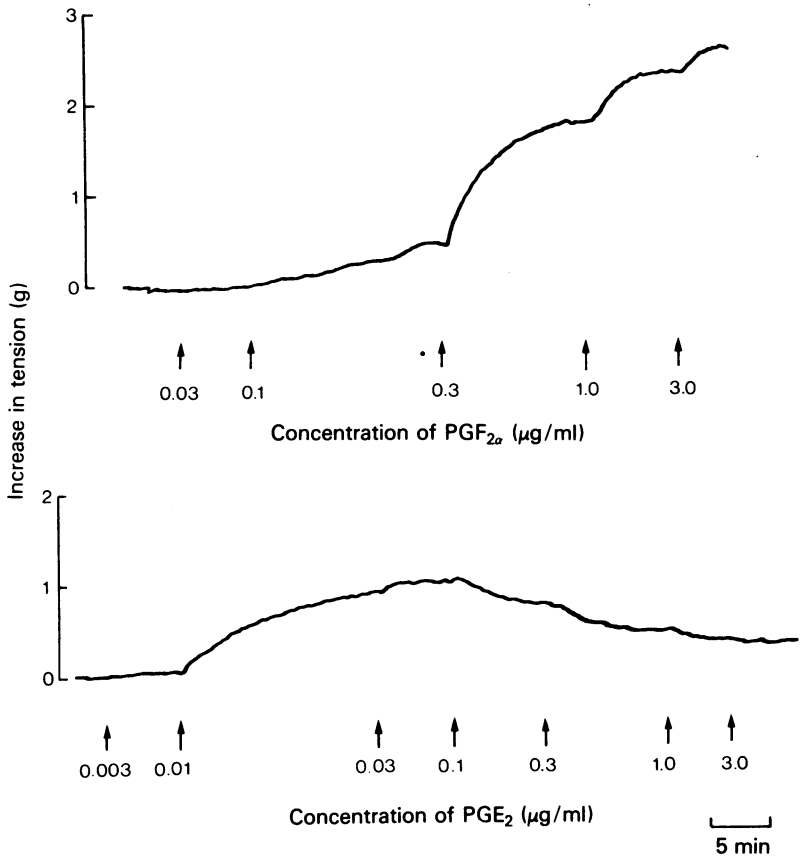

Figure 1 Guinea-pig isolated tracheal strip. Cumulative concentration-effect curves to prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) and PGE_2 on the same preparation in the presence of indomethacin (1 μg/ml). $PGF_{2\alpha}$ causes only contractile responses. PGE_2, at the lower concentrations (0.01 to 0.03 μg/ml), contracts the preparation, and at the higher concentrations (0.1 to 3.0 μg/ml), relaxes it. The maximum contraction obtained with PGE_2 is smaller than that obtained with $PGF_{2\alpha}$.

supports the suggestion of Douglas (1976) that spontaneous tone may be caused by an E-series prostaglandin, probably PGE_2.

We have confirmed the observations of Omini, Moncada & Vane (1977) that PGI_2 contracts guinea-pig isolated trachea, both in the absence and presence of tone. Thus, if PGI_2 has any relaxant activity on the trachea, its potency must be very low relative to the E-series prostaglandins. PGI_2 is only 5 to 10 times less potent than PGE_2 in relaxing isolated vascular strips (Omini *et al.*, 1977) suggesting that the relaxant potencies of prostaglandins on vascular and airway smooth muscle are not necessarily correlated.

Two of the compounds that we have examined, $PGF_{2\alpha}$ acetal and Wy 17186 have been shown to have thromboxane A_2-like platelet aggregating and vasoconstrictor actions (Portoghese, Larson, Abatjoglou, Dunham, Gerrard & White, 1977; MacIntyre, Westwick & Williams, 1978). Thromboxane A_2 has been shown to contract guinea-pig isolated trachea (Svensson, Strandberg, Tuvemo & Hamburg, 1977). It is therefore possible that $PGF_{2\alpha}$ acetal and Wy 17186 contract the trachea by a thromboxane-like mechanism.

Human isolated airway smooth muscle resembles guinea-pig isolated trachea in having spontaneous tone which can be reduced by prostaglandin synthetase inhibitors (Collier & Sweatman, 1968; Dunlop & Smith, 1975). The two tissues also resemble each other in so far as human airway smooth muscle is contracted by $PGF_{2\alpha}$ (Collier & Sweatman, 1968) and PGE_2 has both contractile and relaxant actions (Gar-

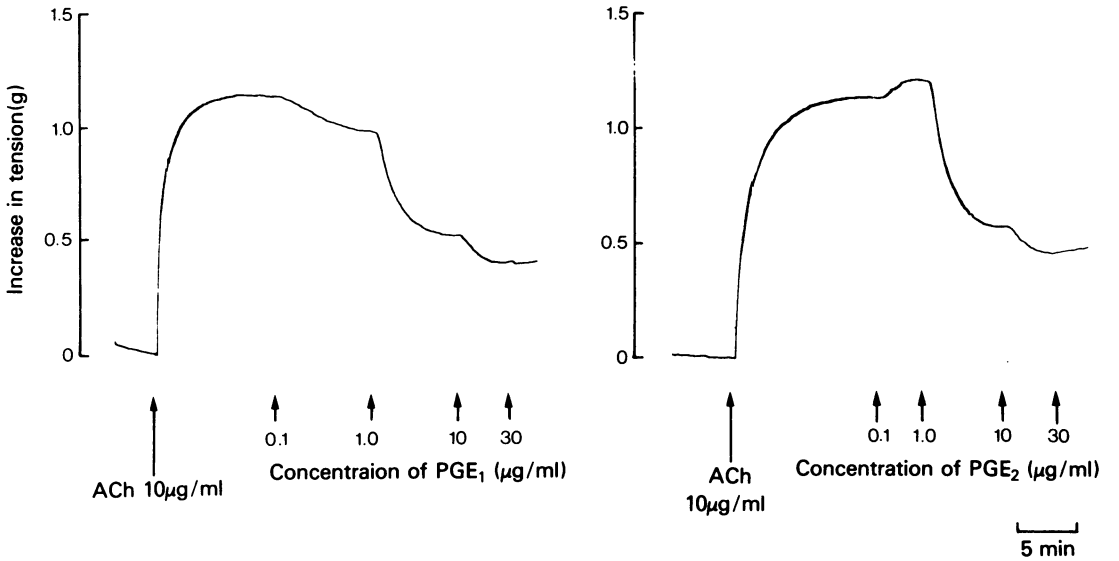

Figure 2 Guinea-pig isolated tracheal strip. Cumulative concentration-effect curves to prostaglandin E_1 (PGE_1) and PGE_2 on the same preparation, in the presence of indomethacin (1 μg/ml) and acetylcholine (ACh, 10 μg/ml). PGE_1 causes only inhibitory responses, whereas PGE_2 contracts the preparation at the lowest concentration (0.1 μg/ml), and relaxes it at higher ones (1.0 to 30 μg/ml). Neither PGE_1 nor PGE_2, even at the highest concentration, completely abolished the ACh-induced tone.

diner, 1975). Furthermore, $PGF_{2\alpha}$ causes bronchoconstriction in humans *in vivo* (Hedqvist, Holmgren & Mathé, 1971; Smith & Cuthbert, 1972) and E-series prostaglandins, although usually considered to be bronchodilators (Cuthbert 1975), have been shown to cause bronchoconstriction in a number of studies in man (Smith, 1974; Mathé & Hedqvist, 1975; Smith, Cuthbert & Dunlop, 1975). Similarly, $PGF_{2\beta}$

Table 2 Relaxant actions of prostaglandins on guinea-pig isolated tracheal strips with tone induced by acetylcholine (10 μg/ml)

Prostaglandin	EC_{30} μg/ml* (95% c.l.)	*Equipotent concentrations* (95% c.l.) [PGE_1 = 1]	n
A_1		Variable†	5
A_2	21.9 (13.5–35.6)	171 (84–350)	5
B_1	10.9 (9.9–11.9)	46.9 (31.4–70.2)	4
B_2	9.0 (3.5–23.2)	42.5 (16.3–111.1)	4
E_1	0.17 (0.15–0.19)	1	45
E_2	0.33 (0.29–0.37)	2.3 (1.9–2.8)	5
$F_{1\alpha}$	NA		5
$F_{2\alpha}$	NA		4
$F_{2\beta}$	8.2 (5.5–12.2)	27.1 (11.8–62.1)	4
I_2	NA		4
$F_{2\alpha}$ acetal	NA		2
Wy 17186	NA		3

* Concentration giving a response 30% of the maximum response to PGE_1 NA = A response 30% of the maximum to PGE_1 was not achieved. † In three experiments, PGA_1 caused small relaxations, less than 30% of the PGE_1 maximum, in concentrations up to 30 μg/ml. In the remaining 2 experiments, PGE_1, 30 μg/ml, gave relaxations 68 and 84% of the maximum response to PGE_1 and was respectively 22 and 29 times less potent than PGE_1.

has been reported to cause both bronchoconstriction (Hamosh & Taviera Da Silva, 1975) and bronchodilatation (Svanborg, Hamberg & Hedqvist, 1973) in man. The bronchoconstriction caused by E-series prostaglandins in man has been attributed to a reflex effect (Cuthbert, 1969) or to the production of a bronchoconstrictor metabolite (Smith, 1973). However, since these compounds have a contractile action on guinea-pig and human airways smooth muscle *in vitro* (Lambley & Smith, 1975; Gardiner, 1975; this study), a direct bronchoconstrictor action seems a more probable explanation. Indeed, the mixed dilator and constrictor actions of E series prostaglandins may be one reason why they have proved to be unsatisfactory bronchodilators. Although some of the prostaglandins we have tested had contractile but no demonstrable relaxant activity, none had only relaxant activity. However, since the contractile and relaxant actions of prostaglandins are presumably mediated through different receptors, there is no reason, in principle, why a selective relaxant prostaglandin is not attainable. Such a compound might prove to be a more satisfactory bronchodilator than the prostaglandins that have been tested to date.

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