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European Journal of Pharmacology 333 (1997) 215–221

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Interaction between prostaglandins and selective phosphodiesterase inhibitors in isolated guinea-pig trachea in vitro

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Received 6 February 1997; revised 2 July 1997; accepted 4 July 1997

Abstract

The possible interaction between spontaneously synthesized relaxant prostaglandins and the relaxation produced by three different isoenzyme-selective phosphodiesterase inhibitors was investigated in the isolated guinea-pig trachea in vitro. The relaxant action of siguazodan (phosphodiesterase III inhibitor), rolipram (phosphodiesterase IV inhibitor) and zaprinast (phosphodiesterase V inhibitor) was investigated in preparations with either spontaneously tone alone or in preparations with spontaneous tone and additionally stimulated with histamine (1 μM). In addition, relaxant effects were assessed in preparations without spontaneous tone (inhibited by indomethacin 2 μM) and precontracted with histamine (1 μM) or prostaglandin $F_{2\alpha}$ (10 μM), either alone or in the presence of a non-relaxant concentration (20 nM) of prostaglandin E_2. All three phosphodiesterase inhibitors preferentially relaxed preparations with spontaneous tone and showed increased relaxant effects in preparations with spontaneous tone and additionally stimulated with histamine compared to preparations contracted by histamine alone. This enhanced relaxing effect observed in the presence of initial spontaneous tone was mimicked by exogenous application of prostaglandin E_2 to indomethacin treated preparations either precontracted by histamine or prostaglandin $F_{2\alpha}$. Furthermore, the study revealed marked differences in the relaxant profiles of siguazodan, rolipram and zaprinast, differences which most likely are related to the functional importance of the phosphodiesterase isoenzymes inhibited by these drugs. It is concluded that endogenously synthesized relaxant prostaglandins and exogenously applied prostaglandin E_2 are capable of enhancing the relaxant action of the phosphodiesterase inhibitors siguazodan, rolipram and zaprinast and that cyclooxygenase inhibition is an important way to avoid this interaction in experimental studies of airway smooth muscle relaxants in isolated guinea-pig trachea in vitro. © 1997 Elsevier Science B.V.

Keywords: Smooth muscle, airway; (Guinea pig); Airway tone, spontaneous; Phosphodiesterase inhibitor; Prostaglandin

1. Introduction

Two of the most important factors regulating airway smooth muscle tone are the intracellular concentrations of cyclic AMP and cyclic GMP (Knox and Tattersfield, 1995). These cyclic nucleotides are degraded by the phosphodiesterase enzyme system which consists of at least seven different isoenzymes (Knox and Tattersfield, 1995), and five of them (phosphodiesterase I–V) have been detected in human (Torphy et al., 1993) and guinea pig (Miyamoto et al., 1994) airway smooth muscle. Selective inhibitors of these isoenzymes (particular inhibitors of phosphodiesterase III, IV and V) have attracted considerable interest as potential antiasthmatic drugs because they possess both bronchodilator and antiinflammatory activity (Nicholson et al., 1991; Banner and Page, 1995; Barnes, 1996). Phosphodiesterase III and IV are responsible for the breakdown of cAMP, whereas phosphodiesterase V accounts for the breakdown of cGMP (Torphy and Livi, 1993).

Guinea pigs are often used for pharmacological studies of antiasthmatic drugs and isolated guinea-pig trachea develop a characteristic spontaneous tone when studied in vitro due to the continuous synthesis and release of prostaglandins (mainly prostaglandin $F_{2\alpha}$) (Raeburn et al., 1987; Lindén et al., 1991). Prostaglandin synthesis is increased by pharmacological and mechanical stimulation (Orehek et al., 1975) and seems to be mediated by the second isoform of cyclooxygenase (Charette et al., 1995). Human airways also develop spontaneous tone when studied in vitro, but this tone is most likely mediated by histamine and leukotrienes (Ito et al., 1989; Ellis and Undem, 1994). In

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addition to contractile mediators, guinea-pig and human airways also generate significant amounts of the relaxant prostaglandin E_2 (Raeburn et al., 1987; Pavord and Tattersfield, 1995), which stimulates adenylate cyclase to cause airway smooth muscle relaxation (Barrett-Bee and Green, 1975; Burka and Saad, 1984). This endogenous production and release of relaxant prostaglandins has been shown to be involved in tachyphylaxis to repeated histamine challenge (Manning et al., 1987; Jackson et al., 1988) and could, at least theoretically, interact with the relaxant action of other airway smooth muscle relaxants when studied under conditions without concomitant cyclooxygenase inhibition.

The aim of the present study was to investigate the possible influence of spontaneously synthesized relaxant prostaglandins on the relaxation induced by three potential antiasthmatic isoenzyme-selective phosphodiesterase inhibitors in isolated guinea-pig trachea in vitro. The relaxant profiles of a selective phosphodiesterase III inhibitor (siguazodan; SKF 94836), a selective phosphodiesterase IV inhibitor (rolipram; ZK 62711) and a selective phosphodiesterase V inhibitor (zaprinast; MB 22948) against spontaneous tone, either alone or in combination with additional stimulation with histamine, were studied. The relaxant effects of these drugs were compared to their effects in preparations treated with a cyclooxygenase inhibitor (indomethacin) and precontracted with histamine or prostaglandin $F_{2\alpha}$, either alone or in the presence of a non-relaxant concentration of prostaglandin E_2.

2. Material and methods

2.1. Tracheal preparation and measurement of contractile force

Hartley–Dunkin guinea pigs (SPF quality) of either sex (240–500 g) were stunned by a blow to the neck and exsanguinated. The thorax was opened, the heart was removed and the complete trachea and lungs were transferred to cold (4°C) oxygenated Krebs solution. The trachea was trimmed of fat and connective tissue under a dissection microscope. The middle part of the trachea was cut into six tubular segments comprising two cartilage rings (approximate length 2 mm) and each preparation was transferred to an organ bath (5 ml) containing Krebs solution (37°C; pH 7.4) continuously gassed with a mixture of oxygen (95%) and carbon dioxide (5%). Each preparation was mounted in precision myographs for measurement of isometric force (Nielsen-Kudsk et al., 1986). In one set of experiments preparations were allowed to develop spontaneous tone and after equilibration for 40 min maximal relaxation was produced by addition of theophylline (1 mM). This allowed determination of baseline and adjustment of the passive load to a mean level about 0.6 g (range: 0.5–0.8 g), which had previously been determined from the broad plateau of load–tension diagrams to be optimal for development of active force either spontaneously or in response to the agonists subsequently used (unpublished data). Preparations were then repeatedly washed with Krebs solution to re-establish tone and equilibrated for a further 60 min before start of the experiments. This procedure was found adequate to avoid accumulation of theophylline, which could interact with other airway smooth muscle relaxants. In another set of experiments the cyclooxygenase inhibitor indomethacin (2 μM) was added and was present during the equilibration period of 100 min and throughout the experiments in order to prevent the development of spontaneous tone. Passive load was adjusted if necessary (range: 0.5–0.8 g). During equilibration the Krebs solution was changed frequently before the start of the experiments. Only preparations displaying adequate active tension, either spontaneously or in response to contractile agonists, were included in the experiments. Six experiments were run in parallel and amplified transducer signals were recorded on a six-channel recorder (Graphtec WR3101, Japan).

2.2. Experiments

2.2.1. Preparations with spontaneous tone

The relaxant effect produced by siguazodan (1 nM–10 μM), rolipram (1 nM–0.3 μM) and zaprinast (0.1 μM–1 mM) was either studied in preparations with spontaneous tone or in preparations with spontaneous tone and additionally stimulated with histamine (1 μM). Drugs were added cumulatively and allowed to equilibrate (approximately 10 min) in order to obtain a stable contraction level before the drug concentration was increased. Time-matched control preparations were run in parallel to detect any decline in tone.

2.2.2. Preparations without spontaneous tone

The relaxant effect produced by siguazodan (1 nM–10 μM), rolipram (1 nM–0.3 μM) and zaprinast (0.1 μM–1 mM) was investigated in preparations submaximally precontracted with either histamine (1 μM) or prostaglandin $F_{2\alpha}$ (10 μM). Phosphodiesterase inhibitors were studied either in the absence or in the presence of a non-relaxant concentration of prostaglandin E_2 (20 nM). Prostaglandin E_2 was added when contractions had stabilized and was allowed to equilibrate (15 min) before the start of experiments. Phosphodiesterase inhibitors were added as described above.

2.3. Data analysis and statistics

All data are expressed as means ± S.E.M. Relaxant effects were calculated as percentage reduction in tone relative to the contraction prior to addition of relaxant drug. A return of tone to baseline was taken as 100% relaxation. Concentration–effect curves were made and

pharmacodynamic parameters were derived by fitting the Hill equation ($E = E_{max}/(1 + 10^{((\log EC50 - \log C) \times S)})$) to mean data, using iterative, non-linear regression analysis. GraphPad Prism® version 2.01 (GraphPad Software, USA) was used for the computer-fitting procedure. E_{max} is the theoretically maximal relaxant effect, EC_{50} the concentration (C) at which $E = (1/2)E_{max}$ and S the Hill coefficient related to the slope of the concentration–effect curve (Barlow and Blake, 1989). The negative logarithm of EC_{50} is termed pEC_{50} (Jenkinson et al., 1995). Statistical comparisons were made by using either two-tailed *t*-test for unpaired data or one-way analysis of variance (ANOVA) with Bonferroni multiple comparison test, both with a significance level of 5%.

2.4. Drugs and solutions

The drugs used were: histamine dihydrochloride, prostaglandin E_2, indomethacin, zaprinast (Sigma, UK), prostaglandin $F_{2\alpha}$ (dinoprost; Upjohn, Belgium), siguazodan (SKF 94836; gift from SmithKline Beecham Pharmaceuticals, UK) and rolipram (ZK 62711; gift from Schering AG, Germany).

Histamine (10 mM), prostaglandin $F_{2\alpha}$ (1 mM) and prostaglandin E_2 (10 mM) were dissolved in distilled water. Indomethacin (8.38 mM) was dissolved in 5% $NaHCO_3$. Zaprinast (10 mM) was dissolved in 0.1 M NaOH. Siguazodan (4 mM) was dissolved in 92% dimethylsulfoxide (DMSO). Rolipram (1 mM) was dissolved in 50% ethanol. The maximal bath concentration of DMSO in experiments involving siguazodan was 0.23% and the maximal bath concentration of ethanol in experiments involving rolipram was 0.15‰. All stock solutions were kept at −70°C until use and then further diluted in saline (0.9%).

The composition of the Krebs solution (in mM) was: NaCl 118.0, KCl 4.6, $CaCl_2$ 2.5, $MgSO_4$ 1.15, $NaHCO_3$ 24.9, KH_2PO_4 1.15 and glucose 5.5.

3. Results

3.1. Contractile responses and effect of prostaglandin E_2 pretreatment

All preparations not treated with indomethacin developed spontaneous tone (2.38 ± 0.11 g, $n = 21$, with reference to the theophylline-induced relaxation) which was stable throughout the duration of the experiments. Stimulation of these preparations with histamine (1 μM) only produced a slight, non-significant further increase in tone (2.45 ± 0.12, $n = 21$). Indomethacin (2 μM) totally prevented the development of spontaneous tone. In indomethacin-treated preparations histamine (1 μM) and prostaglandin $F_{2\alpha}$ (10 μM) both produced tonic contractions (histamine: 1.99 ± 0.15 g, $n = 17$ and prostaglandin $F_{2\alpha}$: 2.76 ± 0.13 g, $n = 14$) which were stable throughout the experimental period. Prostaglandin $F_{2\alpha}$-induced contractions were significantly greater than those induced by histamine ($P < 0.01$).

Pretreatment with prostaglandin E_2 (20 nM) resulted in a slight increase in histamine-induced tone, whereas prostaglandin $F_{2\alpha}$-induced tone was slightly decreased (histamine + prostaglandin E_2: 2.22 ± 0.15 g, $n = 14$ and prostaglandin $F_{2\alpha}$ + prostaglandin E_2: 2.35 ± 0.14 g, $n = 13$). Both these alterations were non-significant.

Control experiments involving cumulative addition of either DMSO or ethanol resulted in minor, non-significant relaxant effects only at the highest vehicle concentrations used. These effects were not modified by pretreatment with prostaglandin E_2 (20 nM) (data not shown).

3.2. Effects of phosphodiesterase inhibitors in preparations with spontaneous tone

Both siguazodan and zaprinast produced dose-dependent and complete relaxation of tracheal preparations with spontaneous tone. Rolipram, in the concentration range 1 nM–0.3 μM, produced a monophasic, dose-dependent relaxation which at the highest concentration was $63.2 \pm 13.0\%$ ($n = 8$).

The potency of all three phosphodiesterase inhibitors and the E_{max} value for rolipram were significantly higher against spontaneous tone than against spontaneous tone combined with additional histamine stimulation (cf., Fig. 1A and Table 1). In the later preparations siguazodan produced a dose-dependent relaxation which plateaued at about 96% whereas E_{max} for rolipram was only $32.0 \pm 2.5\%$ ($n = 6$). Zaprinast produced dose-dependent and complete relaxation of preparations with spontaneous tone and additionally stimulated with histamine.

Computer-derived pharmacodynamic parameters are given in Table 1 and concentration–effect curves are shown in Fig. 1.

3.3. Effects of phosphodiesterase inhibitors in preparations without spontaneous tone

3.3.1. Histamine-induced tone

Compared to the relaxant effect in preparations with spontaneous tone and additionally stimulated with histamine, siguazodan displayed a significantly reduced maximal relaxant effect and a significantly less steep concentration–effect curve in preparations contracted by histamine. As a result, both the relaxant effect in response to low concentrations (1 nM–0.1 μM) and the pEC_{50} for siguazodan in histamine-contracted preparations were increased (cf., Fig. 1B and Table 1). The relaxant effect of rolipram was reduced in histamine-contracted preparations compared to its effects in preparations with spontaneous tone and additionally stimulated with histamine; however, derived pharmacodynamic parameters were not significantly

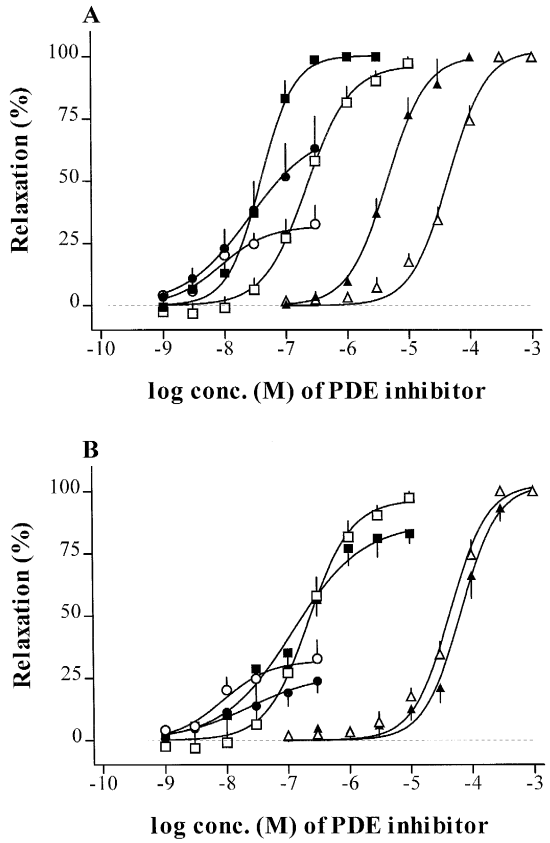

Fig. 1. Concentration–effect data and corresponding curves obtained by computer fitting for the relaxant action of siguazodan (■, □), rolipram (●, ○) and zaprinast (▲, △) in isolated guinea-pig trachea. (A) relaxant effects against spontaneous tone (filled symbols) compared to effects in preparations with spontaneous tone and additionally stimulated with histamine (1 μM) (open symbols). (B) relaxant effects against preparations with spontaneous tone and additionally stimulated with histamine (1 μM) (open symbols) compared to preparations without spontaneous tone (due to indomethacin (2 μM) pretreatment) contracted by histamine (1 μM) (filled symbols). Error bars represent S.E.M.

different (cf., Table 1). Zaprinast produced dose-dependent and complete relaxation of histamine-contracted preparations and the concentration–effect curve was slightly, but significantly, displaced to the right (1.5×) compared to the concentration–effect curve for preparations with spontaneous tone and additionally stimulated with histamine (cf., Table 1 and Fig. 1B).

Pretreatment of histamine contracted preparations with prostaglandin E_2 resulted in a significantly steeper concentration–effect curve and a significant elevation of E_{max} for the relaxant action of siguazodan without a change in its potency. Prostaglandin E_2 pretreatment also significantly increased the maximal relaxant action of rolipram, but did not affect the potency or the steepness of the concentration–effect curve for this drug. The concentration–effect curve for zaprinast was significantly displaced to the left (2.3×) without there being significant alterations in E_{max} and S values following pretreatment with prostaglandin E_2.

Concentration–effect curves are shown in Fig. 2 and derived pharmacodynamic parameters given in Table 1.

3.3.2. Prostaglandin $F_{2\alpha}$-induced tone

In preparations precontracted with prostaglandin $F_{2\alpha}$ siguazodan produced dose-dependent relaxation with a maximum at about 84% (cf., Table 1). The relaxant effect of rolipram was very limited to only 8.2 ± 1.3% ($n = 4$) in response to 0.3 μM, whereas zaprinast produced dose-dependent and complete relaxation.

Table 1
Pharmacodynamic parameters (pEC_{50} ($= -\log(EC_{50})$), E_{max} and S) and S.E.M. obtained by iterative, non-linear regression analysis of mean concentration effect data for the relaxant action of siguazodan, rolipram and zaprinast in isolated guinea-pig trachea

	pEC_{50}	E_{max}	S	n
Spontaneous tone				
Siguazodan	7.41 ± 0.03 [a]	100.6 ± 1.1	1.59 ± 0.15	6
Rolipram	7.59 ± 0.08 [a]	70.8 ± 3.5 [a]	0.81 ± 0.07	8
Zaprinast	5.35 ± 0.03 [a]	100.6 ± 1.8	1.35 ± 0.12	7
Spontaneous tone + histamine				
Siguazodan	6.65 ± 0.04 [b]	96.6 ± 2.0 [b]	1.23 ± 0.11 [b]	6
Rolipram	8.06 ± 0.13	32.0 ± 2.5	1.11 ± 0.28	6
Zaprinast	4.35 ± 0.06 [b]	102.7 ± 2.5	1.41 ± 0.21	9
Histamine				
Siguazodan	6.92 ± 0.09	87.0 ± 3.2	0.76 ± 0.10	6
Rolipram	7.64 ± 0.27	26.5 ± 4.5	0.75 ± 0.21	5
Zaprinast	4.18 ± 0.05	102.5 ± 2.5	1.43 ± 0.19	6
Histamine + prostaglandin E_2				
Siguazodan	6.97 ± 0.02	100.8 ± 0.8 [c]	1.10 ± 0.05 [c]	4
Rolipram	8.22 ± 0.04	44.0 ± 1.2 [c]	1.21 ± 0.12	4
Zaprinast	4.54 ± 0.04 [c]	102.1 ± 1.7	1.34 ± 0.15	6
Prostaglandin $F_{2\alpha}$				
Siguazodan	6.88 ± 0.08	83.9 ± 4.2	1.20 ± 0.22	5
Rolipram	7.21 ± 0.39	9.1 ± 3.6	1.39 ± 1.08	4
Zaprinast	4.69 ± 0.04	102.7 ± 2.0	1.48 ± 0.17	5
Prostaglandin $F_{2\alpha}$ + prostaglandin E_2				
Siguazodan	6.80 ± 0.04	96.5 ± 1.5 [d]	1.17 ± 0.10	4
Rolipram	8.04 ± 0.09	34.1 ± 1.9 [d]	0.89 ± 0.13	5
Zaprinast	4.69 ± 0.03	102.4 ± 1.6	1.54 ± 0.13	4

The relaxant effects were studied in preparations with spontaneous tone, either alone or additionally stimulated with histamine (1 μM), or in preparations without spontaneous tone (in the presence of indomethacin (2 μM)) precontracted with either histamine (1 μM) or prostaglandin $F_{2\alpha}$ (10 μM). The influence of pretreatment with a non-relaxant concentration (20 nM) of prostaglandin E_2 was also studied in preparations precontracted with either histamine (1 μM) or prostaglandin $F_{2\alpha}$ (10 μM).

[a] $P < 0.05$ compared to preparations with spontaneous tone additionally stimulated with histamine (1 μM).

[b] $P < 0.05$ compared to preparations without spontaneous tone precontracted with histamine (1 μM).

[c] $P < 0.05$ compared to preparations precontracted with histamine (1 μM) without prostaglandin E_2 pretreatment.

[d] $P < 0.05$ compared to preparations precontracted by prostaglandin $F_{2\alpha}$ (10 μM) without prostaglandin E_2 pretreatment.

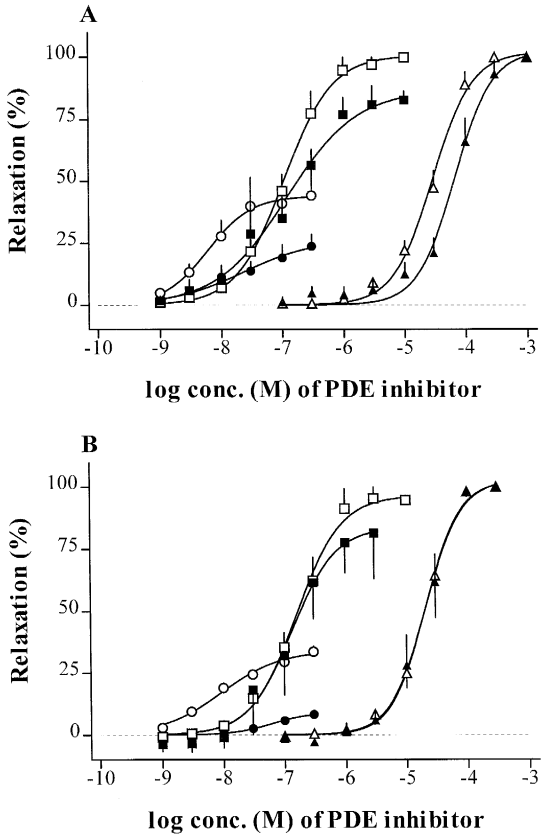

Fig. 2. Concentration–effect data and corresponding curves obtained by computer fitting for the relaxant action of siguazodan (■, □), rolipram (●, ○) and zaprinast (▲, △) in isolated guinea-pig trachea treated with indomethacin (2 μM). (A) Relaxant effects against histamine-induced tone either in the absence (filled symbols) or in the presence (open symbols) of prostaglandin E_2 (20 nM). (B) Relaxant effects against prostaglandin $F_{2\alpha}$-induced tone either in the absence (filled symbols) or in the presence (open symbols) of prostaglandin E_2 (20 nM). Error bars represent S.E.M.

Pretreatment with prostaglandin E_2 resulted in a significant increase of the maximal relaxant effect of both siguazodan and rolipram without there being any significant alterations in other pharmacodynamic parameters for these drugs (cf., Table 1). In contrast to the observed effects in histamine contracted preparations (see above) the relaxant action of zaprinast was unaltered by the pretreatment with prostaglandin E_2 of preparations contracted with prostaglandin $F_{2\alpha}$.

Computer-derived pharmacodynamic parameters are given in Table 1 and the corresponding concentration–effect curves shown in Fig. 2.

4. Discussion

To our knowledge, this is the first study investigating the pharmacodynamic interaction between endogenous relaxant prostaglandins and the relaxant action of isoenzyme-selective phosphodiesterase inhibitors in guinea-pig trachea. In isolated human large bronchi contracted by carbachol, the cyclooxygenase inhibitor meclofenamic acid has been reported to be without effect against rolipram- and siguazodan-induced relaxations (Torphy et al., 1993). However, the present study clearly revealed an influence of endogenous relaxant prostaglandins by demonstrating, for all three phosphodiesterase inhibitors, a preferential relaxant action against spontaneous tone and a difference between their relaxant actions in preparations contracted by histamine and in preparations with spontaneous tone and additionally stimulated with histamine (cf., Table 1 and Fig. 1). The manner in which prostaglandin E_2 augmented phosphodiesterase inhibitor induced relaxation in histamine-contracted preparations further confirms these findings (compare Fig. 1B and Fig. 2A). The greater augmentation seen with prostaglandin E_2 pretreatment compared to spontaneous tone and additional stimulation with histamine presumably indicates that the concentrations of prostaglandin E_2 at the receptor site is lower when caused by endogenous prostaglandins synthesized in situ than when caused by a bath concentration of 20 nM. The prostaglandin E_2 concentration at the receptor has not been determined, but in human airway epithelial lining fluid it is around 50 nM (Pavord and Tattersfield, 1995) and in vitro bath concentrations measured under basal conditions in guinea-pig trachea are sub-nanomolar (Raeburn et al., 1987; Hay et al., 1988). Both these concentrations are most likely underestimates of the real concentration at the receptor.

Furthermore, the present study showed marked differences in the relaxant profiles of siguazodan, rolipram and zaprinast in isolated guinea-pig trachea, and this most likely relates to the functional importance of the different phosphodiesterase isoenzymes in regulating guinea-pig airway tone. Although the rank order of potency, measured by pEC_{50} value, (rolipram > siguazodan > zaprinast) was independent of whether tracheal tone was spontaneous or induced by histamine or prostaglandin $F_{2\alpha}$, the maximal relaxant effects (E_{max}) were clearly different. Zaprinast produced complete relaxation independent of the contractile stimulus, whereas siguazodan and rolipram were less effective against histamine- and in particular prostaglandin $F_{2\alpha}$-induced tone. However, the most striking difference was seen between the maximal relaxant action of siguazodan and rolipram in all preparations studied (cf., Table 1). Rolipram has been reported to show a biphasic concentration–effect curve in guinea pig (Harris et al., 1989; Cortijo et al., 1993; Planquois et al., 1996) and human (De Boer et al., 1992; Turner et al., 1994) airways. This was confirmed in preliminary experiments (data not shown), but we studied only the first phase (1 nM–0.3 μM) in our experiments, since the second phase (> 1 μM) is most probably due to non-selective phosphodiesterase inhibition or another non-specific action (De Boer et al., 1992; Cortijo et al., 1993; Turner et al., 1994). Both phosphodiesterase III (inhibited by siguazodan) and phosphodiesterase IV (in-

hibited by rolipram) are responsible for the degradation of cAMP, and the discrepancy in the relaxant profiles of siguazodan and rolipram can presumably be explained by differences in K_m values of these isoenzymes for cAMP (Torphy and Livi, 1993). Phosphodiesterase III has a 15-times lower K_m for cAMP than phosphodiesterase IV (Torphy and Livi, 1993) and it has been suggested that phosphodiesterase III is associated with the basal turnover of cAMP, whereas phosphodiesterase IV is linked to cAMP accumulation in response to exogenous stimuli (Tomkinson et al., 1993; Turner et al., 1994; Planquois et al., 1996). This theory is supported by our results showing: (1) a difference in maximal relaxant effect between rolipram and siguazodan, (2) a greater E_{max} for rolipram in preparations with spontaneous tone compared to agonist precontracted preparations and (3) a marked enhancement of rolipram-induced relaxation by prostaglandin E_2 pretreatment in histamine- and prostaglandin $F_{2\alpha}$-contracted preparations.

Although zaprinast is a selective inhibitor of cGMP breakdown through phosphodiesterase V, both spontaneously in situ synthesized prostaglandins and exogenously applied prostaglandin E_2 were able to potentiate the zaprinast-induced relaxation in preparations contracted by histamine. This could be explained by increased cGMP levels inhibiting phosphodiesterase III (Torphy and Livi, 1993), and thereby suppressing the breakdown of cAMP produced in response to prostaglandins, as shown for the interaction between sodium nitroprusside and rolipram in guinea-pig trachea (Turner et al., 1994). The lack of prostaglandin E_2-induced potentiation of the effects of zaprinast in prostaglandin $F_{2\alpha}$-contracted preparations is not in accordance with this theory. However, this could be explained by an interaction between prostaglandin E_2 and $F_{2\alpha}$ at different prostaglandin receptors affecting basal cGMP levels.

In conclusion, the present study showed marked differences in the relaxant profiles of the potential antiasthmatic drugs siguazodan, rolipram and zaprinast in isolated guinea-pig trachea, differences which presumably reflect the functional importance of the phosphodiesterase isoenzymes selectively inhibited by these drugs. Moreover, the study revealed that endogenously synthesized relaxant prostaglandins and exogenously applied prostaglandin E_2 are capable of enhancing the relaxant action of siguazodan, rolipram and zaprinast. This stresses the methodological importance of cyclooxygenase inhibition when investigating the pharmacodynamic action of airway smooth muscle relaxants on response to exogenously applied contractile agonists in isolated guinea-pig trachea. Furthermore, endogenous prostaglandin E_2 has been hypothesized to protect against bronchoconstriction and airway inflammation (Pavord and Tattersfield, 1995). The possible clinical importance of an interaction with isoenzyme-selective phosphodiesterase inhibitors with regard to these effects needs further study.

Acknowledgements

This study was supported by a grant from the foundation of the Danish National Association against Lung Diseases. The skilful laboratory work carried out by laboratory technician Henriette Gram Johanson is greatly appreciated.

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