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Prostaglandin E_1 enhances the histamine induced stimulation of the mucociliary activity in the rabbit maxillary sinus

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Prostaglandin E_1 enhances the histamine induced stimulation of the mucociliary activity in the rabbit maxillary sinus. J. Dolata.
ABSTRACT: Inflammatory mediators are released in the airways during both inflammatory and allergic reactions, and many of these mediators affect mucociliary activity. To discover whether mucociliary activity is changed by a combination of mediators, the interaction between prostaglandins and histamine or methacholine was studied *in vivo* in the rabbit maxillary sinus. We used a photoelectric technique and recorded frequency changes induced by tested substances. Prostaglandins E_1 and $F_{2\alpha}$ (PGE_1 and $PGF_{2\alpha}$) were given as *ia.* infusions followed by bolus injections of histamine or methacholine. Infusion with PGE_1 (0.1 $\mu g \cdot kg^{-1}$) enhanced the stimulating effect of a subsequent injection of histamine (10 $\mu g \cdot kg^{-1}$), maximum stimulation being 33±6% compared to 14±4% after histamine alone (p=0.02). When the histamine injection was given 20 min after PGE_1 no enhancement was observed. PGE_1 did not enhance the stimulating effect of methacholine. In contrast to PGE_1, $PGF_{2\alpha}$ failed to enhance the effect of histamine. It is proposed that a role of PGE_1 is to modify the mucociliary response to other mediators released during inflammatory and allergic reactions.
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One of the primary functions of the mucociliary system is to defend the organism from noxious and toxic stimuli reaching the airways during respiration. The mucociliary system may respond with changes in the ciliary activity, in the quantity and physical properties of mucus and periciliary fluid, or a combination thereof [1].

Previous experiments have revealed several inflammatory mediators that stimulate mucociliary activity [2–5]. Prostaglandins, a group of substances belonging to these mediators, are membrane derived and synthesized from polyunsaturated fatty acids by the enzyme cyclooxygenase. Prostaglandins of the E-series and $F_{2\alpha}$ occur in and can be synthesized by the mucosa of the upper respiratory tract. *In vivo* experiments have proved histamine to be more potent than prostaglandins of the E-series (PGE_1 and PGE_2) and prostaglandins $F_{2\alpha}$ ($PGF_{2\alpha}$) in stimulating mucociliary activity whereas *in vitro* experiments using tracheal explants have shown the opposite potency [2].

Inflammatory and allergic reactions are frequent in both the upper and lower airways and during these reactions different inflammatory mediators are likely to be released simultaneously, *eg.* histamine, prostaglandins and leukotrienes [6–9]. The release of histamine and prostaglandins is linked in an intricate manner as shown in experiments using lung tissue and human eosinophils [10–12]. Conceivably these mediators may interact in the modulation of the mucociliary activity during physiological and pathophysiological conditions in the airways. There are also reports concerning the interaction between other inflammatory mediators *in vitro* and the resulting effect on ciliary activity, for example the leukotriene D_4-induced stimulation of ciliary activity which depends on activation of the enzyme involved in prostaglandin synthesis, cyclooxygenase, and possibly also on the generation of prostaglandins [3]. In the lower airways administration of prostaglandin D_2 (PGD_2) to asthmatic subjects enhances the bronchoconstrictor effect of both histamine and the cholinergic agonist methacholine [13].

For a better understanding of the pathophysiology of inflammatory and allergic diseases in the airways more knowledge is needed not only of the effect of the individual mediators on the mucociliary defence system, and especially the mucociliary activity, but also whether this effect can be modified by interactions between different mediators.

The aim of the present investigation was therefore to study: 1) if prostaglandins with known cilioexcitatory effect influence histamine-stimulated mucociliary activity, 2) if a prostaglandin with known cilioexcitatory effect influences methacholine-stimulated mucociliary activity.

Method

The animal care followed the rules issued by the Swedish National Board of Agriculture and was approved by the Board's animal research ethical committee.

The experiments were performed on rabbits of both sexes weighing 2.1–3.0 kg. For details of anaesthetic and surgical techniques see HYBBINETTE and MERCKE [14]. The animals were anaesthetized with urethane, a substance known not to influence the mucociliary activity. The test substances were given *ia.* as bolus injections of 0.2 ml *via* a retrograde cannula in the feeding artery of the maxillary sinus. ECG and rectal temperature were monitored and body temperature was maintained at 37–38.5°C by a heating pad.

The mucosa in the maxillary sinus was exposed through a trepanation hole which in turn was covered with an antimist window. A light beam was aimed at the mucous membrane and the mucociliary activity, (*ie.* the mucociliary wave frequency) visible as flickering in the light reflection was picked up with a photoelectric technique and recorded on an ink writer. The recordings were analysed by a computerized frequency calculator, the mucociliary wave frequency being expressed as waves per min and calculated every 10 s during challenges and at intervals of 1 min otherwise. The induced frequency changes were expressed as percentages of the mucociliary wave frequency (frequency zero level) at the time of administration of the tested substances. The maximum mucociliary wave frequency change during the first 5 min after a challenge was calculated, and this time interval was also used when calculating the area under the curve.

The following drugs were used: prostaglandin E_1 (Prostivas®, Upjohn, USA), prostaglandin $F_{2\alpha}$ (Amoglandin®, Kabi Vitrum, Sweden), histamine dihydrochloride (Sigma, USA), methacholine chloride (Tokyo Kasei Kogyo Comp. Ltd, Japan). Prostivas® is a 0.5 mg·ml^{-1} ethanol solution of PGE_1; immediately before each experiment a small volume of the stock solution was diluted in saline to the appropriate concentration. Amoglandin® is a 5 mg·ml^{-1} aqueous solution of $PGF_{2\alpha}$; further dilutions were made in saline. Siliconized glassware and polypropylene tubes were used to prevent adsorption of the prostaglandins to glass and plastic surfaces. Methacholine and histamine were diluted in physiological saline to the appropriate concentrations. The doses are expressed as concentrations of each respective salt.

Experimental procedure

1) In 6 rabbits an infusion of PGE_1 was immediately (within 5 s) followed by a 0.2 ml bolus injection of histamine at a dose of 10 µg·kg^{-1}. The dose of PGE_1 was 0.1 µg·kg^{-1}, given as an *ia.* infusion of 2 ml during 5 min.

2) In 6 rabbits an infusion of PGE_1 was followed by a 0.2 ml bolus injection of histamine at a dose of 10 µg·kg^{-1} given about 20 min (15–22 min) after the end of the PGE_1 infusion. The dose of PGE_1 was 0.1 µg·kg^{-1}, given as *ia.* infusion of 2 ml during 5 min.

3) In 6 rabbits an infusion of $PGF_{2\alpha}$ was immediately followed by a 0.2 ml bolus injection of histamine at a dose of 10 µg·kg^{-1}. The dose of $PGF_{2\alpha}$ was 1.0 µg·kg^{-1}, given as an *ia.* infusion of 2 ml during 5 min.

4) In 6 rabbits an infusion of PGE_1 was immediately followed by a 0.2 ml bolus injection of methacholine at a dose of 0.5 µg·kg^{-1}. The dose of PGE_1 was 0.1 µg·kg^{-1}, given as *ia.* infusion of 2 ml during 5 minutes.

Control experiments with methacholine alone were run prior to the infusion of PGE_1 in the 6 rabbits that were challenged with methacholine after PGE_1 infusion. This could be done since the stimulating effect of methacholine on the mucociliary activity does not show tachyphylaxis [15]. The control experiments with histamine had to be run in 6 other rabbits since there is tachyphylaxis in the response to histamine [5]. The ethanol concentration in the infusion experiments with PGE_1 was negligible (<0.05%). The doses of the respective prostaglandin were chosen so that the basal mucociliary activity would not be significantly affected. The doses of methacholine and histamine were selected from previously obtained dose-response curves in order to produce about half of the maximum possible stimulation for the two respective agonists [5, 15].

The results are expressed as mean and standard errors of the mean (SEM). Peak responses and areas under the curves were statistically evaluated using Student's t-test for paired or unpaired data respectively. P-values smaller than 0.05 were considered significant.

Table 1. – The mucociliary activity (waves·min^{-1}) in the four different experimental groups (mean±SEM) at the start of the prostaglandin infusion and immediately before challenges with histamine or methacholine.

	Before infusion	Before challenge	p
group 1 PGE_1-histamine	1313±52	1292±45	>0.5
group 2 PGE_1-histamine (20 min later)	1319±66	1260±69	>0.5
group 3 $PGF_{2\alpha}$-histamine	1345±97	1301±66	0.31
group 4 PGE_1-methacholine	1198±21	1258±25	0.16

PGE_1: prostaglandin E_1; $PGF_{2\alpha}$: prostaglandin $F_{2\alpha}$

Results

The spontaneous variation in mucociliary activity in nonstimulated rabbits prior to challenges was 6±1%, n=16.

Infusion with PGE_1 or $PGF_{2\alpha}$ in the doses applied did not change the mucociliary activity in the intervals before or at the time of the challenge with histamine or methacholine (table 1). Nor did the mucociliary activity

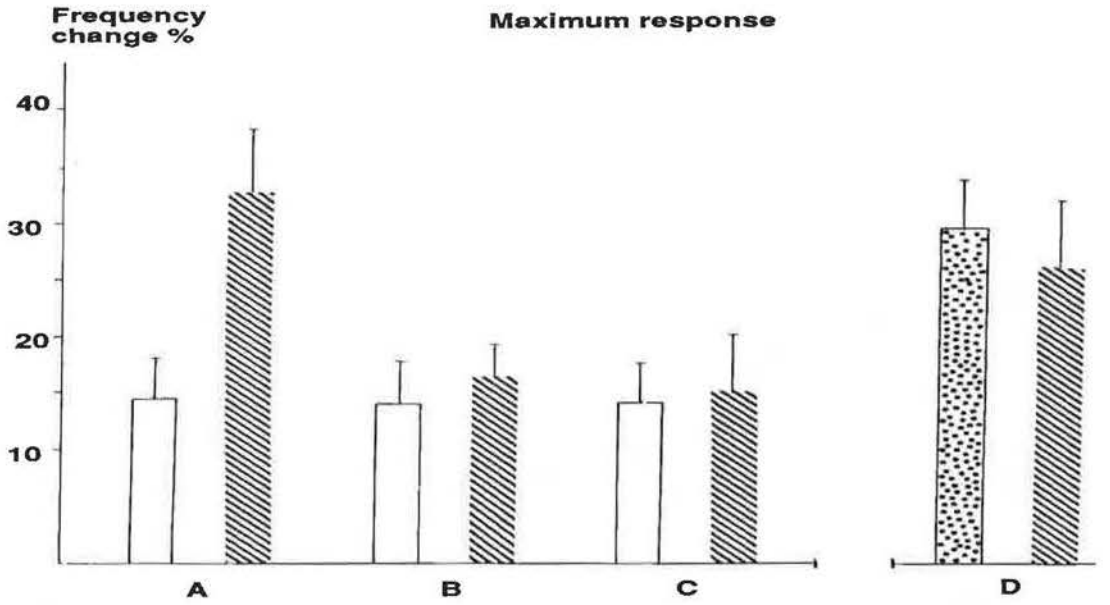

Fig. 1. – The maximum mucociliary response to challenges with histamine (10 μg·kg^{-1}) or methacholine (0.5 μg·kg^{-1}) following infusions of prostaglandins in four experiment series. The results are expressed as mean±SEM, n=6 in each experiment group. Hatched bars refer to challenges after prostaglandin infusion, open bars refer to control experiments with histamine, the dotted bar refers to control experiments with methacholine. A: histamine given immediately after infusion of PGE_1 (0.1 μg·kg^{-1}); B: histamine given about 20 min after infusion of PGE_1 (0.1 μg·kg^{-1}); C: histamine given immediately after infusion of $PGF_{2\alpha}$ (1.0 μg·kg^{-1}); D: methacholine given immediately after infusion of PGE_1 (0.1 μg·kg^{-1}).

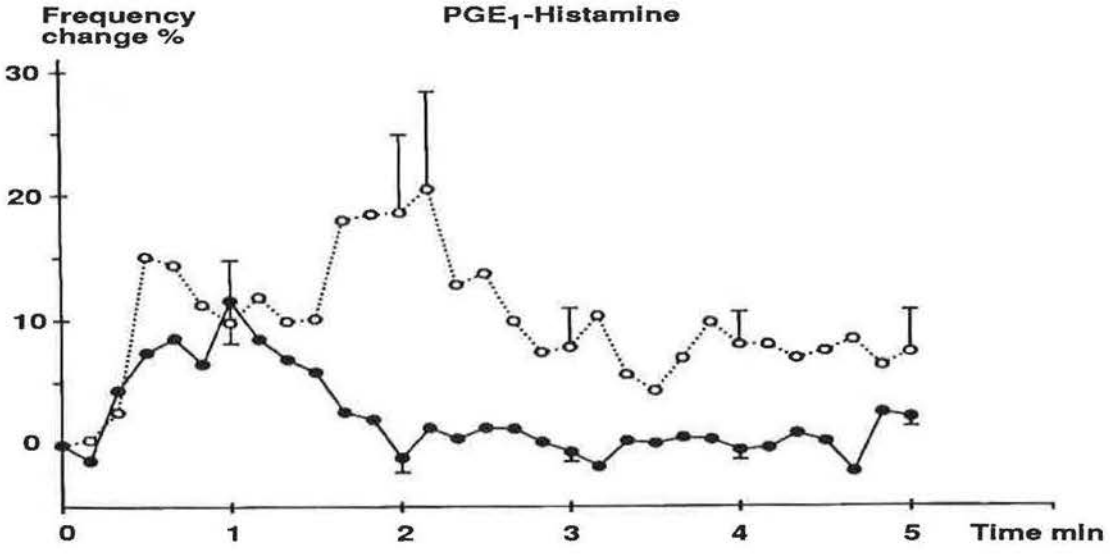

Fig. 2. – The time-course curve for the effect of histamine in the dose 10 μg·kg^{-1} given immediately after infusion of PGE_1 (○····○). The control experiments with histamine alone were run in 6 other rabbits (●——●). The results are expressed as means±SEM. Frequency zero level was 1292±45 waves·min^{-1} in the infusion experiments and 1213±65 waves·min^{-1} in the control experiments (p=0.34).

before the histamine and methacholine challenges differ from mucociliary activity prior to the control experiments with these substances.

When histamine was injected immediately after the infusion of PGE_1 its stimulating effect on the mucociliary activity was enhanced. The maximum response was 33±6% after the PGE_1 infusion compared to 14±4% in the control experiments (p=0.02) (fig. 1 A). This enhancement was also evident when the areas under the curves were compared (p=0.02). Analysis of the time-course for the histamine induced stimulation after the PGE_1 infusion showed that the maximum stimulation was delayed and the response prolonged compared to the control experiments (fig. 2).

When histamine was injected 20 min after the infusion of PGE_1 the stimulating effect of histamine was not enhanced. The maximum response was 16±3% after the PGE_1 infusion compared to 14±4% in the control

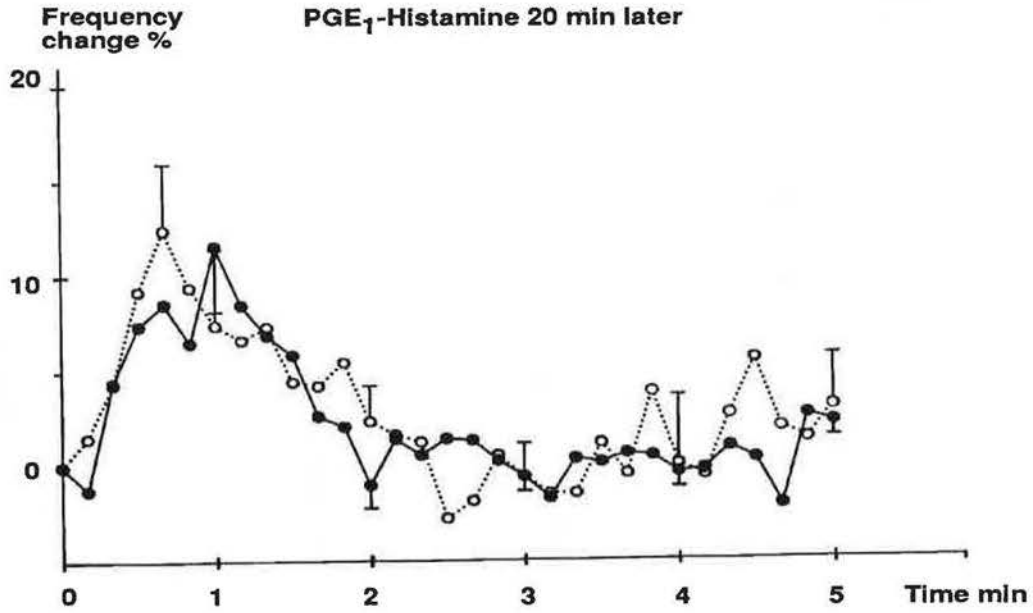

Fig. 3. – The time-course curve for the effect of histamine in the dose 10 μg·kg^{-1} given 20 min after infusion of PGE_1 (o·····o). The control experiments with histamine alone were run in 6 other rabbits (●——●). The results are expressed as means±SEM. Frequency zero level was 1260±69 waves·min^{-1} in the infusion experiments and 1213±65 waves·min^{-1} in the control experiments (p=0.34).

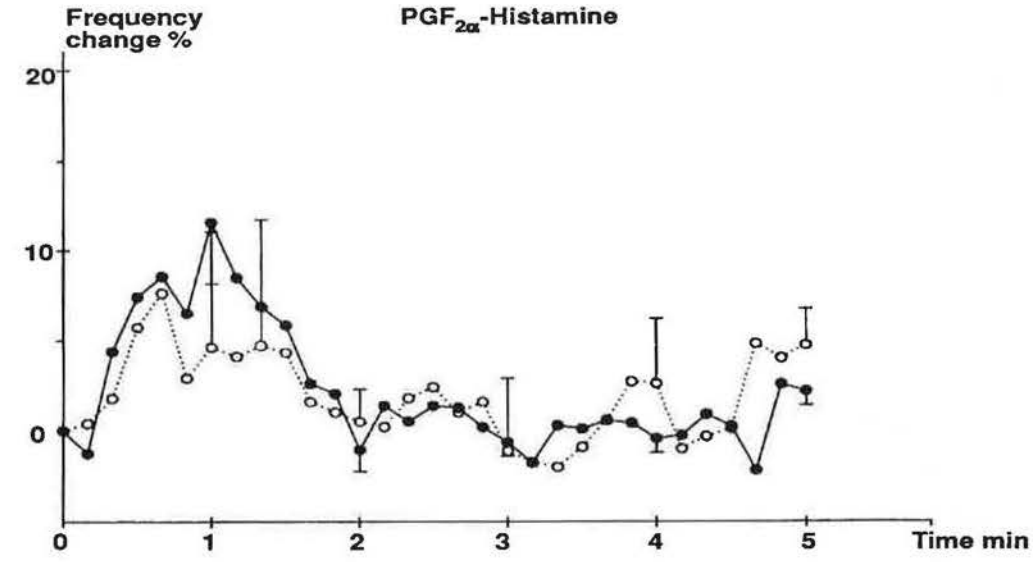

Fig. 4. – The time-course curve for the effect of histamine in the dose 10 μg·kg^{-1} given immediately after infusion of $PGF_{2\alpha}$ (o·····o). The control experiments with histamine alone were run in 6 other rabbits (●——●). The results are expressed as mean±SEM. Frequency zero level was 1301±66 waves·min^{-1} in the infusion experiments and 1213±65 waves·min^{-1} in the control experiments (p=0.36).

experiments (p>0.5) (fig. 1B). The time-course curves in these experiments did not differ significantly (p>0.5 for the areas under the curves) (fig. 3).

Infusion with $PGF_{2\alpha}$ immediately before injection of histamine did not affect the stimulating effect of histamine on the mucociliary activity. The maximum response was 15±5% after the $PGF_{2\alpha}$ infusion compared to 14±4% in the control experiments (p>0.5) (fig. 1C). The time-course curves in these experiments did not differ significantly (p>0.5 for the areas under the curves) (fig. 4).

When methacholine was injected immediately after the infusion of PGE_1 its stimulating effect on the mucociliary activity was not changed.The maximum response was 26±6% after the PGE_1 infusion compared to 29±5% in the control experiments (p=0.48), (fig. 1D). The time-course curves in these experiments did not differ significantly (p>0.5 for the areas under the curves) (fig. 5).

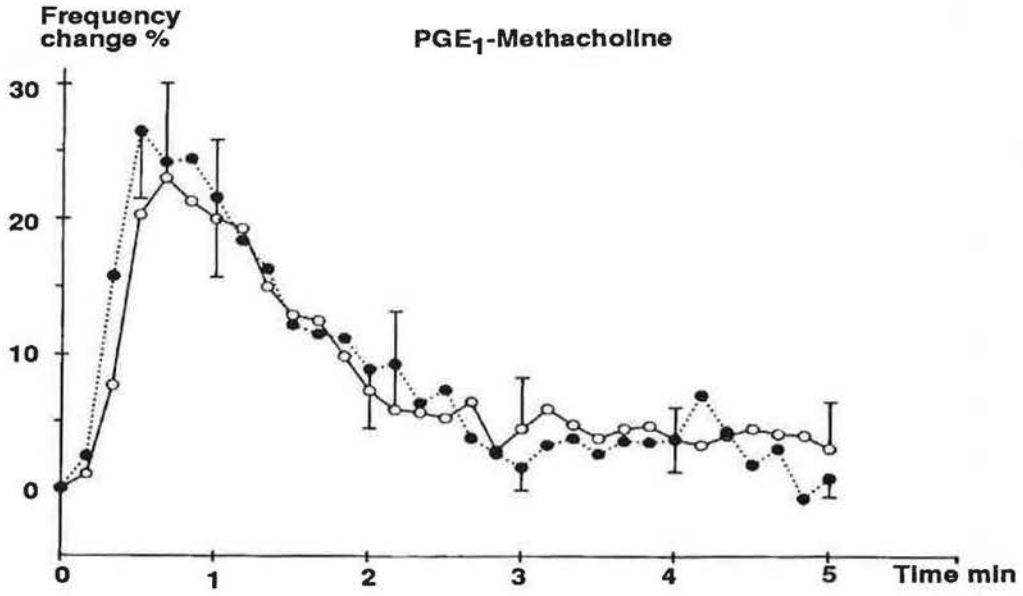

Fig. 5. – The time-course curve for the effect of methacholine in the dose 0.5 μg·kg^{-1} given immediately after infusion of PGE_1 (o·····o). The control experiments with methacholine alone were run in the same rabbits (●——●). The results are expressed as mean±SEM. Frequency zero level was 1258±25 waves·min^{-1} in the infusion experiments and 1251±53 waves·min^{-1} in the control experiments ($p>0.5$).

Discussion

There are few reports concerning interaction between inflammatory mediators and their effects on the mucociliary system. Therefore, the present results will be discussed mainly in the light of reported interactions in other organ systems.

There is substantial evidence of the involvement of many different mediators in inflammatory processes [16]. Histamine, a well known inflammatory mediator, is released during allergic reactions in the nasal mucosa [8]. The mobilization of histamine is thought to take place simultaneously with a release of prostaglandins and leukotrienes, lipid acid metabolites by the cyclooxygenase and lipoxygenase enzyme systems, respectively [8, 9].

The widespread occurrence of prostaglandins in animal tissue together with their mode of action in a wide range of physiological systems has led to the proposition that these substances may have a general function as modulators of cellular responses to a variety of stimuli [17]. Some authors have pointed out that an important role for prostaglandins may be an alteration of the threshold response of components of inflammation [18, 19]. Thus, there are possible interactions between prostaglandins and other inflammatory mediators in the upper airways. Such interactions have been proved valid in other organ systems. For example, in the lower airways PGE_1 has been found to modulate the release of histamine from human lung tissue, an effect mediated by changing intracellular levels of cAMP [10]. YEN *et al.* [12] reported that perfusion of histamine to guinea pig lung increased the release of $PGF_{2\alpha}$ and prostaglandins of the E-series, an effect mediated by H_1 and H_2 receptors respectively. While causing bronchoconstriction and releasing $PGF_{2\alpha}$, histamine simultaneously releases PGE_1 which is a bronchodilatator and also counteracts further release of histamine [10]. These results indicate that the release of histamine and prostaglandins is linked in a complicated way in the airways.

Prostaglandins of the E-series enhanced the histamine-induced increase in vascular permeability in the skin of guinea pigs and rats [20, 21] and they also sensitize the nerve receptors to the analgetic and pruretic effects of histamine in man [18, 22].

In the present study preinfusion of PGE_1 in doses too low to significantly alter the mucociliary activity increased the sensitivity to the subsequent histamine challenge but did not affect the response to methacholine. This enhancement was only noticeable when the histamine injection was given immediately after concluding the PGE_1 infusion. It did not occur when histamine was given about 20 min after the end of the PGE_1 infusion. This interaction between a prostaglandin and histamine is in accordance with FULLER *et al.* [13] who found that PGD_2 administered as an inhalation enhanced the bronchoconstrictor effect of histamine when these mediators were given simultaneously to asthmatic subjects, but not when histamine was given a while after the PGD_2 inhalation. A similar enhancement by prostaglandins of histamine's effects in the airways was reported by WALTERS *et al.* [23] and HEATON *et al.* [24] who both found that $PGF_{2\alpha}$ increased airway responsiveness to histamine in healthy humans.

The lack of enhancement of the histamine induced effect after preinfusion with $PGF_{2\alpha}$ underlines the differences between this prostaglandin and PGE_1. They are known to possess different biological properties

[17, 25], in spite of their similar molecular structure. Prostaglandin $F_{2\alpha}$ has even been reported to antagonize some effects of the E prostaglandins [25, 26].

Prostaglandins have been shown to enhance cholinergically mediated mechanisms in other systems, like the airway-responsiveness in dogs and asthmatics [13, 27]. Contrary to these reports PGE_1 did not enhance the methacholine induced stimulation of the mucociliary activity in the present study. The discrepancy between the present findings and previous reports might be due to the use of other prostaglandins than PGE_1 and investigation of other species and organic systems. Cell membrane receptors are not a static population but can change either in numbers or affinity under the influence of their own agonists [28]. An increase in the sensitivity to histamine would suggest either an increase in agonist concentration in the vicinity of the receptors mediating the histamine induced stimulation of the mucociliary activity, or an increase in the activation of the receptor population by a given concentration of histamine [23]. The former is a possible explanation for the enhanced stimulation of the mucociliary activity found by us since pretreatment with prostaglandins of the E-series (but not with $PGF_{2\alpha}$) have been shown to enhance the vascular leakage induced by histamine *in vivo* [20], thus allowing more histamine to leak from the vascular bed and reach the receptors in the tissue. In the present experiments it is unlikely that PGE_1 enhances the histamine effect in an additive fashion since PGE_1 in the dose given did not change mucociliary frequency.

We have previously reported that PGE_1 and $PGF_{2\alpha}$ are moderate *in vivo* stimulators of the mucociliary activity while histamine has a stronger stimulating effect [4, 5]. The present and previous results indicate that during an allergic or inflammatory reaction in the airways, when many different mediators are released simultaneously, the basic role of PGE_1 is probably not to have a direct stimulating effect on the mucociliary activity but instead to modify the mucociliary response to other known stimulators of the mucociliary system. This investigation has only pointed out one interaction between different inflammatory mediators affecting the mucociliary activity. Bearing in mind the growing number of inflammatory mediators being discovered, the possible interactions in various clinical situations are countless.

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La prostaglandine E_1 augmente la stimulation de l'activité muco-ciliaire induite par l'histamine dans les sinus maxillaires du lapin. J. Dolata.

RÉSUMÉ: Les médiateurs inflammation sont libérés dans les voies aériennes, pendant les réactions inflammatoires tant qu' allergiques, et beaucoup de ces médiateurs ont une influence sur l'activité muco-ciliaire. Pour rechercher si l'activité muco-ciliaire est modifiée par une combinaison de médiateurs, l'interaction entre les prostaglandines et l'histamine ou la methacholine a été étudiée *in vivo* dans les sinus maxillaires du lapin. Nous avons utilisé une technique photo-électrique, et enregistré les modifications de fréquence induites par les substances testées. Les prostaglandines E_1 et $F_{2\alpha}$ (PGE_1 et $PGF_{2\alpha}$) ont été données par perfusion, suivie d'une injection en bolus d'histamine ou de methacholine. La perfusion de PGE_1 (0.1 $\mu g \cdot kg^{-1}$) a renforcé l'effet stimulant de l'injection subséquente d'histamine (10 $\mu g \cdot kg^{-1}$), la stimulation maximale de 33±6% s'opposant aux 14±4% obtenus après histamine seule (p=0.02). Lorsque l'injection d'histamine est donnée 20 minutes après la PGE_1, il n'y a pas de renforcement. PGE_1 ne renforce pas l'effet stimulant de la methacholine. $PGF_{2\alpha}$, contrairement à PGE_1, ne réussit pas à renforcer l'effet de l'histamine. L'on propose qu'un des rôles de PGE_1 serait de modifier la réponse muco-ciliare à d'autres médiateurs libérés au cours des réactions inflammatoires et allergiques.
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