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Effect of Prostaglandin F_{2alpha} on the Contractile Tissues of the Respiratory System of the Cat in Experimental Airway Inflammation

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Summary

The *in vitro* reactivity of the smooth musculature of the trachea and lungs to PGF_{2alpha} was studied in control cats and cats with experimental airway inflammation induced by turpentine oil. No changes were found in the reactivity of the tracheal smooth muscle, but the reactivity of the pulmonary tissue was significantly raised compared with the controls. The results indicate that PGF_{2alpha} may play a role in the pathogenesis of bronchial hyperreactivity after airway inflammation.

Key words:
Prostaglandin F_{2alpha} – Airway smooth muscle – Cat – Inflammation

Introduction

Hyperreactivity of the airways due to a raised contraction response of the smooth muscles is a concomitant feature of various diseases of the respiratory tract. It is particularly symptomatic of bronchial asthma. One important finding in recent years has been the demonstration of a close association between inflammation and hyperreactivity of the airways (Holtzman *et al.* 1983, Bánovčin 1983, Holtzman 1985). It is evident that biologically active substances released from various cellular structures play an important role in this connection, including cyclooxygenase metabolites, whose role in the pathogenesis of asthma is still under debate (Abraham and Wanner 1988).

The aim of this study was to determine changes in the reactivity of tracheal smooth muscle preparations and a strip of lung tissue to prostaglandin F_{2alpha} in cats with airway inflammation.

Material and Methods

Adult cats of both sexes weighing 2.0–3.5 kg, bought from private sources, were anaesthetized intraperitoneally with 30 mg thiopental (Spofa). They were then exsanguinated, their thoracic cavity was opened and the trachea and lungs were removed. After the trachea had been stripped of the surrounding connective tissue, a ring about 3 mm wide was cut from the cervical region. Part of the cartilage skeleton was removed from the ring and the remainder was used to attach the preparation in an organ bath. A strip of tissue measuring 20x3x3 mm was excised from the peripheral parts of the diaphragmatic lobe of the lung by the technique of Lulich *et al.* (1976).

The preparations were made fast with a silon fibre in an organ bath in Krebs-Henseleit solution containing (in mmol.l^{-1}): NaCl 112.9, KCl 4.7, $CaCl_2$ 2.8, $MgSO_4$ 0.3, $NaHCO_3$ 24.9, glucose 11.1 (37 °C, pH 7.4) and saturated with 95 % O_2 and 5 % CO_2. After an initial 20 min load of 4 g and a 30 min adaptive pause with a load of 2 g, prostaglandin F_2 was added cumulatively to the organ bath in concentrations of 10^{-10} to 10^{-5} mol.l^{-1} in 0.2 ml volume, always after the response to the preceding concentration was stabilized. Mechanical responses were detected isometrically with a TDA3 static-dynamic tensometric apparatus and were recorded on an MTA 175 KUTESZ linear recorder.

The turpentine airway inflammation model was induced by the method of Korpáš *et al.* (1970). The cats were anaesthetized with thiopental, part of their cervical trachea was dissected out and a cannula was introduced. In freely breathing cats, turpentine oil was introduced through the cannula in the form of a coarsely dispersed aerosol for 2 min (5–6 mg turpentine oil) and the dissection area was sutured. The cats were used for the experiment 48 h after administering the turpentine oil. The presence of an inflammatory process in the airways was verified from changes in the animals' behaviour, by auscultation, from microscopic changes in the tracheal mucosa and lung parenchyma and by histological examination. Only animals in whose respiratory organs inflammation was confirmed both microscopically and histologically were included in the series.

The pD_2 values, as the criterion of the affinity of PGF_{2alpha} for the formation of a drug-receptor complex, were determined by regression analysis. The results were evaluated statistically by Student's t-test. Differences for which p was less than 0.05 were regarded as significant.

Results

Trachea

The reactivity of the tracheal smooth muscle was studied in material from nine healthy cats (Fig. 1). Five specimens responded to the administration of the PGF_{2alpha} by inconstant contraction – in four cases from a concentration of 10^{-6} mol. l^{-1} and in one case from a PGF_{2alpha} concentration of 10^{-8} mol.l^{-1}. The reaction of the other four tracheal smooth muscle preparations to the administration of PGF_{2alpha} was inconclusive.

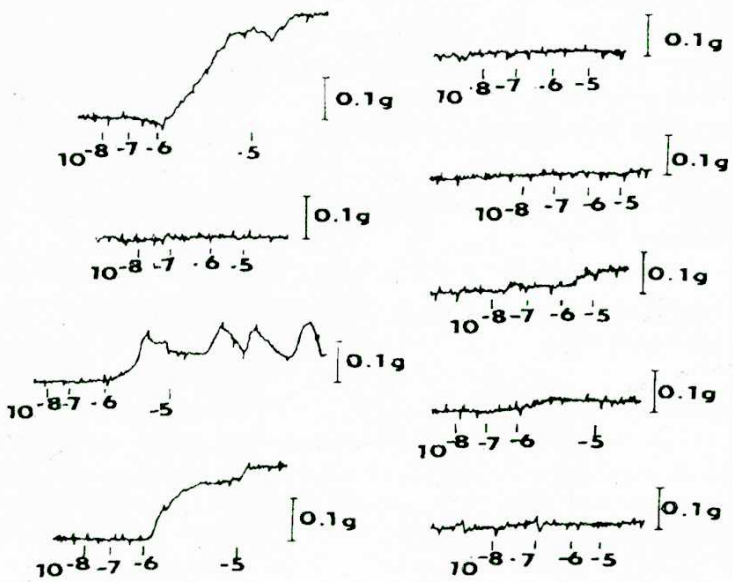

Fig. 1.
Recordings of the reactivity of tracheal smooth muscle preparations from control animals given cumulative doses of PGF_{2alpha} (10^{-8} to 10^{-5} mol. l^{-1}).

The reactivity of the tracheal smooth muscle of cats with airway inflammation to PGF_{2alpha} did not change significantly compared with the control group. Five out of eight specimens reacted by contraction to the administration of PGF_{2alpha} from a concentration of 10^{-6} mol. l^{-1}.

Lung tissue

Unlike the tracheal preparations, the strips of lung tissue (from 10 cats) responded, within the given concentration range (10^{-9} to 10^{-5} mol. l^{-1}), by contraction which was related to the dose (Fig. 2). The amplitude of contraction after a dose of 10^{-5} mol. l^{-1} was 0.61 ± 0.14 g ($pD_2 = 6.38 \pm 0.09$). The reactivity of the lung tissue of cats with turpentine airway inflammation (n=9) to the administration of PGF_{2alpha} was changed. The contraction amplitude increased significantly after all the concentration tested and after a dose of 10^{-5} mol. l^{-1} it represented a value of 0.98 ± 0.12 g. The pD_2 value (6.51 ± 0.08) did not differ significantly from controls, however.

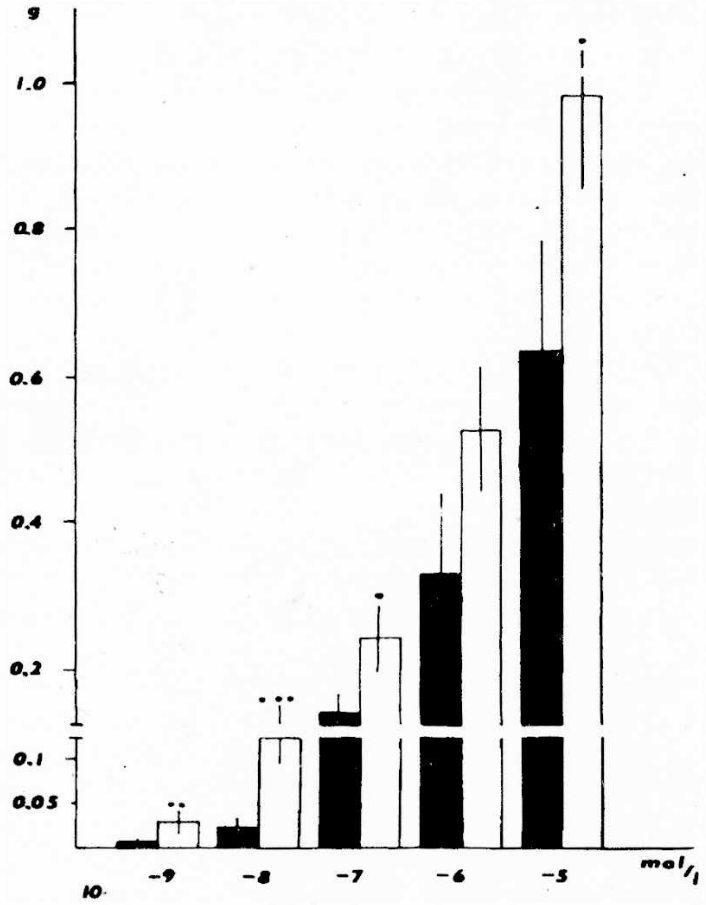

Fig. 2.
Mean amplitudes of contraction of lung tissue strips after cumulative administration of PGF_{2alpha} in doses of 10^{-9} to 10^{-5} mol. l^{-1}. Black columns – normal strips. White columns – inflammation.

Discussion

In general, PGF_{2alpha} is considered to be a bronchoconstrictor substance (Rosenthale 1975, Fleisch 1980). It contrast the smooth muscle of the trachea and strips of lung parenchyma in the guinea-pig, dog (Coloman *et al.* 1981) and man (Ghelani *et al.* 1980). Unlike strips of lung tissue, smooth muscle preparations of the rabbit (Fleisch and Calkins 1976) and cat trachea (Lulich *et al.* 1976) do not respond by a change of the tonus to the administration of PG_{2alpha} *in vitro*. However, in agreement with our findings, Joiner *et al.* (1975) observed isolated contraction of cat tracheal smooth muscle preparations. Hyperreactivity of the airways to PGF_{2alpha} is known both from *in vivo* experiments and from clinical studies (Dahlán *et al.* 1986), but the literature contains no data on its *in vitro* effect on smooth muscle preparations from airway affected by an inflammatory process.

Drazen and Austen (1974) assumed that PGF_{2alpha} influenced the tonus of the airway smooth muscles directly, by activating prostaglandin receptors on the surface of the smooth muscle cells.

The different reactivity of cat tracheal smooth muscle and lung tissue preparations to PGF_{2alpha} and the dose dependence of contraction of a lung tissue strip are indirect evidence that the effect of PGF_{2alpha} is mediated by membrane receptors of the smooth muscle cells. On the other hand, contraction of tracheal preparations was not unequivocally dependent on the dose. This is indicative of possible participation of other mechanisms in prostaglandin contraction – probably by means of the release of endogenous stimulants. An analysis of these, and their role in the contraction of strips of lung tissue require further experiments, however. Since the inflammatory process in the airways did not affect the reactivity of tracheal smooth muscle preparations, we assume that an indirect mechanism of prostaglandin contraction does not participate in the significant increase in contraction amplitude of strips of lung tissue affected by inflammation.

The inflammatory process may affect the physical properties (elasticity) of non-contractile structures of the lung tissue and thus contribute to the raised amplitude of prostaglandin contraction. In another group of experiments on cats, using the same airway inflammation model, we studied changes in the reactivity of smooth muscle preparations to acetylcholine (Bánovčin *et al.* 1987). Since the amplitude of acetylcholine contraction did not increase in strips of inflamed lungs – just as K^+-induced contraction of these preparations did not differ significantly from the controls (unpublished data) – we do not suppose that any change in the physical properties of the lung tissue participates in the increase in prostaglandin-induced contraction.

Membrane receptors are not a stable population. Their number and function are influenced by many factors, including pathological processes. The hypothesis that asthma is caused by depression of the function of inhibitory beta receptors (Szentivanyi 1968) has been reconfirmed. Since then there have been studies on changes in the number and/or function of alpha-adrenergic receptors (Szentivanyi *et al.* 1984), histamine H_1 and H_2 receptors (Chand 1980) and several others.

Since a significant increase in the amplitude of prostaglandin contraction is not associated, in our experiments, with significant differences in the pD_2 values, we assume that the differences found in the response of lung tissue strips are due to increased affinity of the receptors for PGF_{2alpha} and not to changes in their number.

Findings of raised reactivity of the airway smooth muscles to PGF_{2alpha} together with alterations in arachidonic acid metabolism in asthmatics (Green *et al.* 1974) draw attention to the importance of PGF_{2alpha} in the pathogenesis of bronchospasm.

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