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Bradykinin-induced release of thromboxane B_2 into bronchoalveolar lavage fluid of guinea pigs: relationship to airflow obstruction

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Abstract

The aim of this study was to evaluate the role of thromboxane A_2 in bradykinin-induced airflow obstruction in guinea pig in vivo. Airway insufflation pressure (P_i) was measured to assess airflow obstruction and the thromboxane B_2 (a stable metabolite of thromboxane A_2) concentration in bronchoalvelolar lavage fluid was determined by radioimmunoassay. The animals were pretreated with propranolol (1 mg/kg i.v.) and suxamethonium (5 mg i.v.) prior to bradykinin administration. Bradykinin instillation into the trachea (300 nmol) induced a P_i increase (47.5 ± 8.3 cm H_2O versus 23.8 ± 1.5 in sham) and significant thromboxane B_2 release into bronchoalveolar lavage fluid (79 ± 19 pg/ml versus 19 ± 6 in sham). A thromboxane synthase inhibitor (OKY-046, 30 mg/kg i.v.; ((*E-E*)-3-[*p*(1*H*-imidazole-1-yl-methyl) phenyl]-2-propenoic acid hydrochloride mono-hydrate)) or a thromboxane A_2 receptor antagonist (ICI192,605, 0.5 mg/kg i.v.; (4-(*Z*)-6-(2-*o*-chloro-phenyl-4-*o*-hydroxyphenyl-1,3-dioxan-cis-5-yl)hexenoic acid)) reduced the P_i increase evoked by bradykinin (38.7 ± 3.8 and 40.6 ± 3.8 cm H_2O, respectively). OKY-046 abolished the thromboxane B_2 release. A platelet-activating factor receptor antagonist, WEB2086 (1 mg/kg i.v.; (3-[4-(chlorophenyl)-9-methyl-6*H*-thienol [3,2-*f*][1,2,4]trizolo-[4,3-*a*][1,4] diazepin-2-yl]1-4-(4-morpholinyl)-1-propanon) did not significantly affect any measured parameter. We conclude that, in guinea pigs, bradykinin-induced airway effects are associated with a local thromboxane A_2 release.

Keywords: Bradykinin; Thromboxane; Airflow obstruction; WEB2086; ICI192,605; OKY-046

1. Introduction

Bradykinin is a nonapeptide, which has been suggested to participate in inflammatory reactions of various diseases, including allergic rhinitis and bronchial asthma (Proud and Kaplan, 1988). Exogenous administration of synthetic bradykinin induces airflow obstruction (Collier et al., 1960) and increases vascular permeability in guinea pig airways (Saria et al., 1983; Erjefält and Persson, 1989; Lötvall et al., 1991).

The bradykinin-induced airflow obstruction has previously been shown to be reduced by a cyclooxygenase inhibitor, suggesting that cyclooxygenase metabolites of arachidonic acid may be involved in the mechanism of obstruction evoked by bradykinin (Collier et al., 1960). The release of cyclooxygenase metabolites has been studied with isolated perfused lung of guinea pig (Bakhle et al., 1985; De Nucci et al., 1986). In this model, bradykinin induces the release of prostaglandin E_2, 6-oxo-prostaglandin $F_{1\alpha}$ (a stable metabolite of prostaglandin I_2) and thromboxane B_2 (a stable metabolite of thromboxane A_2), but not prostaglandin $F_{2\alpha}$. Recently, we have shown that a thromboxane synthase inhibitor (OKY-046) or a thromboxane A_2 receptor antagonist (ICI192,605) reduces bradykinin-induced airflow obstruction to the same degree as a cyclooxygenase inhibitor (indomethacin), suggesting that thromboxane A_2 may be the most important cyclooxygenase metabolite involved in bradykinin-induced airflow obstruction (Arakawa et al., 1992; Kawikova et al., 1993). The aim of the present study was to evaluate whether thromboxane A_2 is released locally in guinea pig airways in response to bradykinin

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in vivo, and to further elucidate the role of thromboxane A_2 in bradykinin-induced airflow obstruction. To do this, airway insufflation pressure (P_i) was recorded as a measurement of airflow obstruction and the concentration of thromboxane B_2 in bronchoalveolar lavage fluid was determined by radioimmunoassay.

2. Materials and methods

This study was approved by the Animal Ethics Committee in Göteborg. We used male Dunkin-Hartley guinea pigs weighing 350–550 g. The animals were anaesthetised with urethane (6 ml/kg of 25% urethane intraperitoneally and additional doses were given as required to maintain adequate anaesthesia).

2.1. Measurement of airflow obstruction

The animals were placed on a heated blanket (Harvard model 50-7061, Harvard Apparatus, Eden Bridge, Kent, UK), which maintained body temperature at approximately 37° C. The left carotid artery was cannulated and the catheter was connected to a pressure transducer (Spectramed, Viggo, Helsingborg, Sweden) to monitor systemic mean blood pressure. Another polyethylene catheter was inserted into the right external jugular vein for the administration of i.v. drugs and fluids. A tracheal cannula (10 mm length and 2.7 mm internal diameter) was inserted into the upper cervical trachea through a tracheotomy, secured with a suture and connected to a constant volume mechanical ventilator (Harvard model 50-1718, Harvard Apparatus, Eden Bridge, Kent, UK). The animals were placed in a supine position at an angle of 20°, with the head at a higher level to allow the instilled material to reach lower airway levels. A tidal volume of 10 ml/kg and a frequency of 60 breaths per min were used. The ventilatory circuit had a total volume of 18 ml. Insufflation pressure (P_i) was measured using a differential pressure transducer (Model FCO40; ± 1000 mm H_2O, Furness Controls, Bexhill, Sussex, UK) which was attached to a catheter connected to a side port of the intratracheal cannula. The signals from the blood pressure transducer were amplified with an analogue preamplifier (Kungsbacka Mät and Registerteknik, Sweden). All the signals were digitised using a 12-bit analog-digital board (National Instruments, Austin, TX, USA) connected to a Macintosh II computer (Apple Computer, Cupertino, CA, USA) and monitored with appropriate software (LabView, National Instruments, Austin, TX, USA).

2.2. Protocol

After preparation, all animals were treated with propranolol (1 mg/kg i.v.) to inhibit adrenergic effects of anaesthesia (Spriggs, 1965) and with suxamethonium (5 mg i.v.) to avoid artefacts of spontaneous breathing. Airway insufflation pressure and mean systemic blood pressure were monitored for 10 min. Then, control animals were given a vehicle for the drug (1 mM $NaHCO_3$ in 0.9% saline for ICI192,605 or pure 0.9% saline for other drugs) and non-control animals were given one of the following pretreatments: ICI192,605 (a thromboxane A_2 receptor antagonist; 0.5 mg/kg i.v.), OKY-046 (a thromboxane-synthase inhibitor; 30 mg/kg i.v.), combination of OKY-046 (30 mg/kg i.v.) and atropine (a muscarinic receptor blocker; 1 mg/kg i.v.), WEB 2086 (a platelet-activating factor (PAF) receptor antagonist; 1 mg/kg i.v.). After another 5 min, bradykinin (300 nmol in 100 μl in 0.9% saline) was instilled into the tracheal lumen or given intravenously (as bolus of 300 nmol in 100 μl of 0.9% saline with subsequent flushing of the catheter with 0.5 ml of 0.9% saline). To evaluate the effect of instillation of 100 μl of a solution into the tracheal lumen, sham stimulation was performed by instillation of 0.9% saline (100 μl) into the trachea. In a separate group, methacholine (1 μg in 100 μl of 0.9% saline) was instilled into the trachea to evaluate whether the release of thromboxane B_2 is specific for bradykinin. The dose of methacholine inducing a degree of airflow obstruction similar to that with 300 nmol of bradykinin, was determined in a preliminary study.

Airway instillation was performed by flushing 100 μl of a solution with 1 ml of air through a needle, directly into the tracheal lumen via the tracheal cannula, with the point of the needle inside the lower part of the tracheal cannula.

After administration of bradykinin, methacholine or sham stimulation, airway insufflation pressure and mean systemic blood pressure were monitored every 15 s over 1 min. Then, bronchoalveolar lavage was performed twice with 2 ml of saline at 37° C containing 10^{-5} M indomethacin (to avoid the release of thromboxane A_2 from different cells during lavage). After lavage, the fluid was centrifuged ($400 \times g$ for 5 min) and the supernatant was immediately frozen at −20° C.

2.3. Measurement of thromboxane B_2 in bronchoalveolar lavage fluid

The quantitative analysis of thromboxane B_2 in bronchoalveolar lavage fluid was performed by using a thromboxane B_2 ^{125}I radioimmunoassay (Amersham International, Amersham, UK). A gamma scintillation counter (LKB Wallac, Wallac, Sollentuna, Sweden) was used for radioactivity measurements.

The assay is valid over a range of 3–400 pg thromboxane B_2/tube. When a higher level was obtained, the sample was diluted and the measurement was repeated. The cross-reactivity of the thromboxane B_2

antiserum of this assay system was 100% for thromboxane B_2, 2.5% for prostaglandin D_2, 0.4% for prostaglandin $F_{2\alpha}$, 0.3% for prostaglandin E_2 and less than 0.15% for prostaglandins $F_{1\alpha}$, E_1, A_2 and 6-keto-prostaglandin $F_{1\alpha}$.

The assays were performed on several occasions. We do not have enough data to perform a statistical analysis of inter-assay differences. However, it seems that the variability in thromboxane B_2 values was due to differences among individual animals rather than inter-assay variation, because the variability of values of thromboxane B_2 in bronchoalveolar lavage fluid in animals given bradykinin into the trachea varied between 50–950, 10–80 and 20–130 pg/100 μl on three different occasions.

2.4. Drugs

The following drugs were used: bradykinin, acetyl-β-methylcholine chloride and urethane (Sigma Chemical Co., Dorset, UK), propranolol (ICI Pharmaceuticals, Macclesfield, Cheshire, UK), suxamethonium (KabiVitrum, Stockholm, Sweden), ICI192,605 (4-(*Z*)-6-(2-*o*-chloro-phenyl-4-*o*-hydroxyphenyl-1,3-dioxan-cis-5-yl)hexenoic acid) – kindly donated by ICI Pharmaceuticals UK, OKY-046 ((*E-E*)-3-[*p*(1*H*-imidazole-1-yl-methyl) phenyl]-2-propenoic acid hydrochloride monohydrate) – kindly donated by Kissei Pharmaceutical Co., Japan, WEB2086 (3-[4-(chlorophenyl)-9-methyl-6*H*-thienol [3,2-*f*][1,2,4]trizolo-[4,3-*a*][1,4]diazepin-2-yl]1-4-(4-morpholinyl)-1-propanon) – kindly donated by Boehring Ingelheim, Germany.

2.5. Data analysis

The data are reported as means ± S.E.M. The peak of airway insufflation pressure (P_i) was used to evaluate the differences in airway obstruction and the mean thromboxane B_2 concentration of two samples of bronchoalveolar lavage fluid was calculated to assess the release of thromboxane B_2 into bronchoalveolar lavage fluid. Non-parametric analysis (Mann-Whitney *U*-test) was used to determine the significance of differences between groups. The Spearman rank correlation coefficient (R_s) was used to evaluate the relationship between peak P_i and thromboxane B_2 concentration in bronchoalveolar lavage fluid. A $P < 0.05$ was considered significant. The data were analysed with a Macintosh computer (Apple Computer, Cupertino, CA, USA) using standard statistical packages (StatView).

3. Results

3.1. Bradykinin intratracheally

Bradykinin instillation into the trachea induced a significant increase in P_i (47.5 ± 8.3 versus 23.8 ± 1.5 cm H_2O after 0.9% saline, $P < 0.05$) and release of thromboxane B_2 into bronchoalveolar lavage fluid (79 ± 19 versus 19 ± 6 pg/ml 0.9% saline, $P < 0.05$). Methacholine instillation caused an increase in P_i similar to that with bradykinin (60.1 ± 8.9 cm H_2O, $P > 0.05$), but no thromboxane B_2 release (19 ± 5 pg/ml of bronchoalveolar lavage fluid, $P < 0.05$) (Fig. 1).

ICI192,605, a thromboxane A_2 receptor antagonist,

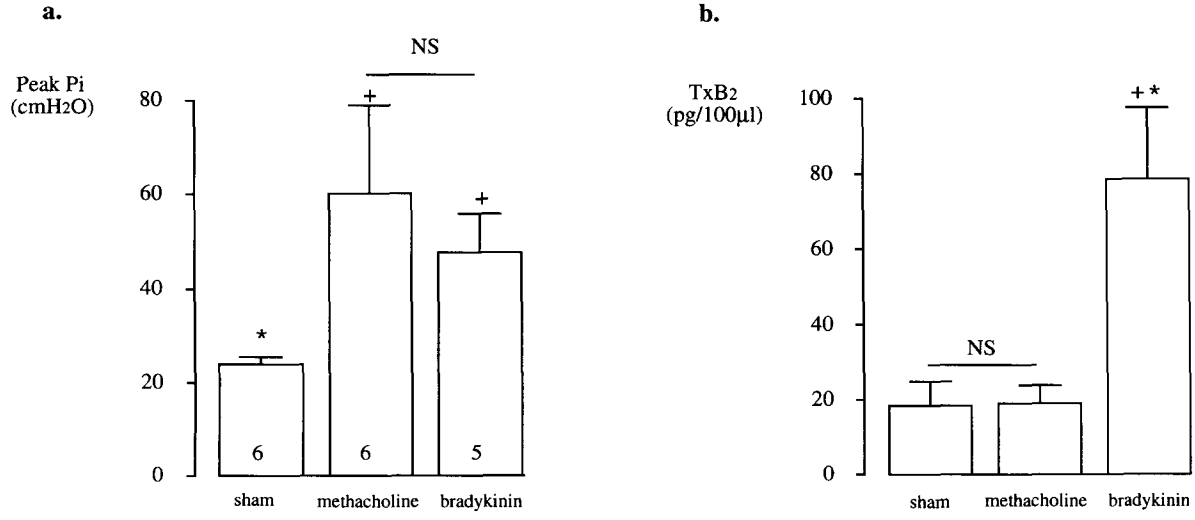

Fig. 1. (a) The peak of airway insufflation pressure (P_i) and (b) concentration of thromboxane B_2 (TXB_2) in bronchoalveolar lavage fluid after instillation of 0.9% saline (sham), methacholine or bradykinin into the tracheal lumen of guinea pig. The numbers in the columns represent the number of animals in each group. $^+$ $P < 0.05$ compared with sham-exposed animals, * $P < 0.05$ compared with methacholine-exposed animals.

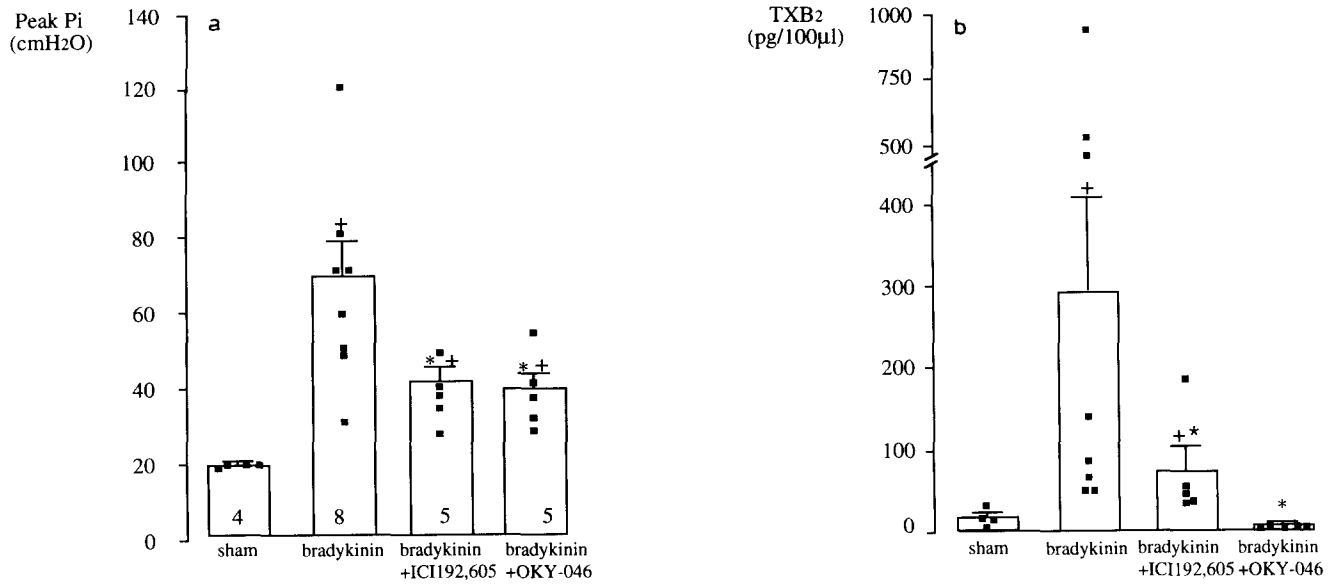

Fig. 2. (a) The peak of airway insufflation pressure (P_i) and (b) concentration of thromboxane B_2 (TXB_2) in bronchoalveolar lavage fluid after instillation of 0.9% saline (sham) and bradykinin into the tracheal lumen in untreated animals or after pretreatment with ICI192,605 or OKY-046. The numbers in the columns represent the number of animals in each group. The closed squares are the individual data. $^{+}$ $P < 0.05$ compared with sham-exposed animals, * $P < 0.05$ compared with bradykinin-exposed untreated animals.

significantly reduced the bradykinin-induced increase in P_i (40.6 ± 3.8 cm H_2O versus 68.1 ± 9.5 cm H_2O in controls, $P < 0.05$). The concentration of thromboxane B_2 in bronchoalveolar lavage fluid was significantly lower in animals pretreated with ICI192,605 than in untreated animals (73 ± 30 and 329 ± 124 pg/ml, respectively, $P < 0.05$) (Fig. 2).

OKY-046, a thromboxane synthase inhibitor, significantly attenuated the bradykinin-induced increase in P_i (38.7 ± 3.8 versus 68.1 ± 9.5 cm H_2O in controls, $P < 0.05$) and abolished thromboxane B_2 release (8 ± 1 pg/ml in bronchoalveolar lavage fluid compared to 295 ± 115 pg/ml in controls, $P < 0.05$) (Fig. 2).

The combination of OKY-046 and atropine caused a reduction of the responses similar to that with pretreatment with OKY-046 alone (Fig. 3).

WEB2086, a PAF receptor antagonist, affected neither the bradykinin-induced increase in P_i (51.8 ± 3.3 versus 51.3 ± 7.4 cm H_2O in controls), nor the thromboxane B_2 release into bronchoalveolar lavage fluid (39 ± 6 compared to 37 ± 1 pg/ml in untreated animals) (Fig. 4).

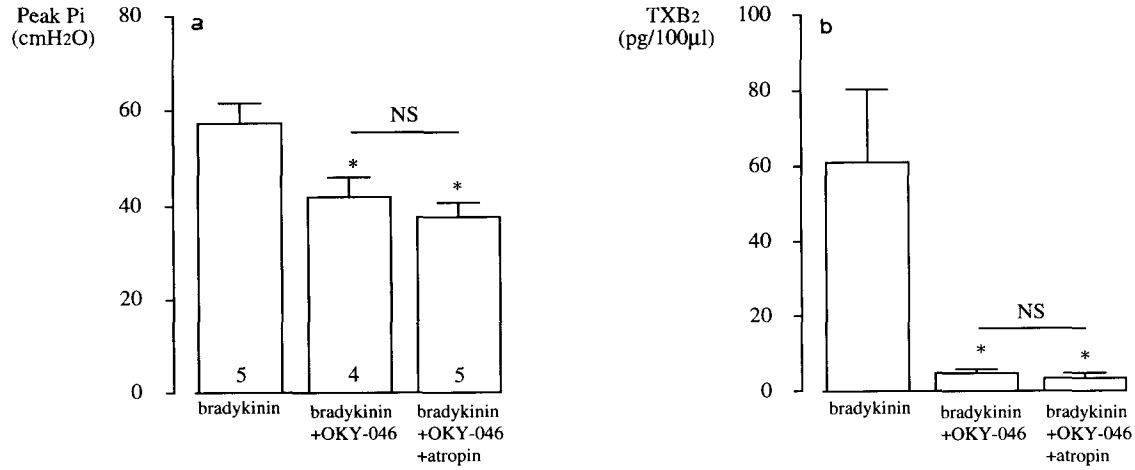

Fig. 3. (a) The peak of airway insufflation pressure (P_i) and (b) concentration of thromboxane B_2 (TXB_2) in bronchoalveolar lavage fluid after instillation of bradykinin into the tracheal lumen in untreated animals and animals pretreated with OKY-046 alone or combination OKY-046 and atropine. The numbers in the columns represent the number of animals in each group. * $P < 0.05$ compared with untreated animals. NS $P > 0.05$.

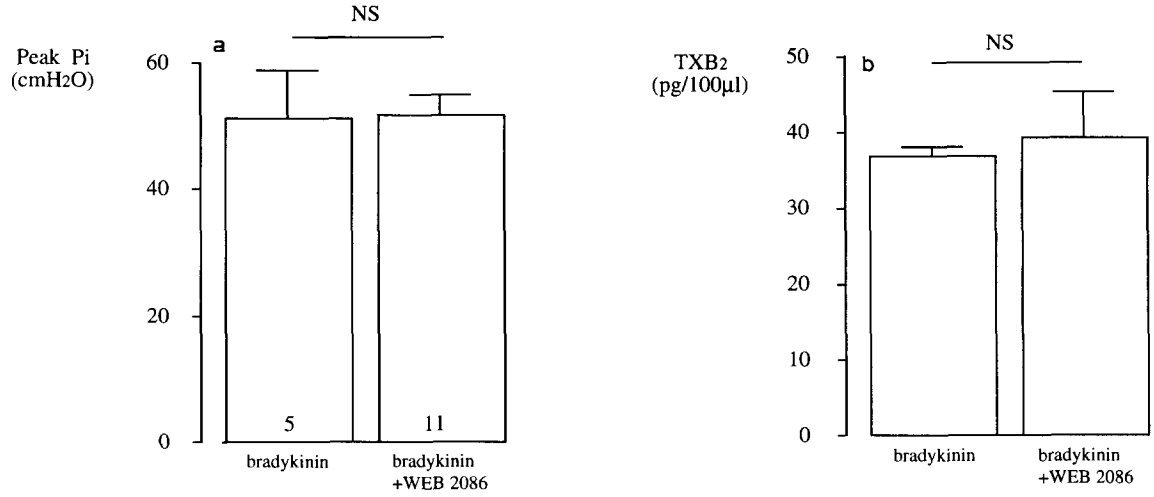

Fig. 4. (a) The peak of airway insufflation pressure (P_i) and (b) concentration of thromboxane B_2 (TXB_2) in bronchoalveolar lavage fluid after instillation of bradykinin into the tracheal lumen in untreated animals and animals pretreated with WEB2086. The numbers in the columns represent the number of animals in each group. NS $P > 0.05$.

3.2. Bradykinin intravenously

Intravenous administration of bradykinin caused a significant increase in P_i (62.9 ± 5 versus 10.9 ± 0.8 cm H_2O in a group given 0.9% saline i.v., $P < 0.05$) and thromboxane B_2 release into bronchoalveolar lavage fluid (114 ± 33 versus 11 ± 2 pg/ml in a group given saline i.v., $P < 0.05$). This increase in P_i was significantly reduced by OKY-046 (40.2 ± 5.1 cm H_2O, $P < 0.05$), but not influenced by WEB2086 (59 ± 6.8 cm H_2O, $P > 0.05$). The bradykinin-induced release of thromboxane B_2 was abolished by OKY-046 (12 ± 4 pg/ml of bronchoalveolar lavage fluid, $P < 0.05$) and not significantly influenced by WEB2086 (111 ± 38 pg/ml of bronchoalveolar lavage fluid, $P > 0.05$) (Fig. 5).

3.3. Correlation

The concentration of thromboxane B_2 in bronchoalveolar lavage fluid correlated significantly with the increase in P_i induced by bradykinin instillation into the trachea ($R_s = 0.69$, $P = 0.002$; $n = 21$) or by intravenous injection of bradykinin ($R_s = 0.77$, $P = 0.02$; $n = 10$).

4. Discussion

Bradykinin instillation into the tracheal lumen of guinea pig causes both airflow obstruction and release of thromboxane A_2 into bronchoalveolar lavage fluid. Thromboxane A_2 release in the airways does not occur

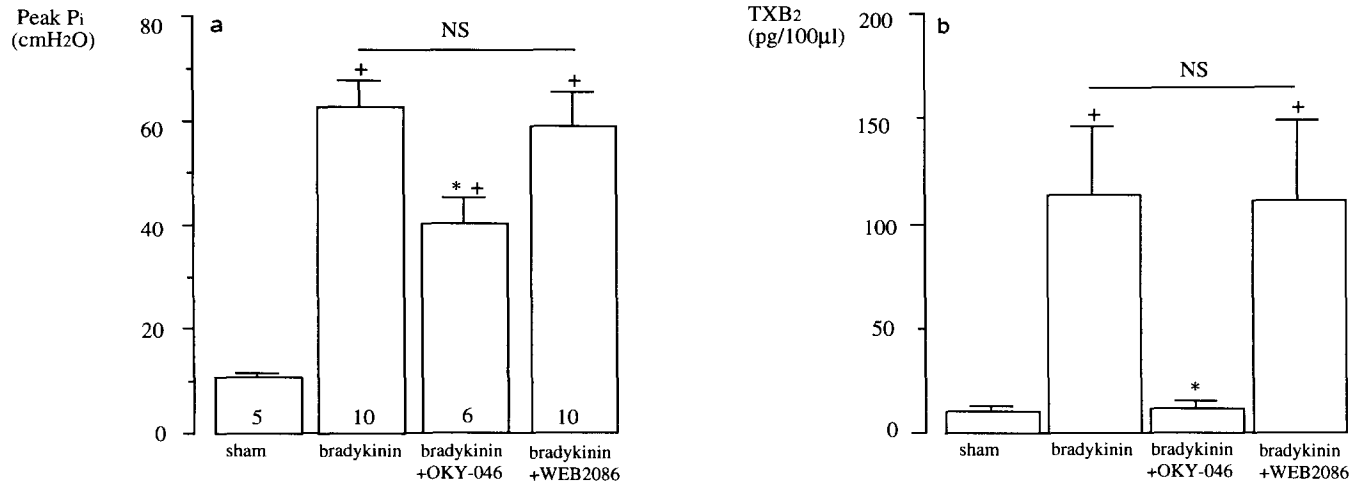

Fig. 5. (a) The peak of airway insufflation pressure (P_i) and (b) concentration of thromboxane B_2 (TXB_2) in bronchoalveolar lavage fluid after intravenous administration of 0.9% saline (sham) and bradykinin in untreated animals or after pretreatment with OKY-046 or WEB2086. The numbers in the columns represent the number of animals in each group. $^+$ $P < 0.05$ compared with sham-exposed animals, * $P < 0.05$ compared with bradykinin-exposed and untreated animals, NS $P > 0.05$.

in response to bronchoconstriction per se, because methacholine instillation causing a similar increase in P_i does not induce thromboxane A_2 release. The released thromboxane A_2 is likely to be responsible for a part of the bradykinin-induced airflow obstruction, because P_i was significantly reduced by both OKY-046 and ICI192,605. There is, however, another mechanism involved in bradykinin-induced airflow obstruction, as apparent from the experiments with OKY-046 that reduced airflow obstruction only partially, despite abolishing thromboxane A_2 release.

The significant reduction of thromboxane B_2 levels in bronchoalveolar lavage fluid of animals treated with ICI192,605 may imply that there exists a positive feedback involved in control of thromboxane A_2 release. Thus, it is possible that instilled bradykinin releases thromboxane A_2 locally, which in turn causes extravasation of plasma (Kawikova et al., 1994; Lötvall et al., 1992). Blockade of such a circle of events by ICI192,605 may explain the attenuation of thromboxane A_2 release by this receptor antagonist. However, other unrelated events such as variability of the response should not be ignored.

We hypothesised that thromboxane A_2 release in airways may be at least a partial consequence of PAF release. The suggestion was based on the following observations. PAF receptor antagonists, as well as inhibitors of cyclooxygenase, thromboxane synthase or antagonists of prostanoid TP receptors partially reduce the plasma extravasation into airway tissue induced by bradykinin (Rogers et al., 1990; Arakawa et al., 1992; Kawikova et al., 1993). Furthermore, the plasma extravasation induced in airways by exogenous PAF is reduced by a thromboxane synthase inhibitor (Tokuyama et al., 1991). However, neither airflow obstruction, nor thromboxane A_2 release is influenced by WEB2086. This negative finding does not seem to be due to the dose of WEB2086, because we used the same dose as did Rogers et al. (1990).

Not only thromboxane A_2, but other mechanisms also seem to be involved in bradykinin-induced airway effects. These mechanisms include activation of cholinergic and sensory nerves (Drazen and Austen, 1975; Saria et al., 1988; Ichinose et al., 1990; Kawikova et al., 1993). It is not clear, however, whether thromboxane A_2 release and activation of nerves are parallel mechanisms, or whether they depend on each other. In the current study, we obtained results showing that inhibition of both cholinergic nerves (by atropine) and thromboxane A_2 production (by OKY-046) did not further reduce bradykinin-induced airflow obstruction more than did inhibition of thromboxane A_2 formation only. Thus, it seems probable that bradykinin-induced activation of cholinergic nerves may be secondary to thromboxane A_2 release. This hypothesis is supported by Chung et al. (1985), who suggested that prostanoid TP receptors are present on prejunctional nerve endings. Also, we have previously shown in in vivo experiments that airflow obstruction induced by U-46619 (a stable thromboxane A_2 mimetic) was slightly, but significantly, attenuated by atropine (Kawikova et al., 1993). Thus, thromboxane A_2 may in part be important for the bradykinin-induced release of acetylcholine in the airways.

Bradykinin also induces the release of other compounds, including different prostanoids (Bakhle et al., 1985; De Nucci et al., 1986), nitric oxide (Schlemper and Calixto, 1994) and histamine (Bueb et al., 1993). All these mediators may modulate the bradykinin-induced airflow obstruction. To understand fully the mechanism and the role of bradykinin in inflammatory processes will require much more knowledge about interactions among these compounds at a cellular and molecular level.

In summary, this study showed that bradykinin induces both airflow obstruction and release of thromboxane B_2 into bronchoalveolar lavage fluid and that thromboxane A_2 partly mediates the bradykinin-induced airflow obstruction in guinea pig. The activation of cholinergic nerves does not seem to be important in the thromboxane-independent part of the airway response induced by bradykinin.

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