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RESPONSE OF HUMAN ISOLATED BRONCHIAL AND LUNG PARENCHYMAL STRIPS TO SRS-A AND OTHER MEDIATORS OF ASTHMATIC BRONCHOSPASM

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1 The responses of human isolated bronchial and lung parenchymal strips to cumulative doses of slow reacting substance of anaphylaxis (SRS-A), histamine, prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) and acetylcholine have been examined, after storing the tissues overnight in Krebs solution at 4°C.

2 Both tissues contracted to all four agonists. The order of potency (as determined by height of maximal contraction) was: bronchial strip: acetylcholine > histamine = $PGF_{2\alpha}$ > SRS-A, and parenchymal strip: $PGF_{2\alpha} \gg$ histamine = SRS-A > acetylcholine.

3 Maximal contractions to SRS-A of both the human bronchial and parenchymal strips were approx. 30% of the maximal contractions produced by the most potent agonist on each tissue ($PGF_{2\alpha}$ on the parenchymal strip and acetylcholine on the bronchial strip). SRS-A, therefore, does not have a powerful direct contractile effect on either parenchymal or bronchial strip of human lung, and is approximately equipotent on both tissues. A part of the broncho-constrictor activity of SRS-A *in vivo* may be mediated via indirect pathways.

4 The selective SRS-A antagonist, FPL 55712, was approximately equipotent in antagonizing contractions induced by SRS-A on both human bronchial and parenchymal strips.

Introduction

Slow reacting substance of anaphylaxis (SRS-A) is believed to be an important mediator of asthmatic bronchospasm in man. It contracts isolated airway tissue from both animals and man (Brocklehurst, 1962; Berry & Collier, 1964; Burka & Eyre, 1977; Drazen, Lewis, Wasserman, Orange & Austen, 1979) and produces bronchoconstriction *in vivo* in guinea-pig (Berry & Collier, 1964; Drazen & Austen, 1974) and monkey (Patterson, Orange & Harris, 1978; Michoud, Pare, Orange & Hogg, 1979). In some asthmatic patients, inhalation of guinea-pig SRS-A resulted in bronchoconstriction whereas normal patients were unaffected (Herxheimer & Stresemann, 1963). In conscious guinea-pigs, SRS-A infused intravenously produced a marked fall in dynamic pulmonary compliance but little change in pulmonary resistance (Drazen & Austen, 1974). This is believed to indicate that in the guinea-pig, SRS-A acts predominantly on peripheral, rather than central airways. In support of this conclusion, isolated lung parenchymal strips of guinea-pig (in which it is believed that smooth muscle of the peripheral airways makes the major contribution to contractile responses: Lulich, Mitchell & Sparrow, 1976; Drazen & Schneider, 1978) are 100 times more sensitive to SRS-A than are tracheal spiral strips (Drazen *et al.*, 1979).

In other species, the pulmonary activity of SRS-A may not be confined to peripheral airways. For example, in anaesthetized monkeys, inhalation of an aerosol of SRS-A produced a significant decrease in compliance and increase in resistance (Patterson *et al.*, 1978). However, tracheal instillation of SRS-A produced a predominant effect of decreased compliance with lesser alterations in resistance (Michoud *et al.*, 1979). The differing effects of SRS-A on pulmonary resistance, *in vivo* may be explained by differences in species, route of administration of SRS-A, and state of consciousness of the animals.

The site of action of SRS-A in human lung is not known. The present study was designed to investigate and compare the responses of human bronchial and lung parenchymal strips to SRS-A, prostaglandin $F_{2\alpha}$

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($PGF_{2\alpha}$), histamine and acetylcholine, all of which may be involved in the pathogenesis of allergic bronchospasm.

Methods

Macroscopically normal specimens of human lung were obtained at the time of surgery (usually for carcinoma of the lung) and transported to the laboratory in a plastic bag, encased in ice within a large Thermos flask.

Suitable bronchi (2 to 5 mm diameter) were located with a probe inserted into the lumen and dissected free of parenchymal tissue. Due to pressure of time, it was not feasible to carry out the experiment on the day the specimens were received. The dissected tissues were therefore stored overnight at 4°C in 25 ml sealed bottles containing Krebs (1950) solution previously gassed with 5% CO_2 in O_2, together with streptomycin sulphate 65 units/ml and benzylpenicillin sodium 500 units/ml. These antibiotics were included to reduce the hazards associated with handling potentially infectious surgical specimens, in line with the general recommendations of the Howie Report (1978).

The composition of the Krebs solution was (g/l): NaCl 5.54, $MgSO_4.7H_2O$ 0.29, KH_2PO_4 0.16, $NaHCO_3$ 2.1, dextrose 2.1, KCl 0.35, $CaCl_2$ 0.28, sodium pyruvate 0.54, sodium fumarate.H_2O 0.84 and sodium glutamate 0.83. Following the technique described by Lulich *et al.* (1976) for isolated lung strips of the cat, parenchymal strips were prepared from full thickness sections of the human lung lobe, cut at right angles to the periphery of the lobe. These strips were stored overnight as described for the bronchi.

Overnight storage of these tissues was not as deleterious as might be imagined. As described later, the responsiveness of the bronchial strips to histamine and acetylcholine was very similar to that described by Dunlop & Smith (1977) and by Rosa & McDowall (1951), who used fresh tissues. In fact, the latter authors state that this tissue continues to react after storage for 48 h in a refrigerator.

Next day the bronchus was cut spirally to produce a strip 2 to 3 mm wide which was sectioned into pieces 2 to 3 cm long. Each individual strip was mounted under an initial tension of 300 mg in a 2 ml organ bath containing Krebs (1950) solution at 37°C, gassed with 5% CO_2 and 95% O_2.

The parenchymal strips were trimmed to approx. 20 × 3 × 3 mm, and mounted under the same conditions as the bronchial strips. All tissues were washed by overflow. Changes in tension of both bronchial and parenchymal strips were recorded semi-isometrically by Statham UC3 force displacement transducers linked to Vitatron chart recorders.

After an equilibration period of 1 h, the maximal response of the bronchial strip to acetylcholine was determined by constructing a cumulative dose-response curve, using final bath concentrations within the range 10 to 1000 μg/ml. Preliminary experiments had shown that acetylcholine produced a greater peak contraction of the bronchial strip than did $PGF_{2\alpha}$, SRS-A or histamine. Acetylcholine was therefore designated the reference agonist for the bronchial strip, and responses to other agonists expressed as a percentage of the maximum to acetylcholine.

Similarly, $PGF_{2\alpha}$ was designated the reference agonist for the parenchymal strip. Preliminary experiments using both individual and cumulative doses had shown that a concentration of 30 μg/ml always produced a maximal response and did not desensitize the tissue to other agonists, confirming the findings of Sweatman & Collier (1968) using human bronchus. Consequently only this single concentration was administered to the parenchymal strip at the beginning of each experiment.

After determining the maximal response to the reference agonist on both parenchymal strip and bronchial strip, the tissue was washed and allowed to recover completely. A cumulative dose-response curve was then established to one or more of the other agonists.

In some experiments, the antagonism of SRS-A by the specific antagonist FPL 55712 (Augstein, Farmer, Lee, Sheard & Tattersall, 1973) was studied. After producing a submaximal contractile response to SRS-A, the tissue was relaxed by the cumulative addition of FPL 55712. The concentration of FPL 55712 required to reverse the response to SRS-A by 50% (IC_{50}) was determined. In all these experiments, the lysine salt of FPL 55712 (i.e. FPL 55712 LL) was used.

Materials

SRS-A was prepared as described by Engineer, Niederhauser, Piper & Sirois (1978) from isolated lungs of guinea-pigs sensitized to egg albumin. The lungs were perfused with Tyrode solution containing indomethacin 1 μg/ml to inhibit the release of prostaglandins and increase the output of SRS-A. The perfusate was collected on ice between 2 and 20 min after antigen challenge. This perfusate was then partially purified by Amberlite XAD-8 chromatography to remove histamine and physiological salts as described by Lee, Fuher, Holroyde, Mann & Bantick (1979), and reconstituted in saline. It was confirmed by bioassay that the perfusate contained no detectable prostaglandins. Potency was assessed by comparison with a laboratory standard of lyophilized unpurified SRS-A, using bioassay on the guinea-pig isolated ileum in the

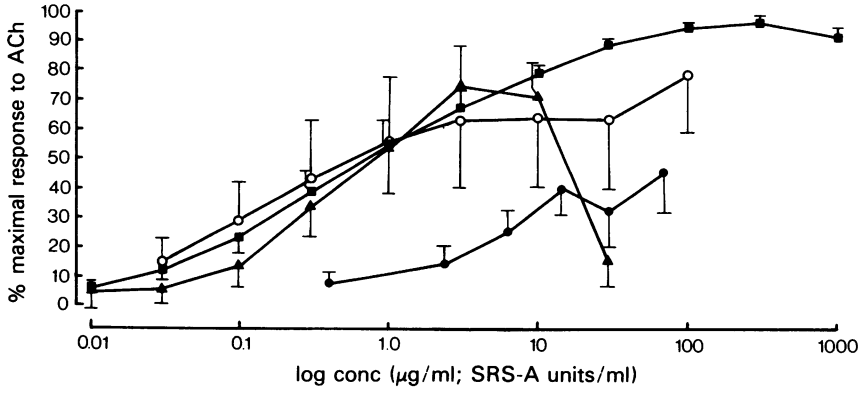

Figure 1 Response of human isolated bronchial strip to acetylcholine (ACh, ■; n = 5–19), histamine (○; n = 3–4), SRS-A (●; n = 5–8) and prostaglandin $F_{2\alpha}$ (▲; n = 3–4). Mean results are shown; vertical lines indicate s.e. mean.

presence of mepyramine 10^{-6} M and atropine 10^{-6} M. The laboratory standard was assigned an arbitrary potency of 100 units/ml. This is approximately equivalent to 0.6 units/ml expressed according to Engineer *et al.* (1978), or 20 units/ml according to Stechschulte, Austen & Bloch (1967).

Drugs Histamine acid phosphate, acetylcholine chloride, atropine sulphate (BDH); indomethacin, egg albumin grades II and III (Sigma); prostaglandin $F_{2\alpha}$ (Cambrian Chemicals); mepyramine maleate (May & Baker); benzylpenicillin sodium, streptomycin sulphate (Glaxo) and FPL 55712 LL, (7-[3-(4-acetyl-3-hydroxy-2-propylphenyloxy)-2-hydroxypropyloxy]-4-oxo-8-propyl-4H-1-benzopyran-2-carboxylic acid, lysine salt) (Fisons) were used.

All drug concentrations are expressed as either the free acid or base.

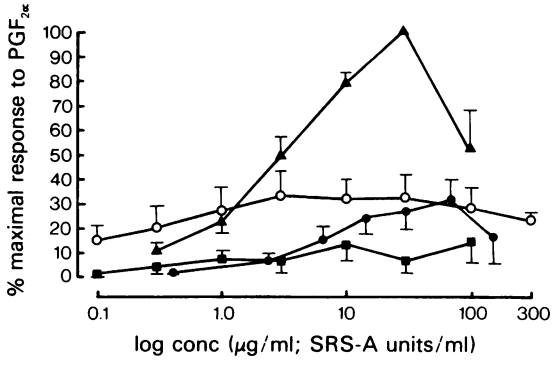

Figure 2 Response of human isolated lung parenchymal strip to prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$, ▲; n = 5–8), histamine (○; n = 3–6), SRS-A (●; n = 4–5) and acetylcholine (■; n = 4–6). Mean results are shown; vertical lines indicate s.e. mean.

Results

Human bronchial strip

Strips were prepared from 19 lung specimens. Responses to all the agonists were generally slow, those to SRS-A being the slowest. Construction of a cumulative dose-response curve to SRS-A often took more than 2 h. For this reason, not all concentrations of all agonists could be tested on each strip.

The maximal tension developed in response to the reference agonist, acetylcholine, was 351.6 ± 64.4 mg (mean ± s.e. mean; n = 19). This was achieved at a concentration of 300 μg/ml. The cumulative dose-response curves to acetylcholine and histamine (Figure 1) were similar, although acetylcholine produced a greater maximal response. The cumulative dose-response curve to $PGF_{2\alpha}$ was similar to those of acetylcholine and histamine up to 10 μg/ml. Increasing the concentration of $PGF_{2\alpha}$ to 30 μg/ml then reversed the previously induced contraction, probably due to tachyphylaxis, as noted by Sweatman & Collier (1968). The dose-response curve to SRS-A displayed a similar slope to those of the three other agonists, but a lower peak response (less than 50% of that to acetylcholine). In some experiments, SRS-A in concentrations greater than 100 units/ml relaxed the tissue.

Human parenchymal strip

Strips were prepared from 18 lung samples. As with the bronchial strips, responses to all agonists were slow, and for this reason not all concentrations of all agonists were tested on each strip. The maximal tension developed to the reference agonist $PGF_{2\alpha}$ was 65.5 ± 8.2 mg (mean ± s.e. mean; n = 16), at a concentration of 30 μg/ml.

Acetylcholine displayed weak activity on this preparation. Histamine was more effective, but no clear dose-response relationship was evident (Figure 2). SRS-A was comparable to histamine in terms of peak tension developed. $PGF_{2\alpha}$ was by far the most potent agonist tested, producing a peak response 3 times greater than that to histamine or SRS-A. As with the bronchial strip, $PGF_{2\alpha}$ produced a bell-shaped dose-response curve, such that increasing the concentration to 100 μg/ml reversed the contraction induced by concentrations up to 30 μg/ml.

Antagonism of SRS-A

As shown in Table 1, FPL 55712 LL antagonized the action of SRS-A to a similar extent on both human bronchial and parenchymal strips.

Discussion

When interpreting the results of this study, it is important to recognize that, although macroscopically normal, the lung samples used were obtained from diseased patients. Furthermore, for practical reasons the tissues had to be stored overnight before use. These qualifications should be borne in mind in the following discussion.

The responses of both bronchial and parenchymal strips to agonists were slow and made the construction of non-cumulative dose-response curves generally impractical. However, preliminary experiments with selected agonists (including $PGF_{2\alpha}$) showed that there was no difference between cumulative and non-cumulative dose-response curves, which agrees with the findings of Drazen & Schneider (1978) using guinea-pig airway preparations.

In general, both human airway preparations responded in some degree to all the agonists tested. However, there were notable differences. Although the bronchus responded well to acetylcholine, the parenchymal strip responded poorly. This contrasted sharply with the reportedly good responsiveness of lung parenchymal strips from other species to cholinomimetics (Lulich *et al.*, 1976; Burns & Doe, 1978; Drazen & Schneider, 1978; Mitchell & Denborough, 1979; Chand, De Roth & Eyre, 1979).

It is possible that parenchymal strips from human lung are histologically different from those of other species. Hence one could suggest that strips from, say, guinea-pig lung contain a greater proportion of central airways which might be expected to be more responsive to acetylcholine. Histological examination of the human parenchymal strips used in these experiments revealed primarily respiratory and terminal bronchioles, alveoli and blood vessels. A similar examination of guinea-pig parenchymal strips revealed mainly small conducting airways, alveoli, and blood vessels in agreement with the findings of Drazen & Schneider (1978) and Mitchell & Denborough (1979). However, the most obvious difference between the two tissues was the presence of large amounts of collagen in the human strips, but very little in the guinea-pig strips. The presence of this non-elastic, non-contractile substance almost certainly explains the generally poor contractility of the human parenchymal strip (this study) in comparison to that of guinea-pig (Mitchell & Denborough, 1979), but does not explain the insensitivity of the human parenchymal strip to acetylcholine when the same tissue responded well to $PGF_{2\alpha}$. It is not clear whether collagen deposition in the human lung was a result of a disease process or the relatively advanced age of most of the patients at the time of surgery. It is conceivable that healthy lung tissue from a young person would more closely resemble histologically that from guinea-pig.

Finally, it is also possible that human lung is quite different from the lung of other species, in that acetylcholine may exert a genuinely selective action on central as opposed to peripheral airways. Although evidence to support or refute this is scant, Dubois & Dautrebande (1958) did observe that inhalation of a carbachol aerosol by human volunteers increased airway resistance but had little effect on dynamic compliance, indicating an action primarily on central airways.

In the present study, $PGF_{2\alpha}$ produced a maximal contraction of the parenchymal strips three times greater than that to histamine or SRS-A. In contrast, Mitchell & Denborough (1979) reported no significant difference in the responses of guinea-pig lung parenchymal strips to histamine or $PGF_{2\alpha}$. This species difference may, once again, be due to the different histological composition of the two preparations.

Table 1 Reversal of response of human airway tissue to partially purified guinea-pig SRS-A by FPL 55712 LL

		IC_{50} (μg/ml)
Bronchial Strip		0.18
		0.21
		0.28
	Mean ± s.e. mean	0.22 ± 0.03
Parenchymal Strip		0.38
		0.22
		0.28
		0.27
		0.52
	Mean ± s.e. mean	0.33 ± 0.05

Results of individual experiments are shown.

In view of the high sensitivity of human parenchymal strips to $PGF_{2\alpha}$, it is noteworthy that sensitized human lung parenchyma releases far more $PGF_{2\alpha}$ when exposed to antigen than does the bronchus, which preferentially releases PGE_2 (Adkinson, Newball, Findley, Adams & Lichtenstein, 1979). It is possible that $PGF_{2\alpha}$ fulfils a major pathophysiological role in small, but not large, airways of human lung.

From the present study, it appears that SRS-A is not a powerful agonist on either bronchial or parenchymal strip of human lung, which contrasts with the widely held belief that human bronchial tissue is particularly sensitive to this agonist. SRS-A also appears to be equiactive on both tissues in comparison to the maximum response produced by the reference agonists (acetylcholine on the bronchial strip and $PGF_{2\alpha}$ on the parenchymal strip). This is in contrast to previous *in vivo* observations which suggest that, at least in the guinea-pig (Drazen & Austen, 1974) and in the monkey (Michoud *et al.*, 1979), SRS-A acts primarily on peripheral airways.

Although SRS-A has long been implicated as an important mediator in asthma, our *in vitro* studies on human airway tissue suggest that its direct contractile actions are not as marked as might be expected. However, asthmatic bronchoconstriction is the result of several mediators acting in concert, so the effects of SRS-A cannot be considered in isolation. For instance, SRS-A can potentiate the effects of other mediators on target tissues (e.g. histamine on guinea-pig ileum: Brocklehurst, 1958) and can also cause the release of other mediators such as prostaglandins (Engineer, Piper & Sirois, 1977) which can themselves induce bronchoconstriction (Berry & Collier, 1964). In the guinea-pig, SRS-A also causes a slight increase in pulmonary resistance; this response is mediated by a vagal reflex (Drazen & Austen, 1975). Furthermore, work in dogs suggests that SRS-A may be implicated in the accumulation of tracheobronchial secretions, which is characteristic of asthma (Wanner, Zarzecki, Hirsch & Epstein, 1975).

Therefore, SRS-A may well play a major role in the pathogenesis of asthma but mechanisms other than a direct contractile action on airway smooth muscle may be more important.

The action of SRS-A on both bronchial strip and parenchymal strip was antagonized by FPL 55712 to a similar extent. The IC_{50} values obtained (Table 1) correlate very closely with the value of 0.25 μg/ml obtained in an earlier study using the human bronchus under slightly different experimental conditions (Sheard, Lee & Tattersall, 1977). It is notable that FPL 55712 is 10 to 20 times more potent in antagonizing the action of SRS-A on guinea-pig ileum, although the ileum is, if anything, slightly less sensitive to SRS-A. This may indicate either that the SRS-A receptors in guinea-pig ileum and human lung are different, or that the receptor in human lung is relatively less accessible to FPL 55712.

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