The contractile action of slow reacting substance of anaphylaxis (SRS-A) on guinea-pig isolated lung strip

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Slow reacting substance of anaphylaxis (SRS-A) causes bronchoconstriction in the guinea-pig (Berry & Collier, 1964). Drazen & Austen (1974) showed that this response comprised a reduction in pulmonary compliance without any change in pulmonary resistance. This suggests a selective constriction of small peripheral, rather than large central, airways. Lulich, Mitchell & Sparrow (1976) have suggested that responses of isolated strips of lung parenchyma to drugs reflect effects on peripheral airways. We have therefore examined the effects of SRS-A on guinea-pig isolated lung strip and compared them with those on guinea-pig isolated ileum, a tissue which is very sensitive to SRS-A (Brocklehurst, 1962).

Preparations were superfused at a rate of 5 ml/min with a modified Krebs solution, gassed with 95% O_2/5% CO_2 and containing atropine (10^{-6}M), mepyramine (3×10^{-6}M) and indomethacin (3×10^{-6}M). Agonists were infused into the superfusion fluid in a volume of 100 µl over a period of 15 s.

Partially purified SRS-A was prepared as follows: peritoneal anaphylactic fluid was obtained as described by Orange, Valentine & Austen (1968) from rats pretreated with indomethacin (1 mg/kg p.o.). This fluid was deproteinised with ethanol. The supernatant was evaporated to dryness, subjected to alkaline hydrolysis (0.1 M NaOH at 37°C for 30 min), evaporated to dryness again and stored as a dry powder at –20°C. Biological activity was expressed in units, 100 units of SRS-A being defined as the quantity necessary to produce a contraction of superfused guinea-pig ileum equal to that produced by 100 ng of PGE_2. This unit is comparable to that defined by Orange & Austen (1969).

SRS-A (3–300 units) caused dose-related contractions of both ileum and lung strip. Sensitivity of the two tissues was similar. Contractions of the ileum were rapid in onset and recovery was complete within 10 min. In contrast, contractions of the lung strip were slow in onset, taking up to 8 min to reach a peak, and recovery was slow, often taking more than 1 h. Responses of both preparations were reduced or abolished by incubation of SRS-A with arylsulphatase (Sigma type V) at pH 5.0 for 2 h, a procedure which inactivates SRS-A (Orange & Austen, 1969). The specific SRS-A antagonist FPL 55712 (Augstein, Farmer, Lee, Sheard & Tatersall, 1973), when infused into the superfusion fluid to give final concentrations of $3 \times 10^{-8} - 10^{-6}$M, antagonised responses of ileum (pA_2 7.5, 95% c.l. 7.3 – 7.7, $n = 12$) and lung strip (pA_2 7.04, 95% c.l. 6.6 – 7.5, $n = 6$) to SRS-A. In both cases the slopes of the Schild plots (Arunlakshana & Schild, 1959) were not significantly different from 1 ($P>0.05$), indicating that the antagonism is competitive. The pA_2 values were however significantly different ($P<0.05$) but further work will be necessary to determine whether this reflects a true difference between the SRS-A receptors in the two tissues.

These results support the suggestion of Drazen & Austen (1974) that SRS-A has a constrictor action on guinea-pig peripheral airways.

References

ARUNLAKSHANA, O. & SCHILD, H.O. (1959). Some quantitative uses of drug antagonists. *Br. J. Pharmac. Chemother.*, **14**, 48–58.

AUGSTEIN, J., FARMER, J.B., LEE, T.B., SHEARD, P. & TATTERSALL, M.J. (1973). Selective inhibitors of slow reacting substance of anaphylaxis. *Nature New Biology*, **245**, 215–217.

BERRY, P.A. & COLLIER, H.O.J. (1964). Bronchoconstrictor action and antagonism of a slow reacting substance from anaphylaxis of guinea-pig isolated lung. *Br. J. Pharmac. Chemother.*, **23**, 201–216.

BROCKLEHURST, W.E. (1962). Slow reacting substance and related compounds. *Progr. Allergy*, **6**, 539–558.

DRAZEN, J.M. & AUSTEN, K.F. (1974). Effects of intravenous administration of slow reacting substance of anaphylaxis, histamine, bradykinin and prostaglandin $F_{2\alpha}$ on pulmonary mechanics in the guinea-pig. *J. clin. Invest.*, **58**, 1679–1685.

LULICH, K.M., MITCHELL, H.W. & SPARROW, M.P. (1976). The cat lung strip as an *in vitro* preparation of peripheral airways: a comparison of β-adrenoceptor agonists, autacoids and anaphylactic challenge of the lung strip and trachea. *Br. J. Pharmac.*, **58**, 71–79.

ORANGE, R.P. & AUSTEN, K.F. (1969). Slow reacting substance of anaphylaxis. *Adv. Immunol.*, **10**, 105–144.

ORANGE, R.P., VALENTINE, M.D. & AUSTEN, K.F. (1968). Antigen-induced release of slow reacting substance of anaphylaxis ($SRS\text{-}A^{rat}$) in rats prepared with homologous antibody. *J. exp. Med.*, **127**, 767–782.