Release of prostaglandins and rabbit aorta contracting substance (RCS) from guinea-pig lung by slow reacting substance of anaphylaxis (SRS-A)

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Guinea-pig lungs previously sensitized to ovalbumin respond to challenge by the release of several mediators including histamine, SRS-A, RCS (thromboxane A_2 (TXA_2) and prostaglandins G_2 and H_2), releasing factor for RCS (RCS-RF) and other prostaglandin-like substances (Piper & Vane, 1969).

SRS-A was prepared from indomethacin-treated isolated perfused lungs from sensitized guinea-pigs as previously described (Engineer, Piper & Sirois, 1976). Histamine was removed and SRS-A concentrated by adsorption onto activated charcoal and elution with 80% ethanol. After evaporation under vacuum the SRS-A was freeze-dried.

Lungs from either sensitized or unsensitized guinea-pigs were perfused with Tyrodes solution via the pulmonary artery at 5 ml/min and the effluent superfused over strips of smooth muscle from guinea-pig ileum, rabbit aorta, rabbit coeliac artery, rat stomach strip and chick rectum. The assay tissues were blocked with mepyramine and hyoscine.

When crude SRS-A was injected directly over the assay tissues it caused contraction of guinea-pig ileum and rat stomach strip but when injected into the pulmonary artery all the assay tissues contracted showing the passage of SRS-A through the pulmonary circulation and the release of RCS and prostaglandin-like substances from the lungs. Following injection of SRS-A into the lungs, RCS-induced contraction of rabbit aorta was matched by injecting PGG_2 over the tissues. Repeated injections of SRS-A released similar amounts of RCS from lungs. Any RCS-RF which might have been present in the samples of SRS-A was destroyed by boiling for 15 min (Flower, Harvey, Moncada, Nijkamp & Vane, 1976) followed by centrifugation for 5 minutes. The biological activity of SRS-A and its ability to release RCS and prostaglandins was unchanged by boiling. Incubation of SRS-A with arylsulphatase for 1 h destroyed the biological activity (Orange, Murphy & Austen, 1974); if the enzyme activity was terminated by boiling, the release of RCS was prevented, but in the absence of boiling there was sometimes a small release, probably due to contamination by RCS-RF. The release of RCS and prostaglandin-like substances by SRS-A was prevented by treating the lungs with indomethacin (1–5 μg/ml) or with dexamethasone (4–40 μg/ml). Furthermore, treatment of the lungs for 15 min with the SRS-A antagonist FPL-55712 (for ref. see Augstein, Lee, Sheard & Tattersall, 1973) (0.1–1.0 μg/ml) also prevented the release of RCS by SRS-A.

These results (a) strengthen the hypothesis that SRS-A released in anaphylaxis (Engineer *et al.*, 1976) might in turn release prostaglandin-related materials to inhibit further release of mediators, and (b) could explain the mechanism of action of steroid and non-steroid anti-inflammatory drugs in acute immunological reactions.

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The relationship between prostaglandin-like substances and SRS-A released from immunologically challenged lungs

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Although the biological activities of certain prostaglandins (PGs), particularly of the F series and slow reacting substance in anaphylaxis (SRS-A) on bronchial smooth muscle are similar, they appear to derive from two different biological precursors. PGs, thromboxanes and hydroxy fatty acids are formed from arachidonic acid by two enzymes, a cyclo-oxygenase and a lipoxygenase, both of which are inhibited by the competitive substrate, eicosatetraynoic acid (TYA). This compound reduced the PGs released on immunological challenge of guinea-pig lungs but did not modify SRS-A release, in contrast to disodium cromoglycate which had the