The effect of arachidonate lipoxygenase substrates and inhibitors on SRS-A release in the guinea-pig lung

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The release of slow reacting substance of anaphylaxis (SRS-A) from guinea-pig lung during antigen challenge is increased by cyclo-oxygenase inhibitors (Engineer, Niederhauser, Piper & Sirois, 1978). This may be a result of inhibition by a cyclo-oxygenase product or re-direction of arachidonic acid (AA) metabolism via the lipoxygenase pathway (Hamberg, 1976; Adcock, Garland, Moncada & Salmon, 1978). Indeed, it has been suggested that SRS-A may be formed from AA by lipoxygenase (Jakschik, Falkenhein & Parker, 1977). The effects of various fatty acids, some of which are substrates for arachidonate lipoxygenase (Nugteren, 1975), on the release of SRS-A were investigated.

Lungs from guinea-pigs previously sensitised to ovalbumin were perfused free of blood and chopped into pieces (1 mm^3). Aliquots (120 mg) were incubated in Tyrode solution at 37°C with or without indomethacin. In each experiment control and test aliquots were from the same lung. Fatty acids and inhibitors were added 30 min before ovalbumin challenge (50 μg/ml) to give a total volume of 3 ml. After 15 min SRS-A released into the supernatant was assayed on superfused longitudinal smooth muscle from guinea-pig ileum in the presence of mepyramine and hyoscine (5×10^{-7} M). Prostaglandin release was estimated in terms of prostaglandin $F_2\alpha$ by radioimmunoassay.

Indomethacin (1 μg/ml) increased the release of SRS-A 81% above control levels. Arachidonic acid (1–50 μg/ml) caused a dose-related increase in SRS-A output up to 162% above control; these doses of AA did not contract the guinea-pig ileum. 5, 8, 11, 14, 17 eicosapentaenoic acid, 4, 7, 10, 13, 16, 19 docosahexaenoic acid and 6, 9, 12 octadecatrienoic acid (10 μg/ml) increased SRS-A release by 100, 22 and 21% respectively. In the presence of indomethacin (1 μg/ml) the release of SRS-A by arachidonic and eicosapentaenoic acids was further increased to 199 and 128%. In all cases, SRS-A was antagonised by FPL 55712 (1 μg/ml). 11, 14 eicosadienoic, 11, 14, 17 eicosatrienoic, 9, 12, 15 octadecatrienoic and oleic acids (10 μg/ml) did not affect the release of SRS-A. In doses of 0.3–100 μg/ml, 12 hydroxy eicosatetraenoic acid (HETE), the stable end-product of action of lipoxygenase on AA, did not potentiate the release of SRS-A. 5, 8, 11, 14 eicosatetraynoic (10 μg/ml) and nordihydroguaiaretic acid (1–50 μg/ml) (Tappel, Lundberg & Boyer, 1953) caused a dose-related inhibition of control release of SRS-A. The release of prostaglandins was unaffected by these doses of nordihydroguaiaretic acid. The indomethacin- or AA-potentiated output of SRS-A was also inhibited by nordihydroguaiaretic acid.

The fatty acids (20:4; 20:3; 20:5 and 22:6) which potentiated SRS-A release have double bonds at n-9 and n-12 (n represents position of double bonds from the terminal methyl group) and are substrates for arachidonate lipoxygenase which has an (n-9) specificity (Nugteren, 1975) whereas the inactive acids are not substrates for this enzyme. Since the output of SRS-A was decreased in the presence of lipoxygenase inhibitors these results suggest that SRS-A release is modulated by some aspect of lipoxygenase action although not affected by the stable end-product HETE.

We thank the M.R.C for a grant and Dr. P. J. Jose for preparing HETE.

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