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Rapid communication

PREVENTION OF ANAPHYLACTIC BRONCHOCONSTRICTION BY A LIPOXYGENASE INHIBITOR

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Important primary mediators in the allergic asthmatic reaction are histamine and slow-reacting substance of anaphylaxis (SRS-A). Until recently metabolites of arachidonic acid were thought to be secondary mediators. However, there have been several indications that SRS-A could be a product of arachidonic acid (Bach et al., 1977; Jakschik et al., 1977). Recently the structure of an SRS from mouse leucocyte mastocytoma has been reported as a novel product of the lipoxygenase pathway of arachidonic acid (Murphy et al., 1979). This substance is now called leukotriene C. It is not known whether leukotriene C is identical to the SRS-A released from the lung.

In this study we investigated the effect of an inhibitor of the lipoxygenase pathway, as well as several 'classic' antagonists of asthmatic mediators on anaphylactic bronchoconstriction.

Male guinea pigs weighing between 300 and 400 g were sensitized with ovalbumin, 100 mg s.c. and 100 mg i.p. and used for the experiment 21-27 days later. Lungs were removed under nembutal anesthesia, suspended in an plexiglass chamber and perfused through the pulmonary artery with Krebs-bicarbonate solution at 10 ml/min. Lungs were rhythmically ventilated (14/min) by an alternating negative pressure of about 11 mm Hg in the artificial thoracic chamber using a Palmer respiratory pump. As a measure of the lung ventilation, the pressure changes in the trachea were recorded by means of a PT5A volumetric pressure transducer (Grass) and displayed on a Grass polygraph. A positive pressure (95% O_2 and 5% CO_2) was continuously maintained in the trachea.

A dose of ovalbumin (0.5-2 μg) was chosen which induced a bronchoconstriction of 20-80%. Accordingly saline (0.9% NaCl solution) or an antagonist was infused in the pulmonary artery for at least 10 min and the dose which induced comparable bronchoconstriction (by doubling doses) was determined again. With this method ovalbumin induced a reproducible bronchoconstriction. Dose-response curves were very steep. Tripling the threshold dose caused 100% bronchoconstriction (complete arrest of lung ventilation).

To investigate which mediator was responsible for the bronchoconstriction, the influence of the H_1-antagonist mepyramine (2×10^{-6} M) and the SRS-A antagonist FPL 55712 (gift of Fisons, England) (1.9×10^{-6} M) was studied. As shown in table 1, histamine seems to play a minor role in the bronchoconstriction since no inhibition occurred with the H_1-antagonist mepyramine. Although not shown in this table, the initial phase of the bronchoconstriction is inhibited, making the curves less steep after mepyramine. In contrast FPL 55712 completely prevented bronchoconstriction, pointing to a major role for SRS-A. Increasing the dose of ovalbumin overcame the inhibition. When mepyramine and FPL 55712 were infused together, the extent of inhibition increased only slightly.

To study whether products formed by the lipoxygenase pathway played a role in the

TABLE 1

Effect of several antagonists on anaphylactic bronchoconstriction in isolated guinea-pig lungs.

Antagonists	Factor of inhibition [1]
Saline	1.2 ± 0.2 (5)
Mepyramine (2×10^{-6} M)	1.3 ± 0.2 (7)
BW 755C (4.4×10^{-5} M)	5.4 ± 1.9 (7) [2]
FPL 55712 (1.9×10^{-6} M)	2.3 ± 0.6 (5) [2]
BW 755C + mepyramine	5.5 ± 1.5 (4) [3]
FPL 55712 + mepyramine	3.1 ± 0.6 (7) [2]
Indomethacin (5.6×10^{-7} M)	0.6 ± 0.1 (5) [2]

[1] The mean of the ratios in individual animals of „the dose of ovalbumin to induce comparable bronchoconstriction before and after the antagonist" is called factor of inhibition.
[2] Levels of significance refer to differences between absolute values before and after the antagonist. $P < 0.05$.
[3] $P < 0.02$.

bronchoconstriction, the lipoxygenase inhibitor BW 755C (gift of the Wellcome Research Laboratories, England) was used (Higgs et al., 1979). As shown in table 1, this compound (4.4×10^{-5} M) completely prevented bronchoconstriction. Doses of ovalbumin had to be increased by a factor 5.5 for the effect to reappear. Addition of mepyramine did not result in additional inhibition.

Since BW 755C also inhibits the cyclooxygenase pathway, the prostaglandin-synthesis inhibitor indomethacin was tested. Indomethacin (5.6×10^{-7} M) however, did not prevent the bronchoconstriction, but even potentiated the response. Presumably therefore prostaglandins do not contribute to the bronchospasm caused by ovalbumin. The potentiation probably is due to an increased liberation of SRS-A after indomethacin (Liebig et al., 1974). A shift of the arachidonic acid metabolism from the cyclooxygenase pathway to the lipoxygenase pathway may explain this phenomen.

In conclusion our results suggest that product(s) formed by the lipoxygenase pathway play a major role in the anaphylactic bronchoconstriction.

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