The biological significance of prostaglandin-like substances released from immunologically challenged guinea-pig lungs

J.R. BOOT, W. DAWSON & D.J. OSBORNE

Lilly Research Centre Limited, Erl Wood Manor, Windlesham, Surrey GU20 6PH

Nine prostaglandin (PG)-like substances have been identified in the perfusate from challenged sensitized guinea-pig lungs perfused *in vitro*. They account for 94% of the total PG-like material released (1.3–1.8 μg/pair of lungs). These figures were derived from 3 groups of 200 guinea pigs and were compared with a non-sensitized group of animals challenged and extracted similarly. No PG-like material was detected in the control perfusate.

These compounds have been tested on a variety of smooth muscle preparations derived from gut and respiratory tree, on pulmonary perfusion pressure *in vitro*, systemic blood pressure on anaphylactic mediator release and on chemotaxis.

Three of the substances, $PGF_{2\alpha}$ (0.6%), 15-oxo $PGF_{2\alpha}$ (6%) and 6-oxo $PGF_{1\alpha}$ (11%) have spasmogenic activity, particularly on respiratory smooth muscle, and each increased pulmonary vascular resistance. 6-oxo $PGF_{1\alpha}$ had $\frac{1}{2}$–$\frac{1}{3}$ the activity of $PGF_{2\alpha}$ in both systems whilst 15-oxo $PGF_{2\alpha}$ had $\frac{1}{10}$–$\frac{1}{3}$ the activity. 6-oxo $PGF_{1\alpha}$ is a novel PG identified in these laboratories (Dawson, Boot, Cockerill, Mallen & Osborne, 1976) and its biological activity is of considerable interest. PGE_2 (1%) and 15-oxo PGE_2 (trace) were the only substances detected which were capable of relaxing bronchial smooth muscle, the latter having the activity of PGE_2.

Thromboxane B_2 (TxB_2), released from challenged chopped lung preparations (Hamberg & Samuelsson, 1974) was also released in this system (30%) and was minimally active on smooth muscle preparations at high (10 μg/ml) concentrations. A metabolite of TxB_2, 15-oxo 13,14-dihydro TxB_2 was also identified (42%) but was devoid of spasmogenic activity. This metabolic conversion of TxB_2 was confirmed using guinea-pig lung homogenates and a high speed supernatant preparation derived from this tissue, both of which converted purified TxB_2 to its metabolite. There was no indication of either the 15-oxo or 13,14-dihydro compounds analogous to the metabolites of the parent PGs.

The 15-oxo 13,14-dihydro metabolites of PGE_2 (trace) and $PGF_{2\alpha}$ (3%) were isolated but were without activity in any of the systems studied.

$PGF_{2\alpha}$ (0.5 μg/ml) and TxB_2 (1–5 μg/ml), increased the synthesis and release of slow reacting substance in anaphylaxis (SRS-A) from challenged guinea-pig chopped lung preparations whilst PGE_2 (0.5 μg/ml) reduced SRS-A release. Sufficient TxB_2 is released on challenge to achieve this concentration in the lung.

There are at least two components of this immunological reaction in which PG-like substances are involved: direct bronchoconstrictor activity of the PGs and the modification of mediator release. Of the nine compounds, only TxB_2 has been shown to be chemotactic (Boot, Dawson & Kitchen, 1976) and could perhaps develop the inflammation commonly associated with allergic responses in the lung. The interaction with the adenyl and guanyl cyclase systems has not been studied but this could be a possible third component of PG involvement (Lichstenstein, Gillespie, Bourne & Henney, 1972).

References

BOOT, J.R., DAWSON, W. & KITCHEN, E.A. (1976). The chemotactic activity of Thromboxane B_2, a possible role in inflammation. *J. Physiol. (Lond.)*, **257**, 47–48P.

DAWSON, W., BOOT, J.R., COCKERILL, A.F., MALLEN, D.N.B. & OSBORNE, D.J. (1976). The release of novel prostaglandins and thromboxanes after immunological challenge of guinea-pig lung. *Nature (Lond.)*, (in press).

HAMBERG, M. & SAMUELSSON, B. (1974). Prostaglandin endoperoxides. VII. Novel transformations of arachidonic acid in the guinea-pig lung. *Biochem. Biophys. Res. Commun.*, **61**, 942–949.

LICHSTENSTEIN, L.M., GILLESPIE, E., BOURNE, H.R. & HENNEY, C.S. (1972). The effects of a series of prostaglandins on *in vitro* models of the allergic response and cellular immunity. *Prostaglandins*, **2**, 519–528.