Prostaglandins and the lung

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Summary

Evidence exists implicating prostaglandins as mediators of asthma and of chronic inflammation in the lung. In addition to their spasmogenic effects, PGs are also potent *in vitro* regulators of mediator secretion by basophils, mast cells, or lymphocytes. These regulatory effects of E-series PGs may have considerable significance in drug design and evaluation in both asthma and chronic inflammation.

PROSTAGLANDINS (PGs) and their metabolites are smooth muscle spasmogens and consequently have been proposed as potential mediators of inflammation in the lung, particularly as mediators of bronchospasm in asthma. Thus, there is evidence of prostaglandin formation by the isolated lung in response to physical, chemical and immunological stimuli. Yet it is increasingly evident that underlying both the bronchial reactivity of asthma and the fibrosis and other features of chronic inflammation, there are regulatory devices which, in normal circumstances, serve to control the intensity and duration of responses, but which may also participate in disease.

In asthma, three lines of evidence suggest PG involvement. Firstly, immunological challenge causes release of PGs and their metabolites in animals (Boot, Dawson and Osborne, 1976) and in man (Grn, Hedqvist and Svanborg, 1974). Secondly, PGE₂ exhibits bronchodilator actions whilst PGF₂ is a potent bronchoconstrictor in asthmatics (Math *et al.*, 1973). Thirdly, aspirin-induced asthma shows cross-reactivity with other acid non-steroidal anti-inflammatory drugs (ANSAIDs) (Szczeklik, Gryglewski and Czemiwska-Mysik, 1975). As bronchodilators, natural and synthetic PGs have proved poorly effective as therapeutic agents, producing only a modest bronchodilatation together with discomforting side effects. The other property of PGs that commands attention is the pronounced capacity of PGE₁ and PGE₂ to inhibit mediator release from mast cells (Lichtenstein, 1973), providing a basis for the ANSAIDs to enhance slow reacting substance

of anaphylaxis (SRS-A) release from passively sensitized lung (Walker, 1973). This may be of relevance to asthma, though it should be noted that classical extrinsic asthma seems unaffected by ANSAIDs and that in allergic responses of guinea-pig skin, PGE₁ potentiates the response (Williams and Morley, 1973), whilst ANSAIDs suppress Type I and Type III responses (Morley and Paul, 1975). This may reflect differences between skin and lung tissues because thromboxane B₂ enhances PG release in lung, but appears inert in skin. The participation of PGs in regulation of allergic responses appears likely, but to date does not appear to have found therapeutic application.

Although considerable evidence has been assembled to support PG involvement in chronic inflammation (Vane, 1976), there has been an emphasis upon rheumatoid arthritis and associated animal models. The isolated rheumatoid synovium produces PGE₂-like material (Kantrowitz *et al.*, 1975) in quantities sufficient to account for symptoms of pain, swelling and erythema. The cellular origin of this material would appear to be the macrophage and the capacity of alveolar macrophages and fragments of lung tissue to produce PGE activity suggests their potential involvement in inflammation. The capacity of macrophage PG production to be stimulated by lymphocyte products (lymphokines) (Gordon, Bray and Morley, 1976) and by macrophage products (C_{3b}) (Schorlemmer *et al.*, 1977) explains how PG formation can be interrelated to the presumed allergic dysfunction. Furthermore, the capacity of PGE₁ and PGE₂ to inhibit lymphokine secretion suggests a mechanism for chronicity, namely, defective reactivity of lymphocytes to endogenous PGE₂. Such a defect has been demonstrated in a series of multiple sclerosis patients (Kirby *et al.*, 1976) and is also evident in cryptogenic fibrosing alveolitis. The therapeutic implications of this relationship between lymphocytes and macrophages remains to be established, but the discomforting prediction that ANSAIDs may exacerbate production of certain mediators has already been demonstrated for

collagenase (Dayer, Robinson and Krane, 1977) and would seem of relevance in drug design.

References

- BOOT, J.R., DAWSON, W. & OSBORNE, D.J. (1976) The biological significance of prostaglandin-like substances released from immunologically challenged guinea-pig lungs. *British Journal of Pharmacology*, **58**, 471.
- DAYER, J.-M., ROBINSON, D.R. & KRANE, S. (1977) Action of anti-inflammatory drugs on synovium. In: *Rheumatoid Arthritis* (Ed. by J. L. Gordon and B. L. Hazleman), p. 117. Elsevier/North-Holland Biomedical Press, Amsterdam.
- GORDON, D., BRAY, M.A. & MORLEY, J. (1976) Control of lymphokine secretion by prostaglandins. *Nature*. London, **262**, 401.
- GRÉEN, K., HEDQVIST, P. & SVANBORG, N. (1974) Increased plasma levels of 15-keto-13,14-dihydro prostaglandin $F_{2\alpha}$ after allergen provoked asthma in man. *Lancet*, **ii**, 1419.
- KANTROWITZ, F., ROBINSON, D.R., MCGUIRE, M.B. & LEVINE, L. (1975) Corticosteroids inhibit prostaglandin production by rheumatoid synovia. *Nature*. London, **258**, 737.
- KIRBY, P.J., MORLEY, J., PONSFORD, J.R. & McDONALD, W.I. (1976) Defective PGE reactivity in leucocytes of multiple sclerosis patients. *Prostaglandins*, **11**, 621.
- LICHTENSTEIN, L.M. (1973). The control of IgE-mediated histamine release: Implications for the study of asthma. In: *Asthma* (Ed. by K. F. Austen and L. M. Lichtenstein), p. 91. Academic Press, London.
- MATHÉ, A.A., HEDQVIST, P., HOLMGREN, A. & SVANBORG, N. (1973) Bronchial hyperreactivity to prostaglandin $F_{2\alpha}$ and histamine in patients with asthma. *British Medical Journal*, **1**, 193.
- MORLEY, J. & PAUL, W. (1975) Evaluation of anti-inflammatory drugs on allergic inflammation. *Proceedings of VIth International Congress of Pharmacology*, Helsinki. Abstract No. 843.
- SCHORLEMMER, H.U., EDWARDS, J.H., DAVIES, P. & ALLISON, A.C. (1977) Macrophage responses to mouldy hay dust *Micropolyspora faeni* and zymosan, activators of complement by the alternative pathway. *Clinical and Experimental Immunology*, **27**, 198.
- SZCZEKLIK, A., GRYGLEWSKI, R.J. & CZEMIAWSKA-MYSIK, G. (1975) Relationship of inhibition of prostaglandin biosynthesis by analgesics to asthma attacks in aspirin-sensitive patients. *British Medical Journal*, **1**, 67.
- VANE, J.R. (1976) The mode of action of aspirin and similar compounds. *Journal of Allergy and Clinical Immunology*, **58**, 691.
- WALKER, J.L. (1973) The regulatory function of prostaglandins in the release of histamine and SRS-A from passively sensitized human lung tissue. *Advances in Bioscience*, **9**, 235.
- WILLIAMS, T.J. & MORLEY, J. (1973) Prostaglandins as potentiators of increased vascular permeability in inflammation. *Nature*. London, **246**, 215.