Release of vaso-active substances from lungs by injection of particles

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The infusion of various suspensions of particles into dog isolated spleens perfused with Krebs solution caused a release of prostaglandins E_2 and $F_{2\alpha}$ into the effluent (Gilmore, Vane & Wyllie, 1969). Infusions of suspensions of particles into perfused lungs from guinea-pigs and rats also caused a release of prostaglandin E_2 (Lindsey & Wyllie, 1970). We have now used the same suspensions (Prosparol and Sephadex G 10) as Lindsey and Wyllie (1970), together with another (Bacto-latex) and have detected the release, not only of prostaglandins but also of rabbit aorta contracting substance (RCS; Piper & Vane, 1969) and possibly histamine.

Lungs were removed from guinea-pigs which had previously been sensitized to ovalbumen and perfused at 5 ml/min with Krebs solution at 37° C via the pulmonary artery. The effluent from the lungs was superfused over a series of assay tissues which included cat terminal ileum, to detect histamine, rabbit aorta, to detect RCS, and rat stomach strip, rat colon and chick rectum, to detect prostaglandins. All the assay tissues except cat terminal ileum were superfused with a mixture of antagonists (Piper & Vane, 1969) which eliminated any activity due to histamine, 5-hydroxytryptamine, catecholamines or acetylcholine. Pulmonary arterial pressure was measured from a side arm of the pulmonary arterial cannula.

Prosparol is a 50% v/v emulsion of arachis oil in water with a particle size of 1–2 μm (Lindsey & Wyllie, 1970). When 0·5–1 ml was injected into sensitized guinea-pig lungs there was a rise in pulmonary arterial pressure of 4–64 mmHg and a release of RCS and prostaglandins. The prostaglandin release when assayed as E_2 ranged from 2 to 20 ng/ml (five experiments). Prosparol given directly to the assay tissues did not cause contraction. The amounts of RCS and prostaglandins released by Prosparol were compared in the same lungs to the amounts released by injection of ovalbumen (10 mg). In all but one instance, the release in anaphylaxis was greater.

Sephadex G 10 has a particle size of 40–120 μm (Lindsey & Wyllie, 1970). When 0·2 ml of a 33% v/v suspension of Sephadex G 10 in Krebs solution was injected into the pulmonary artery, there was also a release of RCS and prostaglandins, but the amounts released were smaller than with Prosparol. In one experiment, a cat terminal ileum was included in the assay system. After injection of Sephadex into the lungs, there was a small release of histamine ($<$0·1 μg/ml) as well as of RCS and prostaglandins.

Bacto-latex 0·81 consists of particles of polystyrene latex of 0·81 μm in diameter. Neither the Bacto-latex suspension nor the suspending fluid affected the assay tissues, but injections of Bacto-latex (0·2 ml) into the pulmonary artery released RCS and prostaglandins into the effluent.

Thus some and possibly all of the mediators of anaphylaxis in the guinea-pig can be released by injection of particles into the sensitized lungs. Some of these mediators have broncho-constrictor and pulmonary vaso-constrictor activity. They may, therefore, be implicated in the changes in lung function which develop after pulmonary embolism in the dog (Thomas, Stein, Tanabe, Rege & Wessler, 1964) and perhaps also in man.

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REFERENCES

GILMORE, N. J., VANE, J. R. & WYLLIE, J. H. (1969). Prostaglandin release by the spleen in response to infusions of particles. In *Prostaglandins, Peptides and Amines*, ed. Mantegazza, P. & Horton, E. W., pp. 21–20. London: Academic Press.

LINDSEY, H. E. & WYLLIE, J. H. (1970). Release of prostaglandins from embolized lungs. In the Press.

PIPER, PRISCILLA J. & VANE, J. R. (1969). Release of additional factors in anaphylaxis and its antagonism by anti-inflammatory drugs. *Nature, Lond.*, **223**, 29–35.

THOMAS, D. P., STEIN, M., TANABE, G., REGE, V. & WESSLER, S. (1964). Mechanism of bronchoconstriction produced by thromboemboli in dogs. *Am. J. Physiol.*, **206**, 1207–1212.

A comparison of the effects of betamethasone and tetracosactrin on hypothalamo-pituitary-adrenal activity in the rat

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Hypothalamo-pituitary-adrenal function may be impaired after therapy with corticosteroids or corticotrophin (ACTH). Hypothalamo-pituitary-adrenal activity was studied in male albino Sprague-Dawley rats which had been given prolonged treatment with betamethasone [Betnesol, Glaxo (40 μg/100 g)/24 h for 2 weeks] in the drinking water, or with tetracosactrin (Cortrosyn Depot, Organon 10 μg/100 g injected subcutaneously once a day).

The growth rate of the rats was impaired less by tetracosactrin than by betamethasone. The normal circadian rhythm and the stress-induced rise in plasma corticosterone concentration were absent following treatment with either the steroid or tetracosactrin. Betamethasone-treated rats showed adrenal atrophy and insensitivity to exogenous corticotrophin, in contrast to tetracosactrin-treated animals, in which there was adrenal hypertrophy and an exaggerated plasma corticosterone rise in response to exogenous ACTH.

Both tetracosactrin and betamethasone cause impairment of hypothalamo-pituitary-adrenal function. The effect of betamethasone is due both to insensitivity of the adrenals to ACTH and to an inability of the hypothalamo-pituitary complex to mobilize endogenous corticotrophin. Tetracosactrin, however, leaves adrenal sensitivity unaffected but inhibits ACTH secretion markedly. The findings suggest that the clinical use of ACTH to aid withdrawal of corticosteroids may be contra-indicated.

The relationship between ascorbic acid concentrations and cortisol production during the development of scurvy in the guinea-pig

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Male guinea-pigs weighing 400 g were fed on an ascorbic acid deficient diet for two weeks with a daily oral supplement of 50 mg of vitamin C, before being given the diet without the supplement for a period of 27 days. Ascorbic acid and cortisol