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Comparison of pulmonary prostaglandin inactivation in normal and sensitized guinea-pig lungs

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Several observations suggest that the process of sensitization as well as of anaphylaxis causes changes in the activity of the pulmonary prostaglandin system of guinea-pigs. Mathé et al (1977) showed that the spontaneous release of immunoassayable prostaglandins (PG) E, $F_{2\alpha}$ and 13,14-dihydro-15-keto $PGF_{2\alpha}$ was greater in sensitized than normal perfused lungs, and increased further upon anaphylactic challenge. Sensitization increased the capacity of lungs to convert arachidonic acid to thromboxane metabolites at the expense of the prostacyclin pathway (Boot et al 1978). Prostaglandin inactivation has been less intensively studied. Piper & Vane (1969) tested PGE_2 and $PGF_{2\alpha}$ inactivation using superfusion cascade bioassay but in a limited series of experiments did not report any differences in lungs from normal and sensitized animals, whereas Kitamura et al (1976) found a substantial decrease in the inactivation of PGE_1 and $PGF_{2\alpha}$.

Using radiochemical assays we have investigated the pulmonary inactivation of prostaglandins $F_{2\alpha}$, E_1 and thromboxane B_2 (TXB_2) in lungs from normal and ovalbumin-sensitized guinea-pigs, both before and after anaphylactic challenge.

Lungs from male Dunkin Hartley guinea-pigs, preinjected 2 to 4 weeks earlier with 0·9% NaCl (saline) or with ovalbumin for sensitization (Mathé et al 1977), were removed and perfused at 10 ml min^{-1} with warmed well-oxygenated Krebs solution essentially as described (Robinson & Hoult 1980). Each lung was perfused six times with 10 ng ml^{-1} tritiated PGE_1 or $PGF_{2\alpha}$ solution (0·02 μCi ml^{-1}) for 2 min periods, three times before and three after injection of 10 mg albumin. Effluents were generally collected for 4 min, although in TXB_2 experiments lungs were perfused once only for 5 min. The extent of conversion to metabolites was measured after ethyl acetate extraction and thin layer chromatography (see Robinson & Hoult 1982). Recovery of tritium label was greater than 90% for $PGF_{2\alpha}$ and PGE_1 and 50–60% for TXB_2.

Table 1 shows that the extent of pulmonary inactivation (measured as conversion to less active 15-keto and 13,14-dihydro-15-keto metabolites, these being the only radioactive metabolites detected) was $PGF_{2\alpha} > PGE_1 > TXB_2$ at this substrate concentration (10 ng ml^{-1} ≈ 30 nM), and that it was the same for all three substrates in lungs from normal and sensitized animals. Thus ovalbumin sensitization does not produce any functional change in pulmonary prostaglandin inactivation.

Table 1. Inactivation of prostaglandins in guinea-pig lungs before and after challenge with 10 mg ovalbumin.

	Percent conversion to metabolites		
	$PGF_{2\alpha}$	PGE_1	TXB_2
Normal lungs:			
pre-challenge	87·3±1·7	69·4±2·9	29·1±3·0
post-challenge	64·9±5·7[a]	57·6±3·6[b]	not tested
Sensitized lungs:			
pre-challenge	79·6±4·2	71·9±2·1	32·4±7·6
post-challenge	59·4±6·1[c]	55·7±4·1[d]	not tested

Results show mean ± s.e.m. for 12 tests on 4 lungs (PGE_1, $PGF_{2\alpha}$) or 10 and 5 tests for TXB_2 on 10 normal and 5 sensitized lungs, respectively. Statistical differences with respect to pre-challenge value: a = $P < 0·002$, b = $P < 0·02$. c = $P < 0·05$, d = $P < 0·01$, Student's unpaired *t*-test.

Following anaphylactic shock in the challenged sensitized lungs there was a significant decrease in $PGF_{2\alpha}$ and PGE_1 inactivation (of 25·4 and 22·5%, respectively) but similar decreases occurred in the normal lungs challenged in this way (Table 1). We believe that this is a non-specific effect indicative of progressive deterioration in the condition of the lung; on reviewing the data concerning the 32 sets of triplicated infusions of PG (16 sets of which were after antigen challenge), we find that the third infusion results in less enzymatic breakdown than the first in 26 cases, although the differences are small.

This impression of progressive deterioration even within the 120-min timescale of these experiments was confirmed by testing $PGF_{2\alpha}$ and PGE_1 inactivation in two sets of triplicated infusions from normal animals, but without injecting ovalbumin after the first set of 3 tests. Breakdown of $PGF_{2\alpha}$ decreased from 84·1 ± 3·7% to 64·5 ± 9·8%, $P < 0·05$, in the second set of infusions; that of PGE_1 decreased from 84·6 ± 3·9% to 63·0 ± 10·2%, $P < 0·05$. Visual inspection showed that lungs became oedematous in all experiments (this can be prevented by adding a colloid oncotic agent such as albumin (Robinson & Hoult 1982), although there can be no direct correlation between the extent of oedema and decreasing capacity to inactivate prostaglandins because, as expected, oedema was greater after anaphylaxis (e.g. wet to dry weight ratio of 18·5 and 11·4 in ovalbumin-challenged anaphylactic or normal

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lungs, respectively, values show mean of 2 measurements after 120 min perfusion).

Bakhle (1982) has shown that oedema induced in the rat in vivo causes a small reduction in the ex vivo pulmonary metabolism of PGE_2. However, there is no systematic study of the effects of oedema on the pulmonary inactivation of prostaglandins despite the fact that cyclo-oxygenase products may be important vasoactive mediators in primary pulmonary or non-cardiogenic oedema (reviewed by Brigham & Ogletree 1981).

We have shown elsewhere that the antigenic challenge elicits an anaphylactic response under the conditions used here (Robinson and Hoult 1980). In parallel experiments in this series we found that release into the effluent of immunoassayable 6-keto $PGF_{1\alpha}$, PGE_2 and $PGF_{2\alpha}$ was greater after antigen challenge in sensitized than in normal lungs ($1{\cdot}19 \pm 0{\cdot}25$ versus $0{\cdot}40 \pm 0{\cdot}07$, $P < 0{\cdot}01$; $0{\cdot}60 \pm 0{\cdot}09$ v. $0{\cdot}36 \pm 0{\cdot}05$, $P < 0{\cdot}05$ and $0{\cdot}27 \pm 0{\cdot}07$ v. $0{\cdot}15 \pm 0.04$, n.s., $n = 16$ from 4 lungs in each group, all values as ng ml^{-1} in perfusates collected 20 to 480 s after challenge). Previous mass spectrometric analysis of anaphylactic guinea-pig lung perfusates has demonstrated these prostaglandins in the same order of abundance (Dawson et al 1976), but we were unable to assay immunologically for thromboxanes and prostaglandin metabolites which are present in larger amounts (Liebig et al 1974; Dawson et al 1976; Mathé et al 1977; Anhut et al 1978).

In summary, by studying the pulmonary inactivation of three prostaglandins we have failed to confirm the preliminary finding of others that this process is altered by sensitization or anaphylactic shock. Small time-dependent reductions in pulmonary degradation always occur in the absence of a colloid oncotic agent and may be related in part to the onset of oedema.

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Rate limiting steps in metabolite kinetics: formation of 5-acetylaminosalicylate after administration of 5-aminosalicylate

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There are numerous examples of commonly prescribed drugs that have clinically important active metabolites (Drayer 1976; Atkinson & Strong 1977). In certain cases these active metabolites have been developed as drugs in their own right. The need to characterize the time course for an active metabolite in the body following administration of the parent drug has necessitated the development of certain pharmacokinetic models. We report information on the formation of the acetyl conjugate of 5-aminosalicylate after intravenous and oral administration of drug. The unusual behaviour apparent is discussed in relation to the more frequently encountered metabolite kinetic profiles.

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Based on mass balance considerations, the rate of change of the amount of metabolite in the body is dependent upon both its formation rate and its elimination rate. Hence

$$V(m).\frac{dC(m)}{dt} = fm.CL.C - CL(m).C(m) \quad (1)$$

where the first term on the right hand side of this equation is concerned with metabolite formation. CL and C are the plasma clearance and concentration of parent drug, respectively, and fm is the fraction of the dose administered which is converted to the metabolite. The second term denotes metabolite elimination where CL(m) and C(m) are the plasma clearance and concentration of metabolite. V(m) is the metabolite volume of distribution.