Time-dependent pro- and anti-inflammatory effects of prostaglandin (PG) E_1 on experimental granulomata in rats

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Locally administered prostaglandins (PGs) inhibit and dietary-induced prevention of local PG synthesis stimulates experimental granuloma production in rats (DiPasquale, Rassaert, Richter, Welaj & Tripp, 1973; Bonta, Parnham & Adolfs, 1977). However, the sensitivity to PGE of the exudative component in carrageenin pouch granuloma is reversed with time (Chang & Tsurufuji, 1976). Therefore, we have studied the possible time dependency of changes in the sensitivity of experimental granuloma formation to inhibition by PGE_1.

Polythene cannulae (inner diameter 0.8 mm) were inserted into polyether sponges (4 × 1.5 × 0.5 cm), which were then implanted sub-cutaneously (2 per rat), under ether anaesthesia, into male Wistar rats (195–250 g), the cannulae being exteriorised at the back of the neck. Two per cent sodium carrageenin (1 ml, with or without PGE_1) was injected into the sponges and the incisions closed by stitching. The animals were balanced according to weight and received subsequent injections (see table 1) through the indwelling cannulae, which were closed with tube sealer after each injection. After killing rats with chloroform, 6 h or 8 days after implantation, sponges and attached tissue were removed. Exudates and cells were collected by centrifugation into 5 ml heparinized saline (Higgs, Harvey, Ferreira & Vane, 1976), total leucocytes counted in a Coulter counter and sponges (plus tissue) dried at 80°C for 24 h before weighing.

PGE_1 (1 μg/sponge), administered with the carrageenin, enhanced exudate production at 6 h from 0.58 ± 0.06 ml (± s.e. mean, $n = 5$) to 0.94 ± 0.10 ml ($P<0.01$). Total leucocyte counts were unaltered (0.81 ± 0.12 (×10^8) cells and 0.65 ± 0.05 (×10^8) cells, respectively). In the same group, after 8 days, PGE_1 treatment significantly increased granuloma formation (table 1). Daily treatment with PGE_1 (1 μg/sponge) on days 1–3, had no effect whatever, whereas the same dose, on days 4–7, inhibited granuloma production, measured on day 8 (table 1). None of the treatments altered exudate volume or leucocyte counts by day 8.

These results indicate that early increases in local PGE potentiate acute exudation and subsequent granuloma formation, whereas, during later stages, PGE inhibits tissue proliferation, as suggested by other data (see Bonta & Parnham, 1977).

Table 1 The effects of locally administered PGE_1 on various parameters of 8 day carrageenin-impregnated sponge granulomata

Treatment	On implantation (day 1)		Days 1–3		Days 4–7	
	Carrageenin only	PGE_1 (1 μg)†	Saline (0.5 ml/day)†	PGE_1 (1 μg/day)†	Saline (0.5 ml/day)†	PGE_1 (1 μg/day)†
Body wt., Day 8(g)	225.6 ± 10.2	231.4 ± 7.4	205.8 ± 4.6	204.6 ± 1.5	208 ± 2.4	202.6 ± 3.3
Exudate vol. (ml)	2.60 ± 0.28	2.94 ± 0.23	2.36 ± 0.21	2.18 ± 0.25	2.52 ± 0.14	3.36 ± 0.58
Total Leucocytes (×10^8)	1.95 ± 0.59	3.18 ± 0.66	2.54 ± 0.70	2.38 ± 0.30	1.94 ± 0.22	2.11 ± 0.24
Dry granuloma wt (mg)	776 ± 69	1013 ± 75**	706 ± 30	630 ± 62	1031 ± 77	798 ± 43**
Dry granuloma wt (mg)/100 g Body wt	348 ± 35	440 ± 34*	343 ± 15	308 ± 31	492 ± 38	395 ± 23**

Values are means ± s.e. mean from 5 animals (10 sponges) per treatment group. Each of the 2 sponges per rat received the same treatment († dose per sponge) and cell counts and exudate volumes were determined using pooled samples from each rat. Significance of differences (saline v. PGE_1) was determined by Student's t test: *$P<0.05$; **$P<0.01$.

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Comparison of the effects of prostaglandin analogues on rabbit platelets, rabbit isolated vascular tissues and rabbit skin microvasculature

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The unstable prostaglandin endoperoxides produce platelet aggregation (Hamberg & Samuelsson, 1974), contract rabbit aorta (Vargaftig & Zirinis, 1973, Willis, 1974), and produce a transient vasoconstriction in the microvasculature followed by a dilatation (Lewis, Westwick & Williams, 1977. Prostaglandin E_2 produces no platelet aggregation, has no activity on rabbit aorta, but it is a potent vasodilator. We have examined a range of stable prostaglandin analogues in order to evaluate their structure-activity relationships to the parent compounds. This has been investigated *in vitro* using rabbit platelet aggregation (Gordon & Drummond, 1974) and isolated vascular smooth muscle (Furchgott & Badrakom, 1953; Bunting, Moncada & Vane, 1976), and *in vitro* by measuring rabbit skin blood flow (Williams, 1976).

The bicyclic compounds resembled the endoperoxides in that they produced aggregation and rabbit aorta contracting activity (see Table 1). ICI 86841 showed less aggregating activity and less activity on blood flow (significant only at high doses). All the bicyclic compounds tested, with the notable exception of azo PGH_2 were active on the rabbit aorta. From the above results it might appear that reductions in blood flow were due to thrombus formation *in vivo*. However, Wy 40659 was a potent aggregatory substance (equipotent with Wy 19110), with no activity on blood flow. Thus, in general, an observed reduction in blood-flow probably represents vasoconstriction. These two compounds (Wy 40659, Wy 19110) had similar activity on rabbit aorta.

For the monocyclic compounds to be potent vasoconstrictors they appear to require both 11-deoxy and 16-methyl groups. Compounds having only 11-deoxy groups, or 15-methyl groups, or 16-methyl groups, were found to be vasodilators. These compounds resembled PGE_2 itself, having poor aggregatory activity, low activity on rabbit aorta, relaxant activity on rabbit mesenteric artery, but potent vasodilatator activity *in vivo*. The exception to this was Wy 18189, which showed some aggregatory activity.

The bicyclic compounds tested resemble the endoperoxides in their structure and aggregatory activity. The correlation with vasoconstrictor activity suggests that native endoperoxides are vasoconstrictors. This probably explains the transient vasoconstriction which we have previously observed with PGG_2.

The lack of correlation between *in vitro* responses (eg to ICI 86841, Wy 40659, Wy 18189) indicates that responses of isolated vascular strips do not necessarily predict microvascular activity *in vivo*.

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