Effects of prostaglandin analogues on rat carrageenan-induced paw oedema

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It has been proposed that prostaglandins are mediators of acute inflammatory responses (Vane, 1972). Prostaglandins are released in inflammatory reactions in animals and man (Willis, 1969; Greaves, Søndergaard & McDonald-Gibson, 1971) and the inhibition of swelling in models such as carrageenan oedema has been correlated with an inhibition of prostaglandin synthesis (Flower, Gryglewski & others, 1972; Smith, Ford-Hutchinson & others, 1974). The administration of prostaglandin E_1 alone into the hind paw of the rat produces only slight oedema (Arora, Lahiri & Sanyal, 1970) and prostaglandins have been reported to play a modulatory rather than a direct role in inflammation. Both prostaglandin E_1 and E_2 greatly potentiate paw oedemas produced by the sub-plantar injection of carrageenan and this action is said primarily to be due to a modulation of kinin activity (Moncada, Ferreira & Vane, 1973; Lewis, Nelson & Sugrue, 1975). Recently it has been suggested that other short-lived, but potentially more active, prostaglandin-type compounds such as the prostaglandin endoperoxides (PGG_2 and PGH_2) may be more important than prostaglandins E_1 and E_2 as mediators of inflammation (Kuehl, Egan & others, 1977). Because of the instability of these compounds it is difficult to investigate their *in vivo* action directly. However, a number of synthetic endoperoxide analogues have been produced which show similar biological activity to the prostaglandin endoperoxides in that they possess rabbit aorta-contracting and platelet aggregatory activity (MacIntyre, Westwick & Williams, 1978a) and these compounds have been used as models to investigate the potential role of endoperoxides in animal models (Frame & Main, 1977).

Oedema formation was induced in the hind paw of female Wistar rats (150–180 g) by the injection of 0·1 ml of a 1% w/v suspension of carrageenan in Tyrode solution. Paw volumes were monitored with a mercury plethysmograph at 15 min intervals for up to 3 h. Prostaglandins and prostaglandin analogues were stored in ethanol and 5 μl aliquots (200 μg ml^{-1}) were added to 1 ml portions of the carrageenan suspension.

The administration of carrageenan in Tyrode produced a reproducible biphasic increase in paw volume which reached a maximum at 5 h. The administration of Tyrode alone produced no change in paw volume. Both PGE_1 and PGE_2, but not 6-oxo-$PGF_{1\alpha}$, (0·1 μg/rat) greatly potentiated the response to carrageenan, the effect with PGE_1 being greater than that observed with PGE_2 (Fig. 1). Unlike previous observations (Moncada & others, 1973; Lewis & others, 1975) a biphasic potentiation of the response was observed. This may reflect the sequential release of mediators reported for this model by Vinegar, Macklin & others, (1974). On this basis the increase observed at 30 min would be due primarily to a potentiation of a histamine response and the peak potentiation at 90 min would represent potentiation of kinin responses.

Three bicylic prostaglandin analogues were tested in the system (15(S)-hydroxy-11α,9α-epoxy-methano-prostadienoic acid (U46619), 15(S)hydroxy-9α,11α-epoxy-methano-prostadienoic acid (U44069) and 15(S)-hydroxy-9α,11α-ethenyl-prostadienoic acid (ICI 86841). These three compounds have been described as endoperoxide analogues and possess endoperoxide-like properties including rabbit aorta contracting, platelet aggregatory and vasoconstrictor activities (MacIntyre & others, 1978a). None of these compounds significantly potentiated the carrageenan paw oedema (Table 1) although U46619 and U44069 significantly reduced the swelling 2 h after the carrageenan injection. In addition, seven other monocyclic PGE_2 analogues and one PGE_1 analogue were tested in the system. All of these compounds produced a similar potentiation of the carrageenan response to that observed for PGE_2 (Table 1). PGE_1 differed from the rest of the series in producing a large early potentiation, possibly reflecting a greater potentiation of a histamine response. In contrast some of the prostaglandin analogues, in particular 11-deoxy-15(S)-hydroxy-15-methyl PGE_2 (Wy 40659) and 11-

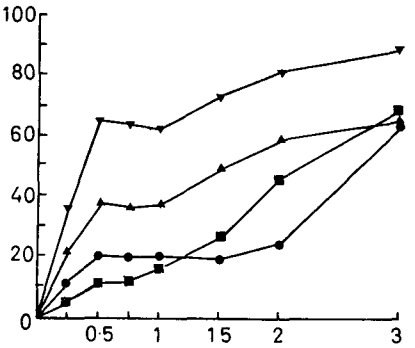

FIG. 1. Increase in paw volume (%) following the injection of carrageenan (1 mg) (■), or a combination of carrageenan (1 mg) and either prostaglandin E_1 (0·1 μg) (▼), prostaglandin E_2 (0·1 μg) (▲) or U46619 (0·1 μg) (●). Abscissa: Time (h).

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Table 1. *Effects of prostaglandins and prostaglandin analogues upon rat carrageenan-induced paw oedema.*

Results are expressed as % increase in paw volume following the injection of carrageenan (1 mg) or combination of carrageenan (1 mg) and a prostaglandin or prostaglandin analogue (0·1 μg) (means ± s.e.). * $P < 0.05$, ** $P < 0.005$ (*t*-test).

	% increase in paw volume	
	0·5 h	1·5 h
Control	10·4±2·2	26·6±3·3
PGE_1	64·4±4·5**	73·0±5·5**
PGE_2	37·3±3·6*	48·8±2·8**
6-oxo-$PGF_1\alpha$	12·8±2·8	28·6±5·1
Bicyclic analogues		
15(S)-Hydroxy-11α,9α-epoxy-methano-prostadienoic acid (U46619)	20·1±4·6	19·5±4·8
15(S)-Hydroxy-9α,11α-epoxy-methano-prostadienoic acid (U44069)	20·8±8·0	24·8±8·0
15(S)-Hydroxy-9α,11α-ethenyl-prostadienoic acid (ICI 86841)	9·5±0·9	32·9±5·8
Monocyclic analogues		
11-Deoxy-15(R)-hydroxy-16(RS)-methyl PGE_2 (Wy 19068)	21·4±4·0*	54·5±5·9**
11-Deoxy-15(S)-hydroxy-15-methyl PGE_2 (Wy 40659)	26·9±2·5**	62·4±7·5**
11-Deoxy-15(RS)-hydroxy-15-methyl PGE_2 (Wy 17186)	16·4±3·8	45·3±6·9*
11-Deoxy-15(S)-hydroxy-15-ethenyl PGE_2(Wy 17256)	26·9±2·7**	62·4±6·3**
15(S)-Hydroxy-15-methyl PGE_2 methylester	28·1±4·8**	49·1±5·4**
11-Deoxy-PGE_2 (Wy 18189)	21·3±2·2*	32·3±4·0
13,14-Dihydro-15(S)-hydroxy-16(R)-methyl PGE_2 methyl ester (ONO 464)	21·4±4·3	31·8±7·6
16-16-Dimethyl PGE_1	23·3±0·6**	46·2±3·7**

deoxy-15(RS)-hydroxy-15-methyl PGE_2 (Wy 17186) were more active against the second phase, presumably the kinin phase.

The present results confirm previous work which demonstrated that prostaglandins potentiate carrageenan-induced oedema. The lack of effect of the bicyclic endoperoxide analogues in the same system suggests that prostaglandin endoperoxides do not have a similar direct role as inflammatory mediators although this does not preclude a role in inflammation for either thromboxanes or free radicals released during the enzymatic conversion of PGG_2 to PGH_2 or thromboxane A_2 (Oyanagui, 1976; Kuehl & others, 1977). It has been suggested that U46619 and U44069 may have thromboxane synthetase inhibitory activity (Sun, 1977) and this may explain the transient anti-inflammatory effects observed with these compounds. All eight monocyclic analogues tested produced similar potentiation of carrageenan-induced oedema, although amongst the eight compounds were those with and without rabbit aorta contracting activity, those that promoted or inhibited platelet aggregation and those that reduced or increased blood flow (MacIntyre & others, 1978a; MacIntyre, Salzman & Gordon, 1978b). There would therefore seem to be no correlation between the effects of prostaglandins on platelet aggregation and their ability to modulate vascular permeability and the results do not support the hypothesis that the modulatory effects of prostaglandins on vascular permeability are due to their vasodilator properties (Williams, 1977).

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