Prostacyclin (PGI_2) potentiates bradykinin-induced plasma exudation in rabbit skin

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Prostacyclin (PGI_2) has hitherto been associated with physiological regulatory processes: prevention of platelet adhesion to vessel walls, and the physiological control of blood flow (Moncada, Gryglewski, Bunting and Vane, 1976). Since E-type prostaglandins have frequently been detected in inflammatory exudates, inflammation might involve a diversion of arachidonate metabolism from the PGI_2 pathway to the PGE_2 pathway, possibly due to the accumulation of hydroperoxy acids which inhibit PGI_2 production *in vitro* (Gryglewski, Bunting, Moncada, Flower & Vane, 1976).

However, recent evidence (Williams. 1976a; Williams, 1977) suggests that the importance of arachidonate metabolism in terms of vascular changes in inflammation, is in the production of vasodilator activity. This vasocilator activity results in a potentiation of the plasma exudation produced by vascular permeability-increasing mediators (which are not products of arachidonate metabolism). The present study in rabbit skin demonstrates that PGI_2, like PGE_2, produces local vasodilatation and potentiation of plasma exudation, and therefore a diversion from the PGI_2 to the PGE_2 pathway is unlikely to account for the vascular manifestations of inflammation. Indeed, PGI_2 itself deserves consideration as an inflammatory mediator.

Local blood flow changes and plasma exudation were measured over a 20 min period, using ^{133}Xe washout, and accumulation of ^{131}I-albumin, as previously described (Williams, 1976b).

Table 1 shows that intradermal injection of PGI_2 produced a dose-related increase in blood flow in skin. The vasodilator potency ratio (PGE_2:PGI_2) in this experiment was approximately 3.

As predicted from the above results, PGE_2 when mixed with bradykinin had potent activity at potentiating plasma exudation. The potentiation potency ratio (PGE_2:PGI_2) was again approximately 3. 6-oxo-$PGF_{1\alpha}$, the stable product of PGI_2, also produced significant vasodilatation and exudation potentiation

Table 1 Prostacyclin (PGI_2)-induced increase in skin blood flow

Agent	*Dose (ng/0.1 ml)*	*Response: Increased blood flow (%)*
PGE_2	1	85.8 ± 5.1
PGE_2	10	160.3 ± 18.0
PGE_2	100	190.0 ± 27.6
PGI_2	3	113.8 ± 15.6
PGI_2	30	165.3 ± 20.9
PGI_2	300	187.5 ± 21.9
Control	—	0.0 ± 7.5
6 oxo $PGF_1\alpha$	1000	40.3 ± 6.9
Control	—	0.0 ± 11.4
		Exudation (µl plasma)
Bk	500	56.6 ± 5.5
PGE_2	100	5.8 ± 1.2
PGI_2	100	6.2 ± 1.6
Bk + PGE_2	500 + 100	164.5 ± 12.4
Bk + PGI_2	500 + 100	132.5 ± 12.5
Bk + PGI_2	500 + 1000	196.2 ± 20.8
Control	—	0.0 ± 1.1
Bk	500	49.3 ± 4.6
6 oxo $PGF_1\alpha$	1000	0.5 ± 1.0
Bk + oxo $PGF_1\alpha$	500 + 1000	60.3 ± 3.4
Control	—	0.0 ± 1.6

Upper: Blood flow increase produced by intradermal injections of prostaglandins compared to saline/buffer controls measured in rabbit skin using ^{133}Xe clearance.
Lower: Plasma exudation produced by intradermal injections of bradykinin/prostaglandin combinations. Control levels (13.8–16.3 µl, approximating intravascular volume) from saline/buffer-injected sites have been subtracted from each value.
All solutions were made up in ice-cold saline containing tris buffer (2.5 mM, pH 7.4) immediately before intradermal injections.
Results: mean ± s.e. mean ($n = 6$ replicate doses/experiment)

at high doses.

The rate of loss of actvity of prostaglandins in the skin was determined by measuring bradykinin-induced exudation in sites pre-injected with prostaglandins at various times. In spite of the difference in stability between PGI_2 and PGE_2 in aqueous solution, the times for half activity loss were similar: PGE_2 18.7 ± 3.0 ($n = 5$) min; PGI_2 12.0 ± 3.0 (n = 3).

These results suggest a possible role for PGI_2 in inflammation.

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A comparison of 3 methods used for measuring the overflow of noradrenaline in the mouse isolated stimulated vas deferens

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The following three methods for measuring the overflow of noradrenaline from the stimulated vas deferens have been used:

(1) Bioassay using the superfused rabbit abdominal aorta (Hughes, 1972).
(2) Radioenzymic method converting released noradrenaline to radioactive adrenaline with phenylethanolamine N-methyl transferase, using [^{3}H]-S-adenosyl methionine as methyl donor. (Henry, Starman, Johnson & Williams, 1975).
(3) Pre-loading with [7–^{3}H]-(-)-noradrenaline.

Measuring:
- (a) Total ^{3}H overflow
- (b) [^{3}H]-catechol overflow
- (c) [^{3}H]-noradrenaline and its metabolites overflowing

(Graefe, Stefano & Langer, 1973).

Methods 1 and 2 have the advantage that they measure only and all of the noradrenaline released from the tissue; whereas method 3(a) commonly used for measuring noradrenaline overflow actually measures labelled noradrenaline only, together with any of its metabolites. Basically therefore, methods 1 and 2 are superior to method 3, but with small tissues such as the mouse vas deferens it is difficult (impossible in our hands) to measure resting overflow.

Method 3 has the advantage of being the most sensitive, but is not applicable to patients whereas method 2 is and has been employed by Sever, Osikowska, Birch & Tunbridge (1977). Method 3(a) is not very informative and may be positively misleading because it measures a number of variables (i.e. radioactive noradrenaline and its metabolites). Thus, Stjärne (1975) and Marshall, Nasmyth & Shepperson (this meeting) using this method in the presence of uptake blockers to try to limit metabolism and to measure release as opposed to overflow, found that clonidine (2.8–11.2nM) did not reduce the overflow of tritium ([^{3}H]-noradrenaline implied in Stjärne's case). However when the tritiated metabolites were separated out as in method 3(c) the noradrenaline overflow was reduced by more than 50% while the overflow of metabolites was increased. Thus though method 3(c) measures only tritiated noradrenaline it does have the advantage that it also measures the tritiated metabolites and is superior to method 3(b) which does not separate the noradrenaline from other catechols.

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