Implications of prostacyclin generation for modulation of vascular tone

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Summary
1. The biotransformation of arachidonic acid and prostacyclin in the circulation was studied in anaesthetized dogs, using the blood-bathed organ technique.
2. In passage through the lungs, arachidonate (50–800 µg kg⁻¹ min⁻¹) was transformed into prostacyclin. No thromboxane A₂ or prostaglandin E₂ could be detected in arterial blood.
3. In dogs treated with indomethacin (5 mg/kg), intravenous infusions of arachidonate had no cardiovascular effects and no prostacyclin was produced. Therefore, the vasodilator effects of arachidonate in vivo may be attributable to prostacyclin formation.
4. Prostacyclin, unlike prostaglandin E₂, is not inactivated by passage across the lungs, and only about 50% disappears in one passage through peripheral vascular beds.
5. Thus prostacyclin released from the lungs could function as a circulating vasodilator and contribute to the regulation of blood vessel tone and blood pressure.

Key words: arachidonic acid, prostacyclin (PGI₂), pulmonary circulation, thromboxane A₂, vasodilatation, vascular tone.

Abbreviations: PGI₂, prostacyclin; PG, prostaglandin.

Introduction
Prostaglandins are important modulators of vascular smooth-muscle tone. PGEs and PGFs have been considered primarily as local hormones producing their effects close to their site of release since they are inactivated in the lungs before reaching the arterial circulation (Ferreira & Vane, 1967; Vane, 1969). It is now known that blood vessels in vitro generate prostacyclin (PGI₂) as the predominant active metabolite of arachidonic acid; prostacyclin, potently prevents platelet aggregation and also induces disaggregation (Moncada, Gryglewski, Bunting & Vane, 1976; Johnson, Morton, Kinner, Gorman, McGuire, Sun, Whittaker, Bunting, Salmon, Moncada & Vane, 1976). In vitro, prostacyclin relaxes arterial smooth muscle from several species (Bunting, Gryglewski, Moncada & Vane, 1976; Dusting, Moncada & Vane, 1977). In vivo, prostacyclin dilates all vascular beds so far studied, including coronary (Dusting, Chapple, Hughes, Moncada & Vane, 1978a), renal (Hill & Moncada, 1978; Bolger, Eisner, Ramwell, Slotkoff & Corey, 1978), mesenteric and hindlimb (Dusting, Moncada & Vane, 1978b). It also induces vagally mediated reflex bradycardia and vasodilatation which contributes to the fall in blood pressure (Chapple, Dusting, Hughes & Vane, 1978).

Arachidonic acid similarly causes hypotension and dilates some vascular beds of the dog (Rose, Johnson, Ramwell & Kot, 1974; Dusting et al., 1978b), but constricts perfused lobes of dog lung (Wicks, Rose, Johnson, Ramwell & Kot, 1976).
Therefore we have investigated the metabolic transformation of arachidonic acid in the circulation of anaesthetized dogs.

Methods

Mongrel dogs of either sex were anaesthetized with thiopentone (25 mg/kg, intravenously) followed by chloralose (60–80 mg/kg, intravenously) and artificially ventilated. Systemic and pulmonary arterial pressures were measured from catheters inserted via a femoral artery and right jugular vein. Other cannulae were inserted into a carotid or femoral artery and jugular vein for withdrawal and replacement of blood.

Arachidonate metabolites were detected by the blood-bathed organ technique (Vane, 1964) by using up to 6 bioassay tissues including rat stomach strip, rat colon and spirally cut strips of rabbit aorta, rabbit coeliac or mesenteric artery and bovine coronary artery, all of which were rendered insensitive to catecholamines and angiotensin II by treatment with phenoxybenzamine (0.1 μg/ml), propranolol (2 μg/ml) and (Sarl-Iles) angiotensin I1 (0.025 pg/ml). In some experiments an incubation coil was interposed between the blood supply and bioassay tissues (Ferreira & Vane, 1967).

Arachidonate and prostacyclin were infused into a femoral vein or into the ascending aorta for 7–15 min.

Results

Arachidonate biotransformation in passage across the lungs

Intravenous infusion of sodium arachidonate (50–800 μg kg⁻¹ min⁻¹) reduced both pulmonary and systemic arterial pressures in proportion to the rate of infusion. During arachidonate infusion there was no change in tone of rabbit aorta, but rabbit coeliac artery, rabbit mesentery artery and bovine coronary artery, all of which were rendered insensitive to catecholamines and angiotensin II by treatment with phenoxybenzamine (0.1 μg/ml), propranolol (2 μg/ml) and (Sarl-Ile) angiotensin II (0.025 μg/ml). In some experiments an incubation coil was interposed between the blood supply and bioassay tissues (Ferreira & Vane, 1967). Arachidonate and prostacyclin were infused into a femoral vein or into the ascending aorta for 7–15 min.

Fig. 1. Bioassay of arachidonate (AA) metabolites after intravenous infusion (IV) in an anaesthetized dog. The records from the top are systemic blood pressure (BP), and changes in tone of spiral strips of rabbit coeliac artery (RbCA) and bovine coronary artery (BCA) superfused with arterial blood from the dog. The effects of arachidonate on bioassay tissues are similar to those produced by infusing prostacyclin (PGI₁) into the blood bathing the tissues (IBB). Indomethacin (INDO) given i.v.) causes continuous contraction of BCA, and abolishes all effects of AA infusion, but does not affect sensitivity of the bioassay tissues to exogenous PGI₁. The time interval between panels is 45 min.

μg), generated by incubation of endoperoxide (PGH₂) with horse platelet microsomes (Needleman, Moncada, Bunting, Vane, Hamberg & Samuelsson, 1976). After indomethacin (5 mg/kg, intravenously) bovine coronary artery contracted continuously and rat stomach strip relaxed, and all effects of arachidonate were abolished (Fig. 1).

Inactivation of prostacyclin in vascular beds

Prostacyclin infused intravenously has to pass through the lungs before assay in femoral arterial blood. Intravenous infusions of prostacyclin (0.1–0.5 μg kg⁻¹ min⁻¹) caused similar decreases in blood pressure and relaxations of rabbit coeliac artery and bovine coronary artery as infusions made into the root of the aorta at the same rates. In contrast, the contraction of rat stomach strip induced by intra-aortic infusion of PGE₂ (0.2 μg kg⁻¹ min⁻¹) could only be matched by intravenous infusions at much higher rates (more than 2 μg kg⁻¹ min⁻¹). Thus, prostacyclin, unlike PGE₂, is not inactivated in passage through the lungs.

Inactivation of prostacyclin in the peripheral circulation was studied by infusing it via a coaxial catheter. Blood for bioassay was withdrawn via this catheter from the ascending aorta. Estimated rates of inactivation of prostacyclin on one complete circulation were 65%, 50% and 45%.
Discussion

In passage across the lungs arachidonate is transformed into a vasodilating prostacyclin-like substance. There was no evidence for significant conversion into other prostaglandins, but when incubated for sufficient time with blood alone, arachidonic acid is transformed into a thromboxane A₂-like substance (Mullane, Dusting, Salmon, Moncada & Vane, 1978). Indomethacin prevents formation of prostacyclin and abolishes the cardiovascular effects of arachidonic acid. Furthermore, the cardiovascular effects of arachidonate are closely mimicked by prostacyclin but not by other bisenoic prostaglandins which are all pulmonary vasoconstrictors (Hyman, Spannhake & Kadowitz, 1978). Therefore, we suggest that the systemic and pulmonary hypotensive effects of arachidonate are attributable to prostacyclin generation.

Prostacyclin is not inactivated by the pulmonary circulation, and only about 50% disappears on crossing peripheral vascular beds. Therefore prostacyclin released from the lungs could have a role in circulatory control. Indeed, Gryglewski, Korbut & Oectkiewicz (1978) and Moncada, Korbut, Bunting & Vane (1978) have presented evidence that the lungs continuously release prostacyclin into arterial blood and inhibition of this release probably accounts for contraction after indomethacin of bovine coronary artery bathed in arterial blood. Therefore prostacyclin, unlike PGE₂, may be a circulating hormone which supplements the vasodilator and antithrombotic effects of prostacyclin generated locally in the walls of the vasculature.

It has previously been suggested that PGE₂ may be an important local modulator of vascular tone and a deficiency of this substance may be partly responsible for the augmented response to vasoconstrictor stimuli in hypertension (Terragno, Crowshaw, Terragno & McGill, 1975; Vane & McGill, 1975). Prostacyclin is generally a more potent vasodilator than PGE₂, and the difference in potency is increased after abolition of endogenous generation by indomethacin or meclofenamate (Dusting et al., 1978a,b; G. A. Higgs, S. Moncada & J. R. Vane, unpublished work). Not only is prostacyclin, and not PGE₂, the predominant cyclo-oxygenase metabolite of arachidonate in blood vessels, but conventional bioassay and chromatographic procedures previously used to identify release of prostaglandin-like substances do not readily distinguish between PGE₂ and prostacyclin or its stable degradation product (6-oxo-
PGE₁α; Moncada & Vane, 1977; Cottee, Flower, Moncada, Salmon & Vane, 1977). Clearly, prostacyclin generation should be taken into account when assessing the contribution of prostaglandin-like substances to the regulation of blood vessel tone and blood pressure.

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References


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