Biotransformation of arachidonic acid in the circulation of the dog

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A major metabolite of arachidonic acid (AA) in blood vessels *in vitro* is the potent vasodilating substance, prostacyclin (PGI_2) (Moncada & Vane, 1977; Dusting, Moncada & Vane, 1978a). AA induces hypotension in anaesthetized dogs (Rose, Johnson, Ramwell & Kot, 1974) and dilates mesenteric and hindlimb vascular beds (Dusting *et al.*, 1978a). However, Wicks, Rose, Johnson, Ramwell & Kot (1976) found that AA caused vasoconstriction in perfused lobes of dog lung. Moreover, incubation of dog platelets with AA *in vitro* generates thromboxane A_2 (Chignard & Vargaftig, 1976) which constricts some vascular beds (Dusting *et al.*, 1978a). Therefore, we have examined the metabolic transformation of AA in blood and the pulmonary vascular bed in dogs.

AA metabolites were detected by the blood-bathed organ technique (Vane, 1964) using blood continuously withdrawn from the carotid artery of chloralose-anaesthetized dogs with up to 6 bioassay tissues including rat stomach strip (RSS), rat colon (RC) and spiral strips of rabbit aorta (RbA), rabbit coeliac (RbCA) or mesenteric (RbMA) artery and bovine coronary artery (BCA). A coil of silicone tubing maintained at 37°C interposed between the blood supply and the bioassay tissues allowed incubation of AA with blood for 0.1–4 minutes. AA (5–10 μg/ml) infused into this coil contracted all tissues, suggesting generation of thromboxane A_2 (TXA_2). Maximum contraction was obtained with an incubation time of 1 minute. TXA_2 (0.1–0.4 μg) also contracted all tissues. The half life of TXA_2 in blood was 30–57 s (5 experiments), a similar value to that in aqueous solutions at 37°C.

The AA-induced contractions were prevented by indomethacin (1 μg/ml blood or 5 mg/kg intravenously). Imidazole (100 μg/ml), an inhibitor of thromboxane synthetase (Moncada, Bunting, Mullane, Thorogood, Vane, Raz & Needleman, 1977), substantially reduced the amount of TXA_2-like material generated.

The bioassay tissues were treated with (Sar^1–Ile^8)-angiotensin II (25 ng/ml), phenoxybenzamine (100 ng/ml) and propranolol (2 μg/ml) to antagonize the effects of released angiotensin and catecholamines. AA (50–800 $\mu g\ kg^{-1}\ min^{-1}$ intravenously) reduced both pulmonary and systemic arterial pressures according to the dose, had no effect on RbA but relaxed RbCA, RbMA and BCA and contracted RSS and RC. The effects could be mimicked by direct infusions of prostacyclin (5–40 ng/ml). All effects of AA were abolished by indomethacin (5 mg/kg, intravenously).

Although AA is transformed into the vasoconstrictor TXA_2 when incubated for sufficient time with blood alone, it is transformed into a prostacyclin-like substance on passage through the lungs. Prostacyclin is not inactivated by the pulmonary circulation (Dusting, Moncada & Vane, 1978b). Thus, prostacyclin released from the lungs could have a circulating function.

References

CHIGNARD, M. & VARGAFTIG, B.B. (1976). Dog platelets fail to aggregate when they form aggregating substances upon stimulation with arachidonic acid. *Eur. J. Pharmac.*, **38**, 7–18.

DUSTING, G.J., MONCADA, S. & VANE, J.R. (1978a). Vascular actions of arachidonic acid and its metabolites in perfused mesenteric and femoral beds of the dog. *Eur. J. Pharmac.* (in press).

DUSTING, G.J., MONCADA, S. & VANE, J.R. (1978b). Disappearance of prostacyclin in the circulation of the dog. *Br. J. Pharmac.*, **62** (in press).

MONCADA, S., BUNTING, S., MULLANE, K.M., THOROGOOD, P., VANE, J.R., RAZ, A. & NEEDLEMAN, P. (1977). Imidazole: A selective potent antagonist of thromboxane synthetase. *Prostaglandins* **13**, 611–618.

MONCADA, S. & VANE, J.R. (1977). Discovery of prostacyclin (PGX): A fresh insight into arachidonic acid metabolism. In *Biochemical Aspects of Prostaglandins and Thromboxanes.* Ed. Karasch, N. & Fried, J., pp. 155–177. London: Academic Press.

ROSE, J.C., JOHNSON, M., RAMWELL, P.W. & KOT, P.A. (1974). Effects of arachidonic acid on systemic arterial pressure, myocardial contractility and platelets in the dog. *Proc. Soc. Exp. Biol. Med.*, **147**, 652–655.

VANE, J.R. (1964). The use of isolated organs for detecting active substances in the circulating blood. *Br. J. Pharmac. Chemother.*, **23**, 360–373.

WICKS, T.C., ROSE, J.C., JOHNSON, M., RAMWELL, P.W. & KOT, P.A. (1976). Vascular responses to arachidonic acid in the perfused canine lung. *Circ. Res.*, **38**, 167–171.