Prostaglandin X, the vascular metabolite of arachidonic acid responsible for relaxation of bovine coronary artery strips

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Both arachidonic acid and prostaglandin E_2 (PGE_2) dilate the coronary vascular bed of most species (see Nakano, 1973), and thus it has been assumed that PGE_2 is the metabolite of arachidonic acid which is responsible for coronary vasodilatation. However, the coronary vascular bed of the rabbit does not respond to PGE_2 (Block, Feinberg, Herbaczynska-Cedro & Vane, 1975) and spirally cut strips of bovine and human coronary arteries are contracted by PGE_2 (and $PGF_{2\alpha}$), whereas arachidonic acid causes relaxation of the same preparations (Kulkarni, Roberts & Needleman, 1976). Recently, we have discovered an unstable intermediate in the metabolism of arachidonic acid (Moncada, Gryglewski, Bunting & Vane, 1976), which we have called PGX. This intermediate is synthesized by an enzyme present in the microsomal fractions of blood vessels and has a striking combination of biological activities including relaxation of vascular smooth muscle and potent inhibition of platelet aggregation. We have now investigated the involvement of PGX in the arachidonic acid-induced relaxation of coronary artery strips of the ox.

The left ramus descendens of the coronary artery and some of its major branches were excised from ox hearts within 2–3 h of slaughter, and generally stored in Krebs' solution at 4°C for 1–2 days before use. Helically cut strips (1–2 cm long) were suspended (initial tension of 2 g) in oxygenated Krebs' bicarbonate solution at 37°C, changes in tension were recorded isometrically on a Grass polygraph.

Arachidonic acid relaxed coronary artery strips (threshold concentration 10–100 μg/ml) but they were contracted by PGE_2 (50–200 ng/ml). The effects of exogenous prostaglandin endoperoxide (PGH_2) were variable. Most strips were relaxed by PGH_2 (20–200 ng/ml). In a few, the relaxation was preceded by a transient contraction, and in others there was only a contraction. Thromboxane A_2 (generated by incubation of PGH_2 with horse platelet microsomes for 2 min at 0°C) caused strong contraction in all strips, the potency being more than double that of PGE_2. Exogenous PGX (20–500 ng/ml) always caused a dose-dependent relaxation, generally being equipotent with PGH_2.

Treatment of arterial strips with indomethacin (1–2 μg/ml) abolished or substantially reduced the relaxation induced by arachidonic acid, but did not affect the small relaxations sometimes produced by high concentrations (50–200 μg/ml) of linoleic acid. Relaxations induced by exogenous PGX were increased after indomethacin, whereas the non-specific relaxation produced by erthrityl trinitrate (1 μg/ml) was not altered.

These findings strongly suggest that PGX is responsible for the relaxation induced by arachidonic acid in bovine coronary artery strips. As prostaglandin endoperoxides are avidly converted into PGX by vascular tissue, and this represents the major pathway of the vascular metabolism of the endoperoxides in man and other species (unpublished observations), it is likely that this intermediate is the active vasodilator principle in the coronary vascular bed of most species.

References

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