DEMONSTRATIONS

Prostaglandin E_2 released from the kidneys of genetic hypertensive rats contributes to the vasoconstrictor supersensitivity to angiotensin II *in vitro*

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Prostaglandin E_2 (PGE_2) causes vasodilation in the kidneys of dogs or cats and when synthesized and released in response to angiotensin II (AII, attenuates the magnitude of the AII vasoconstriction (Aiken & Vane, 1973; Needleman, Johnson, Jakschik, Douglas & Marshall, 1974). However, in rat kidneys, PGE_2 or its precursor arachidonic acid produces vasoconstriction (Malik & McGiff, 1975). An exaggeration of this vasoconstriction due to a relative lack of 15-hydroxyprostaglandin dehydrogenase could be the primary inherited abnormality responsible for hypertension in inbred New Zealand hypertensive (GH) rats (Armstrong, Blackwell, Flower, McGiff, Mullane & Vane, 1976). We have now investigated the possible interactions of AII (Val^5 hypertension II amide, Ciba or Val^3 IIe^5 Cambrian Chemicals) and angiotensin III (AIII) (Des-aspartate AII Ciba; AIII Cambrian Chemicals) with PGE_2 or arachidonic acid in the renal vascular bed of normotensive and GH rats.

Kidneys of male GH rats (indirect systolic blood pressure 160–190 mmHg) weighing 220–260 g and of 17–19 weeks of age were used and compared with those of normotensives (Otago Wistar or Charles River Wistar, 110–130 mmHg) of similar sex and body weight. Both kidneys of each animal were perfused at 20 ml/min *in vitro* and the PGE-like activity in the effluent bioassayed as previously described (Armstrong *et al.*, 1976).

Intra-arterial infusion of arachidonic acid (100–1000 ng/ml) or injections of AII (1.25 ng–80 ng) increased perfusion pressure indicating vasoconstriction. In addition, AII and arachidonic acid released PGE-like activity as shown by contractions of the assay tissues, especially the chick rectum which is insensitive to AII. The vasoconstrictor response to AII or arachidonic acid in preparations from GH rats was approximately 2 times greater than in kidneys from normotensives. Smaller amounts of AII were needed in kidneys from GH rats for the release of PGE-like activity (2.5–5.0 ng) than in preparations from normotensive animals (5–10 ng). AIII also released PGE-like activity, but the kidneys of either group were less sensitive to its vasoconstrictor effects, needing 4 times the dose to give a comparable effect to AII. Indomethacin infusions (1–2 μg/ml) reduced the magnitude of the vasoconstriction to either AII or AIII, prevented the appearance of the PGE-like activity and abolished vasoconstriction induced by arachidonic acid.

These findings indicate that the released PGE-like substance which accompanies the renal vasoconstriction to AII or AIII augments the response. Both the augmentation and the vasoconstriction are greater in kidneys from hypertensive rats. The failure of exogenous PGE_2 (0.1–1.0 ng) in the presence of indomethacin, to potentiate the vasoconstriction to AII is in contrast to findings with noradrenaline (Armstrong *et al.*, 1976) and suggests that AII stimulates vascular sites different from those stimulated by noradrenaline, requiring endogenously synthesized PGs for augmentation. As the kidneys of GH rats were still more sensitive to AII than were the normotensive rats when prostaglandin synthesis had been inhibited by indomethacin, other factors, e.g. structural changes in vessel walls, may also contribute.

References

AIKEN, J.W. & VANE, J.R. (1973). Intrarenal prostaglandin release attenuates the renal vasoconstrictor activity of angiotensin. *J. Pharmac. exp. Ther.*, **184**, 678–687.

ARMSTRONG, J.M., BLACKWELL, G.J., FLOWER, R.J., McGIFF, J.C., MULLANE, K.M. & VANE, J.R. (1976). Genetic hypertension in rats is accompanied by a defect in renal prostaglandin catabolism. *Nature (Lond.)*, **260**, 582–586.

MALIK, K.V. & McGIFF, J.C. (1975). Modulation by prostaglandins of adrenergic transmission in the isolated perfused rabbit and rat kidney. *Circ. Res.*, **36**, 599–609.

NEEDLEMAN, P., JOHNSON, E.M., JAKSCHIK, B., DOUGLAS, J.R. & MARSHALL, G.R. (1974). Renal hormonal interactions and their pharmacological modification. Renin-angiotensin, catecholamines and prostaglandins. In *Recent Advances in Renal Physiology and Pharmacology*, ed. Wesson, L.G. & Fanelli, G.M. pp. 197–214. Lancaster: M.T.P.