Possible contribution of prostaglandins to genetic hypertension in rats: identification of a biochemical lesion

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Prostaglandins (PGs) E_2 and A_2, and the PGE_2 precursor, arachidonic acid, produce vasoconstriction in isolated perfused kidneys of normotensive rats (Malik & McGiff, 1975). PGE_2 is also vasoconstrictor *in vivo* as shown by experiments in which renal blood flow was measured with an electromagnetic flow probe in pithed or anaesthetised rats. Intravenous or intra-arterial PGE_2 (100-3000 ng) reduced renal blood flow (from approximately 10 ml/min to 2 ml/min) whereas acetylcholine bromide (500 ng, i.v.) caused an increase (to 14 ml/min).

The kidney may play a pivotal role in the pathogenesis of hypertension (Guyton & Coleman, 1969). Therefore, we sought possible disturbances of renal prostaglandin mechanisms in male genetic hypertensive rats (indirect systolic blood pressures 160-190 mm Hg) of the New Zealand strain, using Charles River Wistar normotensives (110-130 mm Hg), matched for sex and either age or weight as controls. Both kidneys of each animal were perfused *in vitro* with Krebs solution (gassed with 95% O_2 and 5% CO_2) at 37°C via an aortic cannula (10 ml/min per kidney). The renal effluent was continuously assayed for PG-like activity using the superfused organ technique of Ferreira & Vane (1967). Changes in mean perfusion pressure were measured using a transducer connected to the system proximal to the kidneys.

PGE-like activity, indicated by contraction of chick rectum, was detected in the renal perfusate concomittantly with the pressor responses which followed intra-arterial injections of either (−)noradrenaline bitartrate (200-1600 ng) or angiotensin II amide (5-80 ng). Intra-arterial infusions of indomethacin (1-2 μg/ml) prevented the appearance of the PGE-like activity and reduced the magnitude and duration of the vasoconstriction caused by the pressor agents. Thereafter, potentiation of the pressor effects of noradrenaline occurred when PGE_2 was infused into the kidneys in amounts (100-300 pg/ml) which by themselves had no pressor activity. The renal vasculature of hypertensives released greater amounts of PGE-like activity following intra-arterial vasoconstrictor agents than normotensives of the same age but this difference was not found when kidneys of equal weight were used.

We have also compared in normotensive and hypertensive animals the activity of the enzymes responsible for synthesizing or metabolizing PGs. There was a considerably decreased activity of 15-hydroxyprostaglandin dehydrogenase in the kidneys of genetic hypertensive rats (76.2 ± 2.9 fmol PGE_2 oxidized/mg protein per min, $n = 5$) relative to normotensive animals of similar weight (201.2 ± 3.3 fmol PGE_2 oxidized/mg protein per min, $n = 5$). The difference was also observed when both groups were matched for age. There was no difference between the prostaglandin biosynthetic capacities of hypertensive and normotensive kidneys.

Thus, higher than normal concentrations of PGE_2 may be present in the kidneys of genetic hypertensive rats. As small amounts of PGE_2 potentiate the vasoconstrictor effects of noradrenaline and larger quantities cause vasoconstriction, increased renal levels of the prostaglandin could contribute to the maintenance of the elevated blood pressure. The deficiency in prostaglandin dehydrogenase could be the primary genetic lesion responsible for the development of genetic hypertension in these rats.

References

FERREIRA, S.H. & VANE, J.R. (1967). Prostaglandins: Their disappearance from and release into the circulation. *Nature, Lond.*, **216**, 868-873.

GUYTON, A.C. & COLEMAN, T.G. (1969). Quantitative analysis of the pathophysiology of hypertension. *Circulation Res.*, **24**, Suppl. I, 1-14.

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