Contribution of prostaglandins to the renal vascular supersensitivity to vasoconstrictor agents exhibited by New Zealand genetic hypertensive rats

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Summary

1. Studies were made of the effects on responses to vasoconstrictor agents of prostaglandins released from Krebs perfused isolated kidneys of genetic hypertensive and normotensive rats.

2. Prostaglandin E-like activity, detected by bioassay, was released from kidneys of both groups of rats during the vasoconstriction produced by noradrenaline, angiotensin or prostaglandin F2α.

3. In preparations obtained from hypertensive rats, responses to higher doses of noradrenaline or angiotensin were initially greater than those from normotensive rats and these were then reduced to a greater extent by infusion of indomethacin, which abolished release of prostaglandin E-like activity. Thereafter, in kidneys of either group, vasoconstriction to noradrenaline was potentiated by infusion of prostaglandin E2.

4. We conclude that, in rats, renal prostaglandins released in response to vasoconstrictor agents could augment the effect of such agents and in genetic hypertensive rats release of renal prostaglandins could contribute to the disease.

Key words: genetic hypertension, isolated perfused kidneys, renal prostaglandins, vascular responsiveness, vasoconstrictor agents.

Introduction

Inherited hypertension in man has been attributed to a reduced capacity of the kidneys to regulate extracellular fluid volume at normal arterial blood pressure (Guyton, Coleman, Cowley, Scheel, Manning & Norman, 1972): this could be due to increased renal vascular resistance (Guyton & Coleman, 1969). This hypothesis is strengthened by the finding that in Japanese rats inbred for hypertension, renal vascular resistance and responsiveness to vasoconstrictor agents are greater than normal (Folkow, Hallbäck, Lundgren & Weiss, 1971). Moreover, kidneys of normotensive rats excrete large quantities of urine after their transplantation into hypertensive rats of the Milan strain (Bianchi, Fox, Di Francesco, Bardi & Radice, 1973).

Renal prostaglandins could make an important contribution to the elevated vascular resistance of hypertension as they are released by vasoconstrictor agents and, in rats, themselves produce vasoconstriction and augment responses to noradrenaline and stimulation of renal sympathetic nerves in vitro (Malik & McGriff, 1975).

In view of these observations, we have looked for exaggerated renal vascular responsiveness occurring in New Zealand hypertensive rats and the possible contribution of prostaglandins to any supersensitivity observed.

Methods

Animals

Male genetic hypertensive rats of the New Zealand strain (aged 17 weeks) or normotensive rats (Charles River, aged 10 weeks), both groups of Wistar origin and of similar body weight (220–240 g), were used. Systolic blood pressures, measured by a tail-plethysmograph method in rats immobilized by light ether anaesthesia, were 160–190 mmHg in hypertensive and 110–130 mmHg in normotensive rats.
Kidney perfusion

The two kidneys of each rat were perfused with Krebs solution via a catheter inserted retrogradely into the aorta. After anaesthetizing each rat with chloroform, the lower alimentary tract was removed after ligating and severing the superior mesenteric, coeliac, spermatic and suprarenal arteries. Rats received intravenous heparin (Evans Medical) 100 i.u./100 g and the aorta was tied just below the coeliac artery stump. Kidneys were then flushed with Krebs solution through a polyethylene (pp160) cannula inserted into the aorta. Preparations were rapidly transferred to a covered water-jacketed glass container and perfused with Krebs solution (gassed with O2/CO2, 95:5) at 37°C, a Watson-Marlow roller pump (type MHRE 22) delivering 20 ml/min being used. Composition of the Krebs solution was (mmol/l): NaCl, 119.0; KCl, 4.7; CaCl2, 2.5; MgCl2, 1.2; NaHCO3, 25.0; NaHPO4, 1.2; glucose, 11.5.

Mean renal perfusion pressure was measured with a transducer (Bell and Howell type 4-327-L221) connected to the perfusion system proximal to the kidneys.

Renal vascular responsiveness of normotensive or hypertensive preparations perfused in parallel was assessed by injecting into the arterial supply a series of logarithmically increasing doses of the vasoconstrictor agent in volumes of 0.1-0.4 ml, injected into a port proximal to the roller pump. Indomethacin was dissolved in Tris buffer (pH 7.5) diluted with distilled water to achieve the final concentration. Other drugs were dissolved in Krebs solution. Concentrations are expressed as the salt (-)-noradrenaline bitartrate (Koch-Light Laboratories), angiotensin II amide (Ciba) and indomethacin (Merck Sharp and Dohme).

Kidneys of each preparation weighed approximately 1.5 g in each group.

Assay of prostaglandins

Prostaglandin-like activity in the renal effluent was continuously looked for by allowing the perfusate to superfuse, in series, a rat stomach strip, chick rectum and a rat colon by the method of Ferreira & Vane (1967). Specificity and sensitivity of the assay tissues to prostaglandins were increased by adding a mixture of pharmacological antagonists (Gilmore, Vane & Wyllie, 1968) and indomethacin (2 μg/ml), an inhibitor of prostaglandin synthesis (Vane, 1971), to the perfusate before it superfused the tissues. Changes in tissue length were detected with Harvard transducers (type 386) and each recorded variable was displayed by a Rikadenki KA-41 pen recorder.

The significance of differences between mean responses of normotensive and hypertensive preparations was assessed by using Student’s t-test.

Results

After approximately 35 min from the start of perfusion, the mean (±SEM) resting perfusion pressure in kidneys from genetic hypertensive rats (n = 11) was 90 ± 5 mmHg and those of normotensives 62 ± 4. This difference was significant (P < 0.01). Responsiveness of the renal arterioles of hypertensive rats to each of the agents examined was increased. PGE2 (100 pg/ml to 16 ng/ml) produced vasoconstriction, preparations from hypertensive rats being approximately four times more sensitive than preparations from normotensive rats, as indicated by a lowering of the dose required for a threshold response.

Vasoconstriction and the release of PGE-like activity, as reflected by contractions of the chick rectum and rat stomach strip, occurred during 8 min infusions of PGF2α (100-400 ng/ml). Moreover, PGE-like activity was detected in the renal perfusate accompanying the pressor responses which followed intra-arterial injections of noradrenaline (200-1600 ng), or angiotensin II (5-80 ng). In hypertensive preparations doses of angiotensin (2.5-5 ng) found to be threshold for release of the PGE-like activity were apparently lower than those required for the effect in normotensive rats (5-10 ng). Fig. 1 shows curves relating the increases in perfusion pressure to doses of (a) noradrenaline or (b) angiotensin obtained initially and then in the presence of indomethacin (1-2 μg/ml) and indomethacin and PGE2 (100–300 pg/ml). Vasoconstriction in response to noradrenaline and angiotensin was initially greater in hypertensive rats than in normotensive rats. Intra-arterial infusions of indomethacin prevented the release of the PGE-like activity and reduced responses to either pressor agent, the reduction being greater for hypertensive rats. Thereafter potentiation of the pressor effects of noradrenaline occurred when PGE2 was infused into the kidneys in concentrations (100–300 pg/ml) which by them-

(1) Abbreviations: PGE, PGF2α, prostaglandin E, F2α.
Prostaglandins and renal responsiveness

**Discussion**

These findings indicate that prostaglandins similar to PGE₂ are released from kidneys during the vasoconstriction produced by noradrenaline or angiotensin, thus confirming the observations of others (Leary, Ledingham & Vane, 1974; Aiken & Vane, 1973). Moreover, we have additionally confirmed the observation of Malik & McGiff (1975) that PGE₂ and PGF₂α produce vasoconstriction, and have extended their findings to show that release of PGE-like activity accompanies the response to PGF₂α.

Inhibition of endogenous prostaglandin synthesis by indomethacin was accompanied by reduced vascular responses to either noradrenaline or angiotensin, the effect being greater in hypertensive rats. However, differences were observed between the contribution of the prostaglandin to the responses produced by the two agents. Renal arterioles were sensitized to the constrictor effects of noradrenaline...
by PGE₂ in concentrations which did not by themselves show pressor activity. However, in contrast, responses to angiotensin were not potentiated by these concentrations of this prostaglandin. Nevertheless, PGE₂ when released in sufficient quantities from the kidneys might contribute to the constrictor actions of angiotensin by addition of its constrictor actions to that of the polypeptide. Moreover, prostaglandins may contribute to the supersensitivity to the vasoconstrictor effects of angiotensin since a lower dose of this agent was required in hypertensive preparations for the appearance of prostaglandin-like activity.

These observations support the suggestion of Armstrong, Blackwell, Flower, McGiff, Mullane & Vane (1976) that prostaglandin mechanisms are abnormal in the kidneys of New Zealand genetic hypertensive rats and that prostaglandins may contribute to the disease in these animals. However, as the kidneys of hypertensive rats remained supersensitive to noradrenaline or angiotensin when prostaglandin synthesis has been abolished by indomethacin, other factors, such as increased wall thickness to lumen diameter ratio, may also contribute to the supersensitivity (Folkow, Hallbäck, Lundgren & Weiss, 1970).

References


