Prostaglandin E₂ inhibits and indomethacin enhances noradrenaline release in isolated kidneys of adult spontaneously hypertensive rats

L. C. RUMP, K. WILDE & P. SCHOLLMAYER

Department of Internal Medicine IV, University of Freiburg, Hugstetterstrasse 55, D-7800 Freiburg, FRG

Renal neurotransmission and its modulation by prostaglandin (PG) E₂ (0.06 µM) and indomethacin (10 µM) was investigated in isolated kidneys of adult spontaneously hypertensive (SHR) and normotensive control (WKY) rats. After preincubation with [³H]-noradrenaline the renal nerves were stimulated. The stimulation induced (S–I) outflow of radioactivity was taken as an index of noradrenaline release. The S–I outflow of radioactivity from SHR and WKY kidneys was similar but S–I pressor responses were enhanced in kidneys of SHR. PGE₂ inhibited and indomethacin enhanced the S–I outflow of radioactivity in kidneys of WKY and SHR to a similar extent. This inhibitory effect of PGE₂ is due to activation of inhibitory prejunctional PGE₂ receptors. Neuronally released noradrenaline stimulates a local formation of PGE₂ which then transjunctionally inhibits noradrenaline release. Renal noradrenaline release in the adult SHR and its modulation by PGs is not altered. An enhanced postjunctional responsiveness of the renal vasculature may contribute to the maintenance of hypertension in the adult SHR.

Keywords kidney hypertension noradrenaline release prejunctional receptors prostaglandins

Introduction

An increased renal sympathetic nerve activity may play a role in the pathogenesis of hypertension in experimental animals and humans (Katholi, 1983). Accordingly, an increased rate of renal noradrenaline release has been reported in patients with essential hypertension (Esler *et al.*, 1985). This may be due to an enhanced sympathetic outflow from the central nervous system to the kidneys (Lundin *et al.*, 1984). There may, however, be another explanation. Renal sympathetic nerves possess prejunctional receptor mechanisms which modulate noradrenaline release at the local level of the kidney (Rump, 1987). Altered prejunctional control mechanisms may cause an increase in renal noradrenaline release and this may contribute to the pathogenesis of hypertension. Since PGE₂ is

an important endogenous modulator of renal noradrenaline release (Rump & Schollmeyer, 1989) the effects of PGE₂ and the PG synthesis inhibitor indomethacin on noradrenaline release were investigated in isolated kidneys of SHR and WKY rats.

Methods

Kidneys of SHR (Savo-Ivanovas) and WKY (Charles River) rats 12–14 weeks of age were isolated and perfused with Krebs-Henseleit solution at a constant rate of 5.7 ml min⁻¹ according to a method described earlier (Rump & Majewski, 1987). A bipolar platinum electrode was placed around the renal artery to stimulate

Correspondence: Dr L. C. Rump, Department of Internal Medicine IV, University of Freiburg, Hugstetterstrasse 55, D-7800 Freiburg, FRG

the renal nerves. After preincubation with (-)-[ring-2,5,6-³H]-noradrenaline (2 μ Ci ml⁻¹, 0.05 μ mol l⁻¹) for 15 min 18 consecutive 3 min samples of the effluent were collected. There were two stimulation periods (S₁ and S₂) at 1 Hz for 30 s (1 ms duration, 50 v), 9 and 39 min after commencement of collections of the perfusate, respectively. Drugs were added to the perfusion solution 15 min before S₂. The stimulation-induced (S-I) outflow in S₂ was expressed as a percentage of that in S₁. S-I pressor responses were measured as the maximum increase of perfusion pressure above basal perfusion pressure. All data were analysed by Student's *t*-test. The total uptake of radioactivity of the kidneys was estimated at the end of each experiment. In some experiments the endogenous noradrenaline levels of SHR and WKY kidneys were analysed by high-pressure liquid chromatography. The Krebs-Henseleit solution had the following composition (mmol l⁻¹): NaCl, 118; KCl, 4.7; CaCl₂, 2.5; MgSO₄, 0.45; NaCO₃, 25; KH₂PO₄, 1.03; D-(+)-glucose, 11.1; disodium edetate, 0.067; and ascorbic acid, 0.07. Drugs were: (-)-[ring-2,5,6-³H]-noradrenaline (NEN,

Dreieich, FRG). PGE₂ and indomethacin (Sigma, St Louis (MO), USA). PGE₂ and indomethacin were dissolved in absolute ethanol before being diluted with Krebs-Henseleit solution. The effect of the drugs was always compared with their respective vehicle control.

Results

Systolic blood pressure measured by the tail-cuff method was significantly higher in SHR (205 mm Hg, s.e. mean = 4, *n* = 16) as compared with WKY (124 mm Hg, s.e. mean = 7, *n* = 17). Mean basal perfusion pressure for SHR perfused kidneys was 36.1 mm Hg (s.e. mean = 1.5, *n* = 16) and for WKY perfused kidneys 33.0 mm Hg (s.e. mean = 2.0, *n* = 17). There was a slightly enhanced uptake of radioactivity in SHR (4.6×10^6 d min⁻¹ per kidney, s.e. mean = 0.16, *n* = 7) as compared with WKY (4.0×10^6 d min per kidney, s.e. mean = 0.24, *n* = 8) but tissue levels of endogenous noradrenaline were not different (SHR: 227 ng g⁻¹ kidney wet weight, s.e. mean = 28.5, *n* = 6 vs WKY: 210 ng g⁻¹

Figure 1 Effect of PGE₂ and indomethacin on the S-I outflow of radioactivity from WKY and SHR kidneys preincubated with [³H]-noradrenaline. There were two stimulation periods (S₁ and S₂) each at 1 Hz for 30 s. The S-I outflow of radioactivity is expressed as S₂ as a percentage of that in S₁. Drugs were added 15 min before S₂. There were two sets of experiments. 1) Kidneys of WKY (hatched columns): Control (CON, *n* = 7), PGE₂ (0.06 μ M, *n* = 5) and indomethacin (INDO, 10 μ M, *n* = 5). 2) Kidneys of SHR (stippled columns): Control (CON, *n* = 6), PGE₂ (0.06 μ M, *n* = 4) and indomethacin (INDO, 10 μ M, *n* = 6). Vertical bars represent s.e. mean. *Significant differences from corresponding control, *P* < 0.05, Student's *t*-test.

kidney wet weight, s.e. mean = 37.6, $n = 5$). When the renal nerves were stimulated in the absence of drugs the S-I pressor response in S₁ for SHR kidneys was enhanced (38 mm Hg, s.e. mean = 4.3, $n = 16$) as compared with WKY kidneys (23 mm Hg, s.e. mean = 5.5, $n = 17$). There was no difference in the S-I outflow of radioactivity (SHR: 31465 d min⁻¹, s.e. mean = 2740 vs WKY: 300054 d min⁻¹, s.e. mean = 2922) between both groups. PGE₂ (0.06 µM) present during S₂ decreased the S-I outflow in kidneys of WKY and in kidneys of SHR (Figure 1). Indomethacin (10 µM) present during S₂ enhanced the S-I outflow in SHR kidneys and in WKY kidneys (Figure 1).

Discussion

Kidneys were isolated from 12–14 week old SHR and age matched normotensive control rats and preincubated with [³H]-noradrenaline. The renal nerves were stimulated and the S-I outflow of radioactivity was taken as an index of noradrenaline release (Starke, 1977). In the present study the S-I pressor response to sympathetic nerve stimulation was enhanced in SHR kidneys. An enhanced pressor response to electrical stimulation in sympathetically innervated tissues of the SHR could be a result of an enhanced noradrenaline release due to an altered prejunctional modulation of noradrenaline release (Westfall & Meldrum, 1985). However, in the present study in rat kidney this seems not to be the case since S-I outflow of radioactivity was similar in both groups. Moreover, PGE₂ inhibited

S-I outflow of radioactivity in kidneys of SHR and WKY to a similar extent and this is most likely due to activation of inhibitory prejunctional PGE₂ receptors (Starke, 1977). Thus, prejunctional PGE₂ receptors on renal sympathetic nerves of SHR and WKY seem to operate equally effectively when activated by exogenous PGE₂. The PG synthesis inhibitor indomethacin enhanced noradrenaline release in the present study. This suggests that endogenous PGE₂ locally formed by neuronally released noradrenaline transjunctionally inhibits noradrenaline release via activation of prejunctional PGE₂ receptors. Since indomethacin's facilitatory effect was similar in SHR and WKY kidneys, it may be concluded that transjunctional PG control of renal noradrenaline release is not affected in SHR kidneys. In conclusion, an enhanced postjunctional responsiveness to renal nerve stimulation rather than an enhanced rate of renal noradrenaline release may contribute to hypertension in the adult SHR. However, further experiments in kidneys of young prehypertensive SHR are needed to fully elucidate a role for an altered prejunctional modulation of renal noradrenaline release in the development of hypertension in the SHR.

The work in the authors' laboratory is supported by a grant from the Deutsche Forschungsgemeinschaft (Ru 401/1). We wish to thank Dr L. Hedler (Pharmakologisches Institut, Universität Freiburg) for measuring tissue levels of endogenous noradrenaline. We wish to thank Mr Dörrflinger (Goedecke AG, Freiburg) for measuring systolic blood pressure of SHR and WKY.

References

- Esler, M. D., Hasking, G. J., Willett, I. R., Leonard, P. W. & Jennings, G. L. (1985). Noradrenaline release and sympathetic nervous activity. *J. Hypertension*, **3**, 117–129.
- Katholi, R. E. (1983). Renal nerves and the pathogenesis of hypertension in experimental animals and humans. *Am. J. Physiol.*, **14**, F1–F14.
- Lundin, S., Rickstein, S. E. & Thoren, P. (1984). Renal sympathetic activity in spontaneously hypertensive rats and normotensive controls, as studied by three different methods. *Acta Physiol. Scand.*, **120**, 265–272.
- Rump, L. C. (1987). Modulation of renal noradrenaline release by prejunctional receptor systems *in vitro*. *Clin. exp. Pharmac. Physiol.*, **14**, 423–428.
- Rump, L. C. & Majewski, H. (1987). Modulation of noradrenaline release through α_1 - and α_2 -adrenoceptors in rat isolated kidney. *J. cardiovasc. Pharmac.*, **9**, 500–507.
- Rump, L. C. & Schollmeyer, P. (1989). Effects of endogenous and synthetic prostanoids, the thromboxane A₂ receptor agonist U-46619 and arachidonic acid on [³H]-noradrenaline release and vascular tone in rat isolated kidney. *Br. J. Pharmac.*, **97**, 819–828.
- Starke, K. (1977). Regulation of noradrenaline release by presynaptic receptor systems. *Rev. Physiol. Biochem. Pharmac.*, **77**, 1–124.
- Westfall, T. C. & Meldrum, M. J. (1985). Alterations in the release of norepinephrine at the vascular neuroeffector junction in hypertension. *Ann. Rev. Pharmac. Tox.*, **25**, 621–641.