Table 1 Effect of isoprenaline infusion (0.5 μg kg^{-1} min^{-1}) on systemic haemodynamics and regional vascular resistance in normotensive and hypertensive rabbits

	Normotensive		*Renal hypertensive*	
Haemodynamic variables	*Baseline* ($n = 22$)	*% Change by isoprenaline* ($n = 10$)	*Baseline†* ($n = 7$)	*% Change by isoprenaline* ($n = 7$)
Systemic haemodynamics				
Mean BP (mmHg)	87 ± 3	−4 ± 4	112 ± 4**	−16 ± 4*,**
Heart rate (beats/min)	263 ± 7	+27 ± 4*	229 ± 10**	+43 ± 7*
Cardiac output (ml.min^{-1} kg^{-1})	183 ± 9	+36 ± 6*	108 ± 10**	+38 ± 6*
Systemic vascular resistance (mmHg/ml min^{-1} kg^{-1})	0.49 ± 0.02	−27 ± 5*	1.16 ± 0.1**	−38 ± 3*
Regional vascular resistance (mmHg/ml min^{-1} 100 g^{-1})				
Heart	0.34 ± 0.02	−46 ± 5*	0.58 ± 0.09**	−49 ± 5*
Muscle	9.15 ± 0.48	−28 ± 8*	16.41 ± 2.17**	−30 ± 11*
Skin	9.57 ± 1.15	−49 ± 5*	21.09 ± 3.64**	−59 ± 4*
Fat	5.69 ± 0.85	−59 ± 4*	8.13 ± 2.75	−59 ± 7*
Gastrointestinal tract	1.46 ± 0.11	−8 ± 13	2.45 ± 0.50**	−23 ± 6*

Values are means ± s.e. mean. Renal hypertension was produced by unilateral nephrectomy and cellophane wrapping of the remaining kidney. The animals were studied 5–6 weeks later. †, $n = 16$ for systemic haemodynamics; *, significantly different ($P < 0.05$, two-tailed Mann-Whitney U-test) from corresponding changes induced by saline injection (values not shown in Table); **, significantly different ($P < 0.05$, two-tailed Mann-Whitney U-test) from corresponding values in the normotensive group.

in other regions did not change. The effects of isoprenaline in the hypertensive animals were comparable with those in the normotensives except that the decrease in the mean BP and vascular resistance in the gastrointestinal tract were more prominent.

In conclusion, the present results do not provide any evidence of sub-sensitivity to isoprenaline in the resistance vessels of renal hypertensive rabbits.

References

COHEN, M.L. & BERKOWITZ, B.A. (1976). Decreased vascular relaxation in hypertension. *J. Pharmac. exp. Ther.*, **196**, 396–406.

SAXENA, P.R., VAN BOOM, M., VAN DOORN, K. & CAIRO-RAWLINS, W.I. (1979). Electromagnetic flow probe implantation for cardiac output measurements in rabbits. *J. Pharmac. Meths.* (in press).

Indomethacin and the hypotensive action of captopril in DOCA salt hypertensive rats

C.T. DOLLERY & I. MIYAMORI

Department of Clinical Pharmacology, Royal Postgraduate Medical School, London

The fall in blood pressure caused by the converting enzyme inhibitor captopril (CEI) is associated with a reduction in circulating angiotensin II (Ondetti, Cushman & Burin, 1977). CEI also inhibits the breakdown of bradykinin and this may contribute to its hypotensive effect (Wang, Talamo, Williams & Colman, 1975). As bradykinin may induce prostaglandin synthesis (Murthy, Waldron & Goldberg, 1978), we have studied the effect of prostaglandin synthetase inhibition on the action of CEI in hypertensive rats characterized by a suppressed renin angiotensin system.

Twenty four DOCA salt hypertensive (mean systolic pressure (MSP): 187.6 ± 5.6 mm Hg) male Wistar rats were randomly allocated to one of 4 groups. Captopril (1 mg/kg) was administered to groups I and III and a saline control to groups II and IV. Groups III and IV were pretreated with indomethacin (IND, 25 mg/kg). All doses were administered as an intraperitoneal bolus. Blood pressure fell significantly (mean maximum delta SBP: −23.4 ± 5.0 mm Hg; $P < 0.001$ vs baseline) in group I, reaching a minimum of 30 min after captopril. Pretreatment with IND in group III significantly attenuated this effect

(mean maximum delta SBP: 0.4 ± 9.4 mm Hg; $P < 0.01$ vs group I). There was no significant change in SBP following saline injection in groups II and IV. When the renin-angiotensin system is suppressed, captopril significantly reduces blood pressure by a mechanism that is inhibited by indomethacin.

References

MURTHY, V.S., WALDRON, T.L. & GOLDBERG, M.E. (1978). The mechanism of bradykinin potentiation after inhibition of angiotensin converting enzyme by SQ 14,225 in conscious rabbits. *Circ. Res.*, Suppl. 1, **43**, 40–44.

ONDETTI, M.A., CUSHMAN, D.W. & BURIN, B. (1977). Design of specific inhibitors of angiotensin converting enzyme: A new class of orally active antihypertensive agents. *Science*, **196**, 441–444.

WANG, P.Y., TALAMO, R.C., WILLIAMS, G.H. & COLMAN, R.W. (1975). Response of the kallikrein-kinin and renin-angiotensin systems to saline infusion and upright posture. *J. Clin. Invest.*, **55**, 691–698.

The interaction of antibiotics with ethinyloestradiol in the rat and rabbit

D.J. BACK, A.M. BRECKENRIDGE, FRANCESCA E. CRAWFORD, KAREN J. CROSS, M.L'E. ORME & P.H. ROWE

Department of Pharmacology and Therapeutics, University of Liverpool, P.O. Box 147, Liverpool, L69 3BX

Conjugation is a major route of metabolism of the synthetic oestrogen ethinyloestradiol (EE_2). Conjugates formed in the liver and gut wall may be subsequently available for enterohepatic circulation (EHC). Tritiated EE_2 conjugates were obtained from the bile of 'donor' rats and were then infused into the caecum of 'recipient' rats. Bile was collected from the 'recipient' rats over a period of 6 hours. Radioactivity appearing in the bile of 'recipient' rats is a measure of the extent of deconjugation in the gastrointestinal tract, since only unconjugated steroid can be reabsorbed across the intestinal mucosa. The influence of various antibiotics on the EHC of EE_2 was then studied following pretreatment of 'recipient' animals with ampicillin, a combination of neomycin + lincomycin, or cefoxitin. There was a reduction in the biliary excretion of the radiolabelled drug of 83%, 79% and 81% respectively, with a concomitant supression of the gut microflora (Table 1).

Following the intravenous administration of EE_2 to rabbits, a biphasic decline in plasma concentration of the steroid was found. However, after 7 h a secondary peak was observed in all animals. Pretreatment with the antibiotic combination of neomycin + lincomycin (100 + 100 mg kg^{-1} day^{-1} for 4 days) resulted in a significant decrease ($P < 0.01$) in the area under the plasma concentration time curve ($AUC_{control}$ 61.3 ± 6.2; $AUC_{antibiotic}$ 37.4 ± 5.3 ng ml^{-1} h). Not only was there a reduction in the secondary peak consistent with a reduced EHC, but also a change in the initial disposition of EE_2.

Cefoxitin was generously donated by Merck Sharp & Dohme Limited. We are grateful to Dr Elizabeth Thomas for the bacteriological analysis.

Table 1 Effect of chronic antibiotic treatment on the EHC of EE_2 and the gut microflora

Treatment	*% excretion in bile*	*Caecal flora*
Control	32.6 ± 2.3	LFC + + +; M.An. + + +
Ampicillin (200 mg kg^{-1} day^{-1} for 4 days)	***8.1 ± 2.6	LFC +*; M.An. ±
Neo + Linco (100 + 100 mg kg^{-1} day^{-1} for 4 days)	***6.9 ± 1.7	No LFC; M. An. ±
Cefoxitin (100 mg kg^{-1} day^{-1} for 4 days)	***6.2 ± 1.3	—

LFC—Lactose fermenting coliforms (e.g. E. Coli; Strep. faecalis) M.An.—Mixed Anaerobes (e.g. Clostridia spp., Bacteroides spp.) ± < 10^3/ml; + 10^3–10^5/ml; + + + 10^7–10^{10}/ml.
*** Significantly different from controls, $P < 0.001$.
* Emergence of ampicillin resistant microflora.