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The role of extrarenal prostaglandins in the hypotensive responses to captopril in anaesthetized dogs

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The antihypertensive activity of captopril in man and in various animal models of hypertension (Antonaccio et al 1980) has been attributed to its highly specific inhibitory effect on peptidyl hydrolase, which catalyses the conversion of angiotensin I into the potent angiotensin II (angiotensin converting enzyme, ACE) and degradation of the vasodilator bradykinin (kininase II). In hypertensive patients, the antihypertensive effect of captopril was related to pretreatment plasma renin activity (PRA) and was further enhanced when PRA was elevated with concomitant diurectic therapy (Johnston et al 1980). However, other clinical studies (Bravo & Tarazi 1979) failed to demonstrate any significant relationship between control PRA and the magnitude of blood pressure (BP) lowering by captopril. In addition, captopril lowered BP in patients (Man in 't Veld et al 1980) and dogs (Vollmer et al 1978) without kidneys.

Several lines of recent evidence suggest that kinins (Mimran et al 1980) and prostaglandins (Moore et al 1981) may contribute to the antihypertensive action of captopril in man and in animals. Therefore, we studied the role of kinins and prostaglandins in the antihypertensive action of captopril in dogs that were rendered practically free of plasma renin by previous bilateral nephrectomy, using kinin and prostaglandin synthesis inhibitors.

Methods

Mongrel dogs of either sex, 15–20 kg were bilaterally nephrectomized under thiopentone sodium (20 mg kg^{-1} i.v.) and methoxyflurane and oxygen anaesthesia. Eighteen to 20 h later, the animals were re-anaesthetized with sodium pentobarbitone (30 mg kg^{-1}, i.v.), and artificially respired. Body temperature was kept at 37 °C with a heating pad. The right femoral artery and the right femoral and brachial veins were cannulated to record blood pressure and to administer drugs, respectively. Blood pressure was recorded with a Statham $P_{23}GB$ pressure transducer connected to a Hewlett Packard polygraph. After a 60 min stabilization period a 3 ml arterial blood sample was withdrawn into prechilled EDTA-treated vacutainer tubes for PRA determination, using a New England Nuclear assay kit. All drugs were infused over 5 min unless otherwise noted. The effects of captopril (3 mg kg^{-1}) on blood pressure were measured in 3 separate groups of animals including controls, 15 min after pretreatment with indomethacin (5 mg kg^{-1}), or aprotinin. Aprotinin was infused at the rate of 900 Kiu min^{-1} for 25 min and continued for 5 more min during captopril administration. Kallikrein 0·01 u kg^{-1} was administered as an i.v. bolus before and after aprotinin infusion to assess the degree of inhibition of bradykinin synthesis. The effect of captopril on blood pressure was monitored for 60 min. All data were subjected to analysis of variance; significant differences ($P < 0·05$) were determined by Duncan's multiple range *t*-test (Duncan 1955). All values are expressed as mean ± s.e.m.

Results and discussion

The plasma renin activity expressed in ng AI ml^{-1} h^{-1} was sharply reduced to 0·013 ± 0·011 (n = 7) after bilateral nephrectomy (vs 1·96 ± 0·55 in normal control, n = 10). Following intravenous administration of captopril (3 mg kg^{-1}) to the anephric animals, peak hyptotensive responses (−21 ± 2 mm Hg, n = 5) occurred in 10 min (Table 1). The hypotensive response was significantly ($P < 0·05$) inhibited (−5 ± 1 mmHg; n = 5) when the animals were pretreated with indomethacin, a prostaglandin synthesis inhibitor. Aprotinin, a potent kallikrein inhibitor, reduced depressor reponse to kallikrein (0·01 u kg^{-1} i.v.) from −55 ± 4 mmHg (n = 5) to −20 ± 3 mmHg ($P < 0·05$, n = 5) but failed to alter the BP response to captopril (−21 ± 3 mmHg, n = 5). Neither indomethacin nor aprotinin affected the baseline BP.

As previously reported by Vollmer et al (1978), captopril is able to produce a significant reduction in arterial pressure in anephric dogs. That captopril retains antihypertensive efficacy in the anephric state or in the presence of extremely low plasma renin levels suggests that there is an additional, non-angiotensin mechanism involved.

Aprotinin, a potent kallikrein inhibitor, failed to influence the BP lowering effect of captopril. Similarly, a recent report (Vemulapalli & Chiu 1981) demonstrated that the hypotensive response to captopril in diuretic-treated dogs remained unaffected by aprotinin. The evidence we have obtained does not support significant kinin participation in the antihypertensive effect of captopril (Mimran et al 1980). No explanation can be offered for a discrepant finding (Abe et al 1980) that the vasodepressor effect of a different ACE

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Table 1. Changes in the mean arterial pressure following intravenous administration of captopril (3 mg kg^{-1}) alone and with indomethacin or aprotinin in anephric dogs.

	Δ MBP (mmHg) after captopril					
Baseline BP (mmHg)	+10 min	+20 min	+30 min	+40 min	+50 min	+60 min
Captopril alone						
103 ± 5	−21 ± 2	−17 ± 2	−12 ± 2	−7 ± 1	−6 ± 1	−5 ± 1
Indo. + captopril						
104 ± 4	−5 ± 1*	−7 ± 1*	−7 ± 1*	−6 ± 1	−5 ± 1	−3 ± 1
Aprotinin + captopril						
104 ± 7	−21 ± 3	−17 ± 2	−11 ± 2	−6 ± 1	−3 + 1	−1 ± 1

All values represent mean ± s.e.m. of 5 animals.
* $P < 0.05$, compared with 'captopril alone' or 'aprotinin + captopril' group.

inhibitor (YS-980: (4*R*)-3-[(2*S*)-3-mercapto-2-methyl-propanoyl]-4-thiazolidine carboxylic acid) was blunted by aprotinin in dogs, both compounds being administered via the renal artery.

The effective inhibition of captopril's effect on BP with indomethacin in the anephric state strongly implicates involvement of extrarenal prostaglandins. In doca/salt hypertensive rats, which were also characterized by a low-renin state (0·3 vs 4·4 ng AI ml^{-1} h^{-1} in normal controls), Miyamori et al (1980) showed that the hypotensive effect of captopril was inhibited by indomethacin. Furthermore, a recent clinical study (Moore et al 1981) demonstrated that inhibition of prostaglandin synthesis with indomethacin or aspirin inhibited the depressor response to captopril in some hypertensive patients and appeared to be related to suppression of prostaglandin E2 generation. However, the linking events between ACE inhibition by captopril and activation of vasoactive prostaglandins remain to be elaborated.

In conclusion, the present results indicate that extrarenal prostaglandins, but not kinins contribute significantly to the hypotensive effect of captopril in anephric dogs.

REFERENCES

Abe, Y., Miura, K., Imanishi, M., Yukimura, T., Komori, T., Okahara, T., Yamamoto, K. (1980) J. Pharmacol. Exp. Ther. 214: 166–170

Antonaccio, M. J., Rubin, B., Horovitz, Z. P. (1980) Clin. Exp. Hyperten. 2: 613–637

Bravo, E. L., Tarazi, R. C. (1979) Hypertension 1: 39–46

Duncan, D. (1955) Biometrics 11: 1–42

Johnston, C. I., Millar, J. A., Casley, D. J., McGrath, B. P., Matthews, P. G. (1980) Circ. Res. 46 (Suppl. I) I-128–I-134

Man in't Veld, A. J. Schicht, I. M., Derkx, F. H. M., De Bruyn, J. H. B., Schalekamp, M. A. D. H. (1980) Br. Med. J. 280: 288–290

Miyamori, I., Brown, M. J., Dollery, C. T. (1980) Clin. Exp. Hyperten. 2: 935–945

Mimran, A., Targhetta, R., Laroche, B. (1980) Hypertension 2: 732–737

Moore, T. Z., Crantz, F. R., Hollenberg, N. K., Koletsky, R. J., Leboff, M. S., Schwartz, S. L., Levine, L., Podolsky, S., Dluhy, R. G., Williams, G. H. (1981) Ibid. 3: 168–173

Vemulapalli, S., Chiu, P. J. S. (1981) Pharmacologist 23: 124

Vollmer, R. R., Boccagno, J. A., Harris, D. N., Murthy, V. S. (1978) Eur. J. Pharmacol. 51: 39–45

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The ability of iprindole to antagonize the biochemical central effects of clonidine

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Iprindole, a clinically active antidepressant, has no effect on noradrenaline (NA) or 5-hydroxytryptamine (5-HT) uptake, on monoamine oxidase (MAO) activity or on reserpine effects characteristic of typical antidepressant drugs (Gluckman & Baum 1969; Lahti & Maickel 1971; Rosloff & Davis 1974). Iprindole does not change the brain level of NA or of MOPEG, or the NA turnover (Freeman & Sulser 1972; Rosloff & Davis 1978; Sugrue 1981). Binding studies have also indicated that iprindole has a low activity with respect to α_1, α_2, 5-HT or others receptors (e.g. Peroutka & Snyder 1980; Hall & Ögren 1981). It therefore appears to be a drug with no definite action in an acute experiment.

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In the course of our studies on atypical antidepressants, we have found that iprindole affects changes in the brain 3-methoxy-4-hydroxyphenylethyleneglycol (MOPEG) level and in the utilization of NA (after inhibition of its synthesis), both induced by clonidine. These findings are the subject of the present communication.

Methods

The experiments were carried out on male Wistar rats, 180–220 g. All drugs were given i.p. Iprindole and clonidine were dissolved in 0.9% NaCl (saline). The total MOPEG level was estimated by gas liquid chromatography with electron capture detection as the pentafluoropropionyl derivative, according to Braestrup (1973). The supernatant from the whole brain