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ANGIOTENSIN CONVERTING ENZYME (ACE) INHIBITORS

Michael J. Antonaccio[1]

The Squibb Institute for Medical Research, P.O. Box 4000, Princeton, New Jersey 08540

INTRODUCTION

The primary purpose of this review is to define the development and pharmacology of angiotensin converting enzyme (ACE) inhibitors as a class. Particular attention will be paid to those agents which are considered to be prototypical, as well as those considered to represent significant structural departures from the more established inhibitors. Because of the extraordinary number of papers appearing in continuing rapid succession over a short period of time, and because of the controversy surrounding the mechanism of action of ACE inhibitors in hypertension, no abstracts will be considered in this review. Of necessity, most of the data presented will be on captopril, although the limited available information on MK-421 will also be discussed.

II. RENIN-ANGIOTENSIN-ALDOSTERONE (RAA) SYSTEM

As shown in Figure 1, the RAA system is a closed loop negative feed-back system which responds to a variety of factors that reduce renal perfusion or result in excessive sodium loss, including hemorrhage, heart failure, hypotension, and sodium depletion (1). Release of renin from specialized cells in the kidney initiates the sequence of events illustrated in Figure 1. Renin substrate, angiotensinogen, is circulating in the blood and is acted upon by renin to produce the biologically inactive decapeptide angiotensin I (AI). AI, in turn, is converted to the octapeptide angiotensin II (AII), mainly in the blood, by ACE localized on the endothelium of blood vessels

[1]Current address: Schering Pharmaceuticals, Bloomfield, NJ 07003

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of lung, kidney, and many other organs. The AII now circulating in the blood has three primary actions which counteract the initial stimulus which led to renin release: It causes powerful arterial vasoconstriction; stimulates the synthesis and release of the sodium-retaining steroid, aldosterone, from adrenal glands; and acts directly on the kidney to inhibit sodium excretion. By restoration of pressure, renal blood flow, and/or excessive sodium loss by the actions of AII, the initial stimulus for renin secretion is turned off, aided also by the direct inhibitory effect of AII on renin release. The system is then returned to its original status.

Inhibition of ACE prevents the conversion of AI to AII (Figure 1). In addition, since ACE is the same enzyme as kininase II (2), breakdown of kinins is also inhibited to the extent that they are normally degraded by the enzyme.

III. DEVELOPMENT OF ACE INHIBITORS

ACE is a membrane bound exopeptidase, a peptidyldipeptide carboxyhydrolase (EC 3.4.15.1) that splits off dipeptides from the C-terminal end of peptide substrates [for reviews see (3–7)]. In addition to AI and bradykinin, many other peptides such as leu- and met-enkephalin with widely varying terminal amino acid sequences may serve as substrates for, or inhibitors of,

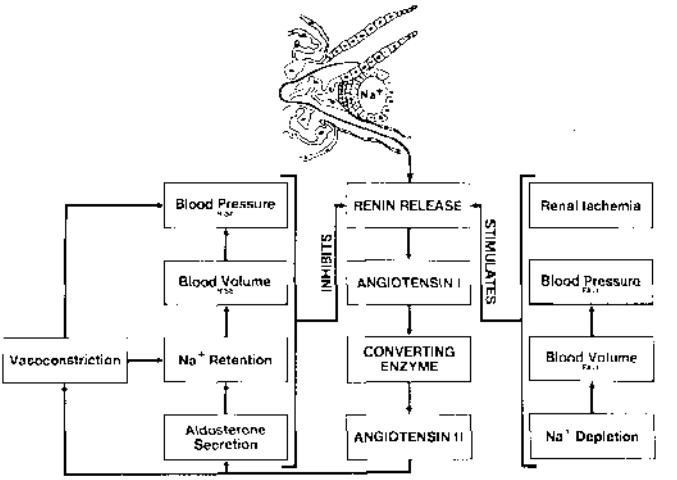

Figure 1 Diagrammatic representation of the juxtaglomerular apparatus and the factors controlling renin release and angiotensin II formation.

ACE. The shortest peptides that serve as substrates or inhibitors of ACE are tripeptides. Thus, as shown in Figure 2, it was suggested that the C-terminal tripeptide residue of substrates and peptide inhibitors, as well as the nonpeptide inhibitors such as captopril, interact with an "obligatory binding site" on ACE, which is necessary for effective binding. Peptide substrates and inhibitors, on the other hand, bind not only to the obligatory binding site of the enzyme but also interact with regions of the enzyme adjacent to the obligatory binding site (Figure 2). The peptide inhibitors can either be a substrate for ACE (as with BPP5a) or not (as with teprotide).

Unlike the peptide inhibitors of ACE, captopril (3-mercapto-2-methyl-D-propanoyl proline; SQ 14,225; Captoten®) is orally active. The conception and design of captopril has been described in detail in several excellent reviews (8–19). Briefly, it was recognized that ACE is a carboxypeptidase similar to carboxypeptidase A, except that the former releases dipeptides and the latter releases single amino acids. The discovery by Byers & Wolfenden (20) that D-2-benzylsuccinic acid was a potent competitive inhibitor of carboxypeptidase A suggested that a similar inhibitor which was one amino acid unit longer might be an analogous inhibitor of ACE. Succinyl-L-proline was the compound first made and tested based on the hypothetical model of ACE and, though a relatively weak inhibitor of ACE, was found to be specific. Many compounds were synthesized, the end result of which was captopril. The salient features of captopril with respect to binding to ACE are (*a*) binding of the sulfhydryl to zinc, (*b*) binding of the proline carboxylic acid to a cationic site on the enzyme, and (*c*) incorporation of the amino acid proline, and a methyl side chain adjacent to proline since the dipeptide sequence Ala- Pro- of BPP5a has the greatest affinity for ACE. The suggested binding of captopril and other inhibitors to ACE is shown in Figure 2. Other inhibitors of ACE very similar to captopril which contain sulfhydryl moieties such as SA-291 or YS-980 (21–24) will not be discussed here. However, several ACE inhibitors have been synthesized which fit the model but do not contain the sulfhydryl moiety. Galardy (25) substituted a phosphoric acid for the thiol group as a strong zinc ligand which resulted in a compound with a K_i which is similar to that of captopril. Captopril and the Galardy compound are considered as being strong zinc binding agents which are dipeptide analogs (Figure 2). Patchett et al (26) synthesized a series of tripeptide analogs which substitute a carboxyl group to bind strongly to the zinc atom of ACE in addition to providing an additional moiety which binds to a subsite on the enzyme to which captopril does not. Finally, Almquist et al (27) synthesized a series of tripeptide, nonsulfhydryl-containing compounds which are considered to be weak zinc binding inhibitors.

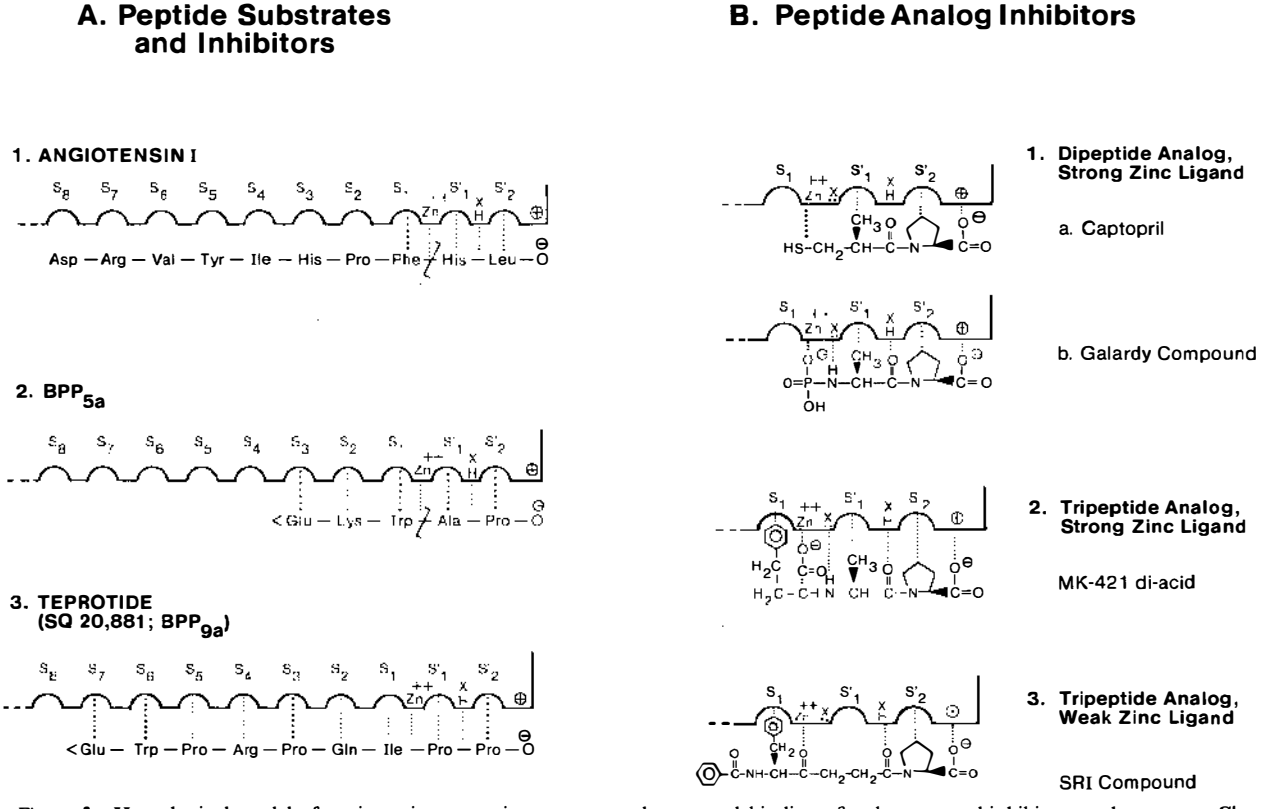

Figure 2 Hypothetical model of angiotensin converting enzyme and suggested binding of substrates and inhibitors to the enzyme. *S'*, obligatory binding site; *S*, additional binding site.

A. Inhibitor Kinetics and Specificity

Teprotide (SQ 20,881; BPP9a), BPP5a, captopril, the diacid of MK-421, and the phosphoryl dipeptide inhibitors are all competitive inhibitors of ACE, whereas the ketomethylene tripeptide analog is a noncompetitive inhibitor. The inhibitory potencies of these compounds against rabbit ACE as well as in the guinea pig ileum assay are shown in Table 1. MK-421 diacid has been reported to be the most potent compound against rabbit lung ACE (26, 28). Teprotide is an unusually poor inhibitor of rabbit lung ACE in comparison to the guinea pig ileum test, whereas the opposite is true for the SRI-ketomethylene analog. The reasons for these differences are not known but could be related to subtle differences in ACE in different tissues and/or to differences in the ability of inhibitors to pass through cellular membranes.

The specificity of the described ACE inhibitors is quite remarkable. They have relatively little or no effect on other proteases, even those with similar activities, such as enkephalinase.

IV. BLOOD PRESSURE EFFECTS OF ORALLY-ACTIVE ACE INHIBITORS

A. Normotensive

In unanesthetized rats, dogs, cats, rabbits, sheep, and man, captopril caused a significant reduction in arterial blood pressure (29–80). MK-421 also decreased blood pressure in normotensive rats and man (76–81). The anesthetized sodium replete dog appears to be particularly sensitive to captopril, since the drug causes a consistent substantial reduction in blood pressure in this species.

Table 1 Activities of inhibitors of angiotensin converting enzyme

Compound	Rabbit lung ACE IC_{50} (nM)	Rabbit lung ACE Ki (nM)	Guinea pig ileum IC_{50} (nM)
Teprotide (SQ 20,881; BPP9a)	550	100	60
Captopril	23	1.7	23
MK–421 di-acid	1.2[a]	—	11
N-α-phosphoryl-L-ala-pro	—	1.4	—
SRI Ketomethylene tripeptide analog	12	—	500

[a] Hog plasma ACE [from (26)].

Procedures which increase plasma renin activity in normotensive animals and in man also enhance the hypotensive activity of both captopril and MK-421, including anesthesia and salt depletion.

B. Hypertension

1. ANIMAL MODELS As shown in Table 2, captopril reduces blood pressure in many animal hypertension models (82–135). In renal hypertension, the initial antihypertensive effect was strongly correlated with predose plasma renin activity (PRA) values (32). However, it is clear that captopril also is very effective in normal renin models of hypertension. Captopril alone had some antihypertensive action in DOCA-salt hypertensive rats with both kidneys intact (112) but was ineffective in uninephrectomized DOCA salt hypertensive rats (83, 91). However, when given in combination with hydrochlorothiazide, captopril caused a significant reduction of blood pressure in this latter model. This effect was not due to increased PRA caused by hydrochlorothiazide and was therefore related to the observed changes in aortic renin values. MK-421 is also effective in reducing blood pressure of conscious two- and one-kidney Grollman hypertensive rats, two- and one-kidney one-clip renal hypertensive dogs, one-kidney one-wrapped hypertensive dogs and SHR (76). Procedures which increased PRA enhanced the antihypertensive effects of both captopril and MK-421 in animal models of hypertension.

In several studies in both renal and SHR, captopril decreased or reversed cardiac hypertrophy (121–124) under circumstances in which α-methyldopa did not. In addition to decreasing established hypertension, captopril is effective in preventing the development of both two-kidney one-clip renal hypertensive rats and dogs as well as SHR (94, 96, 97). Curiously, however, captopril is not effective in preventing the development of one-kidney one-clip renal hypertensive rats or dogs (96, 133, 134).

2. HUMAN HYPERTENSION Captopril is an effective antihypertensive agent in human mild, moderate, severe, and severe treatment-refractory essential, malignant, and renal vascular hypertension, as well as hypertension caused by chronic renal failure, renal parenchymal disease, and renin secreting tumors. It is least effective in primary aldosteronism in which, as in DOCA-salt hypertension in rats, PRA's are very low (137–238). Its efficacy has been demonstrated in many open trials as well as in placebo controlled, double-blind studies. In virtually every study, captopril's antihypertensive effect was enhanced by a diuretic or a sodium restricted diet.

In a representative multicenter open study in a group of 171 patients with hypertension of various etiologies, captopril alone normalized supine dia-

Table 2 Effects of captopril on blood pressure in various animal models of hypertension

Model	Comments	Selected references
A. Renal hypertension		
1. Two kidney, one clip	Effective in acute and chronic phase; prevents development	32, 33, 46, 84, 87, 90, 96
2. Two kidney, two clip	Effective in acute phase; prevents development	83
3. One kidney, one clip	Effective only after several days of dosing; does not prevent development	32, 33, 106
4. Two kidney, one wrap	Effective in acute phase	68
5. Two kidney, two wrap	Effective in acute phase	67, 132
6. One kidney, one wrap	Effective in acute phase	68
7. One kidney, Grollman	Effective in acute phase	68
8. Aoritic coarctation	Effective in acute phase	128
B. Genetic (spontaneous) hypertension (SHR)		
1. Okamoto-Aoki strain	Modest effect acutely; normalization of blood pressure with chronic dosage; prevents development	29, 31, 83, 86, 88, 89, 94, 97, 116
2. New Zealand strain	Effective acutely	82, 117
3. Stroke-prone SHR	Greater reductions in blood pressure than in SHR; decreased incidence of stroke; prevents development	79, 80
C. Steroid hypertension		
1. DOCA-Salt		
a. Two kidney	Modest effect acutely	111, 112
b. One kidney	Inactive	83, 92, 130
c. Heyman nephritis	Effective acutely	130
2. Methylprednisolone, two kidney, salt-depleted	Effective acutely	93
3. Aldosterone, one kidney	Effective after chronic treatment	92
D. Angiotensin II-salt hypertension	Effective after chronic treatment	115
E. Unilateral nephrectomy, salt depletion hypertension	Effective acutely; prevents development	125
F. Psychosocial hypertension	Not effective acutely but normalized blood pressure after 1–7 months	99

stolic blood pressure in 53% and produced at least a 10% reduction in an additional 25% for an overall response rate of 77% (214). An additional 32% required a diuretic or low sodium diet.

In a representative large double-blind placebo-controlled study in essential hypertension including 197 patients, captopril alone or in combination with a diuretic normalized blood pressure in 78% of the patients and reduced supine diastolic blood pressure by at least 10% in an additional 10% for an overall efficacy rate of 88% (142). In this group, 58% received diuretic, 10% were considered nonresponders (less than 10% reduction in supine diastolic blood pressure), and 2% were treatment failures (total lack of response).

The degree of antihypertensive effect of captopril has been reported to be strongly, weakly, and not at all related to predrug PRA. However, there is little doubt that, although captopril is effective in hypertension of low and normal PRA, the drug produces its most dramatic antihypertensive effect in patients with high PRA's. Furthermore, the total number of responders to captopril was directly related to PRA levels, whereas the number of responders requiring diuretic or low sodium diet was inversely proportional to PRA (142).

In patients resistant to standard triple therapy (hydrochlorothiazide or furosemide plus propranolol plus hydralazine) captopril was very effective when given in combination with either a diuretic and/or a beta blocker (186).

Although there is little or no evidence for tolerance or tachyphylaxis to the antihypertensive effects of captopril, captopril may show an unusual triphasic response in high renin patients (174, 208). In these patients, there was a large first dose reduction in blood pressure followed by a return toward control and finally by a gradual further reduction to normotension. These authors also suggested that the blood pressure response to the first dose of captopril can be used to predict the long-term response but that at least 10 days of therapy are necessary to observe the final effect of captopril.

In addition to its efficacy described above, captopril is also dramatically effective in reducing hemodialysis resistant hypertension in end stage renal disease (239, 240). After renal transplantation, captopril, but not alprenolol, reduced hypertension in normal and high renin patients (241). In patients with scleroderma renal crisis resistant to multidrug antihypertensive therapy, captopril was again dramatically effective in controlling blood pressure and stabilizing renal function (242, 243). Captopril has also been given to anephric patients. In several studies by one group of investigators, captopril decreased blood pressure only after fluid and salt depletion (244–246), whereas Leslie et al (247) found a slight increase in blood pressure after captopril in anephric patients.

V. HEMODYNAMICS

Captopril reduces blood pressure by reducing total vascular resistance.

A. Animal Models

In conscious SHR, acute or chronic oral administration of captopril decreased blood pressure and either increased or had no significant effect on cardiac output, resulting in a decrease in total peripheral resistance (95, 104, 116). Heart rate, plasma volume, and oxygen consumption were unchanged. Blood flows to heart, brain, lungs, liver, spleen, kidneys, stomach, intestine, muscle, and skin either increased or did not change.

In SHR receiving captopril for a week, the addition of guanethidine to these rats enhanced the hemodynamic changes induced by captopril, suggesting that compensatory sympathetic reflexes tend to buffer the cardiovascular changes caused by captopril (95).

In normotensive anesthetized dogs, intravenous captopril decreased blood pressure and systemic and pulmonary arterial pressures, and increased cardiac output thereby causing a decrease in systemic and pulmonary vascular resistances (49). A sustained tachycardia was also observed with a small transient increase in coronary sinus blood flow. Cardiac oxygen metabolism and efficiency were unchanged.

In other studies in anesthetized dogs, intravenous captopril decreased blood pressure without changing heart rate (42–44, 61). Pressure flow curves in perfused hind limbs were shifted significantly to the right by captopril, indicating a decrease in hind limb vascular resistance. Neither bilateral nephrectomy nor functional surgical denervation prevented the decrease in blood pressure or hind limb vascular resistance caused by captopril. Similarly, treatment of dogs with the AII antagonist saralasin did not alter the hypotensive action of captopril, leading these authors to suggest that the hemodynamic effects of captopril were unrelated to inhibition of the RAA system. Virtually identical results and conclusions were obtained in anesthetized normotensive and New Zealand genetically hypertensive rats (115). In both rats and dogs, the intra-arterial administration of captopril into the vascularly isolated hind limb caused significant reductions in perfusion pressure.

B. Human Hypertension

In both human essential and renovascular hypertension, acute or chronic administration of captopril consistently reduced blood pressure by reducing total peripheral resistance, while cardiac output remained either unchanged or increased (160, 176, 181–184, 231, 233, 248). Similarly, pulmonary vascular resistance decreased after chronic but not acute captopril therapy,

suggesting both arterial and venous dilatation. Heart rate was unchanged in these patients.

The hemodynamic effects of captopril were significantly correlated to predrug PRA values (181, 233, 248) or plasma AII levels (182–184) in most studies but not all. Tarazi et al (233) found that this correlation became much weaker after chronic therapy.

Plasma volume was only slightly altered after captopril therapy, an effect attributed to the sustained reductions in aldosterone while on captopril (160, 176, 233).

After comparable reductions in diastolic blood pressure with either captopril or standard triple therapy in hypertensive patients, forearm vascular distensibility, basal blood flow, and hyperemic blood flow were all significantly increased in the captopril treated group in comparison with the triple therapy group (200).

VI. RENAL HEMODYNAMICS, RENAL FUNCTION AND ELECTROLYTE BALANCE

A. Animal Studies

In both conscious and anesthetized normotensive sodium replete dogs, intravenous or intra-arterial captopril decreased blood pressure modestly, increased renal blood flow, and decreased renal vascular resistance (34, 61, 72, 126, 149–251). Qualitatively similar but quantitatively greater results were seen in two-kidney, one-clip conscious hypertensive dogs (251). Clappison et al (34) found no change in glomerular filtration rate (GFR).

In sodium deficient conscious normotensive dogs, continual intravenous infusion of captopril decreased blood pressure and increased renal blood flow markedly, and increased urinary sodium excretion while urinary potassium excretion was unaltered (36, 50–56). GFR decreased whereas serum sodium and potassium were unchanged.

In another study in conscious dogs in which sodium intake was controlled at 5–500 meq/day, captopril decreased blood pressure, GFR, and filtration fraction at low sodium intakes but these all tended to reverse as sodium intake increased (38).

In normotensive anesthetized rats, captopril decreased blood pressure and increased renal blood flow both in sodium replete and deplete states (57, 252). Outer cortical flow was increased more than inner in sodium replete rats whereas the opposite was found in sodium deplete rats. GFR was unchanged by captopril in sodium deplete rats whereas sodium and water excretion were markedly increased after chronic treatment.

In SHR, captopril also increased renal blood flow (94, 104). However,

either little or no changes in potassium or urinary volume were observed in SHR on captopril (86, 116). In contrast, captopril consistently increased sodium excretion and urinary volume in acute and chronic two-kidney and one-kidney, one-clip renal hypertensive rats (32, 33, 122).

B. Human Hypertension

In most studies in human essential hypertensive patients on an unrestricted sodium diet, captopril increased renal blood flow, while decreasing blood pressure, and had no effect on GFR (166, 223, 253, 254). As a consequence, filtration fraction decreased. Urinary sodium excretion was unchanged while potassium excretion was decreased. In one study in five essential human hypertensive patients, captopril decreased GFR while having no effect on renal blood flow. In renvascular hypertensive patients, captopril caused a small decrease in GFR (223).

In other studies in hypertensive patients, captopril had little or no effect on sodium or potassium excretion or on serum sodium or potassium levels (163, 200, 201, 204, 210, 212, 217, 218). Some studies have reported a small but significant increase in serum potassium concentration (155, 210, 211).

Interestingly, a significant increase in urine flow, sodium and potassium excretion in sodium replete normotensive volunteers in whom captopril did not reduce blood pressure has been reported (260).

VII. MECHANISM OF ACTION AS AN ANTIHYPERTENSIVE AGENT

Captopril can act to reduce blood pressure by inhibiting the RAA system or enhancing the kallikrein-kinin-prostaglandin system.

A. Effects of Captopril in the RAA System

Inhibition of ACE in animals and humans results in several consistent, well-described, and understood actions on the RAA system.

1. Inhibition of the AI pressor response. Administration of captopril inhibits the pressor response to AI in normotensive rats, dogs, cats, rabbits, monkeys, sheep, and man in doses ranging from 0.01–0.1 mg/kg i.v. and 0.1–1.0 mg/kg p.o. (18, 26, 28, 35, 41, 45, 59, 61–63, 73, 93, 249–251, 255–259, 269, 279, 283, 290, 294, 297, 298, 304; see also 30, 31, 66, 68, 69). Similar results had been obtained in hypertensive rats and dogs (96, 107, 108, 133, 136). MK-421 and its diacid parent compound both inhibited pressor responses to AI in rats and dogs. The diacid given intravenously was about 12 times more potent than captopril in rats and

dogs, whereas MK-421 was 8.6 and 4.6 times more potent than captopril in rats and dogs, respectively (26, 28, 76). *N*-α-Phosphoryl-L-ala-pro was claimed to inhibit the AI pressor response in rats but no data were given (25).

2. Reduction in AII production with consequent increases in AI (see 15, 30, 31, 50–56, 66–68).
3. Increased plasma renin activity due to both a loss of feedback inhibition by reduced AII levels, as well as an increase in sympathetic activity caused by the reduction in blood pressure (see 30, 31, 66–69).
4. Reduction in aldosterone synthesis and release consequent to AII formation (see 15, 30, 31, 50–56, 66–69).

B. Effects of Captopril on the Kallikrein-Kinin-Prostaglandin System

1. Enhancement of hemodynamic and other responses to exogenously administered kinins. Since ACE and kininase II are the same enzyme, it is readily understood that ACE inhibition will result in the enhancement of effects of exogenously administered kinins to the extent that kinins are ordinarily the substrate for ACE. Many studies have shown that captopril or MK-421 enhance the effects of bradykinin (26, 28, 30, 31, 66–69, 261, 262). In particular, Murthy et al (62) showed that the renal prostaglandins contributed to the enhanced hypotensive response to bradykinin after captopril, an effect suggested to be specifically mediated by the increased production of prostacyclin.
2. Plasma kinin levels. These have been reported to be both increased (54, 263, 205, 206) or, usually, unchanged (178, 201–203, 213, 260, 263, 264–268) after captopril. It would be surprising to find increased kinin levels after captopril since these agents are local rather than circulating substances, and since many other enzymes different from ACE are capable of inactivating them.
3. Urinary kinin levels. In two studies in which they were measured, urinary kinin levels rose after captopril (263, 269).
4. Urinary kallikrein. Kallikrein activity is consistently reduced after captopril (54, 131, 269, 270), possibly as a consequence of reduced aldosterone levels or negative feedback by kinins.
5. Captopril and kallikrein inhibitors. Inhibition of kinin synthesis by inhibition of kallikrein and the nonspecific protease inhibitor aprotinin prior to captopril administration did not alter captopril's ability to reduce blood pressure in SHR's (30) or sodium depleted dogs (51). However, infusion of aprotinin into high renin hypertensive patients whose blood

pressure had already been reduced by captopril resulted in a partial reversal of the antihypertensive effect, whereas no effect of aprotinin was observed in normal and low-renin hypertensive patients. Similar reversal of the antihypertensive effect of captopril by aprotinin was found in low and normal hypertensive patients but not in high-renin patients (216, 220, 271).

6. Antibodies of kinins. Antikinin globulins did not alter the reduction in blood pressure caused by captopril in normotensive sodium depleted rats, whereas they partially blunted the antihypertensive effect of captopril in acute two-kidney, one-clip renal hypertensive rats (189).

C. Prostaglandins

The involvement of prostaglandins in the effects of captopril is implicated by virtue of the fact that kinins are potent stimulators of prostaglandin synthesis and release (272). However, the effects of captopril on prostaglandins are inconclusive.

1. EFFECTS ON PLASMA AND/OR URINARY PROSTAGLANDINS AND/OR METABOLITES Captopril has been reported to increase (75, 137, 273, 274), decrease (210), or have no effect on prostaglandin synthesis (138–141, 159, 269). In several studies, inhibition of the synthesis of prostaglandins subsequent to captopril partially reversed captopril's antihypertensive effect (65, 137–139, 274–276), whereas pretreatment or addition of prostaglandin synthesis inhibitors had no effect in other studies (29, 83, 277). Several studies have shown that AI and AII release prostaglandins into the circulation and that captopril prevents only the effect of AI (278–281).

It seems clear from the above that the precise antihypertensive mechanism(s) of captopril remains unresolved but that it is primarily a result of ACE inhibition. The kidneys appear to be necessary for the antihypertensive effects of ACE inhibitors but the adrenals do not.

VIII. CENTRAL EFFECTS

A. Cardiovascular

Direct administration of captopril into the ventricular system of normotensive cats and rats as well as in SHR markedly decreased the pressor responses elicited by centrally administered AI and renin but did not alter the pressor response to centrally administered AII (101, 282–284). The pressor response to intravenous AI was not altered by centrally administered captopril unless fairly high doses were used which allowed the drug to leak into the peripheral circulation.

The intravenous administration of captopril did not alter the pressor response to centrally administered AI (283–285), suggesting that little or no captopril penetrated from the periphery into the ventricular system of rats or cats.

The central administration of captopril had no effect on blood pressure of normotensive rats (101–103, 180). In contrast, administration of relatively high doses of captopril (0.3–2.0 mg/kg) directly into the ventricular system of both renal and SH rats caused a modest reduction in blood pressure (101–103, 127, 180), most of which could not be accounted for by leakage of captopril into the periphery.

B. Drinking and Vasopressin

Orally administered captopril consistently caused an increase in water drinking behavior in normotensive (32, 286) as well as SH rats (33, 89, 94). However, no effect was observed in one-kidney, one-clip renal hypertensive rats (32). Captopril also increased the spontaneous appetite of rats for NaCl solutions (287). This increased drinking behavior after captopril may be related to vasopressin, since captopril decreased vasopressin levels in SHR (89) and depressed drinking in rats lacking vasopressin (288).

In rats in which activation of the RAA system, either peripherally or centrally, induced drinking, captopril inhibited stimulus-activated thirst (33, 286, 289–291).

IX. SYMPATHETIC FUNCTION, CATECHOLAMINE LEVELS, REFLEXES, AND VASCULAR RESPONSIVENESS AFTER ACE INHIBITION

A. In Vitro

The effects of captopril on the responsiveness of isolated vascular preparations are not consistent; some investigators reported inhibitory effects and others reported no change. For example, superior mesenteric rat arteries perfused with a captopril-containing solution inhibited the pressor responses to both norepinephrine and KCl (292). Similarly, perfusion of intact excised rat kidney with a captopril-containing perfusate caused a decrease in the pressor responses to norepinephrine and AII but not to serotonin (293).

On the other hand, strips of thoracic rabbit aorta, rat portal vein, and several nonvascular smooth muscles showed no inhibition of responses to norepinephrine, AII, and several other agonists (70). A similar lack of effect of captopril was observed for cat superior mesenteric artery to AII (294).

In SHR treated for up to 6 months with captopril, responses of aorta to norepinephrine and KCl were not affected (295). In addition, very high concentrations of captopril directly into the organ bath had no effect either on the contraction of SHR aorta to norepinephrine or on relaxation to nitroglycerin (295).

Ito et al (296) reported that the sodium and potassium content of aorta from SHR were reduced after 6 weeks of treatment with captopril and suggested that this constituted a restoration of membrane function in vascular smooth muscle which could contribute to the antihypertensive effect of the drug.

B. In Vivo

In normotensive rats, cats, dogs, rabbits, and humans, acute captopril treatment had either no effect on, or slightly enhanced pressor responses to, AII (36, 297–299). Similar results were obtained in hypertensive rats (107, 300, 301).

Pressor responses to norepinephrine also were not affected by acute treatment with captopril in normotensive rabbits, dogs, rats, as well as hypertensive rats (36, 297–299). In normotensive rats treated for 5 days, the pressor response to AII was unaltered whereas that to norepinephrine was reduced (297).

In SHR treated daily for 1 day to 6 months with captopril, pressor responses to sympathetic nerve stimulation in the subsequently pithed rats were markedly inhibited but cardiac responses were unaffected (300, 301). Pressor responses to injected norepinephrine and AII were not inhibited after a single dose of captopril but were significantly depressed after chronic dosing. It was suggested that high doses of captopril had a selective inhibitory effect on vascular responses to sympathetic nerve stimulation but not on cardiac responses. Furthermore, part of this effect was determined to be prejunctional in nature.

In essential human and renovascular hypertensive patients, captopril did not cause orthostatic hypertension nor did it interfere with the reflex sympathetic response to tilt (159, 176, 217–219, 233).

In anesthetized dogs, captopril inhibited both reflex dilatation and constriction in the perfused hind limb to systemic increases and decreases in blood pressure, respectively (44).

Captopril did not affect plasma catecholamine levels in hypertensive animals or human hypertensive patients nor did it interfere with catecholamine release caused by head-up tilting in patients (106, 159, 210, 213, 217–219).

X. SHOCK

Captopril is beneficial in hemorrhagic shock in cats. Captopril infusion resulted in a higher postoligemic mean arterial blood pressure than vehicle treated cats, decreased accumulation of cathepsin D and myocardial depressant factor, increased lysosomal stabilization, enhanced adrenal gland blood flow, and increased survival time, effects probably related to the reduction of AII formation by captopril (294, 302–304).

XI. CONGESTIVE HEART FAILURE

In early studies in dogs, captopril was found to be beneficial in high output failure (305) and in a model of low cardiac output (36). In the former, captopril decreased blood pressure, plasma aldosterone concentrations, creatinine clearance, and filtration fraction, whereas PRA increased and sodium excretion was unchanged (305). In dogs with thoracic-caval constriction, captopril decreased blood pressure, plasma aldosterone concentrations, and filtration fraction (36). Sodium excretion and PRA increased, whereas clearance of PAH and creatinine did not change.

In human patients with severe congestive heart failure resistant to therapy with diuretics and digitalis glycosides, captopril has proven to be particularly effective. The drug consistently increased cardiac output and/or index as well as stroke volume and/or index in these patients while decreasing myocardial oxygen consumption, pulmonary capillary wedge pressure, right atrial pressure, left ventricular filling pressure, systemic blood pressure, and vascular resistance, good evidence of improved left ventricular function (306–318). Despite the reduction in blood pressure, heart rate and plasma catecholamines were consistently decreased probably because of the improved hemodynamic pattern (318). Improvement in exercise time and in clinical functional classification according to the NYHA criteria also occurred after captopril (307, 311, 316). No tolerance to these effects was observed. Kidney function was also improved along with increases in urinary sodium excretion, probably because of aldosterone reductions and hemodynamic improvement.

In addition to the effects of captopril on the arterial system, the drug also decreased venous tone in congestive failure patients (307, 318), the mechanism of which is unclear.

XII. SUMMARY

Angiotensin converting enzyme inhibitors represent a new class of agents which were designed to retain only that unique property. Because of this inhibition, administration of these agents results in the significant reduction

of elevated blood pressure of various etiologies and in the amelioration of symptoms associated with congestive heart failure resistant to digitalis glycosides and diuretics. The mechanism(s) of action is not entirely certain but almost certainly resides in the inhibition of ACE. Certainly, the future will see still further advances made in this therapeutic area as well as with other inhibitors of the renin-angiotensin system.

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