Relative Lipophilicities and Structural–Pharmacological Considerations of Various Angiotensin-Converting Enzyme (ACE) Inhibitors

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Lipophilicities of seven structurally diverse angiotensin-converting enzyme (ACE) inhibitors, *viz.*, captopril, zofenoprilat, enalaprilat, ramiprilat, lisinopril, fosinoprilat, and ceronapril (SQ29852), were compared by determining their octanol–water distribution coefficients (*D*) under physiological pH conditions. The distribution coefficients of zofenopril, enalapril, ramipril and fosinopril, which are the prodrug forms of zofenoprilat, enalaprilat, ramiprilat, and fosinoprilat, respectively, were also determined. Attempts were made to correlate lipophilicities with the reported data for oral absorption, protein binding, ACE inhibitory activity, propensity for biliary excretion, and penetration across the blood–brain barrier for these therapeutic entities. Better absorption of prodrugs compared to their respective active forms is in agreement with their greater lipophilicities. Captopril, lisinopril, and ceronapril are orally well absorbed despite their low lipophilicities, suggesting involvement of other factors such as a carrier-mediated transport process. Of all the compounds studied, the two most lipophilic ACE inhibitors, fosinoprilat and zofenoprilat, exhibit a rank-order correlation with respect to biliary excretion. This may explain the dual routes of elimination (renal and hepatic) observed with fosinoprilat in humans. The more lipophilic compounds also exhibit higher protein binding. Both the lipophilicity and a carrier-mediated process may be involved in penetration of some of these drugs into brain. For structurally similar compounds, *in vitro* ACE inhibitory activity increased with the increase in lipophilicity. However, no clear correlation between lipophilicity and ACE inhibitory activity emerged when different types of inhibitors are compared, possibly because their interactions with enzymes are primarily ionic in nature.

KEY WORDS: angiotensin-converting enzyme (ACE) inhibitors; lipophilicity; distribution coefficient; oral absorption; biliary excretion; structure–activity correlation.

INTRODUCTION

Since the discovery of captopril (1), angiotensin-converting enzyme (ACE) inhibitors have emerged as an important class of antihypertensive agents for the treatment of high blood pressure and congestive heart failure. Many ACE inhibitors have been approved for medical use or are in various stages of development (2). These compounds generally belong to three chemical categories, *viz.*, sulfhydryl, carboxyalkyl dipeptide, and phosphorus-containing types (3). These inhibitors differ in their rate and extent of oral absorption, duration of action, protein binding, mode of elimination, etc. (2). The inhibitors have also been differentiated by their selective inhibition of ACE in physiologically important target organs, such as aorta, heart, kidney, lung, serum, and brain (4). The possible difference in activity of ACE inhibitors in the brain attracted added attention after it was reported that ceronapril (SQ29852) and captopril increased adoptive and cognitive processes of learning and prevented scopolamine-induced impairment in mice (5), possibly by inducing central cholinergic activity.

The structure–activity relationships were studied by several investigators to explain differences among various ACE inhibitors (4,6,7). The lipophilicity plays an important role in membrane penetration, tissue and protein binding, etc. (8), and has been correlated with activities of various drug molecules (9,10). However, no systematic study on the relative lipophilicities of different ACE inhibitors has been reported. Ondetti (7) used octanol–water partition coefficient values which had been calculated theoretically in his structural relationship studies, and Gohlke *et al.* (11) attempted to correlate lipophilicities of three ACE inhibitors of carboxyalkyl dipeptide type with their ability to penetrate the blood–brain barrier. It has also been suggested that lipophilicity may be a factor in the biliary excretion of certain ACE inhibitors (12,13). In the present study the octanol–water distribution coefficients under various pH conditions were determined for seven ACE inhibitors representing sulfhydryl, carboxyalkyl dipeptide, and phosphorus-containing types, and attempts made to correlate these with their reported oral absorption, enzyme inhibitory activity, plasma protein binding, mode of elimination, potential for crossing the blood–brain barrier, etc. The names and structures of the compounds studied are given in Fig. 1. Four of these inhibitors, namely, enalaprilat, fosinoprilat, ramiprilat and zofenoprilat are used clinically in prodrug forms. Therefore, the distribution coefficients of their prodrugs were also determined and considered in arriving at structure-activity relationships.

MATERIALS AND METHODS

Materials

Captopril, fosinopril sodium, fosinoprilat, zofenopril calcium, zofenoprilat (arginine salt), and ceronapril were produced by the Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, NJ. Enalapril, enalaprilat, and lisinopril were supplied by Merck and Co., Rahway, NJ, and ramipril and ramiprilat were supplied by Hoechst-Roussell Co., Somerville, NJ.

Determination of the Distribution Coefficient

The *n*-octanol–water distribution coefficients were determined in the pH range of 1 to 7 using the general procedure developed by Leo *et al.* (14). The aqueous media used

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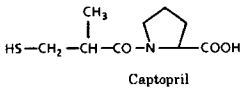
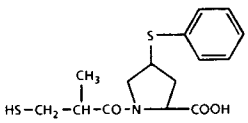
ACE Inhibitors Prodrugs

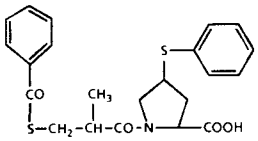
I. Sulfhydryl Type



Captopril

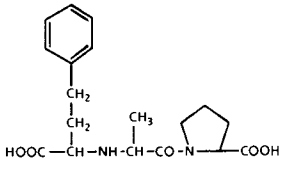


Zofenoprilat

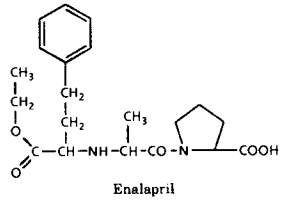


Zofenopril

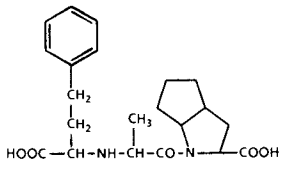
II. Carboxyalkyl Dipeptide Type



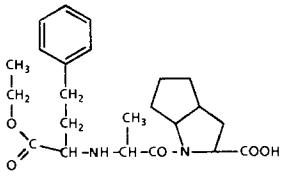
Enalaprilat



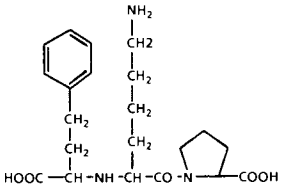
Enalapril



Ramiprilat

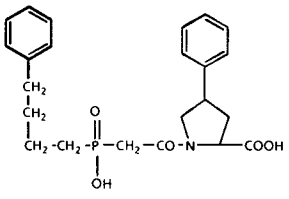


Ramipril

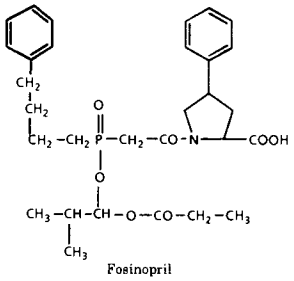


Lisinopril

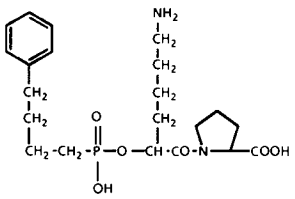
III. Phosphorus-containing Type



Fosinoprilat



Fosinopril



Ceronapril

Fig. 1. Structures of ACE inhibitors and prodrugs used.

were 0.1 and 0.01 *M* HCl, 0.035 *M* phosphate buffer, pH 3, 0.1 *M* acetate buffers, pH 4 and 5, and 0.035 *M* phosphate buffers, pH 6 and 7. Ionic strengths of aqueous phases were adjusted, when necessary, to 0.1 using KCl. Prior to use, the octanol phase was saturated with the appropriate aqueous phase, and the aqueous phase with octanol. A known amount of a compound was dissolved in the aqueous phase prior to equilibration with octanol, except for fosinoprilat, zofenoprilat, and their prodrugs under low-pH conditions, where the aqueous solubilities of these compounds were very low. At pH 5 and lower, fosinoprilat, zofenoprilat, and their prodrugs were first dissolved in octanol and then equilibrated with the aqueous phase. The equilibration was achieved by placing the two phases in a 50-ml centrifuge tube fitted with a Teflon stopper and inverting the same repeatedly for about 300 times. The mixture was then centrifuged (2000 rpm), and the aqueous phase was analyzed for drug concentration. When the drug was initially dissolved in the aqueous phase, the distribution coefficient (D) was calculated using the equation,

$$D = \frac{V_w(C_{w1} - C_{w2})}{V_o C_{w2}} \quad (1)$$

where V_w and V_o are the volumes of the aqueous and octanol phases, respectively, and C_{w1} and C_{w2} are, respectively, the initial and final concentrations of a compound in the aqueous phase.

When a compound was initially dissolved in the octanol phase, the concentration in octanol after equilibration was calculated by subtracting the amount of the drug that had partitioned into the aqueous phase. In this method the volumes of the two phases and the concentrations of drugs were adjusted such that the concentration of a particular drug in the aqueous phase was below its saturation solubility.

Assay Methods

The samples were analyzed by HPLC, under the assay conditions given in Table I. The HPLC system consisted of a Waters autoinjector (WISP 710B), an Altex pump (110A), a UV detector (SF 783, Kratos), and μ-Bondapak column (Waters). The data were analyzed by computer using an integration software package (PeakPro, Beckmann).

RESULTS AND DISCUSSION

Distribution Coefficients

The octanol–water distribution coefficients (D) of the ACE inhibitors captopril, zofenoprilat, enalaprilat, ramiprilat, fosinoprilat, ceronapril, and lisinopril as well as those of the prodrugs zofenopril, enalapril, ramipril, and fosinopril in the pH range of 1 to 7 are given in Table I. All the compounds studied possess ionizable groups and, in solution, can exist as nonionic and ionic species depending on the pH. Some of the structures can also exist as zwitterionic species. The data for enalaprilat, ramiprilat, and their prodrugs are shown graphically in Fig. 2 to indicate the influence of isoelectric pH on the distribution coefficient and to facilitate estimation of the distribution coefficient values for the zwitterionic species of these molecules.

The changes in distribution coefficients of the sulfhydryl-type compounds, captopril, zofenoprilat, and zofenopril, with respect to pH are in agreement with the change in concentrations of nonionized species of the molecules (pK_a ~3.5). A comparison of the $D_{o/w}$ values of the nonionized species of captopril and zofenoprilat indicates that the 4-substitution of the proline residue of captopril with a phenylthio group results in about a 70 times increase in lipophilicity. Further, the prodrug zofenopril, which is the *S*-benzoyl ester of zofenoprilat, is over 150 times more lipophilic than the active moiety.

The bell-shaped curves exhibited by the pH–distribution coefficient plots of the carboxyalkyl dipeptide-type compounds enalaprilat and ramiprilat (Fig. 2) indicate that the maxima in their lipophilicity may possibly be related to the formation of zwitterionic species. Each of these compounds contains two carboxyl and one basic (–NH–) functionality. The carboxyl group in the proline moiety, based on structural similarity with captopril, is expected to have a pK_a value of about 3.5. The alkylcarboxyl group, because of the electrostatic repulsion of the carboxyl proton by the neighboring positively charged –NH– group, would have a pK_a value less than that of the proline carboxyl group. This value is estimated to be between 2 and 2.5 (15). The pK_a value for the –NH– functionality has been reported to be 7.2 (3). By averaging the pK_a values of the acidic groups, the isoelectric pH (pH_I) for enalaprilat and ramiprilat is calculated to be about 3. Thus, as shown in Fig. 2, there is a good agreement between pH_I and pH of the maximum distribution coefficient for both enalaprilat and ramiprilat.

The maxima in distribution coefficients of enalapril and ramipril also appear at their isoelectric pH's (Fig. 2). Each of these molecules has two ionizable groups. The pK_a value of the carboxyl group in the proline moiety, as mentioned above, is 3.5, and due to the effect of esterification on the basicity of the –NH– group, its pK_a value is reduced to 5.5 (3). The pH_I is, therefore, ~4.5, which is also the pH at which the maximum distribution coefficient for each of these compounds was observed.

Since enalaprilat, ramiprilat, enalapril, and ramipril remain ionized and/or protonated throughout the pH range studied, the distribution coefficients of their nonionized species could not be determined experimentally for the purpose of comparing their lipophilicities. The distribution coefficients at pH_I were, therefore, used to compare the lipophilicities of these molecules. Such a comparison is reasonable because the net charges of the molecules at their respective pH_I are zero. The comparison of the distribution coefficients at pH_I in Fig. 2 shows that the introduction of a bicyclic ring in place of the proline moiety makes ramiprilat and ramipril approximately 13 times more lipophilic than enalaprilat and enalapril, respectively. Additionally, enalapril and ramipril are three times more lipophilic than enalaprilat and ramiprilat, respectively, thus showing the influence of prodrug formation.

Unlike other ACE inhibitors, lisinopril has four ionizable groups, *viz.*, $-NH_2$, –NH–, proline–COOH, and alkyl–COOH, with the estimated pK_a values of 10.5, 7.6, 3.5, and

Table I. Octanol–Water Distribution Coefficients of Various ACE Inhibitors and Prodrugs Under Different pH Conditions (μ = 0.1)[a]

Compound	pH 1	2	3	4	5	6	7
Captopril	2.18 (1.99, 2.01, 2.35, 2.35)[b]	1.93 (1.78, 1.97, 1.97, 1.98)	—	0.40 (0.39, 0.41)	0.05 (0.05, 0.05)	0.007 (0.007, 0.007)	0.004 (0.004, 0.004)
Zofenoprilat	145 (141, 149)	136 (133, 138)	—	28.8 (26.4, 26.8, 28.0, 31.3, 31.6)	4.6 (4.3, 4.5, 4.7, 4.9)	1.16	0.22 (0.20, 0.20, 0.27)
Zofenopril	25,000 (24,600, 26,000)	25,000 (22,100, 27,200)	21,000 (18,700, 19,100, 23,000, 23,400)	3150 (2900, 3000, 3300, 3400)	470 (460, 470, 470, 480)	78	35 (31, 38)
Enalaprilat	—	0.24 (0.24,0.24, 0.24, 0.24)	0.28 (0.24, 0.26, 0.30, 0.31)	0.033 (0.033, 0.032)	0.0024 (0.027, 0.022)	—	<0.001
Ramiprilat	1.65 (1.68, 1.62)	2.33 (2.29, 2.36)	3.40 (3.40, 3.39)	0.71 (0.071, 0.71)	0.15 (0.15, 0.15)	—	0.011 (0.009, 0.013)
Lisinopril	0.06 (0.06, 0.06)	0.10 (0.09, 0.10)	<0.001	<0.001	<0.001	—	<0.001
Enalapril	0.33 (0.33, 0.33)	0.36 (0.30, 0.36, 0.41)	0.52 (0.48, 0.50, 0.52, 0.58)	0.85 (0.84, 0.85)	0.76 (0.74, 0.77)	—	0.071 (0.070, 0.071)
Ramipril	3.56 (3.56, 3.56)	2.91 (2.84, 2.97)	5.65 (5.62, 5.68)	10.2 (9.8, 10.6)	10.2 (10.2, 10.2)	—	1.39 (1.33, 1.44)
Fosinoprilat	—	4450 (4400, 4500)	1590 (1470, 1700)	21.4 (19.7, 20.9, 22.3, 22.5)	0.73 (0.72, 0.72, 0.72, 0.74)	—	0.33 (0.32, 0.32, 0.33, 0.36)
Fosinopril[c]	>100,000	>100,000	—	>100,000	84,000	14,000	500
Ceronapril	0.13 (0.11, 0.14)	0.09 (0.07, 0.10)	0.053 (0.048, 0.057)	0.021 (0.019, 0.019, 0.021, 0.023)	0.0020 (0.0016, 0.0019, 0.0020, 0.0026)	—	<0.001

[a] The drug solutions were analyzed by HPLC using μ-Bondapak phenyl columns (Waters) at 30–40°C. For captopril, fosinopril, fosinoprilat, zofenopril, and zofenoprilat, a 15 × 3.9-cm column was used, and for others the column size was 30 × 3.9 cm. Except for ramiprilat and ceronapril, the mobile phases used were mixtures of methanol, water, and 85% (w/w) H_3PO_4 at the following ratios: captopril, 45:55:0.05; zofenoprilat and zofenopril, 68:32:0.2; enalaprilat, 45:55:0.05; lisinopril and enalapril, 60:40:0.05; ramipril, 55:45:0.05; fosinoprilat, 68:32:0.2; and fosinopril, 72:28:0.2. A 55:45 mixture of 0.005 *M* H_3PO_4 (pH 3) and methanol was used for ramiprilat, and for ceronapril it was a 75:25 mixture of 0.01 *M* $NH_4H_2PO_4/H_3PO_4$ buffer (pH 2.1) and acetonitrile. The wavelength of detection was 215–220 nm.

[b] Individual distribution coefficient values are given in parentheses.

[c] Each fosinopril distribution value is the average of at least two individual values.

~2.5, respectively. The multiple charges and the absence of a pH_I throughout the pH range studied may be responsible for the low distribution coefficient values of lisinopril shown in Table I. Among all ACE inhibitors studied, fosinoprilat is the most lipophilic. Its high distribution coefficient value at pH 7 has been attributed to the formation of an ion pair (16). The presence of an aminobutyl side chain and the phosphonic acid group in place of phosphinic acid group renders ceronapril much less lipophilic than fosinoprilat.

Relationship of Lipophilicity with Pharmacological Activity

A comparison of the lipophilicities of various ACE inhibitors and prodrugs with some of their reported biopharmaceutical and pharmacological properties is given in Table II.

Oral Absorption. Four of the ACE inhibitors studied (zofenoprilat, enalaprilat, ramiprilat, and fosinoprilat) are administered orally as inactive prodrug esters (zofenopril, enalapril, ramipril, and fosinopril, respectively) which are deesterified by enzymes present in blood, liver, or other tissues (2). Better absorption of the prodrugs compared to their respective active moieties may be due to one or more of the following factors: (i) All the prodrugs have higher distribution coefficients than their respective active moieties, thus increasing their passive absorption; (ii) the prodrug formation alters the charge densities of enalaprilat and ramiprilat molecules by increasing the pH_I and shifts the maxima in the distribution coefficient profiles from pH 3 to pH 4.5, which would make the pH of the small intestine more favorable for the absorption of prodrugs; and (iii) factors other than lipophilicity, *viz.*, a peptide carrier system, may be responsible for the better oral absorption of prodrugs such as enalapril (25) and ramipril than their respective active forms. The good oral absorption of lisinopril, ceronapril, and captopril despite low lipophilicities are in agreement with the postulation by Amidon and his co-workers (25–27) that a possible amino acid carrier-mediated system may be involved in the absorption of these compounds.

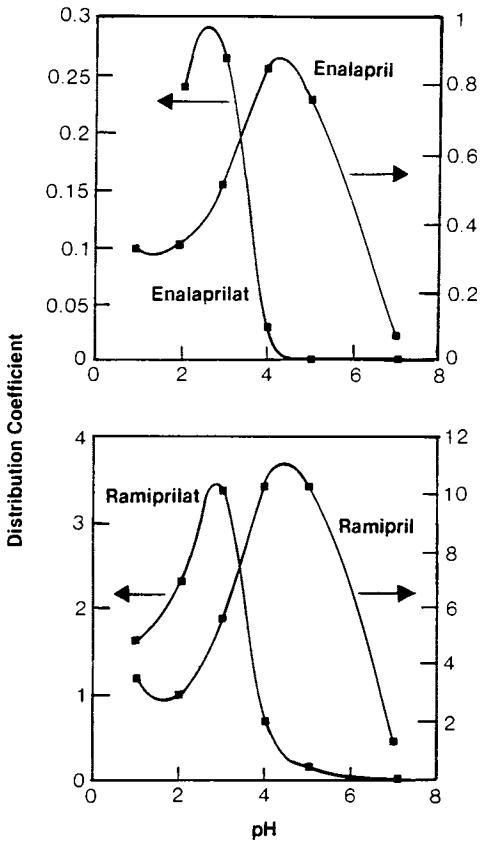


Fig. 2. pH–distribution coefficient profiles of enalaprilat, enalapril, ramiprilat, and ramipril. The arrows indicate appropriate ordinates for distribution coefficient values.

Protein Binding. There is a general agreement between lipophilicity and protein binding within each type of ACE inhibitors. Thus, zofenoprilat, ramiprilat, and fosinoprilat exhibit higher protein binding than captopril, enalaprilat, and ceronapril, respectively. Lisinopril, being very hydrophilic, is not protein bound. It is not clear, however, why the protein binding of ceronapril is much higher than that of lisinopril. An interaction between serum protein and the nonpolar end of ceronapril is a possibility.

ACE Inhibitory Activity. The lipophilicity may be involved in differentiating the ACE inhibitory activities of structurally similar molecules only. Thus, it may be noted in Table II that when the lipophilicity of a molecule is increased by chemical substitution in the proline residue (captopril vs zofenoprilat, enalaprilat vs ramiprilat), the enzyme inhibitory activity is increased. ACE and its inhibitors interact at several sites, and interactions at some of the sites are ionic in nature (e.g., zinc binding), while at others they may be van der Waals type (1,3). It appears from the above results that the potency of a molecule may be increased with the increase in hydrophobic interaction by chemical modification. No clear correlation, however, emerges when distribution coefficients and activities of different classes of ACE inhibitors are compared, possibly because of the difference in the ionic component of drug–enzyme interaction.

Biliary Excretion. The fecal excretions of fosinoprilat and zofenoprilat after intravenous administration are 46 and 16%, respectively, indicating that these two compounds undergo biliary excretion. Since fosinopril and zofenoprilat are much more lipophilic than the other inhibitors studied, there appears to be a correlation between the lipophilicity and the biliary excretion of ACE inhibitors. Recently, Carr *et al.* (13) also reported that FPL 63547, a lipophilic ACE inhibitor, has a higher biliary excretion in rats than do hydrophilic enalaprilat and lisinopril. The high biliary excretion of fosinoprilat

Table II. Comparison of Distribution Coefficients (*D*) of Selected ACE Inhibitors with Biopharmaceutical and Pharmacological Properties in Humans

Compound	Distribution coefficient: Nonionized species	Distribution coefficient: Zwitterionic species	Distribution coefficient: pH 7	Oral absorption in humans (%)	Serum protein binding (%)	*In vitro* ACE inhibition (I_{50}; nmol/L)	Biliary excretion (%)
Captopril	2.2		0.004	60–75 (17)[a]	25–30 (17)	9.7 (4)	0 (17)
Zofenoprilat	150		0.22	ND[b]	95 (18)	1.7 (4)	16 (18)
Zofenopril	25,000		35	96 (18)	ND	NA[c]	NA
Enalaprilat		0.3	<0.001	<10 (17)	40 (19)	2.8 (4)	—[d] (20)
Ramiprilat		3.4	0.011	~5[e] (21)	56 (21)	0.67 (4)	—[f] (21)
Lisinopril		<0.1	<0.001	25–50 (22)	0 (22)	1.4 (4)	0 (22)
Enalapril		0.9	0.07	60–70 (17)	ND	NA	NA
Ramipril		11	1.12	54–65 (21)	ND	NA	NA
Fosinoprilat	5,000		0.33	<5[e]	95 (23)	2.7 (4)	46 (23)
Fosinopril	>100,000		~500	32–36 (23)	ND	NA	NA
Ceronapril	0.1		<0.001	67 (24)	49	34 (4)	0 (24)

[a] The numbers in parentheses are reference numbers.
[b] Not determined.
[c] Not applicable because the compounds are prodrugs.
[d] Low biliary excretion; excreted primarily through kidney.
[e] Based on animal data.
[f] The renal excretion is 56%, compared to 54–65% absorption of ramipril, indicating that the biliary excretion of active ramiprilat in humans may be very small.

provides an alternate route of elimination of the drug beneficial to patients with renal impairment (28).

Penetration of Blood–Brain Barrier. After oral administration of three structurally related compounds, enalapril, ramipril, and Hoe 288, to rats by Gohlke *et al.* (11), the most lipophilic molecule, Hoe 288, exhibited the highest ACE inhibitory activity in the cerebrospinal fluid (CSF), while the hydrophilic enalapril did not shown any activity. The authors also suggested that the administration of an ACE inhibitor as a lipophilic prodrug may enhance its activity in the brain. Being more lipophilic, any intact prodrug remaining in the blood will penetrate rapidly into the brain, where it will subsequently hydrolyze into the active form. In the present study, fosinoprilat–fosinopril is the most lipophilic inhibitor–prodrug pair and, therefore, has the highest potential for diffusion into the brain. Indeed, Cushman *et al.* (4) demonstrated that after a single oral dosing of fosinopril to rats, there was an immediate inhibition of brain ACE which lasted for at least 4 days. Zofenopril and captopril, which are less lipophilic than fosinopril, produced ACE inhibition that persisted for only 8 hr or less. Cushman *et al.* (4) also observed prolonged ACE inhibition with lisinopril and ceronapril, although the onsets were albeit delayed. Since the latter compounds are more hydrophilic than enalaprilat, which did not show any activity in CSF, it is possible that a peptide carrier system present at the blood–brain barrier (29) may be responsible for their penetration into the brain.

CONCLUSIONS

The relative octanol–water distribution coefficients of several angiotensin-converting enzyme inhibitors have been correlated with their oral absorption, protein binding, propensity for biliary excretion, and penetration across the blood–brain barrier. The good oral absorption of captopril, lisinopril, and ceronapril despite their low lipophilicities was attributed to a possible carrier-mediated transport process. The plasma protein binding increased with the increase in lipophilicity of the compounds. The high lipophilicity of fosinoprilat may explain its biliary excretion as well as renal elimination in humans.

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