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Tissue Angiotensin Converting Enzyme Inhibition
Relevant to Clinical Practice?

Kennedy R. Lees, Robert J. MacFadyen, and John L. Reid

Accumulating data indicate that tissue and systemic renin–angiotensin systems may coexist. Evidence supporting the existence of local regulatory systems derives from several sources. Firstly, it has been clearly demonstrated that all components of the renin–angiotensin system are detectable in the tissues of organs such as the brain, heart, lung, kidney, testis, and blood vessels. Secondly, many diverse actions of angiotensin II have been defined in different tissues, all of which have a common mechanism: maintaining or increasing vascular tone, blood volume, or both. Evidence supporting the concept that the local and systemic renin–angiotensin systems are functionally independent includes the discrepancy in the time courses of hemodynamic changes and enzyme inhibition following administration of angiotensin-converting enzyme (ACE) inhibitors; and the observation that ACE inhibitor treatment results in decreases in blood pressure in anephric subjects, who have extremely low circulating concentrations of angiotensin II. These and other data suggest that inhibition of tissue ACE may be as, or more, important than its effects on the more easily measured circulating ACE. This raises the question of whether there are differences among ACE inhibitors in their selectivity for one or more organ systems. Some experimental data indicate that the binding affinity and time course of ACE inhibition can vary from one tissue to another, and among individual agents. Several factors can influence the tissue availability of ACE inhibitors, including the plasma concentration of the drug (or ester prodrug); the rate of conversion of ester to diacid and/or the potential for localized conversion; the relative number of plasma and tissue binding sites for the ACE inhibitor; the rate and route of drug elimination; and the lipophilicity of the drug (or its parent ester). Although the prospect of individualizing therapy by prescribing ACE inhibitors with unique profiles of tissue inhibitory activity is attractive, the clinical relevance and utility of regional ACE inhibition and any differences among ACE inhibitors in terms of tissue selectivity requires further investigation. Am J Hypertens 1990;3:266S–272S

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The role of the renin–angiotensin system as a paracrine or autocrine control mechanism, functionally independent of the endocrine renin–angiotensin system, has recently received extensive attention.[1–7] It is well-known that circulating renin is secreted by the kidney and exerts systemic effects on salt and blood pressure homeostasis. However, it is increasingly believed that there is also local release of renin within tissues. This renin catalyzes formation of angiotensin I, which is converted to angiotensin II by angiotensin converting enzyme (ACE) within the same tissue. The angiotensin II is thought to exert tissue dependent actions, but not to contribute substantially to effects at distant sites.

EVIDENCE SUPPORTING THE CONCEPT OF TISSUE-LOCALIZED RENIN–ANGIOTENSIN SYSTEMS

One of the local effects of angiotensin II may be the control of glomerular filtration pressure within the kidney. Evidence to support this view comes from several sources. Firstly, it is now evident that various components of the renin–angiotensin systems (in addition to renin itself) can be detected in the tissues of many organs (eg, brain, heart, lung, kidney, testis, and blood vessels).[8–16] In addition, the colocalization of messenger RNA for these peptides confirms that local synthesis is possible.[17–19]

Secondly, angiotensin II has diverse actions, the specific functions of which have been defined in a number of tissues (Table 1). The fact that these tissues are involved in maintaining or increasing vascular tone and/or blood volume supports the concept of local regulatory systems, although it does not prove that they are functionally independent.

Discrepancy in Time Course of ACE Inhibition and Hemodynamic Changes The single piece of evidence that is most often interpreted as supporting the argument that tissue ACE may be independent of serum ACE is the discrepancy in the time course of hemodynamic changes compared to the time course of enzyme inhibition following pharmacologic intervention.[2,4,20,21] For example, in a 28 day study in elderly hypertensive patients, maximum plasma concentrations of quinapril and its active metabolite occurred within 2 h postdosing. However, there was no apparent correlation between the plasma drug concentration and the blood pressure lowering effect.[22]

Blood pressure has also been shown to fall after ACE inhibitor treatment, even in anephric subjects with extremely low circulating concentrations of angiotensin II.[4,23] Our detailed knowledge of the regulatory effects of the renin–angiotensin system within the kidney,[24,25] as well as the functional renal impairment that ACE inhibitors may produce in patients with renal artery stenosis,[26–28] favors the argument that local and systemic systems may coexist.

TABLE 1. DIVERSE ACTIONS OF ANGIOTENSIN II

Vascular
Vasoconstriction in resistance vessels, conducting vessels and veins
Mitogenic
Fibrous tissue formation
Enhanced muscle/myosin composition
Hypertrophy or remodelling
Neurogenic
Facilitation of norepinephrine release
Interaction with pre- and postjunctional α-receptors
Parasympathomimetic actions
Membrane
Modulation of ion transport (sodium, chloride and bicarbonate)
Endocrine
Promotes release of aldosterone (potassium-dependent), corticotropin, luteinizing hormone/follicle stimulating hormone, and prolactin
Central nervous system
Promotes thirst
Behavioral effects
Possible central regulation of blood pressure
Renal
Combination of above effects on tubular solute resorption, blood flow, glomerular filtration rate, and cellular structure

LOCALIZED EFFECTS OF RENAL, CARDIAC AND PULMONARY ANGIOTENSIN II

Within the kidney, angiotensin II causes afferent and efferent vasoconstriction, although the greater effect occurs in efferent arterioles. Thus, angiotensin II mediates an increase in glomerular filtration pressure, despite a reduction in blood flow. In addition, the filtration fraction is increased and regional redistribution of flow occurs, reducing flow to the papillary regions.[29] Proximal tubular reabsorption of sodium, chloride and bicarbonate is stimulated by angiotensin II, and medullary blood flow changes may influence the countercurrent mechanism that also contributes to sodium homeostasis.[30] However, the kidney is not typical of other organs, since it has both afferent and efferent arterioles.

In the heart, angiotensin II modulates structure by promoting fibrosis and hypertrophy.[31] Conversely, ACE inhibition in human hypertension can reverse left ventricular hypertrophy.[32,33] Angiotensin II plays a role in inotropy,[34] vasomotor tone,[35] autonomic tone,[36,37] and, possibly, in myocardial conduction.[38]

In the lung, angiotensin II contributes to regional vasomotor tone. Angiotensin converting enzyme is released in response to lung injury[39,40] and chronic hy-

poxia reduces pulmonary ACE and angiotensin II,[41] without affecting other sites.

Angiotensin converting enzyme is present in the vasculature of every organ, and angiotensin II has vasoconstricting effects on conduction vessels, resistance arterioles, and veins. The relevance of aortic or large vessel ACE to flow redistribution is still uncertain.[42] Further evidence is needed if we are to conclude that these individual systems are functionally independent under certain circumstances.

TISSUE SELECTIVITY OF ACE INHIBITORS

The advent of radioligand-binding methods has allowed a comparison of the inhibitory activity of ACE inhibitors in various tissues. For example, Johnston et al[43] determined that the rank order of potency against plasma, as well as against lung, kidney and cardiac ACE, was quinaprilat = benazeprilat > perindoprilat > lisinopril > enalaprilat > fosinoprilat.

As far as the development of new ACE inhibitors is concerned, it is not only important that functional independence be demonstrated, but it will also be necessary to show that agents differ in their selectivity for one or more systems and that this has clinical relevance during chronic therapy.

Factors Affecting Tissue Availability and Selectivity Several factors may potentially influence the tissue availability of ACE inhibitors. These include: 1) the plasma concentration of the drug (and its ester prodrug, when applicable); 2) the rate of conversion of ester to diacid and the potential for conversion to occur locally in tissue sites; 3) the relative number of plasma and tissue-binding sites for the ACE inhibitor; 4) the presence of barriers to diffusion (eg, the blood-brain barrier, the blood-testis barrier); 5) the rate and route of drug elimination; and 6) the lipophilicity of the drug or its parent ester. In practical terms, however, some of these factors are unlikely to be clinically relevant.

The relative proportion of binding sites may affect drug distribution to the tissues, but will not per se alter percentage inhibition of ACE. Similarly, membrane barriers can only protect regions in the short term, unless a mechanism for pumping out the drug coexists, since total impermeability is unlikely.

In practice, therefore, selectivity could be achieved by varying the lipophilicity of a compound and improving tissue penetration. A less likely option is to tailor compounds to inhibit differentially ACE molecules that are structurally distinct.[44]

Evidence for Tissue Specificities of ACE Inhibitors Some experimental data currently suggest that the time course of inhibition of ACE by inhibitors can vary from one organ to another.

Johnston et al[6,43] compared the time course of inhibition of ACE ex vivo in plasma and various tissues. After oral administration of quinapril to rats, there was a substantial reduction in plasma ACE, which was maximal at 1 to 2 h and then decreased to about 25% by 24 h. The degree of ACE inhibition was lower in the lung and aorta, but persisted at an almost constant level for more than 24 h. Similar differences between tissues were seen with the other ACE inhibitors studied, benazepril and perindopril.

A temporal dissociation between pulmonary and plasma ACE inhibition has been reported by Chen et al[45] and Jackson et al,[46] dissociation between vascular and plasma ACE by Unger et al[47] and Jackson et al,[46] dissociation between cardiac and plasma ACE by Unger et al[47] and Chevillard et al,[48] and dissociation of renal from plasma ACE by Jackson et al[46] and Kamei et al.[49] Jackson's work suggests that pulmonary ACE inhibition is more protracted than that of vascular tissue or kidney.[46]

Do Structural Differences Between Tissue-Specific ACE Contribute to Differences Between ACE Inhibitors? As regards the structure of ACE in different sites, it appears that pulmonary ACE is very similar to soluble (ie, plasma) ACE.[50] Indeed, it has been suggested that circulating ACE derives from vascular endothelium primarily in the lung. Renal ACE is also very similar in structure.[51] There is limited evidence for a different primary[52] and tertiary[53] structure of cardiac ACE in the rabbit and rat, respectively. The similarities between ACE structures from different sites effectively outweigh the minor differences that have been detected, however. The minor dissimilarities relate primarily to the parts of the molecule that link to the plasma membrane, which are unlikely to influence enzyme activity or inhibitor binding.

Variability in the dissociation constants for ACE derived from different tissues has been demonstrated, but it is unclear whether these differences are due to inherent properties of the active site of ACE or to extrinsic factors (eg, the lipid content of the local environment).

The magnitude of these differences is small,[54] and is not sufficient to account for the variability in inhibition that has been observed between groups of tissues ex vivo.[44] Delayed tissue penetration is the likely explanation, particularly since the different tissues can all be inhibited in vitro by the diacid inhibitor perindoprilat.[44]

Under steady-state conditions, tissue concentrations of an ACE inhibitor should approximate plasma concentrations, unless the ACE is in a strongly lipid environment. Any acute tissue selectivity that is demonstrated may be irrelevant during chronic dosing.

DURATION OF ACTION AND PHARMACOKINETICS

The effects of almost all ACE inhibitors on plasma ACE appear to be dissociated from the pharmacokinetics of the drug. It can be demonstrated, however, that the

pharmacokinetics of ACE inhibitors are the function of simple linear pharmacokinetics of elimination superimposed upon saturable binding to circulating ACE[55] or circulating and tissue ACE.[56] The time course of drug-binding naturally follows that of ACE inhibition very closely.[55]

The Implications of Excess Circulating and/or Tissue ACE Since ACE is not a rate-limiting enzyme in the renin–angiotensin system[57] (ie, since an excess of ACE is normally present), a significant decline in the concentration of angiotensin II occurs only after substantial inhibition of ACE.[58] Sensitive and specific assays for angiotensin I and II can demonstrate that effective inhibition of ACE recovers before inhibition measured by artificial substrate methods has returned to normal.[58] It has been suggested that any attempt to measure the time course of clinically relevant ACE inhibition must take into account relative concentrations of angiotensin I and angiotensin II.[58]

Excess enzyme capacity may also explain the apparently idiosyncratic response of some patients to their first dose of an ACE inhibitor.[59–62] It has been suggested that first-dose hypotension is not prevented by dose reduction within the normal range of doses used.[63] Nevertheless, there are claims that the incidence of first-dose hypotension may be lower when lower doses of drug are administered.[60,64] It is suggested that hypotension may not be a concentration-related event. Supporting evidence is sometimes quoted in the form of a blood pressure profile, which shows a steady but gradual decline followed by a precipitous fall in blood pressure, despite a smooth and modest rise in drug concentration at that time. Falls in angiotensin II concentration have been demonstrated to be associated with hemodynamic changes.[60]

A further area of potential concern is the extent to which excess tissue ACE may be present. It seems feasible that 30% inhibition of preexisting ACE activity in one tissue may significantly influence angiotensin II production locally, whereas 70% inhibition in another tissue that has a relative excess of ACE may produce little effect on angiotensin II. Limited experimental evidence from the isolated rat kidney suggests that ACE may be rate-limiting under the conditions described.[65] Although published ratios of angiotensin I to angiotensin II collected from renal venous blood in humans are consistent with a similar situation in the human kidney,[66] the assays employed were less specific than those now available.[67] Further investigation is required, not only into the ACE and renin activity in tissues; and not only into plasma ACE activity as measured by angiotensin I to angiotensin II ratios; but into tissue ACE activity as measured by angiotensin I to angiotensin II ratios.

CLINICAL RELEVANCE OF PHARMACOKINETICS

We believe that ACE inhibition with presently available compounds will always be dose-related, provided that the appropriate dose range is selected for study and for clinical use. Secondly, we assume that concentrations of drug need to be interpreted in the light of saturable binding to ACE, both in plasma and in tissues. Thirdly, there is likely to be a critical ACE activity in individual patients that could be measured by an artificial substrate method, which represents the point at which ACE becomes the rate-limiting enzyme. This may be considered the minimum effective point for drug action.

This "set-point" becomes clinically important when it lies on the steep portion of a log concentration-response curve, and varies according to renin activity. In other words, increased plasma renin activity (PRA) will increase the angiotensin I concentration and thus "sensitize" the system to ACE inhibition.[68]

Finally, we propose that many of the difficulties in interpreting drug concentration or ACE inhibition data in relation to blood pressure effects can be alleviated by using an approach that models the hysteresis between concentration and effect. This method has been successfully used for other antihypertensive drugs,[69] and has been empirically applied to ACE inhibitors with some success.[70,71]

We are presently combining the above-mentioned assumptions to study the hemodynamic response to several ACE inhibitors during acute administration in patients at high risk of first-dose hypotension (eg, elderly, diuretic-treated patients with chronic congestive heart failure). The important aspects of the protocol are: 1) the double-blind, randomized allocation of treatments; 2) the inclusion of a placebo arm; and 3) the frequent monitoring of drug concentration, ACE activity, and blood pressure/heart rate responses under realistic clinical conditions.

Preliminary results confirm that the placebo response is often substantial. This alters interpretation of the extent and timing of responses to ACE inhibition, and demonstrates that anecdotal reports of changes occurring during an idiosyncratic hypotensive response should be viewed cautiously.

CONCLUSIONS

Inhibition of tissue ACE may be more important than effects on the easily measured, circulating ACE. From the clinical viewpoint however, there is presently no evidence of any clear-cut difference between ACE inhibitors in terms of their profile of activity. The known differences in onset and duration of action are related to pharmacokinetic properties. Considerable information may still be derived about the effect of these drugs from

observations of circulating ACE activity, although further investigation of regional effects in humans using modern techniques[7] may radically alter our concept of the pathophysiology of the renin–angiotensin system.

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