Localization of Angiotensin Converting Enzyme in Rat Heart

Hiroshi Yamada, Bruno Fabris, Andrew M. Allen, Bruce Jackson, Colin I. Johnston, and Frederick A.O. Mendelsohn

Angiotensin converting enzyme (ACE) was localized in rat heart by quantitative in vitro autoradiography with $^{125}$I-351A as the radioligand. The binding association constant ($K_a$) of the radioligand was measured in membrane-rich fractions of atrium, ventricle, and lung by a radioinhibitor binding assay. A single class of high-affinity binding sites was detected in each tissue, and a significant difference was found between $K_a$ values for atria and ventricles with a rank order of atria > lungs > ventricles. For autoradiography, coronal sections (10 μm) of the frozen heart were incubated with $^{125}$I-351A and exposed to x-ray film. The autoradiographs were quantitated by computerized image analysis. The highest density of ACE in the heart was found on valve leaflets (aortic, pulmonary, mitral, and tricuspid), which contrasted markedly with very low ACE labeling in the endocardium. The coronary arteries also showed dense labeling of ACE. The right atrium had a moderate density of ACE, which was higher than the left atrium and the ventricles. Both the endothelial and adventitial layers of the aorta and pulmonary artery displayed high densities of ACE, with very low density in the media. ACE was not detected in either the sinoatrial node or atrioventricular node. These results reveal a markedly nonuniform localization of ACE in the rat heart and suggest possible sites for local angiotensin II generation and bradykinin or other peptide metabolism. (*Circulation Research* 1991;68:141-149)

Components of the renin-angiotensin system, including renin, angiotensinogen, angiotensin converting enzyme (ACE), angiotensin I (Ang I), angiotensin II (Ang II), and Ang II receptors, have been found in cardiac tissue.1,2 Intracardiac conversion of Ang I to Ang II has been demonstrated in isolated perfused rat heart,3 and pretreatment of the rat with an ACE inhibitor blocks this conversion, suggesting that tissue ACE plays a role in this local generation of Ang II.3 Also, beneficial effects of ACE inhibition in myocardial ischemia have been reported in the isolated perfused rat heart.4,5 In this preparation, local inhibition of ACE with specific inhibitors reduced reperfusion arrhythmias, increased coronary flow, and improved energy metabolism and cardiodynamics. Also, ACE inhibition was shown to reduce infarct size in dogs6 and to attenuate left ventricular remodeling in rats with chronic myocardial infarction.7 These effects may be due to modulation of the action of local Ang II and bradykinin8 as well as inhibition of the facilitatory effect of the Ang II on adrenergic neurotransmission.9 These experimental results are supported by clinical observations that treatment with ACE inhibitors successfully reduces the frequency of ventricular ectopic rhythms and improves cardiodynamics in patients with severe heart failure.10 Recently, ACE inhibitors have been shown to improve mortality rates in patients with congestive cardiac failure.11,12 However, localization of ACE in the heart has not been reported. In view of the clinical and experimental importance of cardiac ACE, we undertook localization of ACE in the rat heart by in vitro quantitative autoradiography. Also, the binding properties of cardiac ACE were tested by a radioinhibitor binding assay in subcellular membrane fractions.

**Materials and Methods**

**Radioligand Preparation**

The radioligand used to label ACE was $^{125}$I-351A. 351A is a tyrosyl derivative of lisinopril, a potent competitive inhibitor of ACE. 351A was iodinated by the chloramine T method and separated from free $^{125}$I by SP Sephadex C25 (Pharmacia LKB, Uppsala, Sweden) column chromatography.13 The binding properties of this radioligand have been published previously.14 The purity of the radioligand was examined by high-performance liquid chromatography, and a single peak

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of activity was obtained. The stability of \(^{125}\text{I}-351\text{A}\) has been previously investigated.\(^{15}\) The specific activity of the iodinated 351A was 1,600 \(\mu\)Ci/µg.

**Radioinhibitor Binding Assay**

**Tissue preparation.** Lungs and hearts were collected from male Sprague-Dawley rats (250–300 g), which were killed by decapitation. The hearts were immediately divided into right and left atria, right and left ventricles, and valve structures and were stored along with aorta and lung tissue at \(-80^\circ\text{C}\) until assayed. The tissues were thawed, homogenized in 0.05 M Tris buffer containing 0.3% bovine serum albumin, 75 mM NaCl, and 50 M \(\text{ZnSO}_4\), pH 7.0, for 10 seconds with an Ultra Turrax T-25 (13,500 rpm; Janke and Kunkel GmbH Co. KG, FRG) and centrifuged for 15 minutes at \(4^\circ\text{C}\) (1,800g). The pellets were resuspended in the same buffer, centrifuged twice, and used immediately for assay. The final pellets were diluted in the buffer to obtain approximately 30% binding of the added \(^{125}\text{I}-351\text{A}\).\(^{16,17}\) Protein concentration ranged between 0.01 mg/ml (lung) and 2.9 mg/ml (left ventricle).

Estimation of equilibrium association constant and binding specificity for angiotensin converting enzyme radioligand. Binding association constants (\(K_a\)) of the ACE inhibitors 351A, benazeprilat, perindoprilat, lisinopril, and fosinoprilat were calculated from results of competition of the unlabeled inhibitors for \(^{125}\text{I}-351\text{A}\) binding to the membrane-rich fraction. Duplicate tubes contained 300 \(\mu\)l tissue preparation, approximately 0.07 \(\mu\)Ci/ml \(^{125}\text{I}-351\text{A}\) (\(-70 \text{ pM}\)), and known concentrations of the unlabeled inhibitors to obtain final concentrations of the drugs ranging between \(10^{-11}\) and \(10^{-8}\) M. After equilibration for 24 hours at \(20^\circ\text{C}\), 1 ml ethanol was added to separate bound \(^{125}\text{I}-351\text{A}\) from free \(^{125}\text{I}-351\text{A}\), and the tubes were vortexed and centrifuged at 1,800g for 5 minutes. The supernatant was discarded, and the pellet was counted in a gamma counter.

The results were analyzed by an iterative model-fitting computer program, LIGAND.\(^{17}\) For this purpose, results from multiple experiments were first analyzed simultaneously. To compare the \(K_a\) values obtained from analysis of tissues from each of the four cardiac chambers and lung, the simultaneous analysis was performed by first permitting the \(K_a\) parameters to assume their optimal values and then repeating the analysis constraining pairs of \(K_a\) values to share a common value. Deterioration of the overall goodness of fit was evidence that the \(K_a\) values differ and was determined by analysis of variance of the model fits by the program. The statistical significance values quoted refer to \(F\) values for the difference in fit of the two models.\(^{17}\)

**In vitro autoradiography.** After the rats were killed, the hearts were quickly removed with trachea and esophagus attached, rinsed in cold saline, and dissected into atria and ventricles at just below the atrioventricular junction. Each chamber was filled with Tissue Tek, Miles Inc., Elkhart, Ind., to prevent collapse. Both parts of the heart were snap frozen in isopentane on dry ice (\(-40^\circ\text{C}\)) and stored at \(-80^\circ\text{C}\).

For the study of the sinoatrial node, the junctional part of the right atrium and superior vena cava were removed. For the atrioventricular node, the intraventricular septum was removed with the upper one fourth of interventricular septum.

Serial cryostat sections of 10 \(\mu\text{m}\) were cut in the coronal plane, thaw mounted onto gelatin-coated slides, dried in a desiccator at \(4^\circ\text{C}\) overnight under reduced pressure, and stored at \(-80^\circ\text{C}\) in sealed boxes with silica gel.

For autoradiography, a previously published procedure with \(^{125}\text{I}-351\text{A}\) was used.\(^{13}\) The sections were preincubated in 10 mM sodium phosphate buffer containing 150 mM NaCl and 0.2% bovine serum albumin, pH 7.4, for 15 minutes at \(20^\circ\text{C}\) and then incubated in the buffer containing approximately 0.3 \(\mu\)Ci/ml of \(^{125}\text{I}-351\text{A}\) for 1 hour at \(20^\circ\text{C}\). Nonspecific binding was determined in parallel incubations containing 1 mM EDTA, which abolishes ACE activity\(^{18}\) and radioligand binding to ACE.\(^{13}\) After incubation, the sections were transferred through four successive 1-minute washes of buffer without bovine serum albumin at \(0^\circ\text{C}\). The slides were dried under a stream of cold air, loaded into x-ray cassettes, and exposed to Agfa Scopix CR3B film (Agfa-Gevaert Ltd., Mortsel, Belgium) for 2 days at room temperature.

\(^{125}\text{I}\) radioactivity standards were exposed to the same film in parallel with tissue sections. These were prepared as follows.\(^{19}\) Twenty-micrometer sections were cut from a 5-mm-diameter brain core that had been snap frozen in isopentane at \(-40^\circ\text{C}\). The sections were then thaw mounted onto gelatin-coated slides and air dried. A range of known \(^{125}\text{I}\) radioactivity standards was applied to the brain disks in a volume of \(5 \mu\text{l}\) and dried. The area of these sections was measured using the image analyzer, and radioactivity on the brain disks was expressed as disintegrations per minute per unit area.

Quantitation of binding density was performed using an MCID computer image analyzer system (Imaging Research Inc., Ontario, Canada) running on a modified IBM-XT computer. The radioactivity standards were corrected for decay and fitted to calibration curves by the computer to convert optical density values of each pixel into \(^{125}\text{I}\) radioactivity (disintegrations per minute per square millimeter).

Alternate sections were stained with hematoxylin and eosin for anatomical orientation. In the case of the conduction system, alternate sections were also stained for acetylcholinesterase\(^{20}\) to assist in identifying the sinoatrial and atrioventricular nodes.

**Results**

**Binding Parameters of \(^{125}\text{I}-351\text{A}\) in Different Cardiac Chambers**

The values of \(K_a\) and concentration of binding sites for 351A for different cardiac chambers and lung are presented in Table 1. Both atria have significantly
higher $K_A$ values for 351A than do the ventricles ($p<0.01$). There was no significant difference in $K_A$ between the right and left atria. Also, the $K_A$ values for the right and left ventricles were not significantly different. The $K_A$ for lung was intermediate between atria and ventricles. The atria have a significantly larger number of binding sites than the ventricles ($p<0.01$), and for both the atria and the ventricles, binding densities were higher in the right-sided chambers ($p<0.01$). However, the overall densities were only 10% of that found in lung homogenate.

In a separate group of three rats, the mitral and tricuspid valves and adjacent tissue were dissected free, and binding site density was estimated in pooled tissue. This was compared with pooled tissue from lung, aorta, and left ventricle from these animals. Binding site density (femtomoles per milligram of protein) was 68 in the preparation from valves, 17 in ventricle, 552 in aorta, and 3,308 in lung.

The specificity of $^{125}$I-351A binding to a right atrial membrane-rich fraction is shown in Figure 1. A range of chemically distinct ACE inhibitors displaced the radioligand binding completely and did so with potencies that parallel their antacatalytic activity.$^{16}$ The properties of $^{125}$I-351A binding to other tissues have been published and strongly suggest that $^{125}$I-351A is a specific radioligand for ACE.$^{13-15}$ Identical rank orders of potency were observed in each of the other three cardiac chambers.

In autoradiographic incubations containing 1 mM EDTA or 1 mM lisinopril to evaluate nonspecific binding, the radioligand binding was completely displaced and no visible image was obtained on the x-ray films. The autoradiographs presented therefore represent specific binding only.

**In Vitro Autoradiographic Localization of Angiotensin Converting Enzyme in the Heart**

**Overall distribution of angiotensin converting enzyme in heart and great vessels.** Figure 2A shows an autoradiograph of the most rostral coronal section of the rat heart and great vessels. It includes the ascending aorta, descending aorta, pulmonary artery, right atrium, and left atrium. These large vessels display a high density of ACE, in both their adventitial and endothelial layers. The media has only a low density of ACE. The binding pattern of the ligand is uniform in endothelium and slightly granular in the adventitia. ACE density in the right atrium is moderate and heterogeneous and is higher than in the left atrium (Table 2), confirming the membrane binding results. The esophagus and trachea show moderate to high densities of ACE in their serosal layers.

The next most rostral section (Figure 2B) also contains the major arteries and both right and left atria. ACE distribution and its intensity in ascending and descending aorta and pulmonary artery are similar to that in Figure 2A. The difference of ACE density between the right and left atria is now more apparent. The right atrial appendage has a higher density of ACE than does the rest of the right atrium.

Figure 2C is a coronal section at the level of the pulmonary valve and just above the aortic valve. A very high density of ACE was found in the pulmonary valve leaflets, which show homogeneous labeling through the whole thickness of the leaflets. In the pulmonary artery at this level, ACE densities in the endothelial layer are lower than in the sections more distal from the heart. The endothelium of the ascending aorta still shows high ACE density. ACE labeling was maximal in the mid portion of the right atrial appendage (compare Figure 2B with Figures 2A and 2C).

![Figure 1](http://circres.ahajournals.org/)

**Figure 1.** Competition curves of $^{125}$I-351A binding from rat right atrium angiotensin converting enzyme (ACE) by five different ACE inhibitors.
FIGURE 2. Autoradiographs (left panels) and hematoxylin and eosin–stained sections (right panels) of coronal sections of rat heart. Sections (10 μm thick) were incubated with $^{125}$I-351A for the autoradiographs, and the alternate sections were stained with hematoxylin and eosin. Each pair of autoradiograph (left) and stained section (right) shows the same level of the heart. The photomicrographs show three representative levels of a rat heart from rostral (panels A and D) to caudal (panels C and F). AAO, ascending aorta; DAO, descending aorta; PA, pulmonary artery; RA, right atrium; LA, left atrium; OES, esophagus; TR, trachea; PV, pulmonary valve. Magnification, ×8.0.
TABLE 2. Angiotensin Converting Enzyme Densities in Rat Heart Analyzed by Quantitative In Vitro Autoradiography

<table>
<thead>
<tr>
<th>Structure</th>
<th>Density (dpm/mm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atria</td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>387.9±47.1</td>
</tr>
<tr>
<td>Left</td>
<td>163.3±5.9</td>
</tr>
<tr>
<td>Ventricles</td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>145.8±2.9</td>
</tr>
<tr>
<td>Left</td>
<td>140.0±5.1</td>
</tr>
<tr>
<td>Valves</td>
<td></td>
</tr>
<tr>
<td>Aortic</td>
<td>752.5±45.0</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>825.4±11.7</td>
</tr>
<tr>
<td>Mitral</td>
<td>793.3±126.2</td>
</tr>
<tr>
<td>Tricuspid</td>
<td>802.1±65.9</td>
</tr>
<tr>
<td>Coronary artery</td>
<td>571.7±65.4</td>
</tr>
<tr>
<td>Aorta</td>
<td></td>
</tr>
<tr>
<td>Endothelium</td>
<td>545.5±69.2</td>
</tr>
<tr>
<td>Adventitia</td>
<td>632.9±47.1</td>
</tr>
<tr>
<td>Pulmonary artery</td>
<td></td>
</tr>
<tr>
<td>Endothelium</td>
<td>525.0±49.9</td>
</tr>
<tr>
<td>Adventitia</td>
<td>533.8±33.2</td>
</tr>
</tbody>
</table>

Values are mean±SEM.

The next section (Figure 3A) now includes the aortic valves, the pulmonary outflow tract, a portion of a pulmonary artery, and both atria. At this level, a very high density of ACE on both the pulmonary and aortic valves can be observed. The right and left atria now have only light labeling of ACE. The endothelial layer of the ascending aorta shows less ACE density than in the more rostral sections.

In the ventricles, both the mitral valves and tricuspid valves have a very high density of ACE labeling (Figures 3B and 3C), as was seen for the pulmonary and aortic valves. The ventricular myocardium shows a low, but detectable, density of ACE. The endocardium contains ACE at slightly higher levels than does the ventricular myocardium (Figures 3B and 3C) but is clearly much less than the endothelium of the large vessels (Figures 2A–2C). Scattered throughout the myocardium are linear streaks of high ACE activity; these correspond to sections of coronary arteries (Figures 3B and 3C).

ACE in the conduction system. Figure 4a shows a hematoxylin and eosin-stained section of the sinoatrial node. The nodal artery is a landmark useful in locating the sinoatrial node. The sinoatrial node is more clearly demonstrated by cholinesterase histochemistry in Figure 4b, where the sinoatrial node is seen surrounding the inflow of the superior vena cava into the right atrium. ACE labeling (Figure 4c) was seen in the endothelial lining of the superior vena cava but was conspicuously absent from the sinoatrial node. ACE labeling of the surrounding right atrial myocardium and endocardium can be seen in Figure 4c.

Figures 4d and 4e show sections at the junction of the interatrial septum (above) and interventricular septum (below) with the atrioventricular node visible on both hematoxylin and eosin staining (Figure 4d) and more readily on cholinesterase histochemistry (Figure 4f). ACE labeling is very sparse at this level, being low but detectable in the ventricular and atrial myocardium, but is conspicuously absent from the atrioventricular node.

Discussion

There is emerging evidence for the existence of an independent tissue renin-angiotensin system in several organs. Components of the renin-angiotensin system have been found in tissues such as the brain, kidney, adrenal gland, testis, arterial wall, and heart.1

In the heart, both renin and angiotensin mRNAs have been found.21,22 Intrinsic renin21,23 as well as ACE activity were demonstrated, and Ang I and Ang II have been extracted and quantitated in heart.24,25 Local conversion of Ang I to Ang II was demonstrated in isolated perfused rat heart2 and guinea pig atria.26 Also, Ang II receptors have been demonstrated in cultured myocytes.27

Possible functions of the cardiac renin-angiotensin system include coronary vasoconstriction, positive inotropic and chronotropic actions,26 and effects on the cardio sympathetic nervous system and cardiac conduction tissue.2 During reperfusion after myocardial ischemia, peptides regulated by ACE, including Ang II and bradykinin, may influence the frequency of ventricular arrhythmias8 and myocardial metabolism.9 In this case, an important role for local ACE has been revealed by using ACE inhibitors. Also, Ang II may be capable of stimulating cardiac hypertrophy.28,29 All these actions may be initiated by either circulating or locally formed Ang II.

The presence of ACE activity in the heart is well recognized.3,26 However, its localization has not been previously reported. Our results indicate higher levels of ACE in the atria compared with ventricles and higher levels in the right atrium compared with the left. The patterns of ACE labeling on autoradiography revealed that ACE is localized in myocardium, with only low levels in the endocardium. The significance of atrial ACE is unclear, although it appears to participate in local Ang II production in guinea pig heart30 and rabbit heart.24 Interestingly, higher concentrations of Ang II have been detected in the right atrium than the left atrium in monkey heart25; this difference parallels the difference in ACE levels found in the present study.

Although the physiological significance of the vascular renin-angiotensin system is still not clear, previous reports suggest that Ang II is probably locally generated in the vascular wall.31 We have observed a high density of ACE in the adventitial and endothelial layers of the major arteries, which agrees with previous results obtained with [³H]captopril as a radioligand.32 We also observed a decline of endothelial ACE density toward the proximal end of the aorta and pulmonary artery. This gradient in ACE density extends into the heart, with very low ACE labeling in the ventricular endocardium.
FIGURE 3. Autoradiographs (left panels) and hematoxylin and eosin–stained sections (right panels) of coronal sections of rat heart. Sections (10 μm thick) were incubated with $^{125}$I-35IA for the autoradiographs, and the alternate sections were stained with hematoxylin and eosin. Three representative levels of the heart caudal to the atrioventricular junction are shown. AV, aortic valve; PV, pulmonary valve; LA, left atrium; RA, right atrium; TR, trachea; OES, esophagus; MV, mitral valve; TV, tricuspid valve; RV, right ventricle; LV, left ventricle; CA, coronary artery. Magnification, ×8.0.
Figure 4. Sinoatrial (SA) node and atrioventricular (AV) node of rat heart. The left, middle, and right panels show hematoxylin and eosin-stained sections (panels a and d), acetylcholinesterase histochemistry (panels b and e), and angiotensin converting enzyme autoradiogram (panels c and f). The upper panels show the SA node, and the lower panels the AV node. Three consecutive sections of each structure were treated for hematoxylin and eosin staining, acetylcholinesterase histochemistry, and autoradiography. NA, nodal artery. Magnification, ×50.
A striking finding in the present results is the very dense ACE labeling of all cardiac valves. Although its physiological significance is not known, this may suggest an important role of ACE in the valve leaflets in intracardiac conversion of Ang I as well as degradation of bradykinin and other peptides in the circulation.

Ang I and Ang II reduce coronary blood flow in isolated rat, guinea pig, and rabbit hearts, and pretreatment with ACE inhibitors blocks these effects of Ang I. Indeed, during myocardial ischemia, ACE inhibition increases coronary flow in the isolated perfused heart, resulting in improved energy metabolism and reduced tissue injury. In dogs, captopril treatment significantly reduces infarct size. These observations suggest an important role of locally formed Ang II in the coronary circulation. Because bradykinin also increases coronary blood flow, increased tissue bradykinin concentration may be another factor underlying the vasodilating activity of ACE inhibitors on coronary flow. Heavy ACE labeling in the coronary vessels in the present study strongly supports a local role of vascular ACE in these vessels.

Several factors may contribute to the antiarrhythmic effects of ACE inhibitors after myocardial reperfusion; these include an increase in coronary blood flow, inhibition of Ang II–mediated facilitation of sympathetic nerve transmission, stimulation of prostacyclin synthesis, or decreased effects of Ang II on the conduction system itself. To evaluate the possibility of direct interactions of ACE with the conduction system, detailed ACE localization was investigated on sinoatrial and atrioventricular nodes. Both the sinoatrial and atrioventricular nodal structures seem unlikel. However, ACE localization in the structures that surround the sinoatrial node, including the nodal artery, endothelium of superior vena cava, and the right atrial endocardium, may support indirect effects of ACE inhibitors on the conduction system, which may be mediated by either inhibition of Ang II formation or preservation of bradykinin.

Ang II receptor binding has been demonstrated in cardiac myocytes and in high concentration in the conducting system. In our autoradiographic studies, Ang II binding sites were found in low density over atrial and ventricular myocardium and were associated with the media of the great vessels. Dense binding was associated with parasympathetic nerve bundles and some intracardiac ganglia, and moderate density binding was found throughout the conducting system, including sinus node, atrioventricular node, and the atrioventricular bundle. It is clear, therefore, that ACE and Ang II receptors are not closely colocalized in the heart. Nevertheless, many sites of ACE localization are very close to putative sites of action of Ang II, as revealed by Ang II receptor binding sites.

Locally generated angiotensin may play a role in the regulation of cardiac and vascular hypertrophy. Vascular smooth muscle cells and cardiac myocytes in culture are stimulated by angiotensin. In cardiac hypertrophy after left ventricular infarction or after aortic banding, ACE content is increased in the hypertrophic myocardium. Treatment with ACE inhibitors prevents this hypertrophy and is associated with normalization of ACE content.

Other than Ang I or bradykinin, ACE is known to metabolize peptides such as substance P, neurotensin, enkephalin, and luteinizing hormone-releasing hormone by cleavage of carboxy-terminal dipeptides or tripeptides. These peptides are known to occur in cardiac nervous tissues and to have cardiovascular effects. Therefore, the physiological and pathophysiological significance of ACE in the heart may result from the metabolism of these peptides as well as Ang I and bradykinin.

The characterization of the radioligand binding in membrane fractions reveals a higher \( K_a \) in the atria compared with the ventricles. This suggests that ACE may differ in its properties in the atria as compared with the ventricles.

The present results therefore show a markedly nonuniform distribution of ACE in the rat heart and suggest several possible sites that may be important loci where ACE inhibitors may exert their local effects on cardiac function.

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