In Vivo Labeling of Angiotensin II Receptors with a Carbon-11-Labeled Selective Nonpeptide Antagonist

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Angiotensin II (ANG II) initiates a variety of physiological effects by binding to high affinity receptors. Two ANG II receptor subtypes, AT1 and AT2, have recently been identified. This study was undertaken to evaluate [^{11}C]L-159,884, an AT1 subtype selective nonpeptide antagonist, as a potential PET tracer. **Methods:** Carbon-11-L-159,884 was prepared by alkylation of the nor precursor with [^{11}C]methyliodide and was studied for its in vivo binding characteristics, biodistribution and kinetics in mice. The effects of PD-123319, an AT2-selective ANGII antagonist, as well as those of alpha- and beta-adrenergic drugs on [^{11}C]L-159,884 binding were investigated also. **Results:** Administration of the AT1 antagonists resulted in dose-dependent inhibition of [^{11}C]L-159,884 binding in the kidneys, the organ with the highest density of AT1 receptors. Inhibition was also observed in the lungs and the heart. Adrenergic drugs did not influence [^{11}C]L-159,884 binding to AT1 receptors. Kinetic studies showed rapid tracer uptake in the liver, kidneys, lungs and heart. Excretion of the radioactivity occurred primarily through the intestinal tract (>20% in 90 min), with less than 8% excreted through the urine. **Conclusion:** The results suggest that [^{11}C]L-159,884 binds in vivo to AT1 receptors in mouse kidneys, lungs and heart. This radiotracer appears to be a promising candidate for studying ANG II receptors in vivo by PET.

Key Words: angiotensin II receptors; carbon-11-L-159,884; PET

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The octapeptide angiotensin II (ANG II) is the biologically active component of the renin-angiotensin system. This hormone plays a pivotal role in the regulation of cardiovascular, renal and endocrine functions (*1*). ANG II exerts its biological effects through the stimulation of specific membrane-bound receptors located on a variety of tissues and organs including the adrenal glands, kidneys, smooth muscle, heart, lungs, liver, pituitary and neurons in the central and peripheral nervous systems (*2–5*).

Although peptide analogs of ANG II have been shown to be potent and specific antagonists of ANG II at its receptor (*6*), their short action and partial agonist properties have limited their application as research tools and therapeutic agents. A breakthrough came with the independent discovery of two unique series of nonpeptide compounds that interfere with ANG II at its binding sites. The prototypes of these two series of compounds are losartan (DuP-753, MK-954) (*7*) and PD-123177 (and the related PD-123319) (*8*).

Recently, evidence for two distinct subtypes of ANG II receptors has been obtained based upon their differential affinities for nonpeptide antagonists such as DuP-753 and its active metabolite, EXP3174, compared to PD-123177 and analogs (PD-121981 or WL-19) or the peptide CGP-42112A (*9–13*). The ANG II receptor subtype having a high affinity for DuP-753 has been designated as AT1, and the receptor subtype having a high affinity for PD-123177 and analogs or CGP-42112A as AT2 (*14*). Numerous studies have shown that the AT1 receptor mediates the vast majority of the ANG II-induced biological effects, while the physiological role of the AT2 receptor subtype remains to be established.

The nonpeptide ANG II receptor antagonists have proven to be especially useful tools with which to explore the actions of ANG II and to define ANG II receptors. In this study, the in vivo binding characteristics, biodistribution and kinetics of [^{11}C]L-159,884 ([^{11}C]*N*-[[4′[(2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl) methyl] [1,1′-biphenyl]-2-yl] sulfonyl]-4-methoxybenzamide), a new, potent and selective nonpeptide antagonist of AT1 subtype, were investigated in mice. The results of this study suggest that [^{11}C]L-159,884 is a promising candidate as a PET radiotracer for studying ANG II receptors in vivo.

MATERIALS AND METHODS

Synthesis and Purification of Carbon-11-L-159,884

The development and detailed synthesis of [^{11}C]L-159,884 has been described elsewhere (*15*), but a brief summary of its preparation for this study is described here. The desmethyl precursor L-162,914 and authentic L-159,884 were prepared by Merck Research Laboratories (West Point, PA) and their syntheses are described elsewhere (*15*). Carbon-11-carbon dioxide was produced by 16 MeV proton bombardment of a nitrogen gas target using a Scanditronix RNP-16 biomedical cyclotron; it was subsequently converted to [^{11}C]methyl iodide following the procedure described by Dannals et al. (*16*).

A 1-ml V-vial was charged with 1 mg (1.85 μmole) of L-162,914. The precursor was dissolved in 200 μl of dimethyl formamide (DMF) and 1.9 μl (1.0 eq.) of tetrabutylammonium hydroxide (1.0 *M* in methanol) was added. The vial was sealed and cooled to −78°C. Carbon-11-methyl iodide was transferred into the reaction vessel by a stream of nitrogen carrier gas. When the radioactivity in the solution reached a plateau, the stream of nitrogen was stopped, and the vessel was submerged in an 80°C water bath. After 3 min, the reaction mixture was diluted with 200 μl of HPLC solvent, consisting of 45:55 acetonitrile-to-water (0.1% trifluoroacetic acid). The mixture was then injected onto an Alltech Econosil C18 (10 μ, 250 mm × 10 mm) semipreparative column and eluted at a rate of 10 ml/min. The effluent from the column was monitored with a UV—and an on-line radioactivity detector. The radioactivity peak corresponding to [^{11}C]L-159,884 (t_R = 6.1 min, k′ = 4.6) was collected in a round bottom flask and the solvent was evaporated to dryness in a rotary evaporator. The residue was dissolved in 7 ml of sterile saline and passed through a sterile, pyrogen-free filter (0.2 μm; Gelman Acrodisc®, Ann Arbor, MI) into an evacuated vial. The solution was diluted with 3 ml of 8.4% sterile aqueous sodium bicarbonate. The radioactivity

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TABLE 1
Tissue Distribution of [^{11}C]L-159,884 in Mice

Organ	Percentage of injected dose per gram*				
	5 min	15 min	30 min	60 min	90 min
Blood	0.88 ± 0.19	1.32 ± 0.44	0.86 ± 0.14	0.91 ± 0.17	0.97 ± 0.05
Brain	0.13 ± 0.02	0.44 ± 0.15	0.36 ± 0.09	0.37 ± 0.09	0.38 ± 0.06
Heart	1.34 ± 0.03	1.55 ± 0.22	1.35 ± 0.37	1.32 ± 0.03	1.16 ± 0.11
Lungs	2.76 ± 0.33	3.02 ± 0.37	2.19 ± 0.55	2.23 ± 0.24	2.18 ± 0.50
Liver	43.85 ± 3.78	33.51 ± 3.76	21.29 ± 1.69	9.95 ± 2.61	7.72 ± 0.89
Spleen	1.44 ± 0.21	2.36 ± 0.55	2.39 ± 0.07	2.95 ± 0.18	2.66 ± 0.18
Kidneys	4.76 ± 0.21	5.61 ± 0.51	5.31 ± 1.16	4.83 ± 0.36	3.87 ± 0.24
Testes	0.19 ± 0.03	0.38 ± 0.05	0.29 ± 0.03	0.40 ± 0.06	0.36 ± 0.09
Bone	0.77 ± 0.11	1.17 ± 0.13	1.05 ± 0.12	1.04 ± 0.05	0.93 ± 0.05
Muscle	1.12 ± 0.27	0.92 ± 0.14	0.86 ± 0.25	0.86 ± 0.09	0.76 ± 0.05

*Mean of four mice at each time ± 1 s.d.

was measured, and a 100-μl aliquot was removed for determination of specific activity.

The specific activity was determined as follows: A 100 μl aliquot of the final preparation of known radioactivity was injected onto an Alltech Econosil C18 column (Deerfield, IL 10 μ, 250 mm × 4.6 mm). A mobile phase of 45:55 acetonitrile-to-water (0.1% trifluoroacetic acid) at a flow rate of 4 ml/min was used to elute the radioligand (t_R = 2.6 min, k′ = 2.9). The area of the UV absorbance peak at 254 nm corresponding to carrier product was measured by an automated integrating recorder and compared to a standard curve relating mass to UV absorbance. The specific activity at end of synthesis (EOS) ranged between 1045–3000 mCi/μmole; mean specific activity (mean ± 1 s.d.; n = 12) was 1791 ± 513 mCi/μmole.

Pharmaceuticals

L-159,282, L-159,884, L-159,913, L-159,689 and EXP3174 were donated by Merck Research Laboratories; PD-123319 was provided by Parke-Davis Pharmaceutical Research Division (Ann Arbor, MI); and prazosin was purchased from RBI, (Natick, MA). DL-propranolol HCl and yohimbine HCl were purchased from Sigma Chemical Co. (St. Louis, MO).

Drug solutions were freshly prepared on the day of the experiment. L-159,282, L-159,884, L-159,913, L-159,689 and EXP3174 were dissolved in 15% saturated $NaHCO_3$/35% normal saline/50% water. PD 123319 and propranolol were dissolved in saline. To dissolve yohimbine and prazosin, acidified saline was used, and the solution heated for 5 min at 70°–80°C.

Biodistribution and In Vivo Kinetics

Animals were housed and cared for according to standards recommended by the NIH *Guide for the Care and Use of Laboratory Animals.* Male CD-1 mice, weighing 24–30 g, were injected intravenously through the tail vein with approximately 200 μCi (1–2 μg/kg) [^{11}C]L-159,884 in a volume of 0.2 ml. The animals were killed by cervical dislocation at 5, 15, 30, 60 and 90 min after injection. The organs of interest were removed, weighed and the radioactivity in the tissue samples were measured in an automated gamma counter. Aliquots of the injectate were prepared as standards and counted along with the tissue samples. The percentage of the injected dose per gram of tissue (%ID/g) and the percent dose per organ (%ID/organ) were calculated.

In Vivo Binding Inhibition Studies

Drugs, dissolved in 0.1 ml medium were administered intravenously into a tail vein of mice before intravenous injection of approximately 7.4 MBq (200 μCi) (1–2 μg/kg) [^{11}C]L-159,884. L-159,282, L-159,884, L-159,913, L-159,689 and EXP3174 were injected 10 min before tracer administration. Prazosin, propranolol, yohimbine and PD-123319 were injected 15 min before tracer administration. Sixty minutes after [^{11}C]L-159,884 injection, the animals were killed by cervical dislocation. Thereafter, the chest was opened, the thoracic aorta cut and a blood sample was obtained rapidly from this pool. By bleeding into the chest, we reduced the amount of blood left in the kidneys. The brain, heart, lungs, liver and kidneys were removed and prepared along with the blood sample as described above.

Statistics and ED_{50} Calculations

Data were analyzed for significant differences by analysis of variance (ANOVA), followed by Dunnett's test. Differences were considered significant at $p < 0.05$. The median effective dose for blocking [^{11}C]L-159,884 binding by 50% (ED_{50}) was calculated from specific binding in the kidneys using log/logit transformation (*17,18*).

RESULTS

Biodistribution and In Vivo Kinetics

The biodistribution, as a function of time after injection of [^{11}C]L-159,884 in mice, is summarized in Tables 1 and 2. Rapid tracer uptake was observed in the kidneys, lungs and heart, followed by a slow clearance. Peak activity in the kidneys, lungs, and heart was 5.6, 3.0 and 1.5 %ID/g, respectively, at 15 min, and 69%, 72% and 75% of the peak activity remained in the respective organs at 90 min after injection. Radioactivity in the blood fell to <1 %ID/g (1.6 %ID in total blood volume) within 5 min after injection. Tissue-to-blood ratios remained high 30–90 min after injection in the kidneys (4.0–6.3) and lungs (2.2–2.5). In the liver, an initial high uptake was followed by a rapid decline of the tracer concentration. More than 20% of the radioactivity accumulated in the intestine over the 90-min observation period while less than 8% was excreted through the urine in 90 min, indicating that excretion of the compound occurred primarily through the hepatobiliary route.

Inhibition of In Vivo Carbon-11-L-159,884 Binding

The specificity of in vivo [^{11}C]L-159,884 binding to ANG II receptors in the kidneys was investigated by pretreatment of the animals with increasing doses of drugs having a known high affinity toward ANG II receptors. The drugs were injected intravenously 10 min before [^{11}C]L-159,884 was administered. Sixty minutes thereafter, the animals were killed and the kidneys were examined for their radioactivity concentrations. The dose-dependent inhibition of specific [^{11}C]L-159,884 bind-

TABLE 2
Tissue Distribution of [^{11}C]L-159,884 in Mice

Organ	Percentage of injected dose per organ*				
	5 min	15 min	30 min	60 min	90 min
Blood	1.64 ± 0.32	2.38 ± 0.79	1.63 ± 0.28	1.69 ± 0.38	1.81 ± 0.11
Brain	0.05 ± 0.01	0.20 ± 0.07	0.15 ± 0.05	0.15 ± 0.04	0.15 ± 0.04
Heart	0.16 ± 0.02	0.16 ± 0.02	0.15 ± 0.04	0.14 ± 0.02	0.13 ± 0.01
Lungs	0.47 ± 0.02	0.51 ± 0.10	0.46 ± 0.09	0.41 ± 0.03	0.40 ± 0.06
Liver	69.87 ± 6.06	45.92 ± 3.35	35.80 ± 3.29	14.77 ± 3.33	11.72 ± 1.41
Spleen	0.21 ± 0.06	0.40 ± 0.15	0.47 ± 0.04	0.62 ± 0.12	0.51 ± 0.05
Kidneys	1.90 ± 0.35	2.02 ± 0.18	1.99 ± 1.00	1.73 ± 0.18	1.45 ± 0.06
Bladder	0.21 ± 0.09	1.26 ± 0.50	3.49 ± 0.90	7.36 ± 2.58	7.53 ± 0.63
Testes	0.03 ± 0.01	0.06 ± 0.01	0.04 ± 0.01	0.05 ± 0.01	0.05 ± 0.01
Stomach	0.87 ± 0.41	0.81 ± 0.11	1.43 ± 0.39	0.97 ± 0.36	0.58 ± 0.10
Intestines	9.12 ± 1.03	16.32 ± 1.97	18.65 ± 4.37	22.87 ± 1.95	21.29 ± 1.59
Carcass	12.27 ± 1.17	15.45 ± 1.24	13.15 ± 2.70	13.44 ± 0.98	12.06 ± 0.53

*Mean of four mice at each time ± 1 s.d.

ing in the kidneys by four ANG II receptor antagonists is presented in Figure 1. Specific binding of [^{11}C]L-159,884 in the kidneys was defined by measuring the reduction in total tracer accumulation by a blocking dose (1 mg/kg) of L-159,282. This dose of L-159,282 resulted in 70% inhibition of total [^{11}C]L-159,884 accumulation. Consequently, nonspecific binding was assumed to be 30% of total radioactivity accumulation. L-159,282 was the most potent inhibitor of [^{11}C]L-159,884 binding, followed by L-159,884 (parent drug), L-159,913 and L-159,689. The median effective dose for blocking [^{11}C]L-159,884 binding in the kidneys by 50% (ED_{50}) was calculated from the inhibition curves. The ED_{50} values for L-159,282, L-159,884, L-159,913 and L-159,689 were 0.02 μmole/kg, 0.085 μmole/kg, 0.18 μmole/kg and 0.57 μmole/kg of body weight, respectively. The ED_{50} values of L-159,282, L-159,913 and L-159,689 have previously been determined in rat kidney by competition for the in vivo binding of [^{125}I][Sar^1, Ile^8]angiotensin II, providing values of 0.0093 μmole/kg, 0.042 μmole/kg, and 0.11 μmole/kg (*19*). The rank order correlation of in vivo affinities provides a linear correlation with $r^2 = 0.99$, which suggests that the receptor site labeled with [^{11}C]L-159,884 in mouse is the same as that labeled via [^{125}I][Sar^1, Ile^8]ANG II in rat (*19*).

After pretreatment of the animals with 1 mg/kg of L-159,282, the total binding was decreased in the kidneys and lungs by 70%, and by 45% in the heart, while radioactivity concentrations in the brain and liver were unaffected by the blocking drug (Fig. 2). The ratios of specific-to-nonspecific binding in the kidneys, lungs, and heart were 2.4, 2.3 and 0.8, respectively. This assumes, that as in the kidneys, complete inhibition of the specific binding of [^{11}C]L-159,884 by 1 mg/kg L-159,282 also occurs in the lungs and heart.

Figure 3 shows the inhibition of [^{11}C]L-159,884 binding by 1 mg/kg L-159,282, EXP3174 and L-159,884 in kidneys, lungs and heart. As expected from the inhibition curves in the kidneys, L-159,282 and EXP3174 were more potent inhibitors of [^{11}C]L-159,884 binding in the lungs and heart than the parent compound L-159,884.

The selectivity of [^{11}C]L-159,884 for the AT1 subtype ANG II receptor was determined by pretreatment of mice with high doses (1–5 mg/kg) of the AT2 selective antagonist PD 123319. This drug did not have any effect on the in vivo [^{11}C]L-159,884 binding in the kidneys, heart and lungs (data not shown). Blood levels of [^{11}C]L-159,884 also remained unaffected by PD

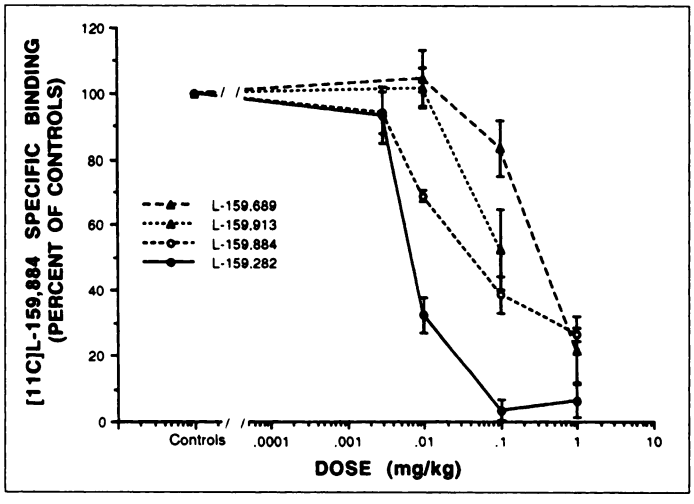

FIGURE 1. Dose-dependent inhibition of [^{11}C]L-159,884 in vivo binding in the mouse kidney by L-159,282, L-159,884, L-159,913 and L-159,689 60 min after tracer administration. Data are means (± 1 s.d.) of %ID/g, expressed as percent of specific binding in the kidneys of control animals. Specific binding was defined as 70% of total [^{11}C]L-159,884 accumulation (see text for details); n = 4 for each dose level.

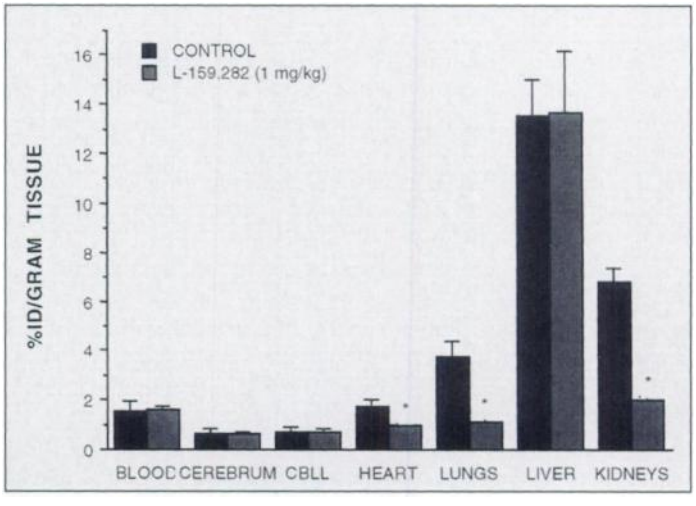

FIGURE 2. Inhibition of [^{11}C]L-159,884 in vivo binding by L-159,282 in various organs 60 min after tracer administration. Bars represent means (± 1 s.d.) of %ID/g. CBLL = cerebellum; n = 4 for each group; *p < 0.001.

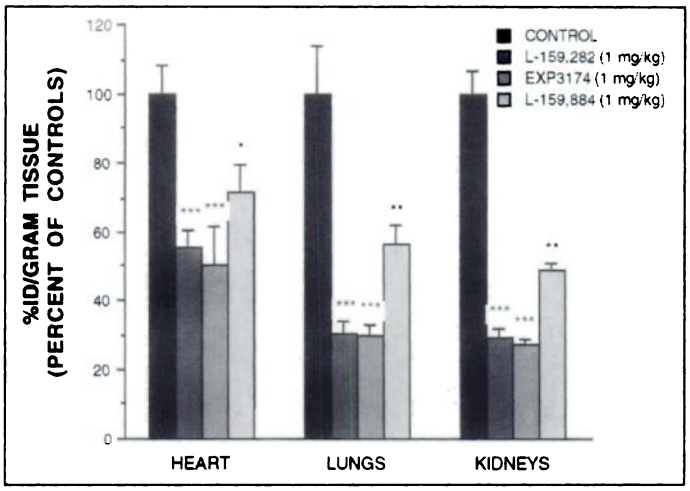

FIGURE 3. Inhibition of [^{11}C]L-159,884 in vivo binding by L-159,282, EXP 3174, and L-159,884 in heart, lungs and kidneys. Data are means (± 1 s.d.) of %ID/g expressed as percentages of controls. n = 4 for each drug. *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

123319 (data not shown). Adrenergic antagonists such as prazosin (α_1), yohimbine (α_2) and propranolol (β) did not influence [^{11}C]L-159,884 binding in the kidneys either (data not shown).

DISCUSSION

The present study was undertaken to evaluate [^{11}C]L-159,884 as a potential PET tracer for imaging ANG II receptors in vivo. We found that:

1. After intravenous injection into mice, [^{11}C]L-159,884 accumulated preferentially in organs or tissues rich in ANG II receptors.
2. The in vivo binding was saturable, as was shown by the ability of L-159,884, the parent drug, to block [^{11}C]L-159,884 binding.
3. In vivo binding was specific since drugs acting at ANG II receptors inhibited [^{11}C]L-159,884 binding.
4. Three antagonists competed with [^{11}C]L-159,884 binding in vivo in an order of potency similar to their ability to block [^{125}I][Sar^1, Ile^8]angiotensin II binding in vivo in rat (*19*).
5. [^{11}C]L-159,884 was selective for the AT1 subtype ANG II receptor; the AT2 specific antagonist PD 123319 did not inhibit its in vivo binding, nor did alpha- and beta-adrenergic drugs.

These results indicate that [^{11}C]L-159,884 binding fulfills the requirements for specific binding to a pharmacological site in vivo: appropriate regional distribution, saturability, selectivity and appropriate pharmacology. Therefore, [^{11}C]L-159,884 binds with high affinity to ANG II receptors in vivo.

Accumulation of [^{11}C]L-159,884 in the kidneys is rapid during the first 5 min after administration (Tables 1 and 2) and remains basically unchanged during the following 60 min. At 5 min postinjection, the amount of metabolites in the peripheral plasma is less than 10%, and at 30 min it is approximately 50% (Szabo et al., unpublished data obtained in dogs, 1994). Thus, metabolism is insignificant during the first few minutes when most of the tracer binding occurs in the kidneys.

Many organs of various species have been examined for a differential distribution of AT1 and AT2 sites. With the use of selective antagonists as tools, AT1 and AT2 receptor subtypes have been shown to occur in the rat brain, and both are widespread (*20–22*). The AT1 receptor subtype predominates in virtually all vascular tissues and is the only type identified in the liver (*4,21*). The AT2 receptor subtype predominates in the rat adrenal medulla, the human uterus, rat ovarian granulosa cells, and some other cell lines (*4,21*). In most other tissues, such as adrenal cortex, kidneys, heart and brain, there appears to be a mixture of both receptor subtypes (*4,21*). It is clear, however, that the precise proportion of sites and even the predominant type can vary as a function of the tissue, the species, and the stage of development. Hence few in vitro and in vivo data are presently available for the systematic comparison of ANG II receptor density between various tissues in the same species. Moreover, receptor binding measured in vitro depends on a number of experimental factors: the ligand used, source of receptor, assay conditions, presence of heterogeneous AT1 or other AT1 receptor subtypes (*20–22*), and other interlaboratory technical variations (*24*). Therefore, it is not easy to quantitatively compare our in vivo data on the distribution of [^{11}C]L-159,884 binding sites in mice with the proportional distribution of ANG II receptors determined in vitro. The regional distribution of [^{11}C]L-159,884 is, however, in general agreement with the distribution of ANG II receptors and corresponds with that of [^{3}H]L-159,884 in rats (Gibson et al., unpublished observations, 1994) and its blockade by L-158,809, a selective AT1 receptor antagonist (*25–26*).

In the present study, cardiac [^{11}C]L-159,884 binding was shown to be relatively low. Several autoradiographic studies have shown uneven distribution of ANG II receptors within the heart, resulting in high levels of ANG II receptors in discrete regions (e.g., parasympathetic and adrenergic nerves, and conduction system) (*27,28*). The technique of measuring tracer binding in the whole heart, as was done in this study, will certainly obscure the heterogeneous distribution of tracer binding and result in overall lower tracer concentrations.

In the rat brain, AT1 and AT2 receptors have been localized and both subtypes have a distinct distribution. AT1 sites predominate in the pituitary, AT2 sites predominate in the thalamus-septum and the midbrain, and a mixture of the two subtypes is found in the hypothalamus (*29*). Autoradiographic techniques have demonstrated the localization of the types to very discrete nuclei (*30*). AT1 sites are concentrated in the subfornical organ, the circumventricular nuclei and other brain regions associated with the central effects of ANG II (*31*). Thus, like in the heart, the receptor-specific binding component may be obscured when the tracer binding is measured in the cerebrum as a whole. No specific binding of [^{11}C]L-159,884 was demonstrated in the cerebellum. This is in agreement with previous results indicating low ANG II specific binding (*29*) or AT2 subtype dominance in the cerebellum (*32,33*). Alternatively, we may not see specific binding in the brain because transfer through the blood-brain barrier of the tracer and inhibitors is too low. Indeed, the concentrations of [^{11}C]L-159,884 in the brain were very small compared to other, successful brain imaging tracers.

While in vitro radioligand binding studies have demonstrated the existence of AT1 subtype receptors in the liver (*34,35*), we found no significant reduction in [^{11}C]L-159,884 concentration in the liver after pretreatment of mice with L-159,282 at the concentration which resulted in maximum inhibition of [^{11}C]L-159,884 binding in the kidneys. A similar result was obtained in the rat liver using [^{3}H]L-159,884 and L-158,809 as a blocker (Gibson et al., unpublished observations, 1995). It is likely that specific binding of this tracer in the liver is obscured by the high concentration of the tracer in the liver as a consequence of its hepatobiliary excretion. Since [^{11}C]L-159,884 is excreted primarily through the hepatobiliary route, the specific-to-nonspe-

cific radioactivity ratio appears to be extremely low in the liver. Thus, the effect of receptor blockade on specific [^{11}C]L-159,884 binding in the liver cannot be discerned. Furthermore, the hepatobiliary excretion seems to be relatively slow in that a significantly high concentration of the radioactivity (10.0 %ID/g) was observed in the liver at times later than 60 min postadministration. The low specific-to-nonspecific radioactivity ratio in vivo might explain the discrepancy between results of in vitro and in vivo studies. Indeed, a preliminary PET study in dogs, performed by our group, has demonstrated inhibition of [^{11}C]L-159,884 binding by L-159,282 in the liver employing a kinetic modeling method in which nonspecific binding is taken into account (*36*). A less likely explanation of our finding is that it may reflect the heterogeneity of AT1 receptor subtypes (AT1A and AT1B), which have been identified in rodents (*37–40*).

Excretion of [^{11}C]L-159,884 was demonstrated to occur primarily through the hepatobiliary route in mice, while a relatively small amount of radioactivity accumulates in the urine. This would be favorable for ANG II receptor imaging studies in the kidneys using [^{11}C]L-159,884 and PET.

The recognized clinical importance of the renin-angiotensin system has expanded continually. In vivo mapping of the ANG II receptor provides a tool to investigate whether abnormalities in this receptor system play a causative role in hypertension, cardiovascular disease, or renal failure. The results from this study indicate that [^{11}C]L-159,884 is a tracer suitable for in vivo labeling of ANG II (subtype AT1) receptors. Thus, with [^{11}C]L-159,884, PET can be used to study physiological and pathological changes of ANG II receptors in humans.

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