Nonpeptide Angiotensin II Receptor Antagonists. IV. EXP6155 and EXP6803


EXP6155 (2-n-butyl-1-[4-carboxybenzyl]-4-chloroimidazole-5-acetic acid) and EXP6803 (methyl 2-n-butyl-1-[4-(2-carboxybenzamido)benzyl]-4-chloroimidazole-5-acetate, sodium salt) are shown to be novel, nonpeptide, antihypertensive, specific angiotensin II receptor antagonists. In rabbit aorta, they competitively inhibited the contractile response to angiotensin II with pA2 values of 6.54 and 7.20 and did not alter the response to norepinephrine or KCl. In guinea pig ileum, both agents blocked the responses to angiotensin I and II and did not alter the responses to bradykinin and acetylcholine. A similar specific angiotensin II antagonism was shown in vivo in the spinal pithed rat model. In renal artery-ligated rats, a high renin hypertensive model, EXP6155 and EXP6803 given intravenously, decreased blood pressure with ED50 values of 10 and 11 mg/kg, respectively. Both compounds did not alter blood pressure when given orally at 100 mg/kg. Unlike saralasin, EXP6155 and EXP6803 given intravenously did not cause a transient increase in blood pressure in the renal artery-ligated and normotensive rats. Our results indicate that EXP6155 and EXP6803 are selective angiotensin II receptor antagonists and antihypertensive agents. Since neither compound had partial agonist activities or bradykinin potentiation effects, unlike the existing peptide angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors, respectively, they may represent preferred probes for studying the physiological roles of angiotensin II. (Hypertension 1989;13:489-497)

The development of specific blockers of the renin-angiotensin system (RAS) has contributed significantly to our understanding of the physiology of this cascade.1,2 However, there are still potential problems in establishing the physiological roles of the RAS from pharmacological data. For instance, angiotensin converting enzyme inhibitors have other actions such as the potentiation of bradykinin in addition to the blockade of the formation of angiotensin II (Ang II) from angiotensin I (Ang I).3 Analogues of renin substrate that appear to be specific inhibitors of renin (see Reference 4) may not totally eliminate the influence of the RAS because nonrenin angiotensin-forming enzymes in certain tissues may produce angiotensin from angiotensinogen (see Reference 5). Selective peptide Ang II receptor antagonists currently available still retain significant agonist properties.6

Recently, we demonstrated that two imidazole analogues, first reported by Furukawa et al,7 were weak but selective Ang II receptor antagonists.8,9 Encouraged by the apparent specificity of these imidazole molecules, we initiated structure-activity studies that led to the synthesis of two new imidazole Ang II receptor antagonists. In this report, we describe the pharmacological characterization of these imidazole functional Ang II antagonists, EXP6155 (2-n-butyl-1-[4-carboxybenzyl]-4-chloroimidazole-5-acetic acid) and EXP6803 (methyl 2-n-butyl-1-[4-(2-carboxybenzamido)benzyl]-4-chloroimidazole-5-acetate, sodium salt). Their structures are shown in Figure 1. Our study indicates that EXP6155 and EXP6803 are selective Ang II receptor antagonists with improved potency over the early imidazole Ang II receptor antagonists. Since neither compound had partial agonist activities or bradykinin potentiation effects, unlike the existing peptide angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors, respectively, they may represent preferred probes for studying the physiological roles of Ang II. It is believed that, using these new promising chemical leads, a better and more potent Ang II receptor antagonist can be designed.
n-C,H,

COOH

COONa

COONa

COONa

\[ \text{FIGURE 1. Chemical structures of EXP6155 and EXP6030.} \]

**Materials and Methods**

**In Vitro Potency and Selectivity Determination—Rabbit Aorta**

The descending thoracic aorta was removed from New Zealand White male rabbits (2-4 kg) (Hazleton Research Products, Inc., Denver, Pennsylvania) after cervical dislocation and cut into helical strips 3-4 mm wide and 15-20 mm long. The helical strips were mounted in 20-ml tissue baths that contained Krebs bicarbonate solution of the following composition (mM): NaCl 118.4, KCl 4.7, KH2PO4 1.2, MgSO4 • 7H2O 1.2, CaCl2 • 2H2O 2.5, NaHCO3 25, dextrose 10.1, CaNa2 EDTA 0.01. The Krebs solution was kept at 37°C and bubbled continuously with 5% CO2 in oxygen. Initial resting tension was set at 2.5 g, and the aortic helical strips were allowed to equilibrate for 90 minutes. At 10-15 minute intervals, the strips were stimulated by adding 50.3 mM KCl to the baths and then washed. At the end of the equilibration period, a control cumulative concentration-contractile response curve for Ang II (3×10⁻¹⁰–10⁻⁷ M) was obtained. The tissue was washed several times until the baseline was reached. Forty-five minutes later, EXP6155 at 3×10⁻⁷, 10⁻⁶, 3×10⁻⁶, or 10⁻³ M was added, and the tissue was incubated with the drug for 15 minutes. The concentration-response curve for Ang II (3×10⁻¹⁰–3×10⁻⁶ M) was then repeated in the presence of EXP6155. In a separate experiment, concentration-response curve for Ang II was determined before and after incubation with 10⁻⁶ M of EXP6155 and EXP6803. The early imidazole Ang II antagonist S-8307 was also included for comparison. The analogue contraction signal was recorded with a Grass force-displacement transducer connected to a Grass polygraph (Grass Instrument Co., Quincy, Massachusetts) and analyzed with a digital computer (Buxco Electronics, Inc., Sharon, Connecticut). Responses were expressed as a percentage of the maximal Ang II response. To measure the potency of the antagonist, the pA2 value of EXP6155 was determined by the Schild equation. Concentration-contractile response curves for norepinephrine and KCl were also examined in the presence or absence of EXP6155 at 10⁻³ M or EXP6803 at 3×10⁻⁶ M to test the specificity of these antagonists. EXP6155 and EXP6803 were dissolved in saline at 1 mg/ml and diluted to the desirable concentration with Krebs buffer.

**In Vitro Potency and Selectivity Determination—Guinea Pig Ileum**

Segments of ileum were removed from male guinea pigs (250–350 g) (Charles River Laboratories, Kingston, New York) after cervical dislocation. Longitudinal muscle strips 15 mm in length were dissected and then mounted in 20 ml tissue baths that contained Krebs bicarbonate solution of the composition as described above. The Krebs solution was kept at 37°C and bubbled continuously with 5% CO2 in oxygen. Initial resting tension was set and maintained at 0.5 g. The strips were equilibrated for 1 hour, and the Krebs solution was replaced every 15 minutes. At the end of the equilibration period, the strips were stimulated by acetylcholine at 3×10⁻⁸ M. The tissue was washed three times and allowed to rest for 5–8 minutes. This procedure was repeated 3–4 times until a consistent contraction was recorded. Ang I (2.6×10⁻⁹ M), Ang II (5.4×10⁻¹⁰ M), bradykinin (1.1×10⁻⁸ M), or acetylcholine (3×10⁻⁸ M) was added to the tissue bath, and the control contractile response was recorded. The concentrations mentioned above represent the EC50 for Ang I, Ang II, and acetylcholine, respectively, and the EC50 for bradykinin. Each strip was tested with one agonist only. The tissue was washed and then incubated with EXP6155 or EXP6803 for 15 minutes before the addition of Ang I, Ang II, bradykinin, or acetylcholine. This procedure was repeated at 15-minute intervals with increasing concentrations of the EXP6155 or EXP6803. Contraction was recorded with a Grass force-displacement transducer coupled to a Grass polygraph. Values of responses were expressed as a percentage change of control response induced by each agonist in the presence of various concentrations of EXP6155 or EXP6803. The inhibitory concentrations of EXP6155 and EXP6803 that inhibited the contractile response to Ang I or Ang II by 50% were determined by linear regression. Test solutions of EXP6155 and EXP6803 were prepared as described above.

**In Vivo Potency and Specificity of Angiotensin II Antagonism**

Male CD Sprague-Dawley rats (300–400 g) (Charles River Laboratories) were anesthetized with...
hexobarbital (150 mg/kg i.p.). After the trachea was cannulated, the animals were pithed through the orbit with a steel rod. Artificial respiration with room air was immediately started using a Harvard rodent respirator at a volume of 1 ml/100 g body wt and at a rate of 70 strokes/min. Animals were kept warm at 37°C by means of thermostat-controlled heating boards. The carotid artery and the jugular vein were cannulated for arterial pressure measurement and intravenous administration of drug. Blood pressure was measured using a Gould pressure transducer coupled to a Grass polygraph. To construct the dose–pressor response curve for Ang II, the agent was injected intravenously in a volume of 0.1 ml/kg, and the catheter was flushed with 0.2 ml saline. For the lower doses of Ang II, which elicited a rise in diastolic pressure of less than 20 mm Hg, full recovery from the response was permitted. For the higher doses, Ang II was injected cumulatively with each successive injection given immediately after the maximal effect of the preceding dose (usually in 10–20 seconds). Only one full dose–response curve was obtained in each rat. Fifteen minutes before injection of Ang II, the animal was pretreated with saline vehicle (1 ml/kg i.v.), EXP6155 (30 or 100 mg/kg i.v.), or EXP6803 (30 or 100 mg/kg i.v.). A similar protocol was also carried out with norepinephrine and vasopressin to determine specificity.

Anti-hypertensive Effect in Conscious Renal Artery-Ligated Hypertensive Rats

Male CD Sprague-Dawley rats (300–350 g) (Charles River Laboratories) were anesthetized with hexobarbital (100 mg/kg i.p.), and being careful not to damage the left kidney or left renal vein, we completely ligated the left renal artery by means of 4-0 silk suture. Six days after the left renal artery ligation, the animals were anesthetized with hexobarbital (90 mg/kg i.p.), and both the right jugular vein and carotid artery were cannulated. The catheters were passed subcutaneously to the dorsal side of the neck and exteriorized. After the animals had completely recovered from anesthesia (at least 2–2.5 hours after the surgery), the carotid catheter was connected to a Gould pressure transducer coupled to a Grass polygraph for monitoring mean arterial pressure (MAP). Heart rate was recorded by the Grass tachygraph.

In the first series of experiments, saralasin (0.01–1 mg/kg), EXP6155 (1–30 mg/kg), or EXP6803 (1–30 mg/kg) was given intravenously in a cumulative manner at intervals of 15 minutes. The ED$_{50}$ of EXP6155 and EXP6803 that decreased MAP by 30 mm Hg was then calculated by linear regression.

In the second group of rats, Ang II was injected (0.1 µg/kg i.v.) before the administration of EXP6155 and subsequently 5 minutes after each successive cumulative intravenous dose of EXP6155 to examine the effectiveness of the antagonist.

In the third group of rats, vasopressin was given (0.03 IU/kg i.v.) before and 5 minutes after each successive dose of EXP6155 to ascertain the specificity of EXP6155.

In the fourth group, renal artery–ligated rats were pretreated with captopril (3 mg/kg i.v.) 30 minutes before the intravenous administration of EXP6155 (30 mg/kg), and the experiment was monitored for an additional hour.

In the fifth group, renal hypertensive rats were dosed orally with EXP6155 or EXP6803 (100 mg/kg) and the experiment was monitored for 2 hours.

Effects in Conscious Normotensive Rats

Male CD Sprague-Dawley rats (300–350 g) (Charles River Laboratories) were surgically prepared with carotid arterial and jugular venous catheters as described above. Saralasin (0.03–1 mg/kg) or EXP6155 (3–100 mg/kg) was given intravenously in a cumulative manner at intervals of 15 minutes.

Statistics

Statistical analyses used were linear regression, the one-way and two-way analysis of variance, and Duncan’s new multiple-range test for multiple comparison. These analyses were carried out by a computer package, Statistical Analysis System (SAS Institute Inc., Cary, North Carolina), in a VAX 8650 computer. The level of significance was taken at $p<0.05$. All data were expressed as the mean±SEM.

Drugs

Acetylcholine, Ang I, Ang II, bradykinin, hexobarbital, norepinephrine, saralasin, and vasopressin were obtained from Sigma Chemical Company (St. Louis, Missouri). S-8307, EXP6155, EXP6803, and captopril were synthesized at E.I. du Pont de Nemours and Company (Wilmington, Delaware).

Results

In Vitro Potency and Selectivity Determination—Rabbit Aorta

In the rabbit aorta, EXP6155 at $3 \times 10^{-7}$ to $10^{-5}$ M caused parallel shifts to the right of the Ang II concentration–contractile response curve and did not alter the maximal response to Ang II (Figure 2). The pA$_{2}$ and the slope of the Schild plot of EXP6155 were 6.54 and 1.02, respectively. A similar result was also obtained with EXP6803 (data not shown) for which the pA$_{2}$ and the slope of the Schild plot were 7.20 and 1.05, respectively. Effects of S-8307, EXP6155, and EXP6803 at $10^{-6}$ M in antagonizing the Ang II response are shown in Figure 3. Perhaps due to a difference in sensitivity of the tissue to Ang II in two separate studies, the control concentration–contractile response curve for Ang II presented in Figure 3 was shifted to the right when compared with that shown in Figure 2. Nevertheless, EXP6155 at $10^{-6}$ M, compared with its own control curve for Ang II, caused a similar degree of antagonism (Figure 3) as before (Figure 2). In this respect, EXP6803 appears to be more potent than S-8307.
and EXP6155. Neither EXP6155 (Figure 2) nor EXP6803 (Figure 4) changed the concentration-response curves for norepinephrine and KCl.

**In Vitro Potency and Selectivity Determination—Guinea Pig Ileum**

In the guinea pig ileum, neither EXP6155 nor EXP6803 altered the contractile responses to bradykinin and acetylcholine, although both compounds effectively inhibited the responses to Ang I and Ang II (Figure 5). The IC$_{50}$ in inhibiting the Ang I response for EXP6155 and EXP6803 was $5.2 \times 10^{-7}$ and $1.3 \times 10^{-7}$ M, respectively. The IC$_{50}$ in blocking the Ang II response for EXP6155 and EXP6803 was $4.3 \times 10^{-7}$ and $6.6 \times 10^{-8}$ M, respectively.

**In Vivo Potency and Specificity of Angiotensin II Antagonism**

In the pithed rat, EXP6155 (30 and 100 mg/kg i.v.) shifted the log dose-pressor response curve for Ang II dose dependently to the right (Figure 6). The mean diastolic blood pressure for the control group and the 30- and 100-mg/kg groups was $37 \pm 2$ (n=8), $31 \pm 2$ (n=4), and $23 \pm 3$ mm Hg (n=3), respectively. The basal diastolic blood pressure after the injection of EXP6155 (100 mg/kg i.v.) was significantly different from control ($p<0.05$). EXP6155 (100 mg/kg i.v.) did not alter the dose-response curves for norepinephrine and vasopressin (Figure 6).

A similar Ang II antagonism was also observed with EXP6803 (Figure 7). The mean diastolic blood pressure for the control group and the 30 and 100 mg/kg groups was $37 \pm 2$ (n=8), $39 \pm 2$ (n=6), and $18 \pm 1$ mm Hg (n=3), respectively. The basal diastolic blood pressure after the injection of EXP6803 (100 mg/kg) was significantly different from control ($p<0.05$). EXP6803 (100 mg/kg i.v.) did not alter the dose-response curves for norepinephrine (Figure 7).

**Antihypertensive Effect in Conscious Renal Artery-Ligated Hypertensive Rats**

As shown in Figure 8, cumulative intravenous injections of EXP6155 and EXP6803 caused a dose-dependent decrease in MAP. Neither EXP6155 nor EXP6803 significantly altered heart rate (data not shown). The calculated intravenous ED$_{50}$ for EXP6155 and EXP6803 was 10 and 11 mg/kg, respectively. Bolus intravenous injections of saralasin (0.01–1 mg/kg) caused an initial and transient increase in MAP and then a latter decrease in MAP (Figure 8). Unlike saralasin, EXP6155 and EXP6803 did not cause a transient increase in MAP (Figure 8).

To study the specificity of Ang II antagonism of EXP6155 in the renal artery-ligated rats, EXP6155 was given intravenously cumulatively (1–30 mg/kg), and its effect on the pressor responses to Ang II and vasopressin was determined. As shown in Figure 9,
Effect of EXP6803 at 3 x 10^{-6} M on log concentration-contractile response curves for norepinephrine and KCl in rabbit aorta. Maximal contractile response to norepinephrine and KCl were 2.02±0.43 g and 2.35±0.29 g, respectively. Values represent mean±SEM (n=3-4).

EXP6155 started to inhibit the pressor response to Ang II significantly at 10 mg/kg. However, EXP6155 did not reduce the response to vasopressin at these doses (Figure 9).

In this hypertensive model, captopril (3 mg/kg i.v.) significantly decreased MAP for at least 90 minutes (Figure 10). EXP6155 (30 mg/kg i.v.) did not cause an additional antihypertensive effect in renal artery-ligated rats that were pretreated with captopril (Figure 10).

Neither EXP6155 (n=4) nor EXP6803 (n=4) (100 mg/kg p.o.) decreased MAP in renal artery-ligated rats (data not shown).

Effects in Conscious Normotensive Rats

As shown in Figure 11, cumulative intravenous injections of EXP6155 (3-100 mg/kg) did not alter MAP. In addition, unlike saralasin, EXP6155 did not increase MAP transiently (Figure 11). A similar result was also observed with EXP6803 (data not shown).

Discussion

Our study indicates that EXP6155 and EXP6803 exerted selective functional Ang II antagonism in various in vitro and in vivo tests. In the rabbit aorta, EXP6155 competitively antagonized the contractile response to Ang II. This functional Ang II antagonism appears to be selective since EXP6155 at a high concentration (10^{-5} M) did not alter the response to norepinephrine, which suggests that EXP6155 is a competitive receptor antagonist of Ang II. A similar selective Ang II antagonism was also observed for EXP6803. Selective Ang II antagonism by EXP6803 and EXP6155 was also supported by the finding that they did not show affinity for prazosin and nitrendipine binding sites in the rat brain and cardiac tissues, respectively. Both EXP6155 and EXP6803 appear to be 10-50-fold...
more potent than S-8307, the first well-characterized imidazole Ang II antagonist.7,8 Based on its pA2 value, EXP6803 is the most potent imidazole Ang II receptor antagonist. Similarly, in the guinea pig ileum, EXP6155 and EXP6803 did not change the contractile responses to bradykinin and acetylcholine but still blocked the responses to Ang I and Ang II effectively. Again, EXP6803 appeared to be more potent than EXP6155 in blocking the response to Ang I or Ang II. Since the responses to bradykinin and Ang I in the guinea pig ileum are commonly used as a means to determine the angiotensin converting enzyme activity,16 our data suggest that EXP6155 and EXP6803 lack angiotensin converting enzyme inhibitory activity, but represent selective functional Ang II antagonists.

In the adrenal Ang II binding assay, EXP6155 and EXP6803 displaced [3H]Ang II from its specific binding sites with IC50 (defined as the concentration of antagonist that inhibits 50% of specific binding of Ang II) values of $1.6 \times 10^{-6}$ and $1.4 \times 10^{-7}$ M, respectively.15 Furthermore, Scatchard analysis revealed that EXP6155 at $10^{-6}$ M increased the dissociation constant for Ang II and did not alter the total number of Ang II binding sites in the rat adrenal, which suggests competitive interaction.15 Thus, the rat adrenal Ang II binding studies confirm the competitive Ang II antagonism by EXP6155 in the rabbit aorta. A similar order of potency in inhibiting specific Ang II binding has been observed.
in rat aortic smooth muscle cells in which EXP6803 was more potent than EXP6155. Whether a similar result would also be obtained for other types of Ang II receptors in the brain, kidney, or heart remains for further investigation. Since different subtypes of Ang II receptors have been reported in different tissues (see Reference 1), this series of imidazole Ang II antagonists would be useful tools to explore the properties of these Ang II receptors.

Similarly, selective Ang II antagonism was also observed in vivo. In the pithed rat, EXP6155 and EXP6803 at 30 and 100 mg/kg i.v. shifted the dose–pressor response curve for Ang II parallel to the right without altering the maximal response to Ang II, which suggests competitive Ang II antagonism. The inhibitory effects of EXP6155 and EXP6803 on the response to Ang II were selective since they did not alter the dose–response curves for norepinephrine or vasopressin. In contrast to the in vitro data, the in vivo potencies of EXP6155 and EXP6803 in blocking the pressor response to Ang II were quite similar. At 100 mg/kg i.v., EXP6155 and EXP6803 caused hypotensive effects in pithed rats, which is probably due to the blockade of the vasoconstrictor effect of endogenous Ang II since the pithed rat is a high renin model.

To examine the antihypertensive effects of EXP6155 and EXP6803, effects of these compounds were studied in renal artery–ligated hypertensive rats. In a typical group of renal artery–ligated hypertensive rats (n=6), MAP and plasma renin activity averaged 175±5 mm Hg and 28.2±6.2 ng Ang I/ml/hr, whereas the MAP and plasma renin activity of a typical group of sham-operated rats...
Mean arterial pressure (mm Hg)

Renal hypertensive rat

Mean arterial pressure (mm Hg)

Normotensive rat

FIGURE 10. Effect of captopril (3 mg/kg i.v.) pretreatment on the blood pressure effects of EXP6155 (30 mg/kg i.v., n=4) and its saline vehicle (1 ml/kg, n=6) in renal artery-ligated rats. Values represent mean±SEM. The antihypertensive effect of captopril was significant for 90 minutes (p<0.05, analysis of variance). There was no significant difference between effect of saline vehicle and that of EXP6155 on mean arterial pressure.

(n=5) were 100±4 mm Hg and 3.9±0.9 ng Ang I/ml/hr, respectively (unpublished data). In addition, we have shown previously that hypertension in this model depends on the activation of the RAS since either captopril given intravenously or saralasin given subcutaneously reduces blood pressure to normotensive levels in these animals.18-19 It should be noted that the intravenous ED50 for EXP6155 and EXP6803 was quite comparable (10 vs. 11 mg/kg, respectively). Thus, unlike the data obtained in vitro, EXP6803 was not more potent than EXP6155 in vivo. Preliminary findings from pharmacokinetic studies with EXP6803 suggest that EXP6803 is rapidly hydrolyzed and eliminated by the bile (unpublished observations). This may partly account for the discrepancy between in vitro and in vivo data. Neither EXP6155 nor EXP6803 was active when administered orally at 100 mg/kg in renal artery-ligated rats.

The mechanism of the antihypertensive effect of EXP6155 and EXP6803 in renal artery-ligated rats is most likely due to the blockade of the vasoconstrictor effect of Ang II. This is supported by our experiments, which show that pretreatment with captopril (3 mg/kg i.v.) effectively abolished the antihypertensive effect of EXP6155. This dose of captopril has been shown previously to be effective in blocking the pressor effect of Ang II.10 The antihypertensive effect of Ang II but not vasopressin in the renal artery-ligated rats. Moreover, even at 100 mg/kg i.v. EXP6155 did not lower blood pressure acutely in normotensive conscious rats whose blood pressure was not influenced by the RAS.19 Therefore, it is unlikely that the compound had additional mechanisms of action unrelated to the suppression of the RAS. In contrast, the early imidazole Ang II antagonist S-8307 (100 mg/kg i.v.) may have mechanisms independent of the Ang II receptor blockade to account for some of its hypotensive effect in rats.8 Thus, EXP6155 appears to be a more specific Ang II receptor antagonist than S-8307.

Although Ang II receptor antagonists have been reported in the literature, they are, in general, peptide analogues of Ang II and thus retain agonist activities.6 We confirmed that intravenous bolus injection of saralasin, one of the peptide Ang II antagonists, exhibited agonist activity in vivo. In the normotensive conscious rat, saralasin given at a low dose of 0.03 mg/kg i.v. increased blood pressure transiently. Even in a high renin model such as the renal artery-ligated rat, saralasin also caused a transient increase in blood pressure at a low dose of 0.01 mg/kg i.v. In contrast, EXP6155 and EXP6803 did not induce pressor responses even at 100 mg/kg i.v. in normotensive rats. Similarly, EXP6155 and EXP6803 did not increase blood pressure transiently
in renal artery-ligated rats. These results indicate that, unlike saralasin, EXP6155 and EXP6803 do not have agonist activities. This finding has an important implication since these nonpeptide Ang II receptor antagonists are the first blockers of the Ang II receptor that are true competitive Ang II receptor antagonists lacking (partial) agonism. Therefore, these Ang II antagonists may serve as the most useful tools to study the physiology of the RAS.

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