ELSEVIER

European Journal of Pharmacology 287 (1995) 163–168

ejp

Responses to L-163,491, a nonpeptide angiotensin II mimic, in the pulmonary vascular bed of the cat

Alan D. Kaye [a,*], Bobby D. Nossaman [a], Salah Kivlighn [b], Ikhlass N. Ibrahim [a], Bracken J. De Witt [a], Philip J. Kadowitz [a]

[a] *Departments of Anesthesiology and Pharmacology, Tulane University Medical Center, New Orleans, LA 70112-2699, USA*
[b] *Merck Research Laboratories, West Point, PA 19486, USA*

Received 6 July 1995; accepted 4 August 1995

Abstract

Pulmonary vascular responses to 5,7-dimethyl-2-ethyl-3-[[2′-[(butyloxycarbonyl)amino-sulfonyl]-5′-(3-methoxybenzyl)-[1,1′-biphenyl]-4-yl]methyl]-3*H*-imidazo[4,5-b]pyridine (L-163,491), a novel nonpeptide angiotensin agonist, and angiotensin IV, the 3-8 amino acid fragment of angiotensin, were compared with responses to angiotensin II. Responses were investigated in the intact-chest cat under conditions of controlled blood flow and intralobar injections of angiotensin II, L-163,491, and angiotensin IV caused dose-related increases in lobar arterial pressure. When comparable in lobar arterial pressure of the three agents were examined, L-163,491 was approximately 3-fold less potent than angiotensin IV and approximately 100-fold less potent than angiotensin II when doses are expressed on a nmol basis. DuP 532, 2-propyl-4-pentafluoroethyl-1-([2′-(1*H*-tetrazol-5-yl)biphenyl-4]-methyl)imidazole-5-carboxylic acid, an angiotensin II AT_1 receptor antagonist, reduced pulmonary vasoconstrictor responses to angiotensin II, angiotensin IV and L-163,491, but did not significantly change pressor responses to serotonin, norepinephrine, or the thromboxane A_2 mimic, U46619. PD 123319, an angiotensin II subtype 2 receptor antagonist, did not significantly change pressor responses to L-163,491, angiotensin II, or angiotensin IV. Captopril, the angiotensin-converting enzyme inhibitor, decreased pulmonary vasoconstrictor responses to angiotensin I and enhanced vasodilator responses to bradykinin, but did not significantly change pressor responses to L-163,491. These data show that L-163,491 has significant angiotensin AT_1 receptor-mediated vasoconstrictor activity in the pulmonary vascular bed of the cat. These data also show that the nonpeptide agonist has 3-fold less activity compared to angiotensin IV and is approximately 100-fold less potent than angiotensin II in the feline pulmonary vascular bed.

Keywords: L-163,491; Pulmonary vascular bed, cat; Angiotensin receptor-mediated response; Captopril; PD 123319; DuP 532

1. Introduction

Angiotensin II is the major active product of the renin-angiotensin system. Angiotensin II has potent vasoconstrictor activity in the pulmonary and peripheral vascular beds. It has been demonstrated that angiotensin II is a more potent vasoconstrictor in the mesenteric, cutaneous and renal vascular beds compared to the skeletal muscle, coronary, pulmonary and cerebral vascular beds (Krasney, 1968; Jarhult, 1971). The recent discovery of nonpeptide angiotensin receptor antagonists has led to the discovery of multiple angiotensin receptor subtypes. The sites having high affinity for DuP 753 (Lorsartan potassium (DuPont-Merck, Wilmington, DE) are designated as angiotensin AT_1 receptors and those having a high affinity for PD 123319 as angiotensin AT_2 receptors. The occurrence of the angiotensin AT_1 and AT_2 receptors binding sites identified appears widespread. The presence and proportion of these receptors vary significantly among different tissues/organs of the same species and within the same tissue/organ of different species (Timmermans et al., 1993; Bumpus et al., 1991; Chiu et al., 1989; Whitebread et al., 1989). The increases in pul-

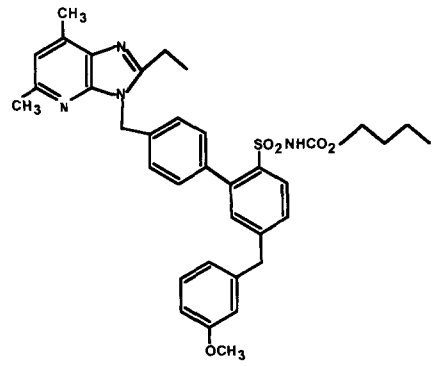
* Corresponding author. Department of Anesthesiology, Tulane University Medical Center, 1430 Tulane Avenue, Box SL-4, New Orleans, LA 70112-2699, USA. Tel.: (504) 588-5069; fax: (504) 584-3501.

SSDI 0014-2999(95)00486-6

monary and systemic vascular resistance in response to angiotensin II are mediated by the activation of angiotensin AT_1 receptors in the cat and rat (McMahon et al., 1992; Nossaman et al., 1994). The increases in pulmonary vascular resistance in response to angiotensin II are modulated by the activation of angiotensin AT_1 receptors in the rat (Nossaman et al., 1995).

In addition to the development of nonpeptide angiotensin receptor antagonists, a new class of nonpeptide receptor agonists has been discovered. 5,7-Dimethyl-2-ethyl-3-[[2′-[(butyloxycarbonyl)aminosulfonyl]-5′-(3-methoxybenzyl)-[1,1′-biphenyl]-4-yl]methyl]-3*H*-imidazo[4,5-*b*]pyridine (L-163,491, Fig. 1) and 5,7-dimethyl-2-ethyl-3-[[4-[2(*n*-butyloxycarbonyl sulfonamido)-5-isobutyl-3-thienyl]phenyl]methyl]imadazo[4,5-*b*]-pyridine (L-162,313) are nonpeptide angiotensin receptor ligands. These compounds have been reported to have agonist activity at the angiotensin AT_1 receptor and both have been shown to have significant pressor activity in the conscious rat (Kivlighn et al., 1995; Huckle et al., 1994). These nonpeptide angiotensin receptor agonists provide a novel approach to the study of the renin-angiotensin system. L-162,313 has approximately equal affinity at both the angiotensin AT_1 and angiotensin AT_2 receptors whereas L-163,491 binds preferentially (approximately 100-fold) at the angiotensin AT_1 receptor and is an agonist at this site, allowing us to observe the effects of angiotensin AT_1 receptor stimulation without concurrent stimulation of the angiotensin AT_2 receptor subtype. However, the effects of L-163,491 on the pulmonary vascular bed have not been determined.

The present study was, therefore, undertaken to investigate responses to recently made available angiotensin peptides such as angiotensin IV, the novel angiotensin nonpeptide agonist L-163,491, and to evaluate the role of angiotensin AT_1 and angiotensin AT_2 receptors in mediating or modulating these responses and other angiotensin peptide actions in the pulmonary vascular bed of the cat under conditions of controlled pulmonary blood flow and constant left atrial pressure. The results of these studies demonstrate that L-163,491 and angiotensin IV have full agonist activity and are 100-fold less potent than angiotensin II. These data also suggest that L-163,491 vasoconstrictor activity appears to be mediated by the activation of angiotensin AT_1 receptors in the pulmonary vascular bed of the cat.



5,7-dimethyl-2-ethyl-3-[[2'-[(butyloxycarbonyl) aminosulfonyl]-5'-(3-methoxybenzyl)-[1,1'-biphenyl]-4-yl]methyl]-3H-imidazo [4,5,-b] pyridine

Fig. 1. Chemical structure of 5,7-dimethyl-2-ethyl-3-[[2′-[(butyloxycarbonyl)aminosulfonyl]-5′-(3-methoxybenzyl)-[1,1′-biphenyl]-4-yl]-methyl]-3*H*-imidazo[4,5-*b*]pyridine (L-163,491).

2. Materials and methods

All experimental protocols were approved by the Advisory Committee for Animal Resources at Tulane University Medical Center. 38 adult cats of either sex weighing 2.8–4.5 kg were sedated with ketamine hydrochloride (10–15 mg/kg i.m.) and were anesthetized with pentobarbital sodium (30 mg/kg i.v.). The animals were strapped in the supine position to a fluoroscopic table, and supplemental doses of anesthetic were administered as needed to maintain a uniform level of anesthesia. The trachea was intubated with a cuffed pediatric endotracheal tube, and the animals spontaneously breathed room air enriched with 100% oxygen at an oxygen flow rate of 150–300 ml/min. Systemic arterial (aortic) pressure was measured from a femoral artery, and intravenous injections were made from a catheter positioned in the inferior vena cava from a femoral vein.

For perfusion of the left lower lung lobe, a specially designed 28-cm 6F triple-lumen balloon perfusion catheter (Arrow International, Reading, PA) was passed under fluoroscopic guidance from an external jugular vein into the pulmonary artery to the left lower lobe. After the animals had been heparinized with heparin sodium (Sigma Chemicals, St. Louis, MO), 1000 U/kg i.v., the lobar artery was vascularly isolated by distension of the balloon cuff of the perfusion catheter. The lobe was then externally perfused by blood pumped from the femoral artery using a Harvard 1210 perfusion pump and infused into the isolated lobar artery via the lumen distal to the occlusion balloon. The perfusion rate was adjusted to approximate mean pressure in the main pulmonary artery and was thereafter not changed during each experiment. The lobar arterial perfusion rate ranged from 30 to 50 ml/min. In some experiments left atrial pressure was measured with a 6F double-lumen catheter (Arrow International, Reading, PA) passed transseptally into the vein draining the left lower lobe. This catheter tip was positioned so the left atrial pressure port on the distal lumen was 1–2 cm into the lobar vein, and the second catheter port was near the venoatrial junction.

When necessary, blood could be withdrawn or infused through this second catheter lumen to maintain left atrial pressure constant. All vascular pressures were measured with Statham P23 or SpectroMed DTX Plus transducers zeroed at right atrial level. Mean pressures obtained by electronic averages were recorded on a Grass model 7 recorder.

The experiments were divided into three groups. In the first two groups of experiments, the influence of 2-propyl-4-pentafluoroethyl-1-([2'-(1*H*-tetrazol-5-yl)biphenyl-4]-methyl)imidazole-5-carboxylic acid (DuP 532; 1 mg/kg i.v.) and PD 123319 (0.5 mg/kg i.a.) on responses to U46619, angiotensin II, angiotensin IV, and L-163,491 were investigated. Responses to DuP 532 and PD 123319 were determined beginning 10–15 min after the blockers were administered. Responses to the vasoconstrictor agents were determined before and after administration of the angiotensin AT_1 or angiotensin AT_2 receptor antagonists. In the last series of experiments the influence of the angiotensin converting enzyme inhibitor, captopril (4 mg/kg i.v.), on responses to angiotensin I, bradykinin, and L-163,491 were investigated. Responses to captopril were determined beginning 10–15 min after the inhibitor was administered. Stock solutions of U46619 (Upjohn, Kalamazoo, MI) were prepared in 100% ethanol at concentrations of 5–10 mg/ml and were stored in a freezer at −20°C. Working solutions were prepared on a frequent basis by dilution of the stock solutions in 0.9% NaCl solution.

Angiotensin I, angiotensin II, bradykinin, norepinephrine hydrochloride, captopril, and serotonin creatinine sulfate (Sigma Chemicals, St. Louis, MO) and angiotensin IV (Bachem Laboratories, Philadelphia, PA) were dissolved in 0.9% NaCl on a frequent basis. PD 123319 was a kind gift from Dr. David Taylor at Parke-Davis laboratories, Ann Arbor, Michigan. PD 123319 and DuP 532 (DuPont-Merck, Wilmington, DE) were dissolved in 0.9% NaCl and were prepared on the day of use. L-163,491 was prepared in 0.1 ml of dimethyl sulfoxide (DMSO) and 0.9 ml of 100% ethanol and was obtained from Dr. Ralph Rivero and Ms. Nancy Kevin at Merck Research Laboratories, Rahway, NJ. All agonists were injected directly into the lobar arterial perfusion circuit on a straight weight basis. Working solutions of all agonists were prepared on a frequent basis, stored in brown stoppered bottles, and kept on crushed ice during experiments.

Blood gases and pH were measured with a Corning model 178 analyzer. All hemodynamic data are expressed in absolute units and are presented as means ± S.E.M. The data were analyzed using a paired *t*-test or an analysis of variance with post-hoc Scheffé's *F*-test (StatView, Abascus Concepts, Berkeley, CA) on a Quadra 660. A $P < 0.05$ was used as the criterion for statistical significance.

3. Results

3.1. Responses to L-163,491, angiotensin II and angiotensin IV and U46619

Responses to the novel nonpeptide selective angiotensin AT_1 receptor agonist, L-163,491 were investi-

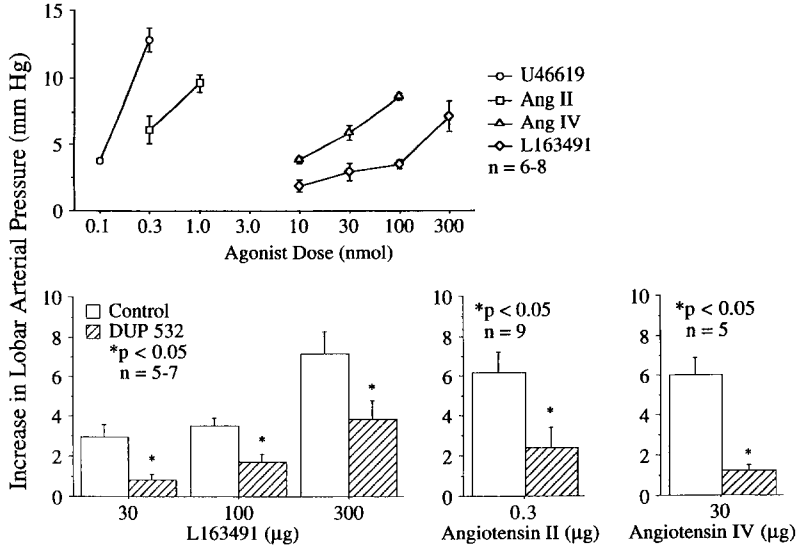


Fig. 2. Upper panel. Dose-response curves comparing increases in lobar arterial pressure in response to injections of L-163,491, angiotensin II, angiotensin IV, and U46619 under low tone conditions. The vasoactive agents were injected directly into the perfused lobar artery, and doses are expressed on a nmol basis. n indicates number of experiments. Lower panel. Influence of DuP 532 on pressor responses to L-163,491, angiotensin II, and angiotensin IV in the pulmonary vascular bed. The agonists were injected directly into the perfused lobar artery, and responses were determined before and beginning 10–15 min after administration of DuP 532 in a dose of 1 mg/kg i.v. *n* indicates number of experiments. * Significantly different from control.

Table 1

	Lobar arterial pressure (mmHg)	Left arterial pressure (mmHg)	Aortic pressure (mmHg)
Control	14±1	3±1	142±6
L163,491 (10 μg)	16±1	3±1	144±4
Control	13±1	3±1	145±6
L163,491 (30 μg)	17±1	4±1	148±8
Control	14±1	3±1	141±7
L163,491 (100 μg)	19±1	3±1	145±8
Control	15±1	3±1	146±8
L163,491 (300 μg)	22±2	4±1	151±7

Values are means (pressure)±S.E.; n, no. of cats. $n = 4–8$

gated in the pulmonary vascular bed of the cat and these results are summarized in Fig. 2. Injections of L-163,491 into the perfused lobar artery in doses of 3–300 μg produced dose-related increases in lobar arterial and aortic pressures without changing left atrial pressures (Table 1 and Fig. 2, upper panel). In terms of relative vasoconstrictor activity in the pulmonary vascular bed, L-163,491 was approximately 3-fold less potent than angiotensin IV and approximately 300-fold less potent than angiotensin II when doses are compared on a nmol basis (Fig. 2). The thromboxane A_2 mimic, U46619, was approximately 3-fold more potent than angiotensin II (Fig. 2). L-163,491 responses were long-acting and returned to baseline within 10 min of injection.

3.2. Influence of DuP 532, PD 123319 or captopril on responses to L-163,491, and to angiotensin peptides

The angiotensin receptor subtype mediating pressor responses to L-163,491 were investigated and these data are summarized in Fig. 2. Following administration of the angiotensin AT_1 receptor antagonist, DuP 532, in a dose of 1 mg/kg i.v., increases in lobar arterial pressure in response to L-163,491 were significantly reduced (Fig. 2, left lower panel). The administration of DuP 532 significantly decreased pulmonary pressor responses to angiotensin II and angiotensin IV (Fig. 2), but did not significantly change pressor responses to serotonin, norepinephrine, or the thromboxane A_2 mimic, U46619 (data not shown).

The effects of the angiotensin AT_2 receptor antagonist PD 123319 on responses to L-163,491 were investigated and these data are summarized in Fig. 3. Following administration of PD 123319 in a dose of 0.5 mg/kg i.a. increases in lobar arterial pressure in response to L-163,491 were not changed significantly (Fig. 3). Administration of the angiotensin AT_2 receptor antagonist did not reduce pressor responses to angiotensin II or angiotensin IV (Fig. 3).

The effects of the angiotensin-converting enzyme inhibitor captopril on responses to L-163,491 were investigated and these data are summarized in Fig. 3. Following administration of captopril in a dose of 4 mg/kg i.v. pressor responses to L-163,491 were not altered whereas the pressor response to angiotensin I was decreased significantly (Fig. 3). The decrease in lobar arterial pressure in response to bradykinin was

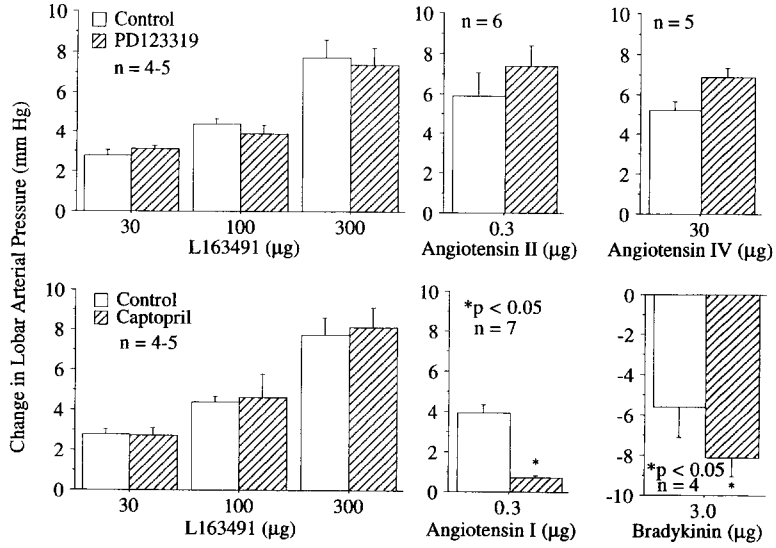


Fig. 3. Upper panel. Influence of PD 123319 on pressor responses to L-163,491, angiotensin II, and angiotensin IV in the pulmonary vascular bed. The agonists were injected directly into the perfused lobar artery, and responses were determined before and beginning 5–10 min after administration of PD 123319 in a dose of 0.5 mg/kg i.a. *n* indicates number of experiments. Lower panel. Influence of captopril on responses to L-163,491, angiotensin I, and bradykinin in the pulmonary vascular bed. The agonists were injected directly into the perfused lobar artery, and responses were determined before and beginning 10–15 min after administration of captopril in a dose of 4 mg/kg i.v. *n* indicates number of experiments. * Significantly different from control.

increased significantly following administration of captopril (Fig. 3).

4. Discussion

The results of the present study show that the novel nonpeptide angiotensin receptor agonist, L-163,491, has significant pressor activity in the pulmonary vascular bed of the cat. In as much as pulmonary blood flow and left atrial pressure were unchanged, the increase in lobar arterial pressure in response to L-163,491 represents an increase in pulmonary vascular resistance. In terms of relative pressor activity in the pulmonary vascular bed, the nonpeptide angiotensin receptor agonist L-163,491 was 3-fold less potent than angiotensin IV, the 3-8 amino acid fragment of angiotensin II, and was approximately 100–300-fold less potent than angiotensin II. Dose-response curves for L-163,491, angiotensin IV, and angiotensin II were parallel in the pulmonary vascular bed of the cat. Angiotensin II is a very potent pressor agent in the pulmonary vascular bed of the cat with activity only 3-fold less than the thromboxane A_2 mimic, U46619, which is the most potent pressor agent in the pulmonary vascular bed of the cat (Kaye et al., 1995).

The angiotensin receptor subtype mediating pressor responses to L-163,491 was investigated using angiotensin AT_1 and AT_2 receptor antagonists and increases in lobar arterial pressure in response to the nonpeptide agonist were reduced by DuP 532 in a dose that attenuated pressor responses to angiotensin II and angiotensin IV (Wong et al., 1991). Pressor responses to L-163,491, angiotensin II, and angiotensin IV were not changed by PD 123319, an angiotensin AT_2 receptor antagonist in a dose that should have an effect on AT_2 receptor mediated responses based on data from binding studies (Timmermans et al., 1992). Higher doses of PD 123319 (2 mg/kg i.a.) produced no significant change in lobar arterial vasoconstrictor response to L 163,491. The results of these studies suggest that increases in lobar arterial pressure in response to the nonpeptide angiotensin receptor agonist, L-163,491, are mediated by the activation of angiotensin AT_1 receptor in a manner similar to that observed with angiotensin II and angiotensin IV in the pulmonary vascular bed of the cat. These results suggest that activation of angiotensin AT_2 receptors play little if any role in mediating or modulating the pressor response to L-163,491 or to angiotensin II or angiotensin IV in the pulmonary vascular bed of the cat. The role of angiotensin-converting enzyme inhibitor in mediating or modulating responses to L-163,491 was investigated and following treatment with captopril in a dose that blocked the pressor response to angiotensin I and enhanced the vasodilator response to bradykinin was without significant effect on the response to the nonpeptide agonist. These results suggest that responses to L-163,491 are independent of the actions of angiotensin-converting enzyme.

Although angiotensin II has potent pressor activity in the pulmonary vascular bed, the role of the peptide and related peptides in the regulation of tone in the pulmonary circulation is unknown. The development of potent selective nonpeptide angiotensin receptor agonists and antagonists may provide the pharmacologic probes by which the role of angiotensin AT_1 and AT_2 receptors in the pulmonary vascular bed may be determined.

The recently discovered class of nonpeptide angiotensin AT_1 receptor antagonists such as DuP 532 which are potent antihypertensive agents, has advanced our understanding of the nature of angiotensin receptors in the pulmonary vascular bed. The present data suggest that angiotensin AT_1 receptors play a dominate role in mediating pressor responses to the angiotensin peptides and L-163,491 in the pulmonary vascular bed of the cat. The data with PD 123319, a selective angiotensin AT_2 receptor antagonist, suggest that pressor responses of L-163,491, angiotensin II, and angiotensin IV are not significantly modulated by the activation of angiotensin AT_2 receptors in resistance vessel elements in the pulmonary vascular bed of the cat.

Angiotensin III can be formed from angiotensin II by an aminopeptidase (Welches et al., 1993); however, the present data and previously published data from this laboratory suggest that this is not a degradation pathway, since angiotensin II and angiotensin III have similar pressor activity in the pulmonary vascular bed of the cat. Thus conversion of angiotensin II or angiotensin III to angiotensin IV results in a marked loss in pressor activity and this pathway could function as an inactivation pathway. Although the present results show that angiotensin IV has less affinity for the angiotensin AT_1 receptor when compared to angiotensin II, angiotensin IV could induce significant vasoconstriction, if this peptide were formed in a large amount, as could occur after treatment with angiotensin-converting enzyme inhibitors.

In conclusion, the present data show that the novel nonpeptide angiotensin receptor agonist, L-163,491, has significant vasoconstrictor activity in the pulmonary vascular bed of the cat and that responses to L-163,491 are mediated by the activation of angiotensin AT_1 receptors. The observation that angiotensin IV has a lower apparent affinity for the angiotensin AT_1 receptor suggests that amino acid residues 2-8 are needed for high affinity binding of the peptide to the angiotensin AT_1 receptor in the resistance vessel elements in the feline lung. These results also suggest that L-163,491 has significant angiotensin AT_1 receptor-

mediated vasoconstrictor activity independent of angiotensin AT_2 receptor activation or angiotensin-converting enzyme inhibition in the feline lung and could be a useful probe for future studies on the role of angiotensin AT_1 receptor-mediated mechanisms in the pulmonary circulation.

References

Bumpus, F.M., K.J. Catt, A.T. Chiu, M. DeGasparo, T. Goodfriend, A. Husain, M.J. Peach, D.M. Taylor and P.B. Timmermans, 1991, Nomenclature for angiotensin receptors. A report of the Nomenclature Committee for the Council for High Blood Pressure Research, Hypertension 17, 720.

Chiu, A.T., W.F. Herblin, R.J. Ardecky, D.E. McCall, D.J. Carini, J.V. Duncia, L.J. Pease, R.R. Wexler, P.C. Wong, A.L. Johnson and P.B. Timmermans, 1989, Identification of angiotensin II receptor subtypes, Biochem. Biophys. Res. Commun. 165, 196.

Huckle, W.R., S.D. Kivlighn, G.G.J. Zingaro, N. Kevin, R.A. Rivero, R.S. Chang, W.J. Greenlee, P.K.S. Siegl and R.G. Johnson, 1994, Angiotensin II receptor-mediated activation of phosphoinositide hydrolysis and elevation of mean arterial pressure by a nonpeptide, L-163,491, Can. J. Pharmacol. 72, 543.

Jarhult, J., 1971, Comparative effects of angiotensin and noradrenaline on resistance, capacitance and precapillary sphincter vessels in cat skeletal muscle, Acta Physiol. Scand. 81, 315.

Kaye, A.D., B.D. Nossaman, I.N. Ibrahim, B.J. DeWitt, C.J. Feng and P.J. Kadowitz, 1995, Analysis of thromboxane receptor-mediated responses in the feline pulmonary vascular bed, Crit. Care Med. 23, 164.

Kivlighn, S.D., W.R. Huckle, G.J. Zingaro, R.A. Rivero, V.J. Lotti, R.L. Chang, T.W. Schorn, N. Kevin, R.J. Johnson, W.J. Greenlee, and P.K.S. Siegl, 1995, Discovery of L-162,313: a nonpeptide that mimics the biological actions of angiotensin II, Am. J. Physiol. (in press).

Krasney, J.A., 1968, Effects of angiotensin on stroke volume and regional blood flow and resistance, Am. J. Physiol. 215, 1454.

McMahon, T.J., A.D. Kaye, R.K. Minkes, B.D. Nossaman and P.J. Kadowitz, 1992, Inhibitory effects of Dup 753 and EXP3174 on responses to angiotensin II in pulmonary vascular bed of the cat, J. Appl. Physiol. 73, 2054.

Nossaman, B.D., C.J. Feng, J.K. Wang and P.J. Kadowitz, 1994, Analysis of responses of angiotensin peptides I, II, III in the isolated rat lung, Am. J. Physiol. 266, L389.

Nossaman, B.D., C.J. Feng, J.K. Wang and P.J. Kadowitz, 1995, Analysis of responses of angiotensin IV: effects of PD 123319 and DuP 753 in the pulmonary vascular bed of the rat, Am. J. Physiol. 268, L302.

Timmermans, P.B.M.W.M., D.J. Carini, A.T. Chiu, W.F. Herblin, P.C. Wong and R.D. Smith, 1992, Angiotensin II receptors and functional correlates, Am. J. Hypertens. 5, 2215.

Timmermans, P.B.M.W.M., P.C. Wong, A.T. Chiu, W.F. Herblin, P. Benfield, D.J. Carini, R.J. Lee, R.R. Wexler, J.M. Saye and R.D. Smith, 1993, Angiotensin II receptors and angiotensin II receptor antagonists, Pharmacol. Rev. 45, 206.

Welches, W.R., K.B. Brosnihjan and C.M. Ferrario, 1993, A comparison of the properties and enzymatic activities of three angiotensin processing enzymes: angiotensin converting enzyme, prolyl endopeptidase and neutral endopeptidase 24.11, Life Sci. 52, 1461.

Whitebread, S., M. Mele, B. Kamber and M. DeGaspar, 1989, Preliminary biochemical characterization of two angiotensin II receptor subtyes, Biochem. Biophys. Res. Commun. 163, 284.

Wong, P.C., S.D. Hart, A.T. Chiu, W.F. Herblin, D.J. Carini, R.D. Smith, R.R. Wexler and P.B.M.W.M. Timmermans, 1991, Pharmacology of DuP 532, a selective and noncompetitive AT_1 receptor antagonist, J. Pharmacol. Exp. Ther. 259, 861.