Journal of Life Science **2010** Vol. 20. No. 6. 831~837 ©JLS / ISSN 1225-9918

Pharmacological Characterization of KR-31125, a Novel Nonpeptide AT1 Receptor Antagonist

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Received February 25, 2010 / Accepted May 13, 2010

KR-31125 (2-butyl-5-dimethoxymethyl-6-phenyl-7-methyl-3-[[2′-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-3H-imidazo[4,5-b]pyridine) is a potent inhibitor of angiotensin II type 1 (AT_1) receptors in human recombinant AT_1 receptors and rabbit aorta. These *in vitro* studies revealed that KR-31125 inhibited specific [^{125}I] [Sar^1, Ile^8]-angiotensin II binding to human recombinant AT_1 receptors in a concentration dependent manner with an IC_{50} value of 19.72±2.65 nM. However, no interaction with AT_2 receptors was detected as displayed by the competition binding of [^{125}I] CGP 42112A to human recombinant AT_2 receptor. The binding action was also confirmed as a competitive mode that was identical to the previously studied compound, losartan. In addition, KR-31125 caused a nonparallel shift to the right in the concentration response curves to angiotensin II with a 30-80% decrease in the maximum contractile responses (pK_B: 7.63). Compared to the previous studies with losartan that showed a parallel right shift in the maximum contractile responses to AII (pA_2: 7.59), KR-31125 presented a different mode of action with a similar potency to losartan. These results demonstrate that KR-31125 is a highly potent and AT_1 selective angiotensin II receptor antagonist that can be applied to the fields of new diagnostic and research tools with upcoming *in vivo* study results.

Key words : KR-31125, antihypertension, angiotensin, AT_1 receptor antagonist, diagnostics

Introduction

Renovascular hypertension is the most common type of secondary hypertension that occurs in 2 to 4 million people in the United States [22]. Especially, the renin angiotensin system plays a major role in the regulation of blood pressure and in the pathogenesis of hypertension [9,15]. The octapeptide angiotensin II is formed *in vivo* by the angiotensin converting enzyme (ACE) catalyzed cleavage of angiotensin II (AII). Although ACE inhibitors have proved to be clinically effective in the treatment of hypertension and congestive heart failure [3,18], some evidence suggests that their unwanted side effects result from a lack of specificity for angiotensin I [4,12]. These problems have asked the development of more selective drugs with effective block the action of AII, including the most recent discovery, Aliskiren, the direct renin inhibitor [13].

The discovery of losartan, an AT_1 receptor antagonist, have revolutionized the development of novel, selective, and orally active antihypertensive agents as those compounds targeted the direct interaction of AII and its receptor [14,17,19]. Currently, losartan is on the market as the first AII receptor antagonist that was launched as a novel antihypertensive agent since proven to be orally active in animals [19,21,20] and humans [5,6,8]. However, there are many candidates developed as me-too approach to losartan, and now those compounds has been expanding the possibility of AII receptor antagonists as the research and diagnostic trials for the early determination of hypertension related pathophysiology, such as in the positron emission tomography imaging [9,22,24].

Before to deploy those compounds in specific applications as tracer ligands, *in vitro* and *in vivo* studies are essential to progress into the pharmacokinetic and toxicological schemes. Therefore, in the present study, the *in vitro* pharmacological properties of KR-31125 as a possible tracer displacing physiologically active AII are presented in comparison with losartan by examining their antagonistic effects on the binding of [^{125}I] [Sar^1, Ile^8]-AII and [^{125}I] CGP 42112A to human recombinant AT_1 and AT_2 receptor subtype, and on the AII-induced contraction of rabbit aortic segments.

Materials and Methods

Chemicals

KR-31125 (2-butyl-5-dimethoxymethyl-6-phenyl-7-methyl-3-[[2′-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-3H-imidazo

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[4,5-b]pyridine, US patent #5691348, Fig. 1), L-158809, PD-123177 and losartan [21] were synthesized at Bio-Organic Science Division, KRICT. Sodium pentobarbital was purchased from Hanlim Pharm. Co. (Seoul, Korea) and ketamine hydrochloride from Yuhan Co. (Seoul, Korea). [Sar^1, Ile^8]-AII, AII acetate, arterenol bitartarate, vasopressin acetate, isoproterenol hydrochloride were purchased from Sigma Chemical Co. (St. Louis, MO, U.S.A.). [^{125}I] [Sar^1, Ile^8]-AII and [^{125}I] CGP 42112A (2200 Ci/mmol) were obtained from PerkinElmer life and analytical sciences (Boston, USA.). KR-31125 and losartan were dissolved in dimethyl sulfoxide and further diluted in the buffer for AII binding assay and for isolated tissue experiments, and dissolved in 0.05 N KOH in saline for the intravenous administration in rats. All chemicals were prepared just before to use.

Radioligand binding assay

For the competition and equilibrium binding studies on AT_1 and AT_2 receptors, human recombinant AT_1 and AT_2 receptor (PerkinElmer life and analytical sciences, Boston, USA) were used to exclude the possible interaction between drugs and other receptors that would exist already in various tissues. Binding assays were performed in 96-well plates by incubating aliquots of the human recombinant AT_1 and AT_2 receptor with 0.21 nM of [^{125}I] [Sar^1, Ile^8]-AII and 0.5 nM of [^{125}I] CGP 42112A, respectively. From the preliminary experiments with those concentrations of radioligands, the binding parameters were well fit to the control data provided by the receptor vendor (data not shown). Test compounds were dissolved at 2.5 mM in dimethylsulfoxide and serially diluted to 10 concentrations for the evaluation of activity in the total assay volume of 250 µl. The assay buffer contained 50 mM Tris, 5 mM $MgCl_2$, 1 mM EDTA and 0.1% bovine serum albumin (pH 7.4). Specific [^{125}I] [Sar^1, Ile^8]-AII and [^{125}I] CGP 42112A binding were determined experimentally from the difference between counts in the absence and the presence of unlabelled AII and [Sar^1, Ile^8]-AII at the concentration of 10 µM, respectively. After incubation at 37°C for 60 minutes (or 180 minutes for AT_2 receptor), the incubation mixtures were filtered through GF/C glass-fiber filters (PerkinElmer life and analytical sciences, Boston, USA) which were presoaked in 0.3% polyethylenimine and rapidly washed nine times with 200 µl of ice cold 50 mM Tris buffer (pH 7.4) using the Inotech harvester (Inotech, Switzerland). The filters were covered with MeltiLex (melted on scintillator, PerkinElmer life and analytical sciences, Boston, USA), sealed in sample bag, followed by drying in the microwave oven, and counted by MicroBeta (PerkinElmer life and analytical sciences, Boston, USA). The assays were performed in three separate experiments run in quadruplicate.

The ability of antagonists to inhibit specific [^{125}I] [Sar^1, Ile^8]-AII and [^{125}I] CGP 42112A binding was estimated by IC_{50} values, which are the molar concentrations of unlabeled drugs necessary to displace 50% of specific binding. The K_i value was calculated from the equation $K_i=IC_{50}/(1+L/K_d)$, where L equals the concentration of [^{125}I] [Sar^1, Ile^8]-AII or [^{125}I] CGP 42112A [2]. The data from binding experiments were analyzed by the nonlinear regression, using the PRISM computer program (GraphPad Software Inc., San Diego, USA).

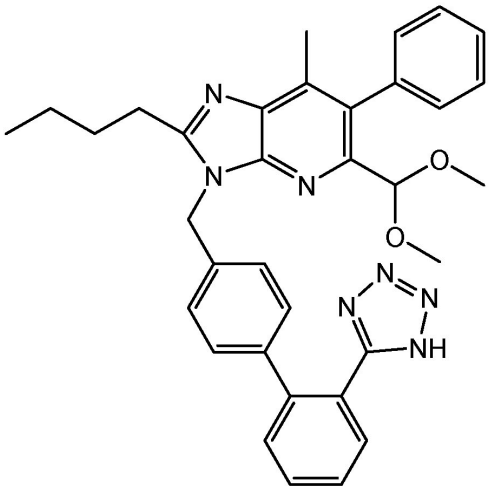

Fig. 1. Chemical structure of KR-31125.

In vitro potency in rabbit aorta

This study conformed to the *Guide for the Care and Use of Laboratory Animals,* published by the U.S. National Institute of Health. The descending thoracic aorta was isolated from male New Zealand white rabbits (2-3 kg, Samyook Experimental Animal Co., Suwon, Korea). The endothelial layer of aorta was destroyed by gentle rubbing of the luminal surface with a cotton swab moistened with Krebs' solution. The aorta was cut into ring segments of 3-4 mm in width, and the vascular rings were mounted in 20 ml organ baths containing Krebs' bicarbonate buffer of the following composition (in mM): NaCl 118, KCl 4.7, $CaCl_2$ 2.5, $NaHCO_3$ 25, $MgSO_4$ 1.2, KH_2PO_4 1.2 and glucose 11.0. The Krebs' buffer was kept at pH 7.4 by continuous bubbling with a gas mixture (95% O_2, 5% CO_2) at 37°C. The isometric

contraction was recorded with force displacement transducers (Grass FT03, Grass Ins., Quincy, U.S.A.) and displayed on a chart recorder (Multicorder MC 6625, Hugo Sachs Electronic, March, Germany).

The rings were allowed to equilibrate for 90 min under a resting tension of 2 g. The first control cumulative concentration-contractile response curve for AII (10^{-10} - 10^{-5} M) was determined to ensure stable reactivity to subsequently added AII. Then, the tissue was washed three times until baseline tension was recovered. After each ring was treated for 30 min with a single dose of KR-31125 (3×10^{-9}, 10^{-8}, 3×10^{-8} M), losartan (10^{-7}, 3×10^{-7}, 10^{-6} M) or vehicle (0.1% dimethyl sulfoxide), the second cumulative concentration-contractile response curve for AII was established. To exclude any influence of multiple dosing with KR-31125 and losartan on the concentration-contractile response curve, each tissue was incubated only with one concentration of the antagonist. Responses from rabbit aorta were expressed as percentage of the maximal AII response obtained from the first cumulative concentration-response curve. The pA_2 values were determined according to the Schild equation with pK_B values being calculated from the equation of [antagonist]/(dose ratio-1).

To test the specificity of KR-31125 as an AII receptor antagonist, the concentration-contractile responses to norepinephrine, $PGF_{2\alpha}$, serotonin and histamine were also examined in the endothelium-removed rabbit aorta in the presence and the absence of KR-31125 at 1 μM. Responses in this study were expressed as percentage of the maximal response obtained from the first cumulative concentration- response curve.

Statistical analysis

All values are expressed as mean±S.E.M. Data were analyzed by Student's t-test or one-way analysis of variance (ANOVA) followed by the Dunnett's test for multiple comparisons (Sigma Stat, Jandel Co., San Rafael, USA). In all comparisons, the difference was considered to be statistically significant at $p<0.05$.

Results

Radioligand binding assay

[^{125}I] [Sar^1, Ile^8]-AII interacted with a single population of binding sites (46.3±0.7 fmol/mg) with the dissociation constant (K_d) of 0.24±0.01 nM in the human recombinant AT_1 receptor. With this receptor preparation, KR-31125, losartan, L-158809 and PD-123177 competed dose-dependently with 0.21 nM [^{125}I] [Sar^1, Ile^8]-AII against the binding sites of the human recombinant AT_1, where they appeared to exhibit monophasic inhibition curves (Fig. 2). The potency of KR-31125 from the radioligand binding assay (IC_{50}=19.72± 2.65 nM) was comparable to losartan (IC_{50}=12.30±1.42 nM) and less than L-158809 (IC_{50}=1.44±0.34 nM) in displacing labeled AII for the human recombinant AT_1 receptor. However, the binding affinity of KR-31125 for the human recombinant AT_2 receptor was not found except for PD-123177 (IC_{50}=4.3±1.4 μM), the known AT_2 receptor specific

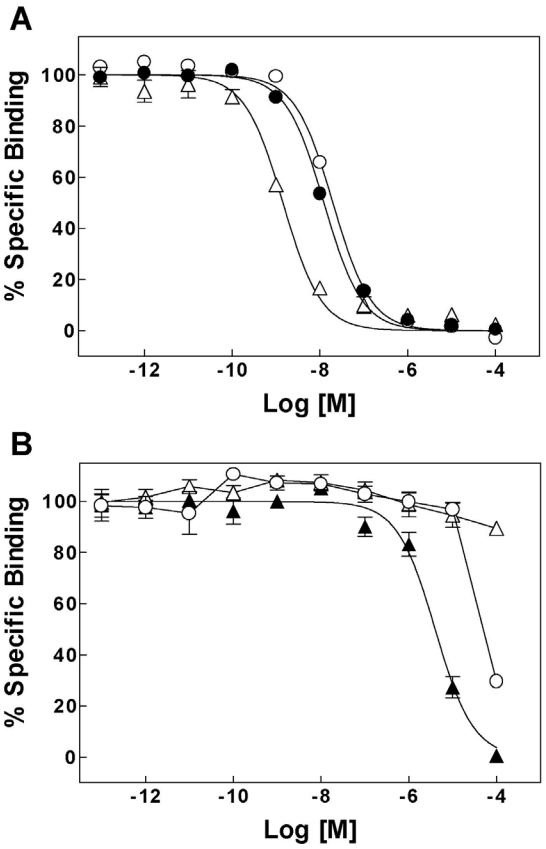

Fig. 2. Inhibition of specific [^{125}I] [Sar^1, Ile^8]-AII binding to human recombinant AT_1 **(A)** and of specific [^{125}I] CGP 42112A binding to human recombinant AT_2 receptor **(B)** by KR-31125 (open circles), losartan (solid circles), L-158809 (open triangles) and PD-123177 (solid triangles), respectively. The dose-response curve for the inhibition of specific binding by these compounds was determined by incubating the radioligand with 10 concentrations of each compound in the medium of receptor source. The data points represent the mean±S.E.M of three separate experiments run in quadruplicate.

antagonist. The pattern of inhibitory sigmoidal curves represented by Hill coefficients for the inhibition by KR-31125, losartan and L-158809 were 1.07, 0.86 and 0.99, respectively. From the results of saturation binding assay using [^{125}I] [Sar^1, Ile^8]-AII in the presence of KR-31125 (1 nM) and losartan (10 nM), these two antagonists did not affect the total number of binding sites labelled by [^{125}I] [Sar^1, Ile^8]-AII, however, increased the dissociation constant of the radioligand by a factor of 1.17±0.31 with KR-31125 and 1.37±0.15 with losartan in a competitive mode (Fig. 3).

In vitro potency in rabbit aorta

In rabbit aorta, KR-31125 and losartan inhibited the AII-induced contractions in a concentration dependent manner, but with different patterns of antagonism (Fig. 4). The concentration-contractile response curve to AII were shifted rightward by different concentrations of KR-31125 (3×10^{-9}, 10^{-8}, 3×10^{-8} M), however, significant reductions in the maximum contractile responses by 34.5, 59.9 and 87.6% at each concentration of KR-31125 were observed. The calculated pK_B value was 7.63±0.28 (Fig. 4A). These reductions of the maximum contractile responses were not found in losartan (10^{-7}, 3×10^{-7} and 10^{-6} M), and produced a parallel rightward shift in the concentration-response curve. The calculated pA_2 value was 7.59±0.12 with the Schild plot slope of 1.34±0.14 (Fig. 4B). With 1 μM concentration, KR-31125 did not change the pattern of concentration response curve to norepinephrine, $PGF_{2\alpha}$, serotonin and histamine in rabbit aortic preparations (Fig. 5).

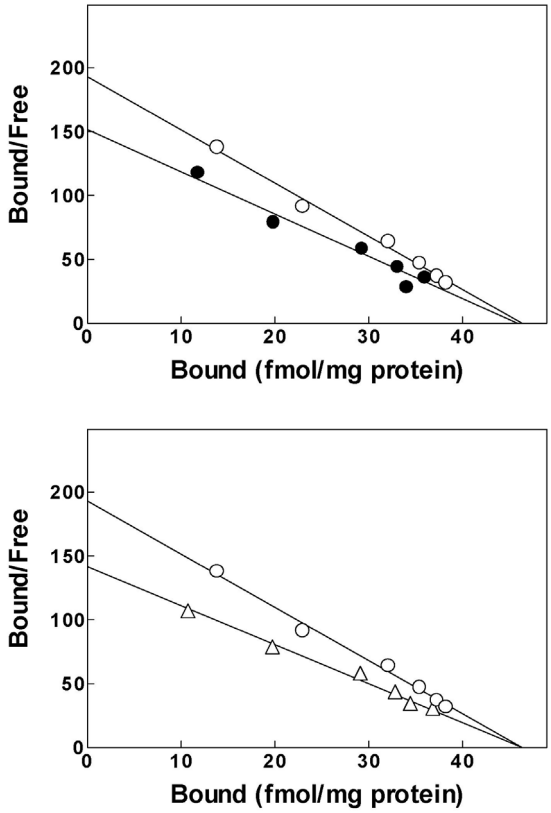

Fig. 3. Scatchard transformations of saturation binding data for specific [^{125}I] [Sar^1, Ile^8]-AII binding to human recombinant AT_1 receptor in the absence (open circles) or presence of KR-31125 (1 nM, solid circles) and losartan (10 nM, open triangles). The data points represent the mean of three separate experiments run in quadruplicate.

Discussion

After the discovery of losartan, the first AT_1 selective receptor antagonist, many me-too candidates had been developed and marketed as antihypertensive therapeutics. However, follow up studies for the use of these antagonist compounds have not been reported as the most trials of AT_1 receptor antagonists were focused only on drug candidates. For the fields of receptor research especially in the well established receptor system such as AII pathway, ligands that can modulate receptor functions are very important tools in various applications based on their structural novelty. Currently, receptor specific ligands have been applying to non-invasive diagnostic studies [9,22-24], cell imaging [1,10], non-radioactive receptor binding tests (Tag-lite technology by Cisbio, Bedford, USA). Therefore, it would be meaningful to revisit the AT_1 selective receptor antagonists to check the adaptability into the recent applications.

The present study presented results from *in vitro* studies of KR-31125 showing that it is a potent and selective AT_1 antagonist comparable to losartan. KR-31125 inhibited the binding of the specifically bound [^{125}I] [Sar^1, Ile^8]-AII in human recombinant angiotensin AT_1 receptor with similar potency to losartan without interaction with human recombinant angiotensin AT_2 receptor, whereas PD 123177, an AT_2 selective antagonist, inhibited the binding of the specifically bound [^{125}I] CGP 42112A. The statistical analysis of the competition curve showed that the binding of KR-31125 represented a pattern of monophasic inhibition implying the interaction with a single class of AT_1 receptor. In the further studies with radioligand saturation experiments, KR-31125 resulted an increase in dissociation constant of [^{125}I] [Sar^1, Ile^8]-AII without reduction in the maximum binding capacity

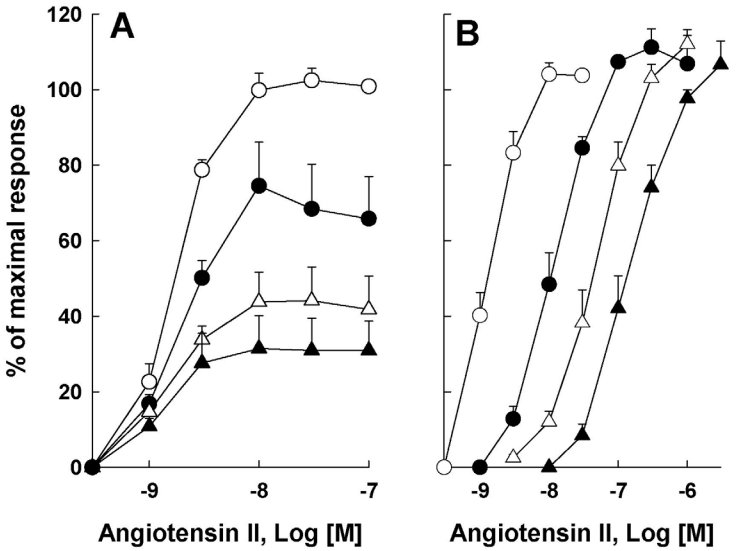

Fig. 4. Effects of KR-31125 and losartan on the concentration-contractile response curve to AII in isolated rabbit aorta. A: KR-31125: Vehicle (open circles), 3×10^{-9} M (solid circles), 10^{-8} M (open triangles), 3×10^{-8} M (solid triangles). B: Losartan: Vehicle (open circles), 10^{-7} M (solid circles), 3×10^{-7} M (open triangles), 10^{-6} M (solid triangles). The data points represent the mean percentage of the maximal response±S.E.M. (n=4-8).

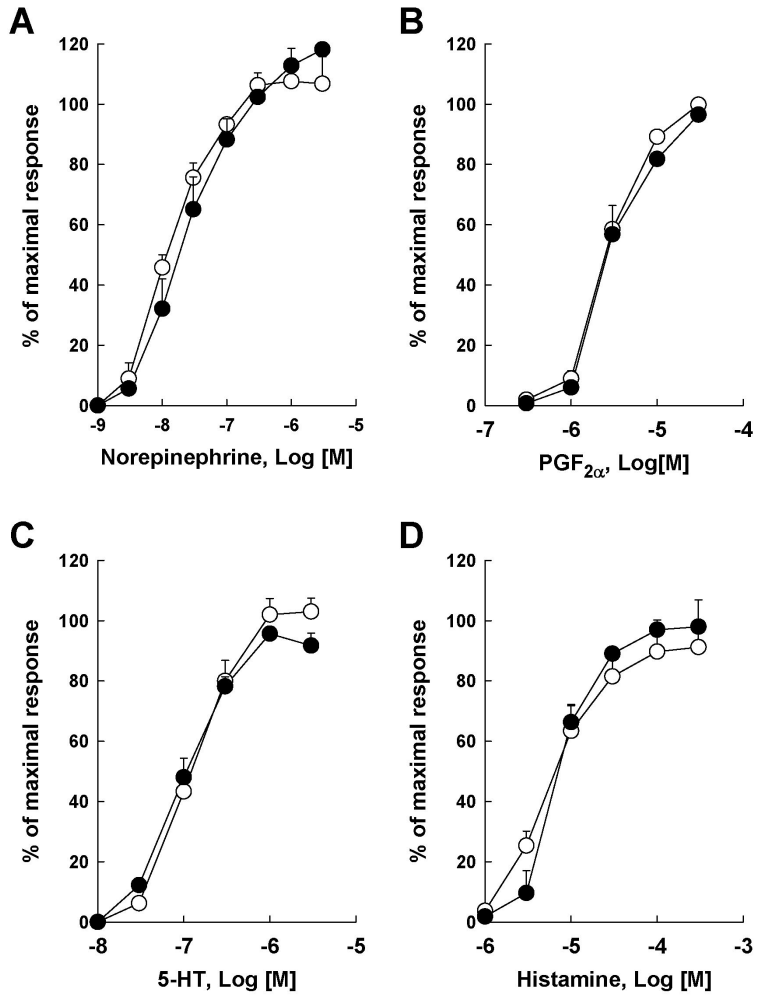

Fig. 5. Effects of vehicle (open circles) and KR-31125 (10^{-6} M, solid circles) on the concentration-contractile response curve to norepinephrine **(A)**, $PGF_{2\alpha}$ **(B)**, serotonin **(C)** and histamine **(D)** in isolated rabbit aorta. The data points represent the mean percentage of the maximal response±S.E.M. (n=4-5).

(B_{max}) of human recombinant AT_1 receptor suggesting that KR-31125 competitively interacted with AT_1 receptors as for losartan.

From *in vitro* functional studies, KR-31125 resulted a rightward shift in the concentration-response curve to AII with a reduction of maximal contractile response by 30 to 80%, suggesting an insurmountable antagonism of AII-induced contraction as seen in BIBR277, GR138950 or EXP3174 [7,16]. These reduced maximum contractile responses were well contrasted with losartan that exerted a parallel rightward shift in the concentration response curve without any changes in the maximal contractile response in rabbit aorta. Previous explanations for this insurmountable antagonism exhibited by AT_1 receptor antagonists were a slow dissociation of the receptor-antagonist complex and allosteric modification of receptors [11,17]. In case of imaging applications, these slow dissociation effects can be a strong point for the development of tracer molecules. The selective and specific interaction of KR-31125 with AII receptors was further substantiated by the results from the functional experiments demonstrating no effects of KR-31125 on the contractile response to norepinephrine, $PGF_{2\alpha}$, serotonin and histamine in the isolated rabbit aorta.

With upcoming results from *in vivo* experiments, pharmacological characteristics of pyridyl imidazole compounds including KR-31125 will be clear enough to expand their possibility for the development of useful ligands to study renin-angiotensin-aldosterone system by fluorescence or radioactive components. In summary, the results from the present study with *in vitro* binding and functional experiments presented that KR-31125 is a potent and selective nonpeptide AT_1 receptor antagonist suggesting its use as a tracer molecule for the research of renin-angiotensin-aldosterone system *in vivo* and *in vitro*.

Acknowledgement

The author would like to thank research teams at Bio-organic science division and pharmacology research center at KRICT for their excellent cooperation.

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초록 : 안지오텐신 수용체 길항제 KR-31125의 특성에 관한 연구

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KR-31125는 피리딜 이미다졸 시리즈 화합물로서 비펩타이드 안지오텐신 수용체 길항제로 새롭게 개발되었다. 동위원소 리간드를 사용한 재조합 수용체 결합실험과 기능성 토끼혈관실험 결과 기존 의약인 로자탄과 동등수준의 수용체 길항효과를 나타내었다. 이러한 KR-31125의 특징들은 제 1형 안지오텐신 수용체에 특이적으로 나타났으며(IC_{50}: 19.72±2.65 nM), 표준물질에 대한 대조실험 결과 제 2형 안지오텐신 수용체에 대한 결합친화력은 발견되지 않았다. 기능성 혈관실험에서 KR-31125가 안지오텐신에 의한 혈관수축 효과를 경쟁적으로 저하시켰지만 표준물질인 로자탄과는 달리 농도가 증가함에 따라 30-80% 정도의 최대 수축효과 감소가 관찰되어 로자탄과는 다른 분자작용 기전을 가진다고 판단된다. 제 1형 안지오텐신 수용체에 선택적으로 작용하는 것으로 나타난 KR-31125는 레닌-안지오텐신-알도스테론 시스템에 대한 연구 및 진단에 폭 넓게 활용될 수 있는 표지자 화합물로 가능성을 넓혀 줄 수 있을 것이라고 판단된다.