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Pharmacological Profile of KR-31125, an Orally Active AT_1 Receptor Antagonist

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In vivo studies of 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) were performed in pithed rats, conscious angiotensin II (AII) challenged normotensive rats, renal hypertensive rats (RHRs) and furosemide-treated beagle dogs. KR-31125 induced a non-parallel right shift in the dose-pressor response curve to AII (ID_{50}: 0.095 mg/kg) with a dose-dependent reduction in the maximum responses in pithed rats. Compared to losartan, this antagonistic effect was about 18 times more potent, presenting competitive antagonism. Other agonists such as norepinephrine and vasopressin did not alter the responses induced by KR-31125. Orally administered KR-31125 had no agonistic effect and dose-dependently inhibited the pressor response to AII with a slightly weaker potency (ID_{50}: 0.25 and 0.47 mg/kg, respectively) in the AII-challenged normotensive rat model, but with a more rapid onset of action than losartan (time to E_{max}: 30 min for KR-31125 and 6 hr for losartan). KR-31125 produced a dose-dependent antihypertensive effect with a higher potency than losartan in RHRs, and these effects were confirmed in furosemide-treated dogs where they presented a dose-dependent and long-lasting (>8 hr) antihypertensive effect with a rapid onset of action (time to E_{max}: 2-4 hr), as well as a 20-fold greater potency than losartan. These results suggest that KR-31125 is a potent, orally active AT_1 receptor antagonist that can be applied to the development of new diagnostic and research tools as an added exploratory potential of AT_1 receptor antagonist.

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

Introduction

The renin angiotensin aldosterone system (RAAS) plays a key role in the development and pathophysiology of hypertension and cardiovascular disease [11]. Although there are other angiotensin peptides with biological effects, angiotensin II (AII) is the major end product of the RAAS [2]. Among receptors for AII, AT_1 and AT_2, AT_1 receptors have been localized in the kidney, heart, vascular smooth muscle cells, brain, adrenal gland, platelets, adipocytes, and placenta. AT_2 receptors are present only at low levels, mainly in the uterus, the adrenal gland, the central nervous system, the heart (cardiomyocytes and fibroblasts), and the kidney [7,14]. However, all the known clinical effects of AII are mediated by the AT_1 receptor as the physiological role of AT_1 receptors is very well documented experimentally and clinically.

In recent years, numerous orally active, selective AT_1 receptor antagonists have been synthetized [15]. As the first drug developed and marketed as an AT_1 receptor antagonist [4,17], losartan is an orally active competitive AII receptor antagonist with selectivity for AT_1 subtype in animals [16,18] and humans [5,10]. It was derived from the Takeda series of 1-benzylimidazole-5-acetic acid derivatives recognized to be weak AII antagonists and has a major active metabolite, EXP 3174 [17,19]. This metabolite is 10 to 20 times more potent than losartan and has a longer duration of action than losartan. Up to date, more than 6 nonpeptide AT_1 receptor antagonists have launched for the treatment of hypertension and other compounds may be to come in the future.

In addition to these drug discovery efforts in the field of AT_1 receptor research, probing molecular changes is expected to assist diagnosis to support prediction, the evaluation of treatment success, and basic research trials for RAAS. These applications of AII receptor antagonists include ongoing trials for noninvasive diagnostics as in positron emission tomography imaging [12,20,22]. Therefore, it is meaningful to consider revisiting AT_1 receptor antagonists as new diagnostic and research tools. 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, US patent #5691348), synthesized in the Korea Research Institute of Chemical Technology (KRICT, Daejeon, Korea), belongs to a novel

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class of nonpeptide AII receptor antagonists with a high affinity for AT_1 receptors. In terms of the development of a biologically active ligand, KR-31125 has a strong point over losartan as it acts by itself but not via its metabolites (data not shown) to exert a potent insurmountable antagonism against contractile responses to AII in various *in vitro* studies (submitted to J. Life Science). Adding to the information that KR-31125 interacted with human recombinant AT_1 receptor in a competitive manner as with losartan (submitted to J. Life Science), the pharmacological profile of KR-31125 was examined in various *in vivo* systems including pithed rats, conscious normotensive rats (AII-challenged), renal hypertensive rats (RHRs), and furosemide-treated dogs.

Materials and Methods

Chemicals

KR-31125 and losartan [18] were synthesized at the Bio-Organic Science Division, KRICT, and were dissolved in 0.05 N KOH in saline and suspended in Tween 80 for intravenous and oral administration, respectively. Ketamine hydrochloride was purchased from Yuhan Co. (Seoul, Korea), and AII acetate from Sigma Chemical Co. (St. Louis, MO, U.S.A.). All chemicals were prepared just before use.

In vivo potency and specificity as AII antagonist in pithed rats

All animal studies conformed to the *Guide for the Care and Use of Laboratory Animals,* published by the U.S. National Institute of Health. Male Sprague-Dawley rats (350-450 g, KRICT) were anesthetized with sodium pentobarbital (35 mg/kg, *i.p.*). After a tracheotomy was performed, artificial ventilation with room air was initiated with rodent ventilator (model 7025, Ugo Basile, Varese, Italy; frequency: 60 cycles/min; stroke volume: 1 ml/100 g body weight). Two polyethylene (PE-50) catheters connected to PE-10 catheter that were filled with heparinized saline solution (20 IU/ml) were inserted into the left femoral artery and vein for recording arterial blood pressure and drug administration, respectively. The arterial catheter was connected to an Isotec pressure transducer (Healthdyne, Georgia, U.S.A.) coupled to a Graphtec Linearcorder (model 3310, Graphtec Corp., Japan). Subsequently, the animals were pithed by inserting and driving a steel rod (2 mm in diameter) via the orbit and the foramen magnum down into the whole length of the spinal canal [6]. The animals were kept warm at 37°C by means of a thermostat-controlled heating pad. Arterial blood pressure was continuously recorded through the whole experiment.

Forty minutes after surgery, when consistent control values for blood pressure were possible to obtain, the experiment was commenced. To construct the dose-pressor response curve for AII, AII (0.01-1,000 μg/kg/0.1 ml, *i.v.*) was injected cumulatively with each successive injection given immediately after the maximal effect of the preceding dose was reached (10-20 sec). After each injection, the catheter was flushed with 0.2 ml of saline. Only one full dose-response curve was obtained in each rat. Fifteen minutes before injection of AII, the animal was pretreated with a single *i.v.* dose of KR-31125 (0.03, 0.1 and 0.3 mg/kg), losartan (1, 3 and 10 mg/kg) and vehicle (0.05 N KOH, 1 ml/kg). A similar protocol was also carried out with norepinephrine, and vassopressin to determine specificity of KR-31125. Full dose-pressor response curves for norepinephrine (0.01 - 100 μg/kg, *i.v.*) and vasopressin (0.01 - 30 IU/kg, *i.v.*) were determined in pithed rats pretreated with KR-31125 (0.3 mg/kg, *i.v.*) or vehicle (0.05 N KOH, 1 ml/kg). The results were expressed as mmHg of diastolic arterial blood pressure. The doses (ID_{50}) of compounds that inhibited by 50% the pressor response to AII (10 μg/kg, *i.v.*) were calculated by linear regression as an indirect measure of antagonism.

Effects in conscious AII-challenged normotensive rats

Male Sprague-Dawley rats (300-350 g, KRICT) were used in this study and the arterial blood pressure was measured as previously described [9]. Briefly, AII (0.1 μg/kg/250 μl) was intravenously administered twice at 20 min intervals to establish a reproducible control AII pressure response. After each injection, the catheter was flushed with 0.2 ml saline. Each rat was then treated with a single oral dose of KR-31125 (0.1, 0.3, 1 mg/kg), losartan (0.1, 0.3, 1, 3 mg/kg) or vehicle (5% Tween 80, 2 ml/kg). After oral administration of test compound, AII was subsequently injected at 30 min intervals for 2 hr and then at 1 hr intervals for the next 6 hr. AII challenges were also repeated 24 hr after oral administration. Results were expressed as percentage inhibition from control responses. The ID_{50} values of compounds, doses that inhibited the maximal AII-induced pressor response by 50%, were determined by linear regression of log dose-response data.

Antihypertensive effects in conscious RHRs

For preparing RHRs, the left renal artery of Sprague-Dawley rats (300-350 g, KRICT) was completely ligated under ketamine (125 mg/kg, i.p.) anesthesia. They were fed normal diet and water *ad libitum* for one week in plastic cages in rooms maintained on 12 hour-light/dark cycles. To measure the arterial blood pressure from RHRs, the animals were prepared as described above and kept moving free in individual cages in a quiet room on the day of the experiment. Then, the arterial catheter was connected to a pressure transducer (CDX-III, Modular Ins., Malvern, PA, U.S.A.) coupled to a physiograph (Modular 8,000 Signal processor, Modular Ins.), and resulting parameters being analyzed and stored by Biowindow program (Modular Ins.). Arterial blood pressure was monitored for 6 hr after single oral administration of KR-31125 (0.3, 1 mg/kg) and losartan (3 and 10 mg/kg). Results were expressed as percentage change from control mean arterial pressure (MAP). The ED_{20} values of compounds, doses that decreased the maximal MAP by 20%, were obtained from linear regression of log dose-response data.

Antihypertensive effects in furosemide-treated dogs

Male beagle dogs (8-12 kg, Samyook Experimental Animal Co., Suwon, Korea) were anesthetized by intravenous injection of sodium pentobarbital (30 mg/kg) into the left cephalic vein. Under the aseptic conditions, the left femoral artery was cannulated with a special chronic catheter device filled with heparin (1,000 IU/ml). The catheter was exteriorized through a subcutaneous tunnel at the back of neck. Two days after catheter implantation, animals were trained to stand in a sling (Daejong Co., Seoul, Korea) for continuous measurement of arterial blood pressure via a Grass P23XL pressure transducer (Grass Ins., Quincy, MA, U.S.A.) followed by continuous recording on a Gould 2,000 physiograph (Gould Inc., Cleveland, OH, U.S.A.). To elevate their plasma renin activity, animals were treated with furosemide at 10 mg/kg twice 18 (given *i.m*) and 2 hr (given *i.v.*) before the experiment, as previously described by Wong et al. [16]. Food and water were withdrawn from these dogs after the first dose of furosemide. Arterial blood pressure was monitored for 8 h after single oral administration of KR-31125 (0.1, 0.3, 1 mg/kg) and losartan (3, 10, 30 mg/kg). Results were expressed as percentage change from control MAP. The ED_{20} values of compounds, doses that decreased the maximal MAP by 20%, were calculated by applying linear regression analysis to log dose-response data.

Statistical analysis

All values are expressed as mean±S.E.M. Data were analyzed by one-way analysis of variance (ANOVA) followed by the Dunnett's test for multiple comparisons (Sigma Stat, Jandel Co., San Rafael, CA, U.S.A.). In all comparisons, the difference was considered to be statistically significant at $p<0.05$.

Results

In vivo potency and specificity of AII antagonist in pithed rats

The mean diastolic arterial pressure was 30.9±4.8 mmHg in pithed rats treated with vehicle (control group) under the experimental conditions used. Baseline values for diastolic arterial pressure were similar in all groups of pithed rats. Cumulatively administered AII induced a gradual increase in diastolic arterial pressure with dose (E_{max}: 112.0±7.5 mmHg; ED_{50}: 0.68±0.05 μg/kg) (Fig. 1A). When KR-31125 was pretreated (0.03, 0.1 and 0.3 mg/kg, *i.v.*), it did not significantly affect diastolic arterial pressure (30.3±5.1, 30.4±3.1 and 30.5±5.1 mmHg, respectively). KR-31125 not only presented a dose-dependent rightward shift in the dose-pressor response curve to AII with ID_{50} value of 0.095 mg/kg, but also significantly decreased the maximal pressor response to AII (E_{max}: 102.0±8.6, 77.0±11.4 and 13.3±3.1 mmHg at 0.03, 0.1 and 0.3 mg/kg, respectively). In case of Losartan (1.0, 3.0 and 10.0 mg/kg, *i.v.*), it slightly lowered diastolic arterial pressure (33.9±3.2, 30.4±1.3 and 23.0±1.4 mmHg, respectively) with dose dependent shift of the dose-pressor response curve to AII in a parallel manner with ID_{50} value of 1.74 mg/kg without any change in the maximal response to AII unlike KR-31125 (Fig. 1B). Especially, KR-31125 did not alter the dose-response curves to norepinephrine and vasopressin at a dose of 0.3 mg/kg *i.v.* (Fig. 2).

Effects in conscious AII-challenged normotensive rats

AII (0.1 μg/kg i.v.) increased diastolic arterial pressure by 45±4 mmHg in conscious normotensive rats. The pressor response was not attenuated during the 24 hr observation period in the vehicle-treated group. Basal arterial blood pressure was not changed by KR-31125 and losartan at any oral doses tested. At the concentrations of 0.1, 0.3 and 1 mg/kg, *p.o*, KR-31125 inhibited the AII-induced pressor response in

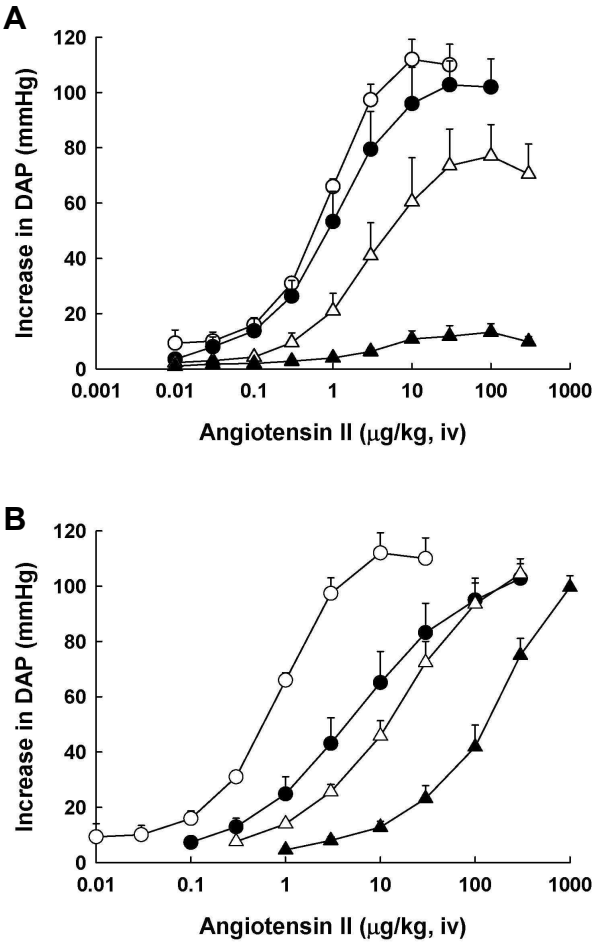

Fig. 1. Effects of intravenously administered KR-31125 **(A)** and losartan **(B)** on the log dose-pressor response curve to AII in anesthetized pithed rat. KR-31125: Vehicle (open circles), 0.03 (solid circles), 0.1 (open triangles) and 0.3 mg/kg (solid triangles). Losartan: Vehicle (open circles), 1.0 (solid circles), 3.0 (open triangles) and 10.0 mg/kg (solid triangles). The data points represent the mean± S.E.M. (n=6-9).

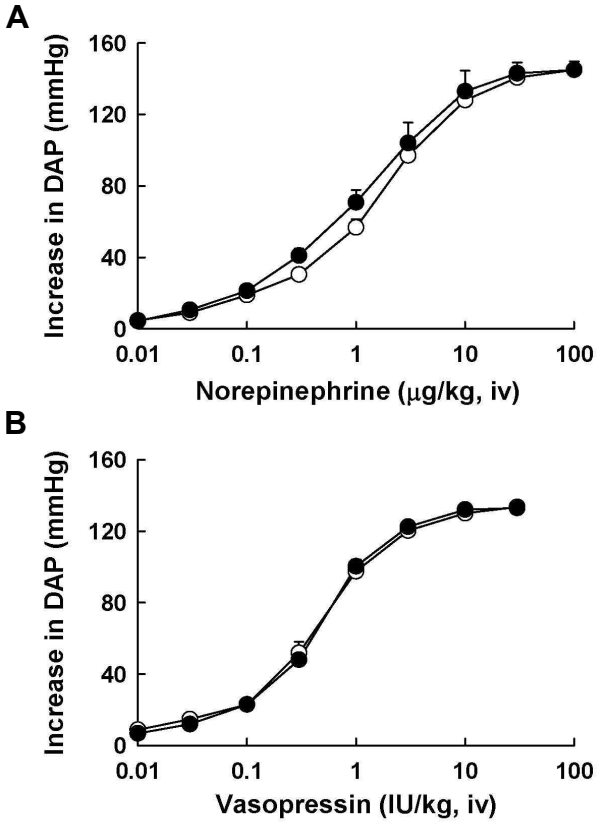

Fig. 2. Effects of intravenously administered vehicle (open circles) and KR-31125 at 0.3 mg/kg (solid circles) on the log dose-pressor response curve to norepinephrine **(A)** and vasopressin **(B)** in anesthetized pithed rat. The data points represent the mean±S.E.M. (n=5-6).

a dose-dependent manner with a rapid onset of action (Fig. 3). Unlike losartan, the first peak effect (E_{max}) of compound was reached 30 min after the administration of higher doses. When orally administered, losartan (0.1, 0.3, 1 and 3 mg/kg, *p.o.*) also inhibited the AII-induced pressor response in a dose dependent manner with a peak response observed between 6-8 hr postdose and the peak inhibitory effect remained unchanged at 24 hr postdose at all doses used except the highest dose (ID_{50} values for KR-31125 and losartan were 0.25±0.06 and 0.47±0.15 mg/kg, respectively).

Antihypertensive effects in conscious RHRs

The results from the oral administration of KR-31125 (0.3 and 1 mg/kg) on MAP in conscious RHRs were shown in Fig. 4A. KR-31125 produced a dose dependent decrease in MAP with a gradual onset of the effect (10 min). The maximum response was reached 4-6 hr postdose depending on the dose used (E_{max}: 45.7% at 1 mg/kg). Persisting antihypertensive effects of KR-31125 were found even at 24 hr postdose at all doses although not significant. In case of losartan (3 and 10 mg/kg) on MAP in conscious RHRs, it produced a dose dependent decrease in MAP (ED_{20} value: 3.36±1.02 mg/kg) with a similar pattern of time course to KR-31125 (time to the onset of the effect and the maximum, Fig. 4B). Losartan maintained antihypertensive effects at 24 hr postdose even at a more significant level.

Antihypertensive effects in furosemide-treated dogs

Oral administration of KR-31125 (0.1, 0.3 and 1 mg/kg) produced a dose dependent decrease in MAP with a gradual onset of the effect (10 min) in furosemide-treated dogs (Fig. 5A). The maximal effect was reached at 2-4 h postdose (E_{max}:

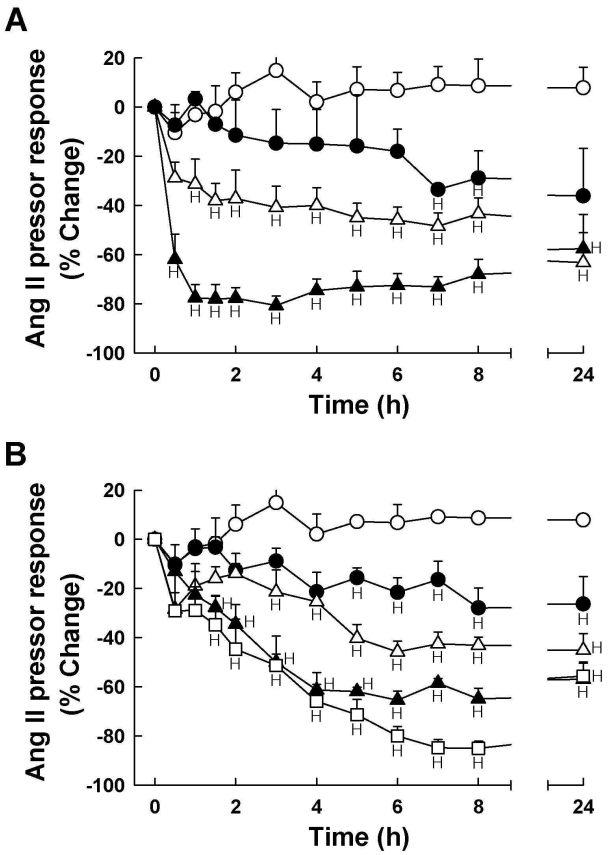

Fig. 3. The inhibitory effects of orally administered KR-31125 **(A)** and losartan **(B)** on the pressor response to AII (0.1 μg/kg, i.v.) in conscious normotensive rat. Vehicle (open circles), 0.1 (solid circles), 0.3 (open triangles), 1.0 (solid triangles) and 3.0 (open squares) mg/kg. The data points represent mean percentage change from control±SEM (n=6-9). $p<0.05$, significantly different from the control.

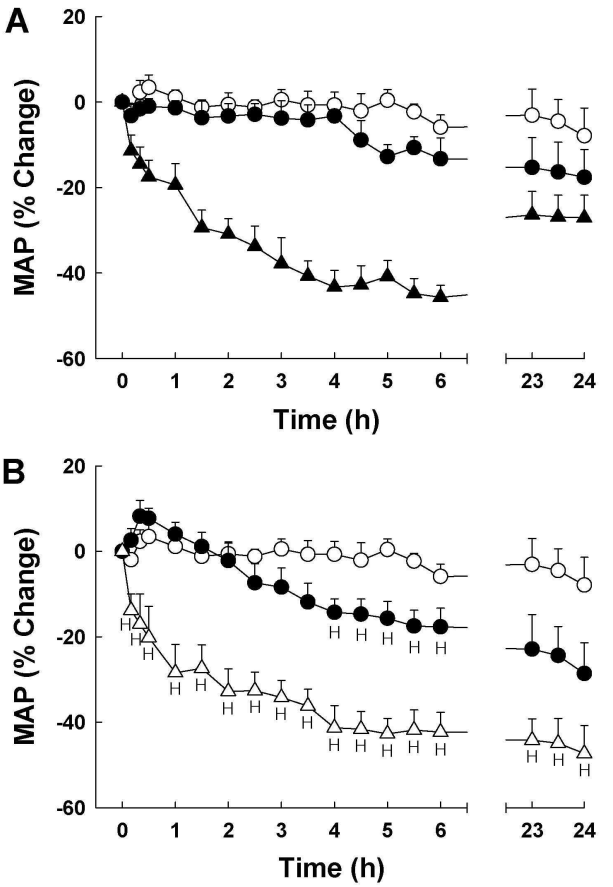

Fig. 4. Effects of orally administered KR-31125 **(A)** and losartan **(B)** on mean arterial pressure (MAP) in conscious renal hypertensive rat. KR-31125: Vehicle (open circles), 0.3 (solid circles), and 1.0 (solid triangles). Losartan: Vehicle (open circles), 3.0 (solid circles), 10.0 (open triangles) mg/kg. The data points represent mean percentage change from control±SEM (n=4-7). $p<0.05$, significantly different from the control.

8.7±1.4, 17.6±2.2 and 33.5±3.4% at 0.1, 0.3 and 1 mg/kg, respectively) and antihypertensive effects of KR-31125 lasted over 8 hr postdose. In case of the orally administered losartan (3, 10 and 30 mg/kg) for furosemide-treated dogs, it produced a dose dependent decrease on MAP with a gradual onset of action within 10 min (Fig. 5B). The maximum effects occurring at 1 hr at doses of 3 and 10 mg/kg and at 5 h postdose at 30 mg/kg (E_{max}: 10.7±2.5, 22.9±2.5 and 28.7±1.2% at 3, 10 and 30 mg/kg, respectively). Persisting antihypertensive effects of losartan (ED_{20}: 8.13±1.02 mg/kg) was observed up to 8 hr postdose ($p<0.05$).

Discussion

The discovery of specific AII receptor antagonists has confirmed the existence of various subtypes of AII receptors [14]. This includes losartan and PD 123177 as the representative antagonists for AT_1 and AT_2. Because of the therapeutic potential, there have been many reports for the development of AII antagonists, especially for the AT_1 receptor. Recently, research communities have started to track their use for experimental applications other than drug discovery trail. Some of those applications include non-invasive diagnostic studies [12,20-22], cell imaging [1,13], non-radioactive receptor binding tests (Tag-lite technology by Cisbio, Bedford, USA). Therefore, gathering pharmacological information for AT_1 receptor antagonists can provide the fundamental checkpoint for the use of AT_1 receptor antagonists as molecular probes that can target the receptor specifically.

The present study presented that KR-31125, a structurally novel nonpeptide AT_1 receptor antagonist, is an orally active, potent antihypertensive agent with long-lasting activity

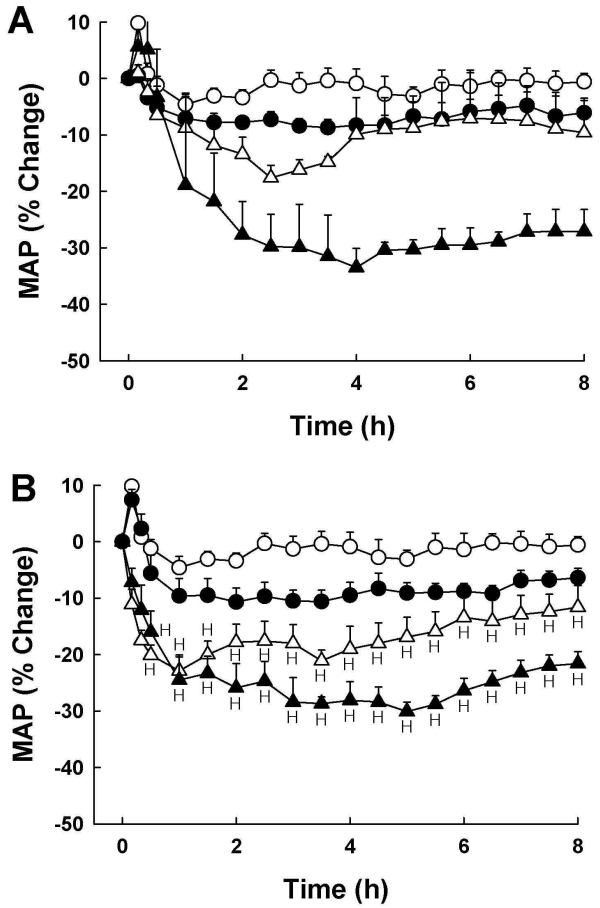

Fig. 5. Effects of orally administered KR-31125 **(A)** and losartan **(B)** on mean arterial pressure (MAP) in conscious furosemide-treated dog. KR-31125: Vehicle (open circles), 0.1 (solid circles), 0.3 (open triangles) and 1.0 (solid triangles) mg/kg. Losartan: Vehicle (open circles), 3.0 (solid circles), 10.0 (open triangles) and 30.0 (solid triangles) mg/kg. The data points represent mean percentage change from control±SEM (n=4-7). $p<0.05$, significantly different from the control.

in rats and dogs. In this report, the hemodynamic profile and the *in vivo* potencies of KR-31125 and losartan were compared in animal models of hypertension where the activated renin-angiotensin system was known to play an important role in the development and the maintenance of the blood pressure. The results from studies with anesthetized pithed rat, KR-31125 caused a rightward shift in the dose-pressor response curve to AII with a dose dependent reduction in the maximum pressor response to AII. However, losartan produced a rightward parallel shift in dose-pressor response curve to AII without reduction in the maximum response in pithed rat as reported by others [3,18]. In addition to the anesthetized pithed rat model, results from studies with conscious AII-challenged normotensive rat indicate the antagonistic action at AII receptor without any agonistic action. KR-31125 exerted a more rapid onset of action and a more rapid arrival at the maximum inhibitory effect compared with losartan. The inhibitory effect of KR-31125 sustained up to 24 hr after oral administration at all doses, whereas the peak inhibitory effect of losartan remained unchanged at 24 hr postdose except the highest dose. The findings from the conscious normotensive rat indicate that KR-31125 exerts long-lasting AII receptor antagonistic effects with a hemodynamic profile somewhat different from that of losartan, and the differences in hemodynamic profile between two compounds may be due to the difference in metabolic change and/or oral absorption, considering the *in vivo* generation of the active metabolite EXP 3174 after oral administration in this species [19]. The potential of KR-31125 as an AT_1 specific ligand was also evaluated in two different animal models; two-kidney, one-ligated RHRs, a high renin model, and the furosemide-treated conscious dogs [8]. In RHRs, orally administered KR-31125 and losartan produced dose dependent antihypertensive effects with a similar hemodynamic profile (gradual onset of the effect, time to E_{max} and long duration of >24 hr). In furosemide-treated dogs, another animal model with high plasma renin level [16], KR-31125 was about 20-fold more potent than losartan in its antihypertensive activity.

Together with *in vitro* experimental results, KR-31125 can be an important ligand to study RAAS and for the development of diagnostic probing tools to label with fluorescence or radioactive materials. In summary, the results from the present study indicate that orally administered KR-31125 exerted significant long-lasting antihypertensive effects in conscious RHRs with higher potency and similar pattern of time course to losartan. In furosemide-treated conscious dogs, orally administered KR-31125 was over 20-fold more potent than losartan in lowering blood pressure with a long duration of action up to 8 hr postdose. These pharmacologic *in vivo* profiles of KR-31125 indicate that this pyridyl imidazole compound is a potent, orally active AT_1 selective antagonist suggesting its use as a tracer molecule for the research of renin-angiotensin-aldosterone system *in vivo* and *in vitro*.

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초록 : 안지오텐신 수용체 리간드 KR-31125의 생체 내 활성에 관한 연구

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피리딜 이미다졸 시리즈의 비펩타이드 안지오텐신 수용체 리간드로 새롭게 개발된 KR-31125에 대한 생체 내 활성을 동물모델에서 검증하였다. 척수장애 동물모델에서 KR-31125는 비대칭 농도의존적으로 로자탄보다 18배 이상의 경쟁적인 혈압강하 효과를 나타내었으며, 기타 수용체 촉진제들의 영향을 받지 않았다. 안지오텐신으로 유도된 정상혈압 쥐모델에서는 대조화합물인 로자탄과 비교하여 경구효과는 동등하였으나 더 빠른 초기효과가 관찰되었다. 또한 신성고혈압 쥐모델에서 KR-31125는 로자탄보다 3배 이상의 지속형 혈압강하 효과를 나타내었고, 이뇨제를 투여하여 레닌을 활성화시킨 개실험 모델에서 KR-31125는 로자탄보다 20배 이상의 지속적인 경구 혈압강하 효과를 나타내었다. 이러한 KR-31125의 생체 내 활성특징은 대사물질을 통하여 효과를 발휘하는 로자탄과 달리 동일물질의 효과에 의한 것으로 고혈압 및 혈관질환과 깊은 관련이 있는 안지오텐신 조절시스템에 대한 세포영상, 비침투성 진단등의 도구물질로서 가능성이 높을 것으로 판단된다.