

Antihypertensive activity of KR-31081, an orally active nonpeptide AT₁ receptor antagonist

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안지오텐신 수용체 리간드 KR-31081의 생체 내 활성에 관한 연구

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Abstract The pharmacological profile of KR-31081, a newly synthesized AT₁ receptor antagonist, was evaluated in pithed rats, conscious renal hypertensive rats (RHRs) and conscious furosemide-treated beagle dogs. In pithed rats, KR-31081 (i.v.) induced a non-parallel right shift in the dose-pressor response curve to angiotensin II (ID₅₀: 0.05 mg/kg) with a dose-dependent reduction in the maximum responses; this antagonistic effect was about 40 times more potent than losartan (ID₅₀: 1.74 mg/kg) which showed competitive antagonism. KR-31081 did not alter the responses induced by other agonists such as norepinephrine and vasopressin. In RHRs, orally given KR-31081 produced a dose-dependent and long-lasting (>24 h) antihypertensive effect with a higher potency to losartan (ED₂₀: 0.30 and 3.36 mg/kg, respectively). In furosemide-treated dogs, orally given KR-31081 produced a dose-dependent and long-lasting (>8h) antihypertensive effect with a rapid onset of action (time to E_{max}: 1-1.5 h) and 20-fold greater potency than losartan (ED₂₀: 0.41 and 8.13 mg/kg, respectively). These results suggest that KR-31081 is a potent, orally active AT₁ receptor antagonist useful for the research and diagnostic tools as an added exploratory potential.

요약 비펩타이드성 안지오텐신 수용체 길항제로 새롭게 개발된 KR-31081에 대한 생체 내 활성을 세가지 동물모델에서 검증하였다. 척수장애 동물모델에서 KR-31081은 로사탄보다 40배 이상의 경쟁적인 혈압강하 효과를 나타내었으며, 신성고혈압쥐 모델에서 KR-31081은 로사탄보다 10배 가량의 지속형 효과를 나타내었다. 또한 개실험에서 구강 투여한 KR-31081은 로사탄보다 20배 이상의 지속적인 혈압강하 효과를 나타내었다. 실험에 사용된 동물 모델 시스템에서 다른 혈관조절물질들과 상호작용을 하지 않는 것으로 나타난 KR-31081은 향후 고혈압 및 혈관질환에 대한 연구 및 진단에 활용될 수 있을 것이라고 판단된다.

Key Words : KR-31081, Antihypertension, Angiotensin, AT₁ receptor antagonist, Receptor ligands, Diagnostics

1. Introduction

It is well known that the major pharmacologic actions of angiotensin II (AII), such as contraction of vascular smooth muscle, aldosterone release from the adrenal gland, and cell proliferation and hypertrophy of

cardiovascular tissues, are mediated by the AT₁ subtype [1, 2]. Therefore, AII receptor antagonists with selectivity for the AT₁ subtype are considered to be useful for the treatment of patients with hypertension accompanying cardiac hypertrophy and vascular thickening. Since the discovery of losartan, the first drug developed and

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marketed as an AT₁ receptor antagonist [3, 4], a growing number of angiotensin receptor antagonists have been introduced. A numerous studies have reported that losartan is an orally active competitive AII receptor antagonist with selectivity for AT₁ subtype in animals [5, 6] and humans [7, 8]. Losartan and its metabolite EXP3174 have been reported to antagonize AII in different ways, showing surmountable and insurmountable antagonism, respectively [4, 9].

Recently, the application of AII receptor antagonists has expanded to ongoing trials for noninvasive diagnostics as in positron emission tomography imaging [10-12], therefore upcoming AT₁ receptor antagonist candidates are important developments as new diagnostic tools in future.

In the present study, the pharmacological profile of KR-31081 was examined in various *in vivo* systems including pithed rats, conscious renal hypertensive rats (RHRs), and conscious furosemide-treated dogs.

2. Materials and Methods

2.1 Chemicals

KR-31081(2-butyl-5-dimethoxymethyl-6-(pyridin-2-yl)-3-[[2'-(1H-tetrazol-5-yl)biphenyl -4-yl]methyl]-3H-imidazo [4,5-b]pyridine, US patent #5691348) and losartan [3] 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.).

2.2 *In vivo* potency and specificity as AII antagonist in pithed rats

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 [13]. The animals were kept warm at 37°C by means of a thermostat-controlled heating pad. Arterial blood pressure and heart rate were continuously recorded through the whole experiment.

Forty minutes after surgery, when consistent control values for blood pressure and heart rate were possible to obtain, the experiment was commenced. To construct the dose-pressor response curve for AII, AII (0.01-1000 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-31081 (0.03, 0.06, and 0.1 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 vasopressin to determine specificity of KR-31081. Full dose-pressor response curves for norepinephrine (0.01 - 300 µg/kg, *i.v.*) and vasopressin (0.01 - 30 IU/kg, *i.v.*) were determined in pithed rats pretreated with KR-31081 (0.1 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 (ID₅₀) 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.

2.3 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 8000 Signal processor, Modular Ins.), and resulting parameters being analyzed and stored by Biowindow program (Modular Ins.). Arterial blood pressure was monitored for 6 h after single oral administration of KR-31081 (0.3, 1, 3 mg/kg) and losartan (3 and 10 mg/kg). Results were expressed as percentage change from control mean arterial pressure (MAP). The ED₂₀ values of compounds, doses that decreased the maximal MAP by 20%, were obtained from linear regression of log dose-response data.

2.4 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 2000 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 h (given *i.v.*) before the experiment, as previously described by Wong *et al.* [5]. 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-31081 (0.3, 1, 3 mg/kg) and losartan (3, 10, 30 mg/kg). Results were expressed as percentage change from control MAP. The ED₂₀ values of compounds, doses that decreased the maximal MAP by

20%, were calculated by applying linear regression analysis to log dose-response data.

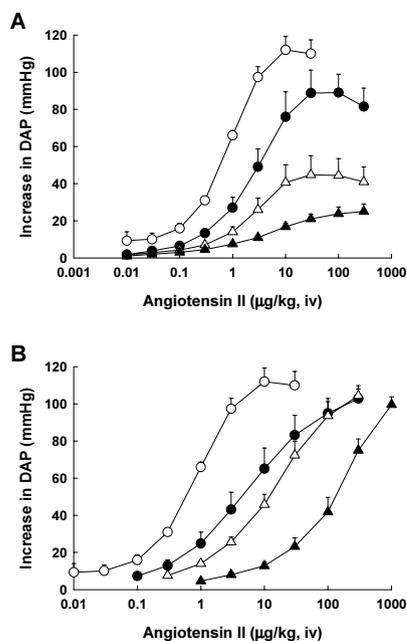
2.5 Statistical analysis

All values are expressed as mean \pm 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 $p < 0.05$.

3. Results

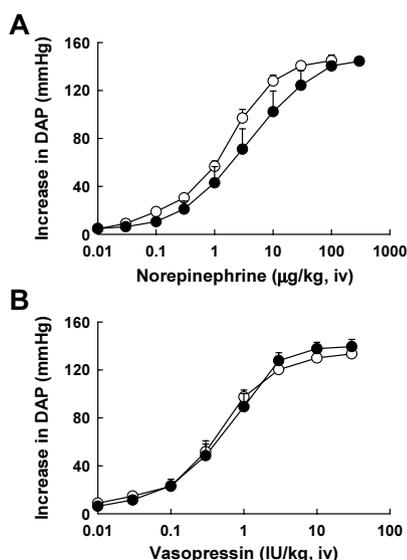
3.1 *In vivo* potency and specificity of All antagonist in pithed rats

In pithed rats treated with vehicle (control group) under the experimental conditions used, the mean diastolic arterial pressure was 30.9 ± 4.8 mmHg.



[Fig. 1] Effects of intravenously administered KR-31081 (A) and losartan (B) on the log dose-pressor response curve to AII in anesthetized pithed rat. KR-31081: Vehicle (open circles), 0.03 (solid circles), 0.06 (open triangles) and 0.1 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 \pm S.E.M. (n=6).

The 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 $\mu\text{g}/\text{kg}$, Fig. 1A). The pretreatment with KR-31081 (0.03, 0.06 and 0.1 mg/kg, *i.v.*) did not significantly affect diastolic arterial pressure (30.3 ± 5.1 , 30.4 ± 3.1 and 30.5 ± 5.1 mmHg, respectively). However, KR-31081 not only caused a dose-dependent rightward shift in the dose-pressor response curve to AII with ID_{50} value of 0.06 mg/kg, but also significantly decreased the maximal pressor response to AII (E_{max} : 89.0 ± 9.9 , 44.8 ± 10.3 and 25.0 ± 4.1 mmHg at 0.03, 0.06 and 0.1 mg/kg, respectively). Losartan (1.0, 3.0 and 10.0 mg/kg, *i.v.*) slightly lowered diastolic arterial pressure (33.9 ± 3.2 , 30.4 ± 1.3 and 23.0 ± 1.4 mmHg, respectively). Losartan dose-dependently shifted to the right the dose-pressor response curve to AII in a parallel manner with ID_{50} value of 1.74 mg/kg, but without any change in the maximal response to AII unlike KR-31081 (Fig. 1B). At a dose of 0.1 mg/kg *i.v.*, KR-31081 did not alter the dose-response curves to norepinephrine, vasopressin (Fig. 2).



[Fig. 2] Effects of intravenously administered vehicle (open circles) and KR-31081 at 0.1 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 \pm S.E.M. ($n=5-6$).

3.2 Antihypertensive effects in conscious RHRs

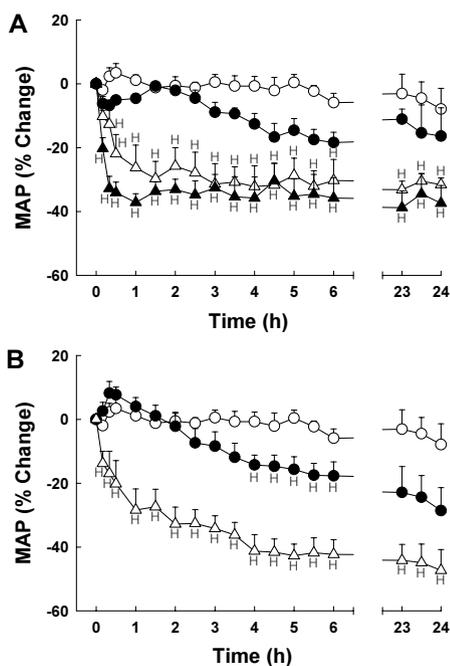
The effects of the orally administered KR-31081 (0.3, 1 and 3 mg/kg) on MAP in conscious RHRs were shown in Fig. 3A.

KR-31081 produced a dose-dependent decrease in MAP with a gradual onset of the effect (10 min), the maximum being reached 4-6 h postdose depending on the dose used (E_{max} : 38.8% at 3 mg/kg). The antihypertensive effects of KR-31081 persisted even at 24 h postdose at all doses although not significant (ED_{20} value: 0.30–0.18 mg/kg). Any significant change in HR was not noted during the period of antihypertensive effect (data not shown). The effects of the orally administered losartan (3 and 10 mg/kg) on MAP in conscious RHRs were shown in Fig. 3B. Losartan 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-31081 (time to the onset of the effect and the maximum). At 24 h postdose the antihypertensive effects of losartan were maintained even at a more significant level.

3.3 Antihypertensive effects in furosemide-treated dogs

The effects of the orally administered KR-31081 (0.1, 0.3 and 1 mg/kg) on MAP in furosemide-treated dogs were shown in Fig. 4A. KR-31081 produced a dose-dependent decrease in MAP with a gradual onset of the effect (10 min), the maximal effect being reached 1-1.5 h postdose (E_{max} : 17.1 ± 7.1 , 27.4 ± 8.6 and $34.4 \pm 1.3\%$ at 0.1, 0.3 and 1 mg/kg, respectively). The antihypertensive effects of KR-31081 (ED_{20} : 0.41 ± 0.17 mg/kg) lasted over 8 h postdose ($p < 0.05$), and these effects were not accompanied by any significant changes in HR at all doses used (data not shown). The effects of the orally administered losartan (3, 10 and 30 mg/kg) on MAP in furosemide-treated dogs were shown in Fig. 4B. Losartan produced a dose-dependent decrease in MAP with a gradual onset of action (within 10 min), the maximum effects occurring at 1 h 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 $28.7 \pm 1.2\%$ at 3, 10 and 30 mg/kg, respectively). The antihypertensive effects of losartan (ED_{20} : 8.13 ± 1.02 mg/kg) persisted at a significant level

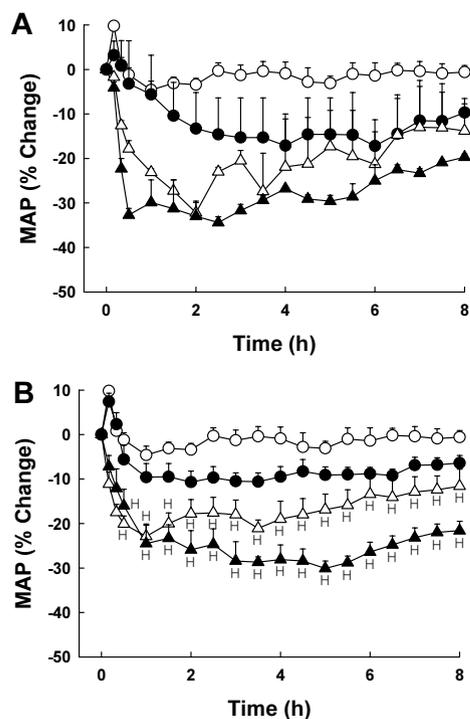
at 8 h postdose ($p < 0.05$).



[Fig. 3] Effects of orally administered KR-31081 (A) and losartan (B) on mean arterial pressure (MAP) in conscious renal hypertensive rat. KR-31081: Vehicle (open circles), 0.3 (solid circles), 1.0 (open triangles) and 3.0 mg/kg (solid triangles). 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 \pm SEM ($n=4-7$). $p < 0.05$, significantly different from the control.

4. Discussion

The results from the present study indicate that KR-31081, a structurally novel nonpeptide AT₁ receptor antagonist, is an orally active, potent antihypertensive agent with long-lasting activity in rats and dogs. In this study, the hemodynamic profile and the *in vivo* potencies of KR-31081 and losartan were compared in several 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.



[Fig. 4] Effects of orally administered KR-31081 (A) and losartan (B) on mean arterial pressure (MAP) in conscious furosemide-treated dog. KR-31081: 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 \pm SEM ($n=4-7$). $p < 0.05$, significantly different from the control.

The results from studies with anesthetized pithed rat, KR-31081 caused a rightward shift in the dose-pressor response curve to AII with a dose-dependent reduction in the maximum pressor response to AII. By contrast, 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 [6, 14].

In the second series of experiments, the potential of KR-31081 as a novel antihypertensive agent was evaluated in two different animal models; two-kidney, one-ligated RHRs, a high renin model, and the furosemide-treated conscious dogs. In RHRs, orally administered KR-31081 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 h). The oral antihypertensive effects of KR-31081 were greater than that of losartan in RHRs. The antihypertensive effects of KR-31081 were further studied in furosemide-treated conscious dogs, another animal model with high plasma renin level [5], to compare the results with those from the rat model of hypertension. In furosemide-treated dogs, KR-31081 was about 20-fold more potent than losartan in its antihypertensive activity in furosemide-treated dogs, probably due to much better bioavailability in dogs (*p.o.* ED₂₀: 0.41 and 8.13 mg/kg, respectively).

Despite the potent antihypertensive activity of KR-31081 in rats and dogs, reflex tachycardia was not observed unlike other types of antihypertensive drugs including β -adrenoceptor blocking agents, calcium channel blockers and potassium channel activators [15-17]. Although the lack of reflex tachycardia in the presence of reduced blood pressure is also observed with blockers of the renin-angiotensin system such as angiotensin-converting enzyme inhibitors and AII receptor antagonists [6, 18-19], the underlying mechanism is still unclear except the possibilities of venous dilatation, the enhanced vagal tone or reduction of the sympathetic baroreceptor response [18]. Together with *in vitro* experimental results, KR-31081 can be an important ligand to study rennin-angiotensin-aldosterone system and for the development of diagnostic tools labeled by fluorescence or radioactive molecules.

In summary, the results from the present study indicate that orally administered KR-31081 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-31081 was over 20-fold more potent than losartan in lowering blood pressure with a long duration of action at least up to 8 h postdose. All these pharmacologic profiles of KR-31081 indicate that KR-31081 is a potent, orally active AT₁ selective receptor antagonist. The research and diagnostic potential of the compound as a novel AT₁ receptor ligand awaits further evaluation in upcoming exploratory studies.

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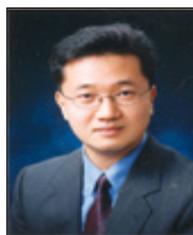
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<Research Interests>

High throughput screening, GPCR biochemistry