

## 신성고혈압 흰쥐 대동맥 평활근에서 세포외 칼륨에 의한 혈관이완반응의 변이

전제열<sup>1</sup> · 염철호<sup>1</sup> · 윤평진<sup>1</sup> · 이정희<sup>1</sup> · 최형호<sup>1</sup> · 박유환<sup>1</sup> · 김진호<sup>4</sup>

### Altered Vascular Response to the K<sup>+</sup>-induced Vasorelaxation in Aortic Smooth Muscle of Renal Hypertensive Rats

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#### ABSTRACT

**Background :** An increase of the extracellular K<sup>+</sup> concentrations up to about 8 mM in the isolated vessels causes relaxation in pre-contracted state. In order to elucidate the mechanisms of K<sup>+</sup>-induced relaxation and compare with that of 2-kidney, 1 clip (2K1C) renal hypertensive rats, we recorded aortic vascular tension using an organ bath study. **Methods :** 2K1C hypertension was made by clipping the left renal artery and age-matched control rats received a sham treatment. Thoracic aortic rings were mounted in tissue baths for measurement of isometric contractile force. **Results :** Exposure to K<sup>+</sup> (from 2 to 8 mM) relaxed a phenylephrine (2 × 10<sup>-6</sup> M)-induced contraction in K<sup>+</sup>-free Krebs-Ringer solution, dose-dependently. Ouabain (10<sup>-5</sup> M) enhanced the K<sup>+</sup>-induced relaxation in above 2 mM K<sup>+</sup>. The K<sup>+</sup>-induced relaxation was still induced in endothelium-denuded condition. Incubation with the K<sup>+</sup> channel blockers such as tetraethylammonium (TEA, 1 mM), glibenclamide (10<sup>-5</sup> M), 4-aminopyridine (3 mM), barium (5 mM) and cesium (2 mM) did not affect on the K<sup>+</sup>-induced relaxation. In renal hypertensive rats, the K<sup>+</sup>-induced relaxation was markedly suppressed and ouabain enhanced it. **Conclusions :** These results suggest that the K<sup>+</sup>-induced relaxation in aorta be mediated by Na-pump independent mechanisms, and the decrease of the K<sup>+</sup>-induced relaxation in the renal hypertensive rats may be a possible mechanism of hypertension. . (Korean Circulation J 2000;30(8):980-988)

**KEY WORDS :** K<sup>+</sup>-induced relaxation · Ouabain · Renal hypertensive rats.

#### 서 론

가

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: 2000 7 15  
: , 501 - 759

375

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가

(vasoactive substances)

1)2) ,

가 가

3) .

가

가

4) .

$K^+$

(resting membrane potential)

$K^+$  가

5) .

$K^+$  가

$K^+$  (K<sup>+</sup> - induced vasorelaxation)

6)7)  $Na^+ - K^+$  adenosinetriphos - phatase (ATPase)(Na - ) 가 가

ouabain 8)9) .

Na -

가 (volume expansion hypertension)

digitalis

Na - 10)11) .

가

$K^+$

가

12 - 14)

15 - 17)

$K^+$

Na -  $Ba^{2+}$

7)18) .

$K^+$

가

대상 및 방법

실험동물

2K1C

Spr -

ague - Dawley ( ) . 150

200 g phentobarbital(50 mg/kg, IP)

0.2 mm silver

clip .

1

4

혈압 및 혈관장력측정

2K1C

phentobarbital heparin

(400 IU/ml) polyethylene tube(PE

60) (press -

ure transducer, Gould, P23Db)

(physiography, Beckman, R511A)

(mean arterial pressure,

MAP) (diastolic pressure + pulse pressure/3)

95% O<sub>2</sub>

5% CO<sub>2</sub> Krebs - Ringer (NaCl 112,

KCl 5, NaHCO<sub>3</sub> 25, KH<sub>2</sub>PO<sub>4</sub> 1.2, MgSO<sub>4</sub> 1.2, ethylenediamine - tetraacetic acid(EDTA) 0.026, CaCl<sub>2</sub> 2.5, glucose 11.5 mM, pH 7.4)

가  
5 mm ring  
37 95% O<sub>2</sub> 5% CO<sub>2</sub> Krebs - Ringer 10 ml  
(force transducer, Grass FT03)  
20  
(passive tension) 2 g  
1

K<sup>+</sup>  
Krebs - Ringer K<sup>+</sup> phenyleph - rine(PE, 2 × 10<sup>-6</sup> M)  
가  
acetylcholine(10<sup>-6</sup> M)  
가  
PE  
가  
15

실험약물 및 통계

4 - Aminopyridine, TEA, barium chloride, cesium chloride, glibenclamide, ouabain, phenylephrine Sigma

meansSEM  
unpaired t - test , p<0.05

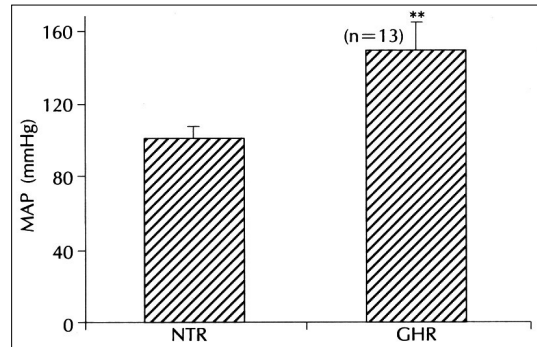
## 실험 결과

정상혈압쥐와 신성 고혈압쥐의 동맥혈압비교

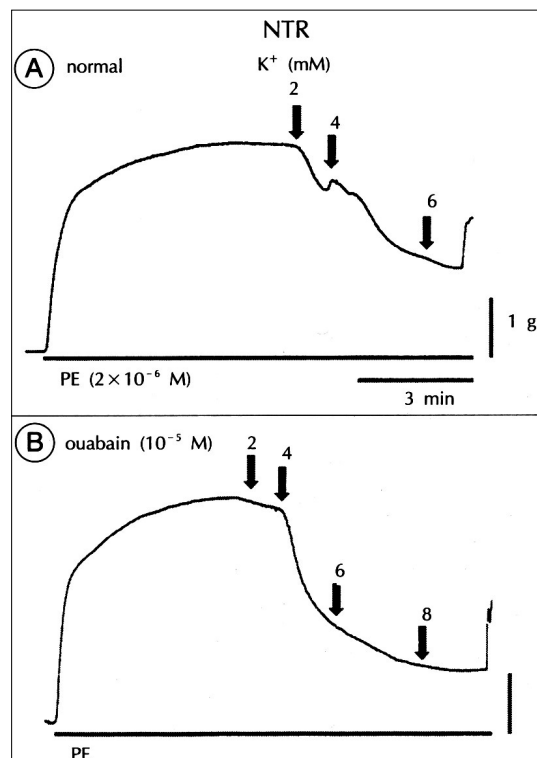
100 ± 5.1 mmHg(n = 15)  
2KIC  
154 ± 10.2 mmHg(n = 13)

가 (Fig. 1).

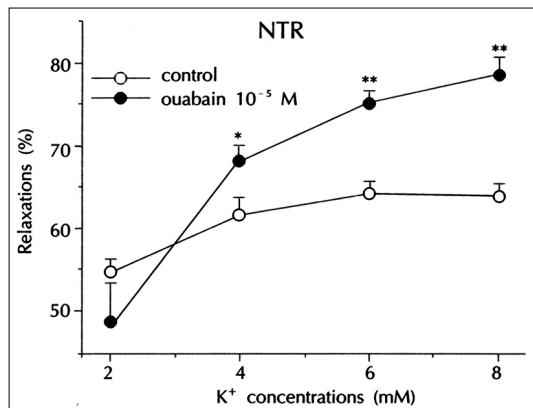
정상혈압 쥐 대동맥에서 K<sup>+</sup>으로 유발되는 혈관이완반응 PE(2 × 10<sup>-6</sup> M)



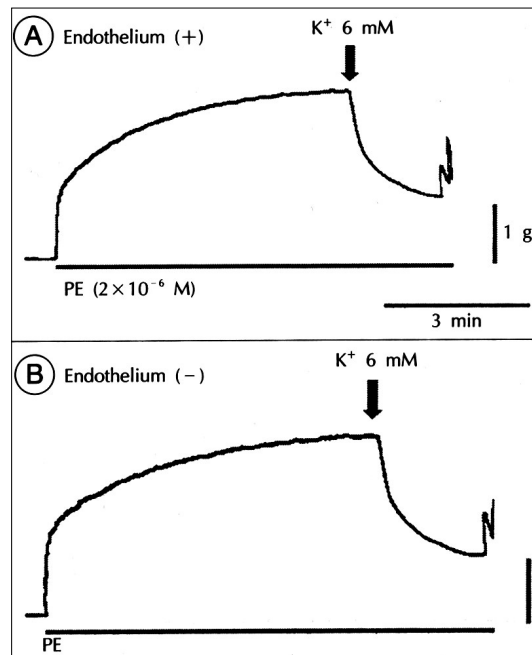
**Fig. 1.** Baselines for mean arterial pressure (MAP) in normotensive (NTR) and 2K1C Goldblatt hypertensive rats (GHR). Values represent mean ± SE. n = number of rats. \*\*p<0.01, compared with NTR.



**Fig. 2.** Tracing of K<sup>+</sup>-induced relaxation of aorta and ouabain effect in NTR. A : Addition of K<sup>+</sup> from 2 to 6 mM to the PE-induced contraction preincubated in K<sup>+</sup>-free solution resulted in relaxation, dose-dependently. B : Such an K<sup>+</sup>-induced relaxation was blocked to 2 mM K<sup>+</sup> whereas more enhanced to above 4 mM K<sup>+</sup>.



**Fig. 3.** A graph summarizing  $K^+$ -induced relaxation and ouabain effect from 2 to 8 mM concentrations in NTR ( $n=8$ ). Ouabain ( $10^{-5}$  M) inhibited  $K^+$ -induced relaxation at 2 mM  $K^+$  whereas increased it at above 4 mM  $K^+$ . Values represent mean  $\pm$  SE.  $n$  = number of rats. \* $p<0.05$ , \*\* $p<0.01$ , compared with control value at each  $K^+$  concentrations.



**Fig. 4.** Effects of endothelium on the  $K^+$ -induced relaxation of aorta in NTR. A : Addition of 6 mM  $K^+$  to the PE-induced contraction preincubated in  $K^+$ -free solution resulted in relaxation in the intact of endothelium. B : The  $K^+$ -induced relaxation was still induced in the removal of endothelium.

Fig. 2A and B

$K^+$

( $K^+$  - free solution) PE

가

$K^+$  2 6 mM

가

Na - 가

ouabain( $10^{-5}$

M) PE 15

2 mM

54  $\pm$  1.8%, 4 mM 62  $\pm$  2%, 6 mM

65  $\pm$  1.6%, 8 mM 65  $\pm$  1.4%

Ouabain

2 mM(47  $\pm$  7%)

(n=8)

(Fig. 3)

$K^+$

가

in

4(68  $\pm$  2%), 6(76

$\pm$  2%), 8 mM  $K^+$  (80  $\pm$  2%)

가

가

가

6 mM

66  $\pm$  1.2%  $K^+$

( $n=3$ )(Fig. 4).

$K^+$ 에 의한 혈관이완반응에 대한  $K^+$  통로 차단제들의 효과

$K^+$

$K^+$

$K^+$

가

TEA(1 mM), glibenclamide( $10^{-5}$  M),

4 - AP(3 mM)  $K^+$

(Fig. 5).

barium(5 mM) cesium

(Fig. 6).

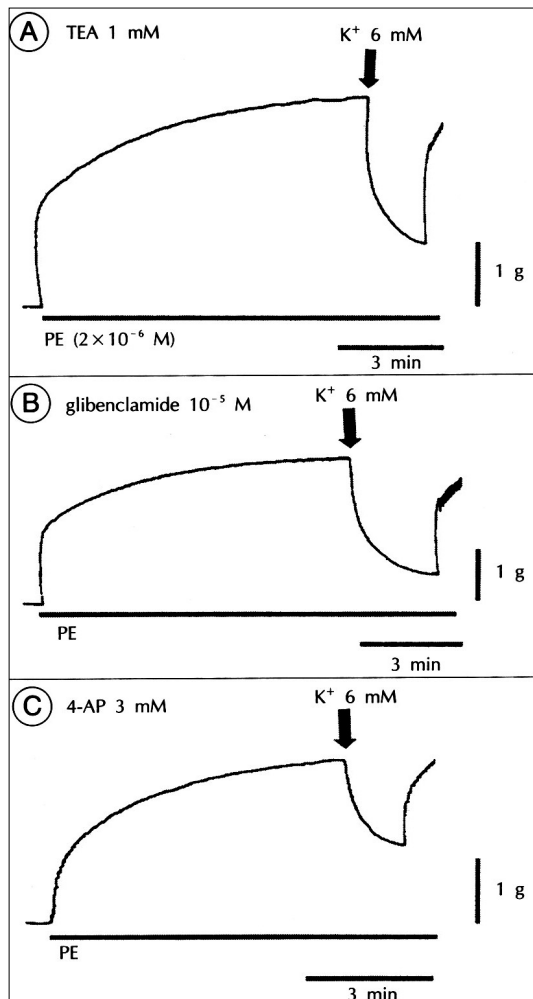
TEA

68  $\pm$  1.8%, glibenclamide

66  $\pm$  2.4%, 4 - AP 62  $\pm$  1.7%,  $Cs^{2+}$

62  $\pm$  2.4%,  $Ba^{2+}$  65  $\pm$  2.3%

(Fig. 7).



**Fig. 5.** Effects of  $K^+$  channel blockers (TEA, glibenclamide and 4-AP) on the  $K^+$ -induced relaxation of aorta in NTR. The  $K^+$ -induced relaxation on the PE-induced contraction was still induced in the pretreatment of TEA (A, 1 mM), glibenclamide (B,  $10^{-5}$  M) and 4-AP (C, 3 mM).

신성 고혈압 쥐 대동맥에서  $K^+$ 에 의한 혈관이완반응

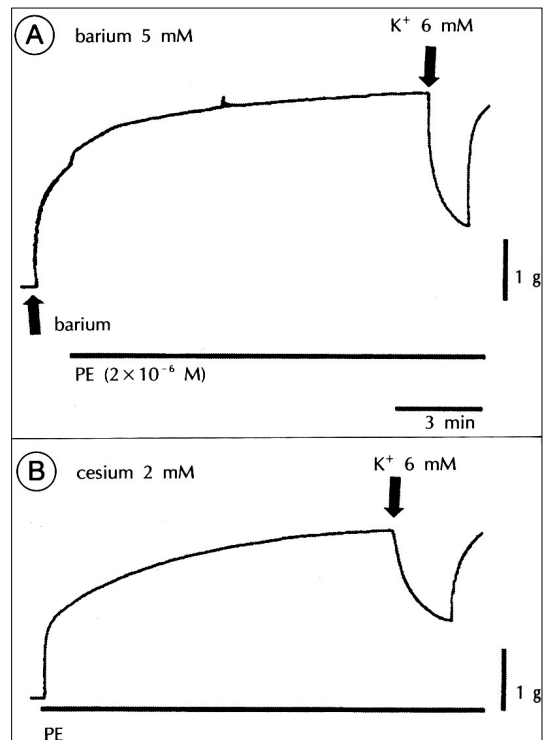
$K^+$

(Fig. 8A and C),

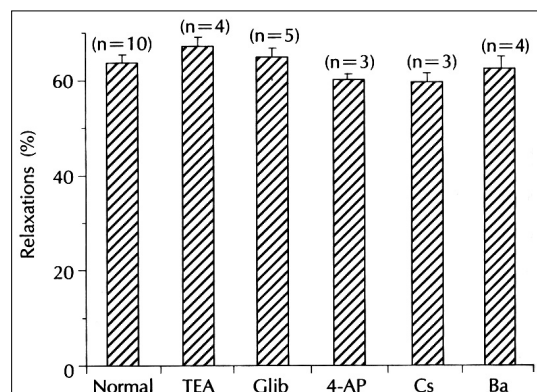
가 ouabain

가 (Fig. 8B). 4 mM  $17 \pm 4\%$ ,  
6 mM  $K^+$

ouabain 4 mM  $53 \pm$   
2%, 6 mM  $60 \pm 0.6\%$   
가 (Fig. 9).



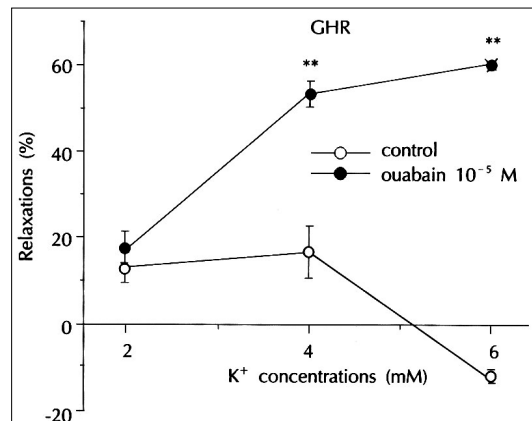
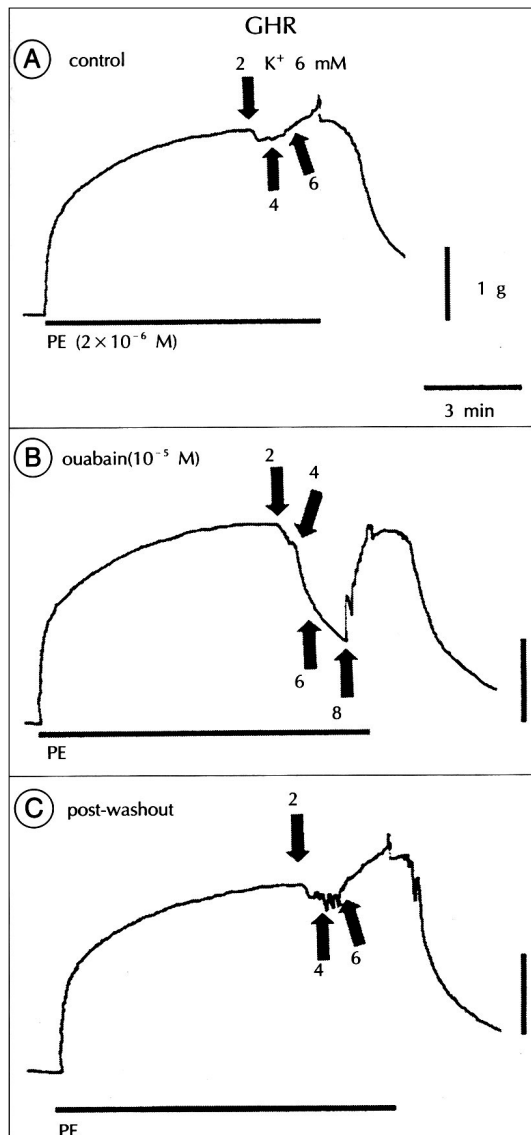
**Fig. 6.** Effects of barium and cesium on the  $K^+$ -induced relaxation of aorta in NTR. The  $K^+$ -induced relaxation on the PE-induced contraction was still induced in the pretreatment of barium (A, 5 mM) and cesium (B, 2 mM).



**Fig. 7.** A bar graph summarizing  $K^+$ -induced relaxation to  $K^+$  channel blockers in NTR. All agents represented statistically non-significance.

고 안

$K^+$   $K^+$  16 mEq  
liter



**Fig. 9.** A graph summarizing  $K^+$ -induced relaxation and ouabain effect from 2 to 6 mM concentrations in GHR ( $n=7$ ). Ouabain ( $10^{-5}$  M) increased the  $K^+$ -induced relaxation. Values represent mean  $\pm$  SE. \*\* $p<0.01$ , compared with co-nrol value at each  $K^+$  concentrations.

Figure 10 illustrates the effect of ouabain on the Na<sup>+</sup>-K<sup>+</sup> ATPase pump. The graph shows the relationship between the concentration of ouabain (mM) on the x-axis and the rate of Na<sup>+</sup> transport (mmol/min/mg protein) on the y-axis. The data points show a hyperbolic relationship, indicating that ouabain acts as a competitive inhibitor of the Na<sup>+</sup>-K<sup>+</sup> ATPase pump. The curve approaches a maximum rate of approximately 1.8 mmol/min/mg protein as the concentration of ouabain increases. The data points are as follows:

Ouabain Concentration (mM)	Na <sup>+</sup> Transport Rate (mmol/min/mg protein)
0	0
0.2	0.2
0.4	0.4
0.6	0.6
0.8	0.8
1.0	1.0
1.2	1.2
1.4	1.4
1.6	1.6
1.8	1.8

Na -  
 K<sup>+</sup> MacCaron 7)21) 25) 26) Na<sup>+</sup> 가 가  
 (Na<sup>+</sup> - activated K<sup>+</sup> channels, K<sub>Na</sub>)가  
 K<sup>+</sup> Na - barium Na - Na<sup>+</sup>  
 K<sup>+</sup> 가 가 Luk Carmelliet 27)  
 digitalis K<sub>Na</sub> 가  
 (Patch clamp method) K<sup>+</sup> Mori 28) ouabain K<sub>Na</sub>  
 barium ouab -  
 K<sup>+</sup> K<sup>+</sup> n K<sup>+</sup>  
 가 22) Luk 가 Na -  
 K<sup>+</sup> Na<sup>+</sup>  
 5)24) K<sub>Na</sub> 가  
 - K<sup>+</sup> (vol - tage - dependent K<sup>+</sup> K<sub>Na</sub>  
 channels, K<sub>V</sub>) - K<sup>+</sup> (Ca<sup>2+</sup> - dendent  
 K<sup>+</sup> channel, K<sub>Ca</sub>)  
 4 - aminopy - ridine TEA ouabain 가 K<sub>Na</sub>  
 ATP - K<sup>+</sup> 가  
 (ATP - dependent K<sup>+</sup> channel, K<sub>ATP</sub>) inward  
 rectifier K<sup>+</sup> channels(K<sub>IR</sub>)  
 가 K<sup>+</sup>  
 glibenclamide barium  
 K<sup>+</sup> Knot 18) Na<sup>+</sup> - K<sup>+</sup> ATPase 가 가 12 - 14)  
 K<sup>+</sup> 6 16 mM K<sup>+</sup> 가  
 ouabain K<sup>+</sup> 15 - 17) MaCarron Halperne<sup>21)</sup> K<sup>+</sup>  
 barium K<sub>IR</sub> Na -  
 TEA, glibenclamide, 4 - AP K<sup>+</sup> Na -  
 ba - Webb 29)  
 rium cesium 가 K<sup>+</sup>  
 가  
 K<sub>IR</sub> Hagen 30) 가  
 K<sup>+</sup> ouabain 가  
 K<sup>+</sup>  
 24) K<sup>+</sup>  
 K<sub>IR</sub> 6 mM  
 Ouabain 2 mM K<sup>+</sup>

가

가 . K<sup>+</sup> TEA, glibenclamide, Na - 4 - AP, barium cesium Na - 2K1C K<sup>+</sup>

Webb Hagen

결 론 :

Na - K<sup>+</sup> K<sup>+</sup> Na - K<sup>+</sup>

가 K<sup>+</sup> Na - 가

가

요 약

연구배경 :

K<sup>+</sup> 가 K<sup>+</sup> 가

방 법 :

clip 4

결 과 :

100 ± 5.1 mmHg  
154 ± 10.2 mmHg

가 K<sup>+</sup>

phenylephrine K<sup>+</sup> 2 8 mM 가

Na - ouabain

2 mM K<sup>+</sup> 가 K<sup>+</sup>

K<sup>+</sup> TEA, glibenclamide, cesium

4 - AP, barium 2K1C K<sup>+</sup>

결 론 :

K<sup>+</sup> K<sup>+</sup> Na - K<sup>+</sup>

가

중심 단어 : K<sup>+</sup> - induced relaxation · Ouabain ·

1997

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