

혈관내피세포 유무에 따른 돼지 관동맥에서의 Endothelin에 대한 반응

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Endothelium-dependent and Independent Responsiveness to Endothelin in Porcine Coronary Artery

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ABSTRACT

Background : The purpose of this study was to investigate the mechanism of endothelium-dependent and independent responses to endothelins (ETs) in porcine coronary artery. **Methods :** The vascular rings of left anterior descending artery or left circumflex artery from 7 pigs were suspended in conventional organ chambers for the measurement of isometric force. To evaluate relaxation responses, vascular rings with endothelium were exposed to ET-1 and ET-3. To evaluate contraction responses, vascular rings with and without endothelium were exposed to ET-1 and ET-3 in the presence or absence of BQ 123 (ET A receptor antagonist) or TAK-044 (ET A and ET B receptor antagonist). **Results :** Transient relaxation responses of vascular rings occurred after exposure of ET-1 and ET-3. These transient responses disappeared after preincubation with N-nitro-L arginine. There was an increased contractions of vascular rings according to increasing concentration of ET-1 and ET-3. The initial responses were enhanced in vascular rings without endothelium in ET-1 and ET-3. In vascular rings with endothelium, the contraction responses were more reduced in vascular rings with preincubation of BQ 123 than in vascular rings without BQ 123 in ET-1. In vascular rings without endothelium, the contraction responses were more reduced in vascular rings with preincubation of TAK-044 than in vascular rings without TAK-044 in ET-1. **Conclusion :** ET B receptor on the endothelium might mediate the transient vasodilator responses to ET-1 and ET-3 through release of nitric oxide in porcine coronary artery. ET A and ET B receptor on vascular smooth muscle cells might mediate vasoconstrictor responses to ETs. (Korean Circulation J 1998;28(12):1993-2001)

KEY WORDS : Endothelin (ET) · Endothelin receptor · Endothelium.

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서 론

4 7 , 80 90%

ET - 2 (intestine) (kidn - ey)

(vascular endothelium) ET - 1

가 , 가 ET - 3 ET - 1

(art - erial wall) ET 2가 ET (type A type B ET receptor)

low - density lipoprotein(LDL), 45,000 50,000 dalton , (growth factor) (receptor)가 50% . Type A ET (ET_A re - ceptor) ET - 3 ET - 1 10

,¹⁾ prostacyclin I₂ , ET -

heparan sulfate가 1 . Type B ET (ET_B (nonthrombogenicity) .²⁾ receptor) ET - 1 ET - 3

가 endothelium - derived ,

relaxing factor(EDRF), endothelin, angiotensin - co - nverting enzyme platelet - derived growth factor ET_B ET - 1 ET - 3 ED -

,^{2 - 4)} , RF prostacyclin

(atherosclerosis), (hyperlipide - mia), , (coronary spasm), ET

(diabetic angiopathy), (thrombosis) (free calcium ion) 가 가 ,

(reperfusion injury) 가 가 ET_A ET_B 가

Endothelin(ET) 가 ET

polypeptide phospholipase C inositol

(vasoconstrictive peptide) 가 1,4,5 - triphosphate diacylglycerol

,⁵⁾ ET 가 ,⁶⁾ ,⁷⁾ ,⁸⁾ ,⁹⁾ ET ,¹²⁾ 가

가 voltage - dependent calcium channel EDRF

. ET 21

3 isotype

가 ,¹⁰⁾ (vascular tone) ,¹¹⁾

isotype ET - 1 ET - 3

endothelin - 1(ET - 1) , end - oth - elin - 2(ET - 2) endothelin - 3(ET - 3) , ET_A

ET 가 ET_B (receptor antagonist) BQ123 ET_A/

ET - 1 ET - 3 , ET - TAK - 044

3 ET - 1 ET - 3

ET isotypes

재료 및 방법		organ chamber
실험대상 및 준비	7 8 20 25 kg	control 1
	Yorkshire 7 Telazol	(equilibration) endo -
	(A.H. Robins, Richmond, VA)100 mg	genous prostanoids 10^{-5} M
	, sodium pentobarbital kg 12.5 mg	indomethacin (Sigma Chemical Company, St.Lou -
		is) 1
		2×10^{-6} M prostaglandin F ₂
		10^{-8} M bradykinin(Sigma Chemical Comp -
		any, St.Louis)
	modified Krebs - Ringer bicar -	
	bonate [(mM) NaCl 118.3, Kcl 4.7, CaCl ₂ 2.5,	가
	MgSO ₄ 1.2, KH ₂ PO ₄ 1.2 NaHCO ₃ 25, glucose 11.1	가 11
	and calcium disodium edetate 0.026 at pH 7.4 (con -	$\pm 3\%$, 가
	trol solution) 37)]	$117 \pm 5\%$
		가 ,
	, 3 4 mm	가
	3 4 cm	organ chamber
	가	이완반응 실험
	control (paper tissue)	가 2×10^{-6} M prostag -
	watchmaker' forcep	landin F _{2a} (Sigma Chemical Company, St.Louis)
Organ Chamber실험	가	10^{-10} to 10^{-7} M ET - 1(Sigma
	10 ml 37 °C control	Chemical Company, St.Louis), ET - 3(Sigma Chemi -
	, PH 7.4 , 95% 5%	cal Company, St.Louis)
	가 가 organ chamber	N - nitro - L - argi -
		nine (Aldrich, Milwaukee)(10^{-4} M)
	(lengthactive tension relation)	ET - 1, ET - 3
	(optimal point)	수축반응 실험
	(lengthactive ten -	가 ,
	sion relation) (optimal point)	ET - 1, ET - 3 concentration - depen -
	60mM KCl	dent 가
ive tension)	(act -	BQ123(Banyu Pharmaceuticals, Tokyo)
		(10^{-6} M, ET _A receptor antagonist) TAK - 044
	6 8 g	(Takeda Chemical Industries, Tokyo) (10^{-9} M, ET _A /
	60 mM KCl	ET _B receptor antagonist)
	100%	실험약제
		Indomethacin

Indomethacin
 Na_2CO_3 sonication
 organ chamber
 final molar(M) concentration
 통계처리
 mean \pm SEM
 2×10^{-6} M prostaglandin F_2
 %
 KCl 60 mM
 %
 t - test P - value가 0.05
 paired

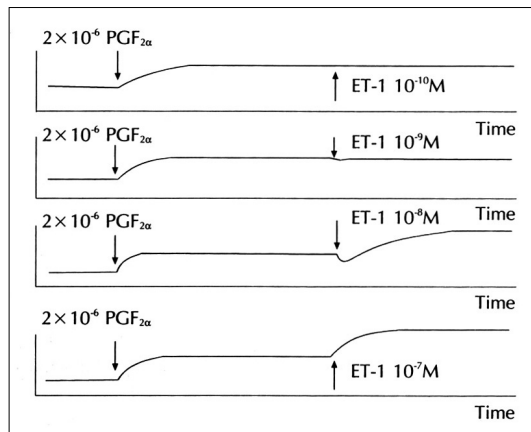


Fig. 1. Relaxation responses to various concentrations of single dose ET-1. Transient relaxation responses to ET-1 (10^{-9} ~ 10^{-8} M) were observed in porcine coronary artery with endothelium.

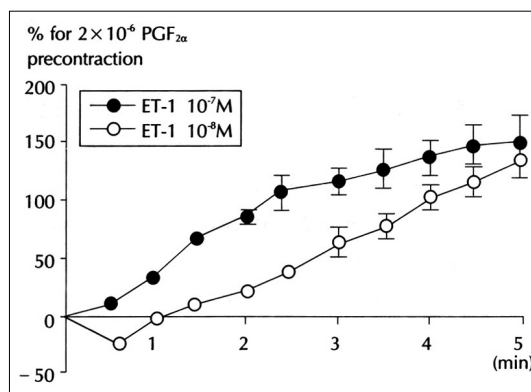


Fig. 2. Time-dependent relaxation responses to ET-1. Transient relaxation responses for 1 minute were observed at dose of 10^{-8} M of ET-1.

결 과

이완반응 실험결과

10^{-9} 10^{-8} M ET - 1 10^{-8} 10^{-7} M ET - 3

(Figs. 1, 2, 3 and 4), N - nitro - L - arginine

수축반응 실험결과

BQ123

ET - 1

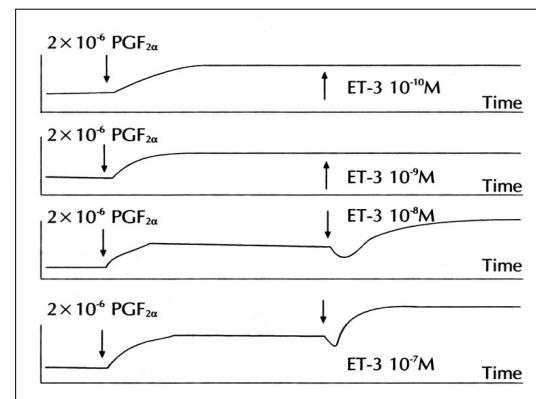


Fig. 3. Relaxation responses to various concentrations of single dose ET-3. Transient relaxation responses to ET-3 (10^{-8} ~ 10^{-7} M) were observed in porcine coronary artery with endothelium.

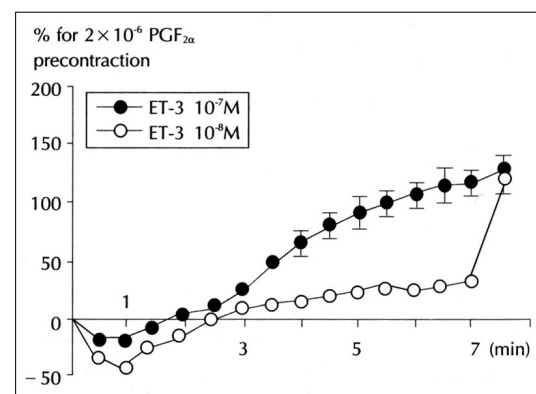


Fig. 4. Time-dependent relaxation responses to ET-3. Transient relaxation responses were observed for 2 minutes at dose of 10^{-7} M of ET-3 and for 3 minutes at dose of 10^{-8} M of ET-3.

$10^{-8.5}$ $10^{-7.5}$ M 가 ($p < 0.05$). BQ123
 가 ($p < 0.05$). BQ123 (Fig. 6).
 가 BQ BQ123 $10^{-8.0}$ ET - 1 TAK - 044
 $10^{-7.5}$ M 가 ($p < 0.05$) $10^{-8.5}$ $10^{-7.0}$ M 가
 (Fig. 5). 가 TAK - 044
 ET - 3 ($p < 0.05$). TAK - 044
 $10^{-8.5}$ $10^{-7.0}$ M 가 가 TAK -
 가 044

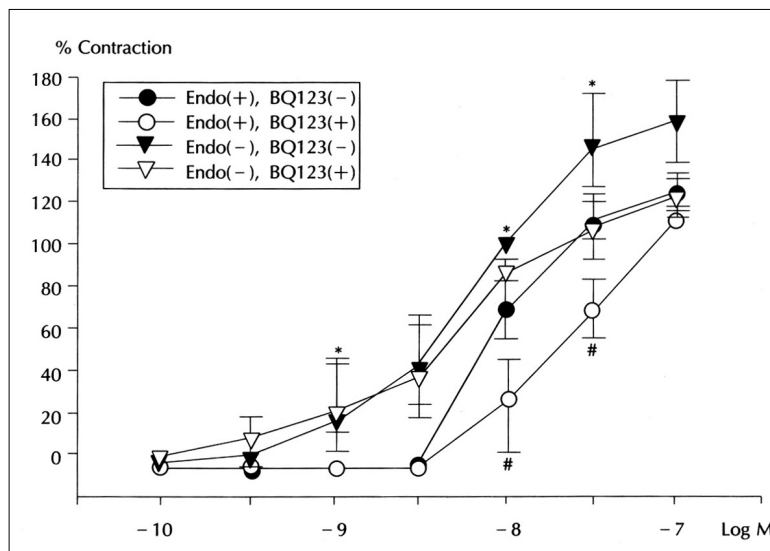


Fig. 5. Contraction responses to ET-1 with or without ETA receptor antagonist, BQ123 (10^{-6} M). The contraction responses were more reduced in vascular rings with endothelium compared with those in vascular rings without endothelium in $10^{-8.5}$ to $10^{-7.5}$ M of ET-1. In vascular rings with endothelium, the contraction responses were more reduced in vascular rings with preincubation of BQ 123 than those in vascular rings without preincubation of BQ 123 in $10^{-8.0}$ to $10^{-7.5}$ M of ET-1 (Endo : Endothelium).
 * $p < 0.05$, Endo (+) vs Endo (-)
 # $p < 0.05$, Endo (+), BQ123 (+) vs Endo (+), BQ123 (-)

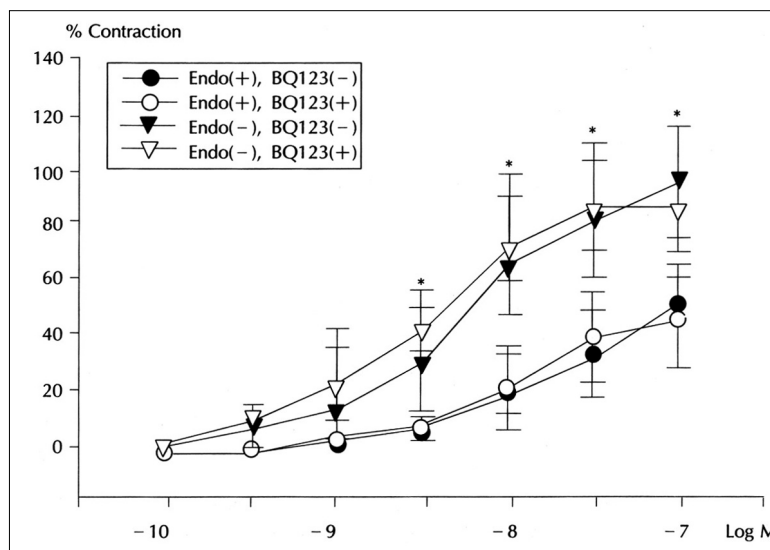


Fig. 6. Contraction responses to ET-3 with or without ETA receptor antagonist, BQ123 (10^{-6} M). The contraction responses were more reduced in vascular rings with endothelium compared with those in vascular rings without endothelium in $10^{-8.5}$ to $10^{-7.0}$ M of ET-3 (Endo : Endothelium).
 * $p < 0.05$, Endo (+) vs Endo (-)

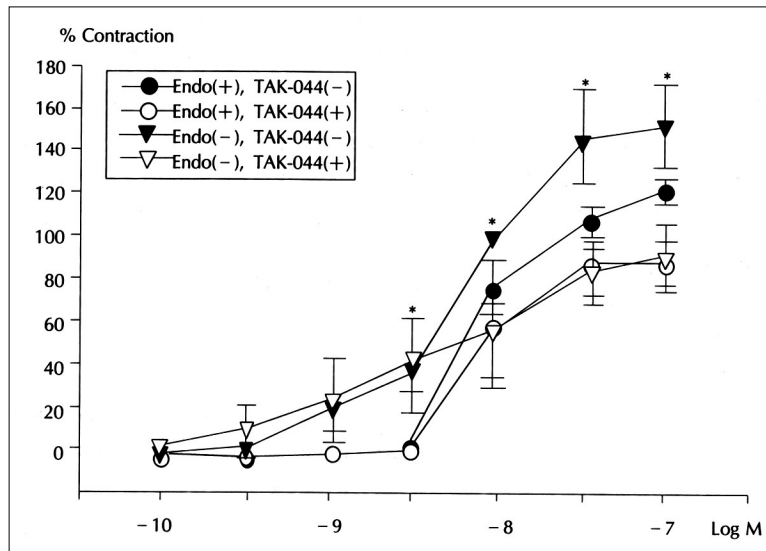


Fig. 7. Contraction responses to ET-1 with or without ETA and ETB receptor antagonist, TAK-044 (10^{-9} M). In vascular rings without endothelium, the contraction responses were more reduced in vascular rings with preincubation of TAK-044 in $10^{-8.0}$ to $10^{-7.0}$ M of ET-1 (Endo : Endothelium). * $p < 0.05$, Endo (+) vs Endo (-) # $p < 0.05$, Endo (-), TAK-044 (+) vs Endo (-), TAK-044 (-)

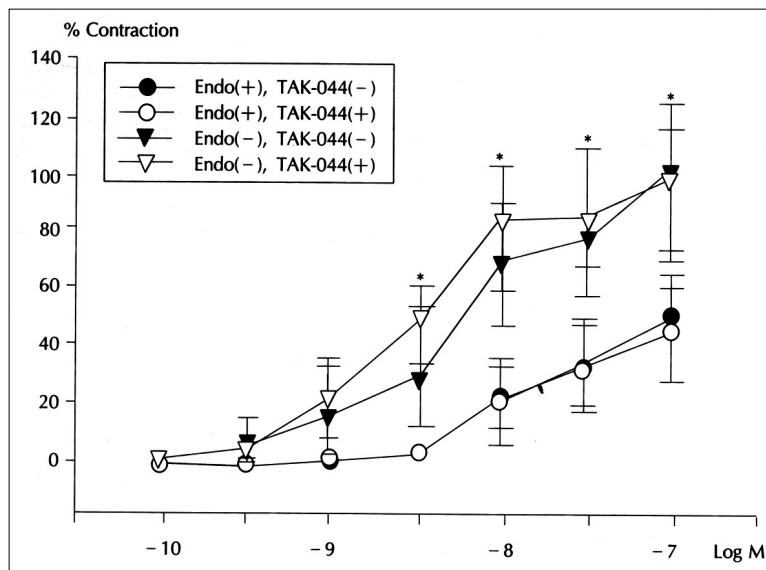


Fig. 8. Contraction responses to ET-3 with or without ETA and ETB receptor antagonist, TAK-044 (10^{-9} M). The contraction responses were more reduced in vascular rings with endothelium compared with those in vascular rings without endothelium in $10^{-8.5}$ to $10^{-7.0}$ M of ET-3 (Endo : Endothelium). * $p < 0.05$, Endo (+) vs Endo (-)

가
 $10^{-8.0}$ $10^{-7.0}$ M
 05)(Fig. 7). TAK - 044
 TAK - 044
 .
 ET - 3
 $10^{-8.5}$ $10^{-7.0}$ M
 .
 (p<0.05). TAK - 044
 (Fig. 8).
 TAK - 044
 가 (p<0.
 고 찰
 EDRF가 ,
 가
 (prostacyclin, EDRF)
 (thr -
 omboxane A₂, ET)
 . ET
 polypeptide ,
 가

(vasospasm) (1.0 3.0 ug) ET_B²²⁾
가 ET ET_B
ET 21 peptide indomethacin
(, , ,) N - nitro - L - arginine ET
, , , , , ,)
isotype(ET - 1, ET - 2, ET - 3) ET_B 가
¹¹⁾ ET epinephrine, angiotensin II, argin- ²³⁾²⁴⁾ N - nitro - L - arginine ET_B
ine, vasopressin, transforming growth factor beta ET
(TGF), thrombin, interleukin - 1 ET - 1²⁵⁾
^{13 - 15)} 가 ET
가 ET ET - 1
가 가 ,
¹⁶⁾
²⁶⁾
(coronary sinus) organ chamber
ET 가 가 ¹⁷⁾ ET
ET 가 가 ,
가
¹⁸⁾ (percutane -
ous transluminal coronary angioplasty) ET N - nitro - L - arginine ET_B
가 가 , nitric oxide 가
¹⁹⁾ ET_B
ET nitric oxide
ET_B 가 가 , BQ123 ET A
(neointima) , ET
가 (left anterior descending
ET B 가 artery) (internal mammary artery)
²⁰⁾ , ET B 가 (pulmoary artery) (sa -
phenous vein)²⁷⁾
²¹⁾ ET - 1
가 ET_A
ET - 1 ET - 3 1 3
nitric oxide BQ123 가
N - nitro - L - arginine . BQ123 가
ET - 1 ET - 3 ni - 044 . ET_A ET_B TAK -
tric oxide 가 TAK - 044 가
ET_B 가 , ET_A 2가 ET
ET ET_B 가 , ET - 1 , ET_B
(agonist) sarafotoxin S6c , ET - 1 ET - 1 ET -
(0.1 0.3 ug) ,

ET_B ET_A

중심 단어 : Endothelin(ET) · ET

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