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Relation between adrenergic neurogenic contraction and α_1-adrenoceptor subtypes in dog mesenteric and carotid arteries and rabbit carotid arteries

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1 We examined the distribution of α_1-adrenoceptor subtypes and their relation to adrenergic neurogenic contraction induced by electrical transmural stimulation in the dog mesenteric and carotid arteries and the rabbit carotid artery.

2 In the dog mesenteric artery, contraction to noradrenaline was competitively inhibited by HV723 ($pK_B = 9.37$) and prazosin ($pK_B = 8.40$). Pretreatment with chlorethylclonidine (CEC) slightly attenuated only the contractions induced by low concentrations of noradrenaline. Contraction induced by electrical transmural stimulation was inhibited at lower concentrations of HV723 than of prazosin.

3 In the dog carotid artery, contraction to noradrenaline was inhibited with higher affinity by prazosin ($pK_B = 9.82$) than by HV723 ($pK_B = 8.47$). Prozosin was also more potent than HV723 in inhibiting the contraction to electrical stimulation. Pretreatment with CEC markedly attenuated or abolished contraction to noradrenaline and electrical stimulation.

4 In the rabbit carotid artery, prazosin inhibited noradrenaline-induced contraction biphasically ($pK_B = 9.91$ and 8.60). After CEC pretreatment, contraction to noradrenaline was attenuated moderately and the high affinity site for prazosin was abolished. HV723 competitively inhibited the noradrenaline response with a similar pK_B value (approximately 8.5) regardless of CEC treatment. Contraction to electrical stimulation was inhibited by prazosin more effectively than by HV723 in preparations not treated with CEC, while it was equipotently inhibited by both antagonists in CEC-treated preparations.

5 These results suggest that the contractions induced by endogenous and exogenous noradrenaline are mediated through the same subtypes of α_1-adrenoceptor distributed in each artery; according to our recent subclassification: α_{1N} subtype in the dog mesenteric artery, α_{1H} subtype in the dog carotid artery and α_{1H} and α_{1L} subtypes in the rabbit carotid artery. Different susceptibility to α_1-adrenoceptor antagonists of sympathetic adrenergic responses in various blood vessels may be related to heterogeneous involvement of distinct α_1-adrenoceptor subtypes in the sympathetic response.

Introduction

Blood vessels are innervated by sympathetic nerves and the muscle tonus is predominantly regulated through α_1-adrenoceptors by noradrenaline released from the nerve terminals (McGrath, 1982; Bülbring & Tomita, 1987). Recently, α_1-adrenoceptors of blood vessels have been classified into three subtypes (α_{1H}, α_{1L} and α_{1N}) by their affinity for α_1-adrenoceptor antagonists (prazosin, HV723) and by their susceptibility to chlorethylclonidine (CEC) (Muramatsu *et al.*, 1990b). The α_{1H}-subtype is the most sensitive to prazosin (pA_2: >9.5) and is selectively susceptible to CEC. The α_{1N}-subtype has a higher affinity for HV723 (pA_2: >9.0) than for prazosin (pA_2: 8.0–9.0), while the α_{1L}-subtype shows low affinity for both the α_1-adrenoceptor antagonists (pA_2: 8.0–9.0). These α_1-adrenoceptor subtypes may co-exist in a single tissue, involved in a contraction induced by exogenous α_1-adrenoceptor agonists (Holck *et al.*, 1983; Flavahan & Vanhoutte, 1986; Flavahan *et al.*, 1987; Muramatsu *et al.*, 1990a). However, it is uncertain which subtype (or subtypes) is activated by endogenous noradrenaline and is involved in adrenergic neurogenic contraction. The present study was carried out to demonstrate the relationship between α_1-adrenoceptor subtypes and sympathetic adrenergic contraction in three arteries (dog mesenteric and carotid arteries and rabbit carotid arteries), in which the noradrenaline-induced contraction has been reported to be caused predominantly through the postulated three different α_1-adrenoceptor subtypes (Muramatsu *et al.*, 1990b).

Methods

Mongrel dogs of either sex (7–15 kg) and male rabbits (2.5–4.0 kg) were used in the present experiments. After being killed under pentobarbitone anaesthesia, dog mesenteric and carotid arteries and rabbit carotid artery were isolated from the animals and cut helically under a dissecting microscope (Muramatsu *et al.*, 1990b). In order to avoid the possible involvement of endothelium-derived relaxing factor in the mechanical response (Furchgott, 1981), the endothelial cells of blood vessels were removed by rubbing them with filter paper. The functional loss of endothelial cells was confirmed by the loss of the relaxant response to acetylcholine (1 μM) in noradrenaline-precontracted arteries (Muramatsu, 1987). Each strip was mounted vertically in an organ bath containing 20 ml Krebs-Henseleit solution of the following composition (mM): NaCl 112, KCl 5.9, $MgCl_2$ 1.2, $CaCl_2$ 2, $NaHCO_3$ 25, $NaHPO_4$ 1.2 and glucose 11.5. The medium was maintained at 37°C, pH 7.4, and was equilibrated with a gas mixture consisting of 95% O_2 and 5% CO_2. The tension was recorded isometrically through a force-displacement transducer. The preparations were equilibrated for 90 min before starting the experiments.

Concentration-response curves for noradrenaline were obtained by adding the drug directly to the bathing media in cumulative concentrations. Desmethylimipramine (0.1 μM), deoxycorticosterone acetate (5 μM), and propranolol (3 μM) were present throughout this series of experiments in order to block neuronal and extraneuronal uptake of noradrenaline and to block β-adrenoceptors, respectively. The concentration-response curves were obtained 6 times in the same strip at 90 min intervals and the third concentration-response curve was used as control. In preliminary experiments, the reproducibility of the concentration-response curves obtained by the third to sixth trials in the absence of α-adrenoceptor antagonist was confirmed (Muramatsu *et al.*, 1990b). The reproducibility was also often checked in paired vehicle experiments. α-Adrenoceptor antagonists were present

for 30 min before and during the concentration-response curves were obtained. The concentrations of α-antagonist were chosen randomly but in sequence from a given concentration to higher concentrations in individual preparations. With chlorethylclonidine (CEC) treatment, the preparations were treated once for 20 min with CEC 50 μM and then washed with the drug-free solution.

The pK_B value was estimated according to Arunlakshana & Schild (1959). Briefly, the concentration of noradrenaline necessary to give a half-maximal contraction in the presence of α-adrenoceptor antagonist was divided by the concentration giving a half-maximal response in the control to determine the agonist concentration-ratio (CR). Data were plotted as the −log antagonist concentration (M) vs the log (CR − 1), and pA_2 values were calculated from Schild plots along mean slope and 95% confidence limits (95% CL) and straight lines were drawn by least square linear regression. When the straight line yielded a slope with unity, the pA_2 value estimated was represented as the pK_B (Arunlakshana & Schild, 1959). The pK_B value for α-adrenoceptor antagonist was also determined for single concentrations of antagonist by concentration-ratio method (Furchgott, 1972).

Electrical transmural stimulation was applied through a pair of platinum-wire electrodes at 10–15 min intervals (Muramatsu *et al.*, 1989). The preparation was placed in parallel between the electrodes. The distance between the electrodes was approximately 2 mm. Stimulus parameters were 0.3 ms duration, frequencies of 20 Hz and supramaximum voltage (10 V) for 10 s. In this series of experiments, DG-5128 (10 μM) and propranolol (1 μM) were added to the bath medium to block prejunctional α_2-adrenoceptors and postjunctional β-adrenoceptors, respectively (Muramatsu *et al.*, 1983; 1989). DG-5128 (10 μM) had no effect on the contractile response to noradrenaline in each preparation. In the experiments with the dog mesenteric artery, α,β-methylene ATP (10 μM) was present throughout the experiments in order to block the sympathetic purinergic component (Muramatsu *et al.*, 1989). No effect of α,β-methylene ATP on noradrenaline-induced contraction was confirmed in the dog mesenteric artery (Muramatsu, 1987).

Experimental values are given as a mean ± s.e.mean or means with 95% confidence limits. Results were analysed by Student's *t* test (unpaired or paired comparison) and a probability of less than 0.05 was considered significant.

Drugs used were: (−)-noradrenaline bitartrate, desmethylimipramine hydrochloride, α,β-methylene ATP (Sigma, St Louis, U.S.A.), deoxycorticosterone acetate, (±)-propranolol (Nacalai, Kyoto, Japan), prazosin (Taito-Pfizer, Tokyo, Japan), chlorethylclonidine dihydrochloride (CEC: Funakoshi, Tokyo, Japan), HV723 (Oshita *et al.*, 1988; α-ethyl-3,4,5- trimethoxy-α-(3- ((2-(2-methoxyphenoxy) ethyl)-amino)-propyl) benzeneacetonitrile fumarate, Hokuriku Seiyaku, Katsuyama, Fukui, Japan), tetrodotoxin (Sankyo, Tokyo, Japan), guanethidine sulphate (Tokyo-Kasei, Tokyo, Japan) and DG-5128 (2-(2-(4,5-dihydro- 1H-imidazol-2-yl)- 1-phenylethyl) pyridine dihydrochloride sesquihydrate, Daiichi Seiyaku, Tokyo, Japan).

Results

Effects of HV723 and prazosin on response to noradrenaline

Noradrenaline produced concentration-dependent contractions in the dog mesenteric and carotid arteries and the rabbit carotid arteries. The concentration-response curves were attenuated by HV723 and prazosin, resulting in a rightward displacement of the curves. Figure 1 shows the Schild plots in three tissues. The slopes of the Schild plots for HV723 were close to unity, indicating that HV723 competitively inhibited the contractile responses induced by noradrenaline in three tissues. The pK_B value for HV723 was 9.37 ± 0.06 in the dog mesenteric artery, which was approximately 1 log unit higher than those in the dog and rabbit carotid arteries (Table 1).

Prazosin also inhibited the noradrenaline response in competitive manner in the dog mesenteric and carotid arteries (Figure 1). The pK_B value for prazosin was greater in the carotid artery than in the mesenteric artery. On the other hand, Schild plots for prazosin in the rabbit carotid artery showed a deviation from a straight line (slope = 0.676, 95% CL = 0.592–0.761), suggesting that the inhibition by prazosin occurred biphasically. Therefore, two different pK_B values (9.91 ± 0.10 and 8.60 ± 0.14) for prazosin were estimated in the rabbit carotid artery (Table 1).

In the preparations pretreated with CEC (50 μM), the noradrenaline-induced contraction was attenuated. However, the extent of the attenuation varied between the tissues tested (Table 2). In the dog mesenteric artery, the contractile response to noradrenaline at concentrations less than a medium effective concentration was significantly reduced. In the dog carotid artery, CEC pretreatment abolished or markedly inhibited the responses to noradrenaline at all concentrations tested. On the other hand, the extent of inhibition in the rabbit carotid artery was intermediate between that in the dog mesenteric and carotid arteries.

HV723 and prazosin competitively inhibited the noradrenaline responses in the dog mesenteric and rabbit carotid arteries which had been pretreated with 50 μM CEC (Figure 1, open symbols), resulting in a pK_B value for an antagonist in each tissue (Table 1). Each value was approximately the same as that in CEC-untreated preparations (except for the high value in the rabbit carotid artery). The antagonist experiments were not carried out in the CEC-treated dog carotid artery

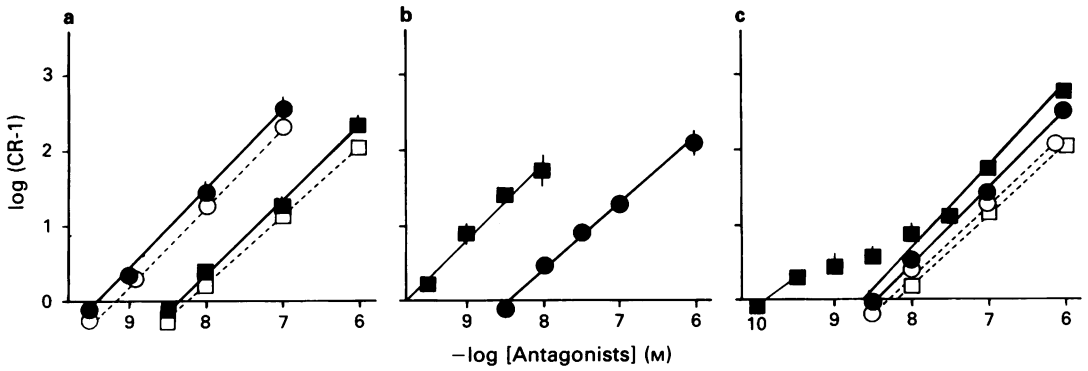

Figure 1 Schild plots for competitive inhibition of noradrenaline contractions by HV723 (circles) and prazosin (squares) in dog mesenteric artery (a), dog carotid artery (b) and rabbit carotid artery (c). Closed symbols, control; open symbols, chlorethylclonidine-treated tissues. Each point is the mean of data obtained from five to six preparations and vertical lines show s.e.mean. For pK_B values and slopes see Table 1.

Table 1 pK_B values and slope factors for HV723 and prazosin in the dog mesenteric and carotid arteries and rabbit carotid artery

	pK_B and slope (95% CL)			
	HV723		*Prazosin*	
	CEC-untreated	*CEC-treated*[a]	*CEC-untreated*	*CEC-treated*[a]
Dog mesenteric artery	9.37 ± 0.06 1.068 (0.978–1.158)	9.29 ± 0.05 0.997 (0.913–1.080)	8.40 ± 0.09 0.954 (0.827–1.082)	8.22 ± 0.05 0.919 (0.837–1.002)
Dog carotid artery	8.47 ± 0.09 0.870 (0.696–1.099)	—[b]	9.82 ± 0.12 1.016 (0.773–1.258)	—[b]
Rabbit carotid artery	8.50 ± 0.05 0.995 (0.921–1.070)	8.33 ± 0.04 0.934 (0.867–1.000)	9.91 ± 0.10[c]	
			8.60 ± 0.14 1.090 (0.920–1.260)	8.25 ± 0.10 0.912 (0.786–1.039)

[a] Experiments were carried out in the preparations which had been treated with 50 μM chlorethylclonidine (CEC) for 20 min beforehand and washed out repeatedly.
[b] Not examined.
[c] Determined from the inhibitory effects of 0.1 and 0.3 nM prazosin.

because of a marked reduction of noradrenaline-induced contraction after CEC-pretreatment (Table 2).

Effects of HV723 and prazosin on adrenergic nerve-mediated contraction

Electrical transmural stimulation at 20 Hz for 10 s produced transient contractions in the dog mesenteric artery (in the presence of 10 μM α,β-methylene ATP), dog and rabbit carotid arteries. These responses were abolished by guanethidine (3 μM) or tetrodotoxin (0.5 μM) ($n = 5$, in each drug and each artery). Pretreatment with 50 μM CEC in the presence of 10 μM DG-5128 and 1 μM propranolol attenuated the contractile response slightly in the dog mesenteric artery, moderately in the rabbit carotid artery and markedly in the dog carotid artery (Figure 2).

HV723 and prazosin inhibited the contractions induced by electrical stimulation in a concentration-dependent manner (Figure 3). In the dog mesenteric artery, the inhibition by HV723 was more potent than that by prazosin, and their inhibitory potencies were not influenced by CEC-pretreatment (Table 3). In the rabbit carotid artery, prazosin was more effective in inhibiting the neurogenic response than HV723 in CEC-untreated preparations, but the inhibition by both drugs was equipotent in CEC-treated arteries. In the CEC-untreated dog carotid artery, prazosin attenuated the contractile response to electrical stimulation at approximately 10 times lower concentrations than HV723.

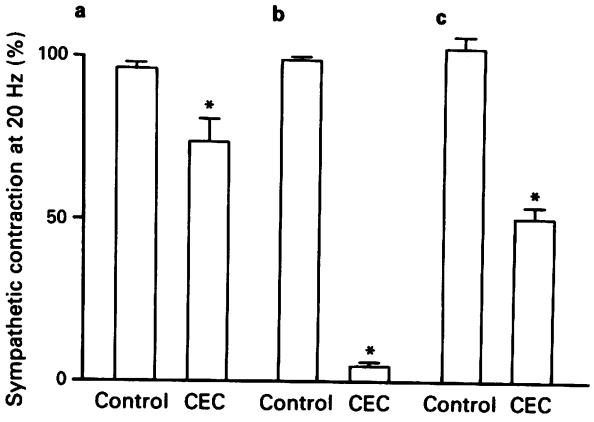

Figure 2 Effects of pretreatment with chlorethylclonidine (CEC) on sympathetic adrenergic contractions induced by electrical transmural stimulation in the dog mesenteric artery (a), dog carotid artery (b) and rabbit carotid artery (c). Contractile amplitude induced by electrical transmural stimulation (20 Hz, for 10 s) is represented as a percentage of the contraction before treatment with CEC (50 μM, 20 min). DG-5128 (10 μM) and propranolol (1 μM) were present throughout this series of experiments. α,β-Methylene ATP (10 μM) was also present in the experiments with dog mesenteric artery. * Significantly different from the time control (control) ($P < 0.05$, unpaired t test). Each value is the mean of 5–6 experiments with s.e.mean shown by vertical lines.

Discussion

As mentioned in the Introduction, α_1-adrenoceptors of blood vessels were recently subclassified into three subtypes (α_{1H}, α_{1L} and α_{1N}) based on the different affinities for α_1-adrenoceptor antagonists (prazosin and HV723) and on the susceptibility to CEC (Muramatsu *et al.*, 1990b). According to the criteria proposed, noradrenaline-induced contractions of the dog mesenteric and carotid arteries seem to be predominantly mediated

Table 2 Effects of chlorethylclonidine (CEC)-pretreatment on noradrenaline contraction in the dog mesenteric and carotid arteries and rabbit carotid artery

Tissue	*Noradrenaline concentration*	*% contraction*[a] *Before CEC*	*After CEC*	*P*[b]
Dog mesenteric artery	0.3 μM	48.8 ± 4.3	35.7 ± 3.8	<0.01
	10 μM	97.5 ± 1.8	94.8 ± 2.1	
Dog carotid artery	0.1 μM	46.0 ± 2.8	0.8 ± 0.4	<0.001
	10 μM	99.3 ± 0.3	24.8 ± 5.6	<0.001
Rabbit carotid artery	0.1 μM	48.4 ± 2.1	3.2 ± 0.9	<0.001
	10 μM	96.3 ± 0.4	88.8 ± 3.8	<0.1

[a] Relative contraction compared with a maximum contraction induced by 100 μM noradrenaline before pretreatment with 50 μM CEC.
[b] Comparison between the values before and after CEC-pretreatment (Student's t test, paired comparison).
Mean ± s.e. of 5 to 6 experiments.

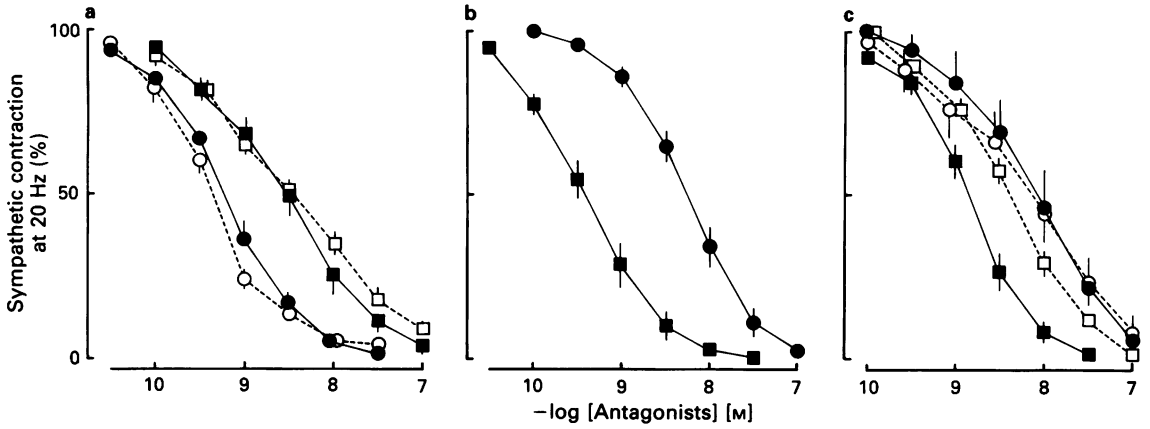

Figure 3 Concentration-response curves for HV723 (circles) and prazosin (squares) in inhibiting the sympathetic adrenergic contraction of the dog mesenteric artery (a), dog carotid artery (b) and rabbit carotid artery (c). Sympathetic adrenergic contraction was elicited by the application of electrical transmural stimulation (20 Hz, 10 s). The contractile amplitude before addition of HV723 or prazosin was taken as 100%. Closed symbols, control; open symbols, CEC-treated tissues. Each value is the mean of 5–6 experiments with s.e.mean shown by vertical lines.

through α_{1N} and α_{1H} subtypes, respectively, because of the high pK_B values for HV723 (9.37) in the mesenteric artery and for prazosin (9.82) in the carotid artery. However, a minor contribution of α_{1H} adrenoceptors cannot be ruled out in the mesenteric artery, where CEC, an inactivating drug of the α_{1H} subtype, slightly but significantly attenuated the contractions induced by low concentrations of noradrenaline. On the other hand, the response to noradrenaline in the rabbit carotid artery was biphasically inhibited by prazosin. Two distinct pK_B values for prazosin (9.91 and 8.60) and a low affinity for HV723 (8.50) suggest that the noradrenaline contraction is mediated through α_{1H} and α_{1L} subtypes in this artery. In fact, CEC selectively inactivated the high affinity site (α_{1H}) detected by prazosin. These results are reminiscent of our recent observations in the rabbit thoracic aorta where noradrenaline causes a contraction through both α_{1H} and α_{1L} subtypes (Muramatsu *et al.*, 1990a). Therefore, it is likely that exogenous noradrenaline acts on the co-existing α_1-adrenoceptor subtypes resulting in a contraction.

Which α_1-adrenoceptor subtypes are involved in the sympathetic contraction induced by endogenous noradrenaline? We analysed sympathetic adrenergic contractions elicited by electrical stimulation in three arteries. Prejunctional α_2-adrenoceptors were blocked by DG-5128 (Muramatsu *et al.*, 1983). The sympathetic purinergic component of the dog mesenteric artery was inhibited by desensitization of P_{2x}-purinoceptor with α,β-methylene ATP (Machaly *et al.*, 1988; Muramatsu *et al.*, 1989). Lack of effects of DG-5128 or α,β-methylene ATP on the responses to exogenous noradrenaline was confirmed. Therefore, under such conditions the contractions elicited by electrical stimulation seem to reflect the adrenergic component of the sympathetic response. In fact, the contractions were completely inhibited not only by tetrodotoxin or guanethidine but also by α_1-adrenoceptor antagonists, prazosin and HV723. However, the inhibitory potencies of prazosin and HV723 varied between the arteries tested and were differently affected by CEC.

In the mesenteric artery, HV723 was several times more potent than prazosin in inhibiting the adrenergic contraction, and the inhibitory potencies of both antagonists were not affected by CEC pretreatment. In contrast, sympathetic adrenergic contractions of the dog carotid artery were inhibited by prazosin with a higher affinity than HV723. Electrical transmural stimulation failed to cause a significant contraction in the CEC-pretreated carotid artery. These results suggest that the sympathetic adrenergic contractions of the dog mesenteric and carotid arteries are predominantly mediated through α_{1N} and α_{1H} subtypes, respectively.

The case of the rabbit carotid artery seems to be more complex. In preparations not treated with CEC, prazosin was an antagonist more potent than HV723. However, a half of the adrenergic contraction in amplitude was inhibited by CEC and the residual response was equipotently inhibited by prazosin and HV723. Therefore, it is likely that the sympathetic adrenergic contraction of the rabbit carotid artery is caused through α_{1H} and α_{1L} subtypes before CEC treatment but only through the α_{1L} subtype after CEC treatment.

In conclusion, the present pharmacological study confirms the presence of three distinct α_1-adrenoceptor subtypes in vascular smooth muscles and, at the same time, shows that such α_1-adrenoceptor subtypes are activated not only by exogenous but also by endogenous noradrenaline. Different sensitivity of sympathetic adrenergic responses to various α_1-adrenoceptor antagonists may reflect heterogeneous involvement of distinct α_1-adrenoceptor subtypes in the sympathetic response.

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Table 3 EC_{50} values for HV723 and prazosin in inhibiting the sympathetic contraction induced by electrical transmural stimulation

	EC_{50} (nM)			
	HV723		*Prazosin*	
Tissue	*CEC-untreated*	*CEC-treated*	*CEC-untreated*	*CEC-treated*
Dog mesenteric artery	0.53 ± 0.07	0.43 ± 0.05	3.80 ± 1.58[b]	2.98 ± 0.54[b]
Dog carotid artery	6.38 ± 1.41	—[a]	0.48 ± 0.14[b]	—[a]
Rabbit coronary artery	10.3 ± 3.04	9.92 ± 3.81	1.54 ± 0.33[b]	4.33 ± 0.77[c]

[a] Not examined.
[b] Significantly different from the corresponding value for HV723 ($P < 0.05$, unpaired comparison).
[c] Significantly different from the value for prazosin in CEC-untreated preparations ($P < 0.05$, unpaired comparison).
Mean ± s.e. of 5 to 6 experiments.

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