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α_1-Adrenoceptor subtypes in the mouse mesenteric artery and abdominal aorta

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1 Subtypes of α_1-adrenoceptor-mediated contractions to noradrenaline in mouse mesenteric artery and abdominal aorta were examined.

2 In mesenteric artery, BMY7378, 5-methylurapidil, WB4101 and prazosin were inhibited contraction to noradrenaline The good correlation for pA_2 values of antagonists in native α_{1D}-(rat thoracic aorta) adrenoceptor subtype and pK_i values in rat cloned α_{1d}-adrenoceptor with the pA_2 values estimated in the mouse mesenteric artery was obtained. However, the pA_2 value for BMY7378 is significantly lower than the accepted value against the α_{1D}-adrenoceptor subtype.

3 In the abdominal aorta, it was obtained the regional difference for the sensitivity for noradrenaline.

4 In the upper abdominal aorta, the good correlation for the pA_2 values of the antagonists in the native α_{1D}-adrenoceptor subtype and pK_i values in the cloned α_{1d}-adrenoceptor with the pA_2 values estimated in the upper abdominal aorta was obtained, and regression line was close to the line of identity.

5 In the lower abdominal aorta, the good correlation for the reported pK_i values in the cloned α_{1a}-adrenoceptor subtype with the pA_2 values estimated in the mouse lower abdominal aorta was obtained, and regression line was close to the line of identity.

6 In conclusion, the present functional data in the mouse suggest that (1) α_{1D}-like adrenoceptors are present in the mesenteric artery, (2) there is the regional difference for the sensitivity for noradrenaline in the abdominal aorta and (3) noradrenaline evokes the contraction mediated through α_{1D}-adrenoceptor in the upper abdominal aorta, whereas there is α_{1A}-adrenoceptor-mediated contraction in the lower abdominal aorta.

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Keywords: α_1-Adrenoceptor; mouse abdominal aorta; mouse mesenteric artery; BMY7378

Abbreviations: BMY7378, (8-(2-4-methoxyphenyl)-1-piperazinyl)-ethyl)-8-azaspiro(4,5)-decane-7,9-dionedihydrochloride; WB4104, 2-(2,6-dimethoxyphenoxyethyl) aminomethyl -1,4-benzodioxane hydrochloride

Introduction

Pharmacological and molecular cloning studies have established operational and structural heterogeneity among the α_1-adrenoceptors (Minneman, 1988; Ford *et al*., 1994; Bylund *et al*., 1994). The α_1-adrenoceptor classification comprises three native subtypes, termed α_{1A}, α_{1B} and α_{1D}, and their cloned counterparts are now designated α_{1a}, α_{1b} and α_{1d} (Bylund *et al*., 1994; Ford *et al*., 1994; Hieble *et al*., 1995b). Various groups have shown that the α_1-adrenoceptor antagonist, prazosin, does not discriminate between these subtypes (Ford *et al*., 1994; Hieble *et al*., 1995a; b; Michel *et al*., 1995). Functional pharmacological studies, however, have resulted in a subdivision of the α_1-adrenoceptors that is based on selectivity of prazosin. Muramatsu *et al*. (1990b; 1995) proposed that the α_1-adrenoceptors can be pharmacologically divided into α_{1H} and α_{1L} subtypes with high ($pA_2 > 9$) and low ($pA_2 < 9$) affinity for prazosin, respectively. The α_{1A-}, α_{1B-} and α_{1D}-adrenoceptor subtypes are all included in the α_{1H}-adrenoceptor subtypes.

Recently, targeted gene disruption has been increasingly used to elucidate the *in vivo* functions of several receptors, including some adrenoceptor subtypes (Link *et al*., 1995; Susulic *et al*., 1995; Macmillan *et al*., 1996; Rohrer *et al*., 1996; Cavalli *et al*., 1997). The potential functional changes occurring in the knockout mice might allow, on one hand, to assign distinct functions to the receptor that has been deleted, and on the other, to test the functional redundancy among receptor subtypes. However, there is little information about the distribution of the α_1-adrenoceptor subtype in the normal mouse.

Therefore, in the present study, we tried to investigate the pharmacological characterization of α_1-adrenoceptor mediated contraction in the normal mouse mesenteric artery and abdominal aorta by calculating the pA_2 values of antagonists against noradrenaline.

Methods

Mechanical responses

Male albino ddY mouse (20–30 g) was killed by a blow on the head and mesenteric artery, upper and lower abdominal

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aorta (see Figure 1) were isolated and dissected free of excess fat and connective tissue. The initimal surface of each artery was gently rubbed with a polyethylene tube to remove the endothelium, and functional loss of endothelial cells was confirmed by the loss of the relaxation response to acetylcholine (1 μM). Each artery was cut into 4 mm ring segments. Each ring segments was suspended in a 20 ml organ bath filled with a Ringer-Locke solution in (mM): NaCl 154, KCl 5.6, $CaCl_2$ 2.2, $MgCl_2$ 2.1, $NaHCO_3$ 5.9 and glucose 2.8 kept at 37°C and bubbled with a mixture of 95% O_2 and 5% CO_2. The tension was monitored continuously and recorded isometrically by a force displacement transducer. Experiments were conducted under the presence of propranolol (10 μM), yohimbine (0.3 μM), desmethylimipramine (0.1 μM) and normethanephrine (1 μM) to block β-adrenoceptors and α_2-adrenoceptors and to inhibit neural and non-neural uptake of noradrenaline, respectively. The strips were allowed to equilibrate for 90 min, were then contracted with noradrenaline (mesenteric artery and upper abdominal aorta; 1 μM, lower abdominal aorta; 10 μM), and allowed to equilibrated for 30 min after wash out. This was repeated until two successive contractions of approximately equal size had been obtained. The resting tension of mesenteric artery and both abdominal aorta were about 0.2–0.3 g. The maximal contractions to noradrenaline of each arteries was about 0.75–1.20 g, and the maximal contraction to noradrenaline were not changed by the presence of antagonists used in present study. The competitive antagonistic activities were expressed as the pA_2 values (negative logarithms of dissociation constant). The concentration-response curves of agonists were obtained cumulatively. The contraction was expressed as a percentage of the maximal contraction produced by the agonists. After determination of control concentration-response curve, the strips were equilibrated with a competitive antagonist for 30 min. Concentration-response curves were then obtained in the presence of the antagonist and procedure repeated with a high (3 fold) concentration of the antagonist in the same preparation. After determination of the control concentration-response curve, two or three successive cumulative concentration-response curves for agonists were determined. For each tissue, pD_2 values and maximum tension for 1st, 2nd, 3rd and 4th concentration-response curve for noradrenaline were not significantly different in preliminaly experiments. The pA_2 values were calculated according to the method of Tallarida *et al*. (1979), which was originally reported by Arunlakshana & Schild (1959).

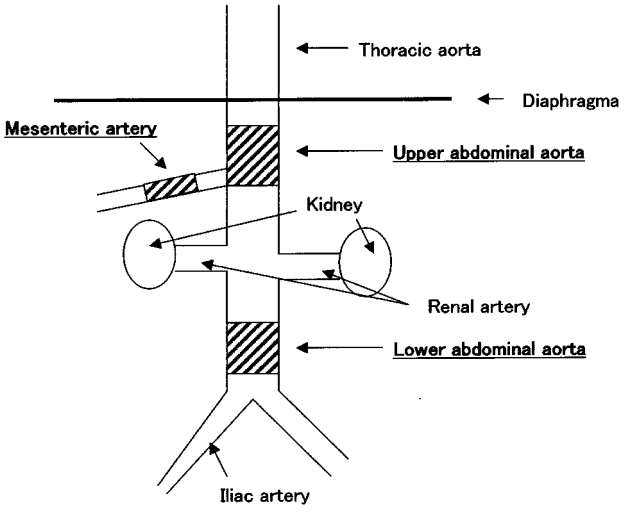

Figure 1 The illustration of the arteries. The underlined arteries are used in the present study.

Data analysis

Numerical results were expressed as means ± s.e.mean and statistical analyses were performed using Student's *t*-test and Dunnett's multiple range test as appropriate. A *P*-value of less than 0.05 was considered a significant difference.

Drugs

The following drugs were used: (−)-noradrenaline bitartrate (Wako-Junyaku, Osaka, Japan); 5-methylurapidil, BMY7378 ((8-(2-(4-methoxyphenyl)-1-piperazinyl)-ethyl)-8-azaspiro(4,5)-decane-7,9-dione dihydrochloride) and WB4101(2-(2,6-dimethoxyphenoxyethyl) aminomethyl-1,4-benzodioxane hydrochloride) (Research Biochemicals, Natick, MA, U.S.A.); prazosin hydrochloride, desmethylimipramine hydrochloride, (±)-normethanephrine hydrochloride, (±)-propranolol hydrochloride and yohimbine hydrochloride (Sigma, St. Louis, MO, U.S.A.).

5-Methylurapidil was dissolved in DMSO (dimethyl sulphoxide) at the initial concentration of 2 mM, and diluted in distilled water. All other drugs were dissolved in distilled water.

Results

Effect of antagonists on noradrenaline-induced contraction in the mouse mesenteric artery

In the mouse mesenteric artery, noradrenaline evoked the contraction in a concentration-dependent manner. The pD_2 value of noradrenaline is 7.51 (Table 1). The responses to noradrenaline were antagonized by the presence of BMY7378 in a concentration-dependent manner. Schild regression analysis carried out for BMY7378 against noradrenaline gave the pA_2 value of 7.69. The slope of the Schild regression line was not significantly different from unity (Table 1, Figure 2). The responses to noradrenaline were also antagonized by prazosin, 5-methylurapidil and WB4101 in a concentration-dependent manner, and Schild regression analyses carried out for antagonists against noradrenaline gave the pA_2 values of 9.93, 7.26 and 9.61, respectively. The slopes of the Schild regression lines were not significantly different from unity, respectively (Table 1, Figure 3).

Correlation coefficients between the mouse mesenteric artery investigated, and native or cloned α_1-adrenoceptor subtypes

We have studied the correlations between the pA_2 values obtained at the present study in the mouse mesenteric artery (Table 1), and the pK_i values for the displacement of [^{3}H]-prazosin or the pA_2 values obtained from the functional analysis in the α_1-adrenoceptor subtypes (Ford *et al*., 1996;

Table 1 The pD_2 values for noradrenaline (NA), the pA_2 values for antagonists against NA and suggested α_1-adrenoceptor subtype in the mouse mesenteric artery, upper and lower abdominal aorta

	Mesenteric artery		*Upper abdominal aorta*		*Lower abdominal aorta*	
Antagonist	*pA_2 value*	*Slope*	*pA_2 value*	*Slope*	*pA_2 value*	*Slope*
Prazosin	9.93±0.19	0.93±0.04	9.65±0.05	0.96±0.05	9.34±0.14	0.97±0.06
WB4101	9.61±0.18	0.93±0.04	9.60±0.07	1.02±0.07	9.40±0.09	0.99±0.04
BMY7378	7.69±0.11	1.10±0.05	8.53±0.12	1.01±0.05	6.00±0.01	1.03±0.02
5-Methylurapidil	7.26±0.04	1.08±0.04	7.45±0.16	1.03±0.04	8.70±0.04	1.04±0.02
pD_2 value for NA	7.51±0.06		7.18±0.01		5.85±0.02	

Each data indicates the mean±s.e.mean of four–five experiments.

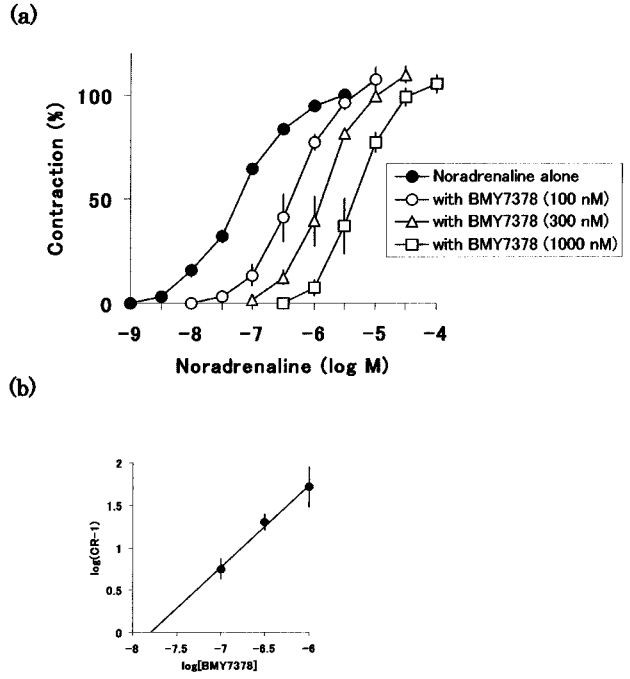

Figure 2 (a) Effects of BMY7378 on noradrenaline-induced contraction in the mouse mesenteric artery. Ordinate: contraction (%), expressed as a percentage of the maximum contraction induced by noradrenaline (3 μM). Abscissa: log concentration (M) of noradrenaline. (b) Schild plot for antagonism of noradrenaline by BMY7378. Ordinate: logarithm of equieffective concentration ratio (CR) of noradrenaline minus 1. Abscissa: log concentration (M) of BMY7378. Each point is presented as mean±s.e.mean of four experiments.

Yamamoto & Koike, 1999). Only those antagonists (BMY7378, prazosin, 5-methylurapidil and WB4101), which were used both by us and previous studies (Ford *et al*., 1996; Yamamoto & Koike, 1999), were included in the analysis.

We obtained the good correlation for the pA_2 values reported in the rat thoracic aorta (α_{1D}-adrenoceptor) and pK_i values reported in rat cloned α_{1d}-adrenoceptor with the pA_2 values estimated in the mouse mesenteric artery (R^2 values were 0.86 and 1.00, respectively, Figure 4), but the slopes of the regression line were significantly different from unity. In contrast, we did not observe any significant correlation for the mouse mesenteric artery with the pK_i values reported in the cloned bovine α_{1a}-, and the pA_2 values reported in the guinea-pig thoracic aorta (α_{1L}-adrenoceptor). Correlation coefficients (R^2 values) against α_{1a}- and α_{1L}-adrenoceptor were 0.34 and 0.28, respectively (Figure 4).

The contractile effects of noradrenaline in the mouse abdominal aorta

In the upper and lower abdominal aorta, noradrenaline evoked the contraction in a concentration-dependent manner, and the pD_2 values are 7.18 and 5.85, respectively (Figure 5).

Effect of antagonists on noradrenaline-induced contraction in the mouse upper and lower abdominal aorta

In the mouse upper abdominal aorta, the responses to noradrenaline were antagonized by the presence of BMY7378 in a concentration-dependent manner. Schild regression analysis carried out for BMY7378 against noradrenaline gave the pA_2 values of 8.53. The slope of the Schild regression line is not significantly different from unity (Table 1, Figure 6). The concentration-response curves for nor-adrenaline were also rightward shifted by the WB4101, 5-methylurapidil and prazosin, respectively. Schild regression analysis carried out for WB4101, 5-methylurapidil and prazosin against noradrenaline gave the pA_2 values of 9.60, 7.45 and 9.65, respectively. The slopes of the Schild regression lines were not significantly different from unity (Table 1, Figure 7).

In the lower abdominal aorta, the concentration-response curve for noradrenaline was also rightward shifted by the BMY7378. However, Schild regression analysis carried out for BMY7378 against noradrenaline gave the pA_2 values of 6.00. The slope of the Schild regression line was not significantly different from unity (Figure 8). The concentration-response curves for noradrenaline were also rightward shifted by the WB4101, 5-methylurapidil and prazosin, respectively. Schild regression analysis carried out for WB4101, 5-methylurapidil and prazosin against noradrenaline gave the pA_2 values of 9.40, 8.70 and 9.34, respectively. The slopes of the Schild regression lines were not significantly different from unity (Table 1, Figure 9).

Correlation coefficients between the mouse upper and lower abdominal aorta investigated, and native or cloned α_1-adrenoceptor subtypes

We obtained the good correlation for the pA_2 values reported in the rat thoracic aorta (α_{1D}-adrenoceptor) and pK_i values reported in rat cloned α_{1d}-adrenoceptor with the pA_2 values estimated in the mouse upper abdominal aorta (R^2 values were 0.93 and 0.87, respectively, Figure 10), and regression line was close to the line of identity.

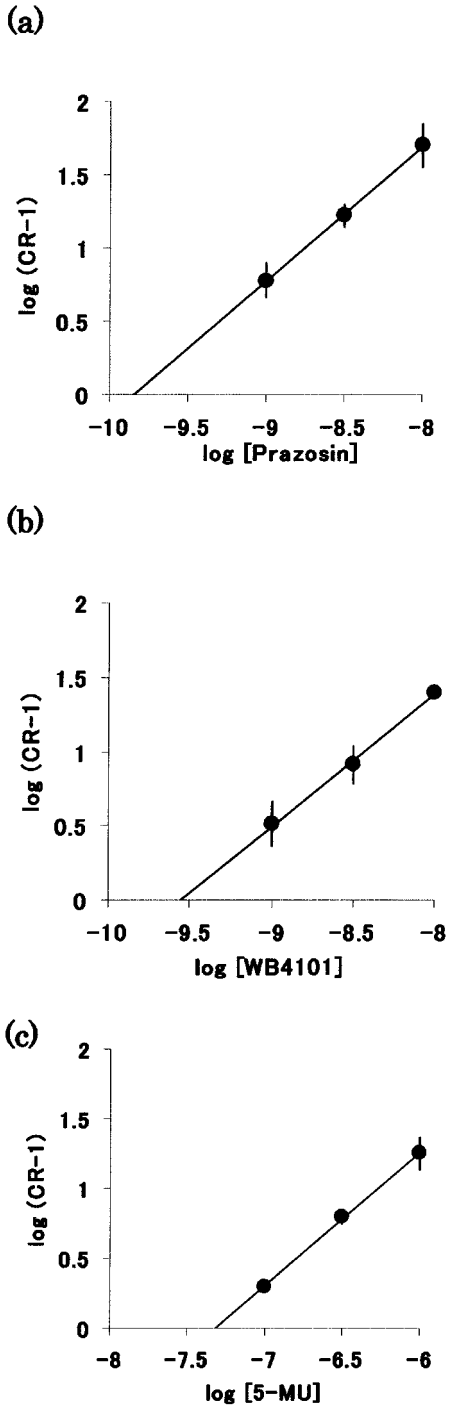

Figure 3 Schild plots for antagonism of noradrenaline by (a) prazosin, (b) WB4101 and (c) 5-methylurapidil (5-MU) in the mouse mesenteric artery. Ordinate: logarithm of equieffective concentration ratio (CR) of noradrenaline minus 1. Abscissa: log concentration (M) of antagonists. Each point is presented as mean ± s.e.mean of four experiments.

On the other hand, we obtained the good correlation for the pK_i values reported in the bovine cloned α_{1a}-adrenoceptor with the pA_2 values estimated in the mouse lower abdominal aorta (R^2 values were 1.00, Figure 11), and regression line was close to the line of identity. The good correlation also obtained the pA_2 values reported in the guinea-pig thoracic aorta (α_{1L}-adrenoceptor) with the pA_2 values estimated in the mouse lower abdominal aorta (R^2 values were 0.98, Figure 11), but the slope of the regression line was significantly different from unity.

In addition, we examined the effect of treatment for irreversible α_{1B}-adrenoceptor alkylating agent, chloroethylclonidine to the noradrenaline-induced contraction in the mouse mesenteric artery, upper and lower abdominal aorta (data not shown). After determination of control concentration-response curves, tissue was treated with 10 μM chloro-ethylclonidine for a total of 60 min; this antagonist was renewed every 10 min to allow for decomposition of the drug in the solution. The concentration-response curve for noradrenaline was 100 fold (mesenteric artery and upper abdominal aorta) and 3 fold (lower abdominal aorta) rightward shifted by the treatment for choloroethylclonidine.

Discussion

We have used BMY7378 in the present study, which is the first selective α_{1D}-adrenoceptor antagonist (Saussy *et al.*, 1994; Goetz *et al.*, 1995), to observe whether the α_{1D}-adrenoceptor subtype is present in the mouse mesenteric artery and abdominal aorta.

In the mesenteric artery, the rightward shift of the concentration-response curve for noradrenaline was observed by the presence of BMY7378 (Table 1, Figure 2). The pA_2 value for BMY7378 from the Schild plot (7.69) is significantly lower than the generally accepted value against α_{1D}-adrenoceptor ($pA_2 = 8.5$, Ford *et al.*, 1996). These results suggest that noradrenaline does not evoke the contraction mediated through α_{1D}-adrenoceptor in the mouse mesenteric artery. However, the pA_2 value of BMY7378 obtained from present study is significantly higher than generally accepted value against α_{1A}-, α_{1B}- and α_{1L}-adrenoceptor subtypes (pA_2 = approximately 6.5, Ford *et al.*, 1996), suggesting the presence of new α_1-adrenoceptor subtype. On the other hand, other antagonists (prazosin, 5-methylurapidil and WB 4101) also inhibited the noradrenaline-induced contraction, and the pA_2 values were 9.93, 7.26 and 9.61, respectively (Table 1, Figure 3). Those values were similar to the pA_2 and pK_i values reported in the rat aortic ring and rat cloned α_{1d}-adrenoceptor (Ford *et al.*, 1996). It was obtained from the good correlation for the affinity values reported in α_{1D}- and α_{1d}-adrenoceptor, but not those in α_{1a}- and α_{1L}-adrenoceptors with the pA_2 values estimated in the mouse mesenteric artery though the slopes of regression lines were significantly different from unity (Figure 4). These results indicate that the pharmacological characterization of α_1-adrenoceptor in the mouse mesenteric artery is most nearly to the α_{1D}-adrenoceptor subtype, but not equality. From these results, it can be suggested that this subtype may be a pharmacologically distinct subtype from α_{1A}-, α_{1B}-, α_{1D}- and α_{1L}-adrenoceptor subtypes or may be a functional phenotype to the α_{1D}-adrenoceptor subtype as reported between α_{1A}- and α_{1L}-adrenoceptors (Ford *et al.*, 1997), this requires further investigation.

In the abdominal aorta, there is the regional difference for the sensitivity to noradrenaline between the upper and lower

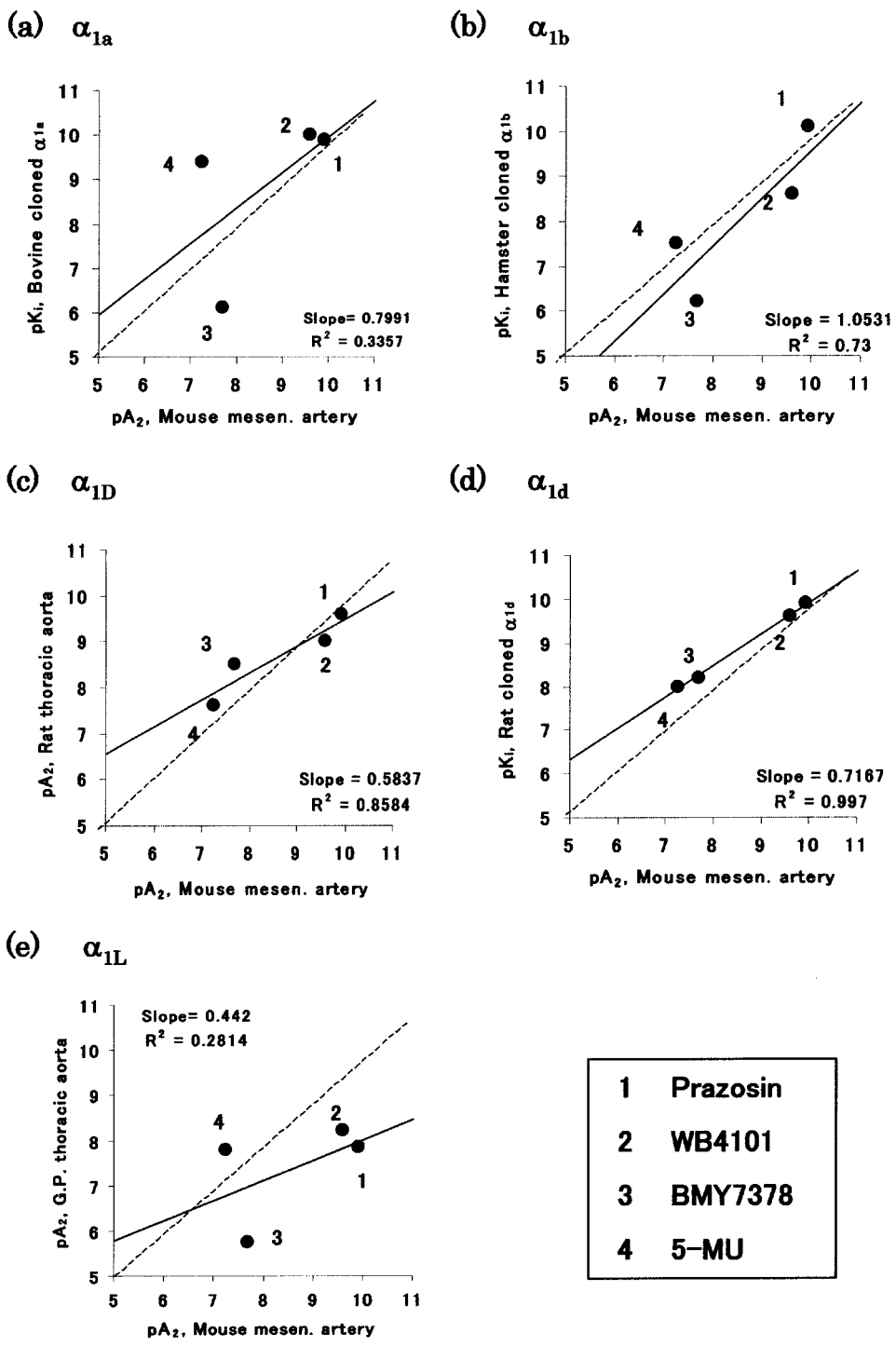

Figure 4 Correlation plots showing the relationship of affinity estimates from *in vitro* functional analysis of mouse mesenteric artery for some antagonists (pA_2) compared with (a) bovine cloned α_{1a}-adrenoceptor (pK_i), (b) hamster cloned α_{1b}-adrenoceptors (pK_i), (c) rat thoracic aorta (α_{1D}-adrenoceptor, pA_2), (d) rat cloned α_{1d}-adrenoceptors (Ford *et al.*, 1996) and (e) guinea-pig thoracic aorta (α_{1L}-adrenoceptor, pA_2) (Yamamoto & Koike, 1999). Cloned mammalian α_{1a}- and α_{1b}-adrenoceptors expressed in rat-1 fibroplasts (Ford *et al.*, 1996). The solid lines were obtained by linear regression, the dashed lines represent the line of identity.

site. The sensitivity to noradrenaline in the upper abdominal aorta was 20 times higher than that in the lower abdominal aorta (Table 1, Figure 5), suggesting the presence of different subtype or difference for receptor density between upper and lower abdominal aorta. In the upper site, the noradrenaline-induced contraction was inhibited by the BMY7378, and the pA_2 value was similar to the generally accepted value against α_{1D}-adrenoceptor (Table 1, Figure 6). WB4101, 5-methyl-

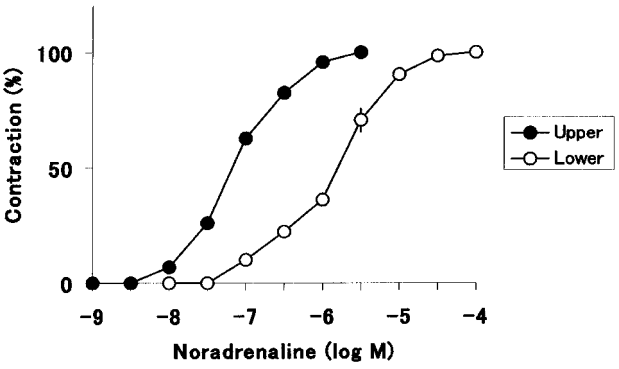

Figure 5 Contractile effect of noradrenaline in the mouse upper and lower abdominal aorta. Each point is presented as mean±s.e.mean of four experiments.

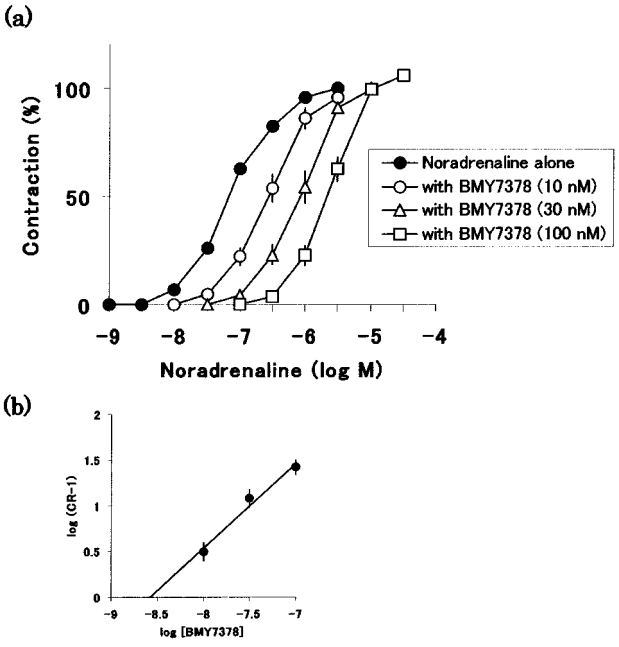

Figure 6 (a) Effects of BMY7378 on noradrenaline-induced contraction in the mouse upper abdominal aorta. Ordinate: contraction (%), expressed as a percentage of the maximum contraction induced by noradrenaline (3 μM). Abscissa: log concentration (M) of noradrenaline. (b) Schild plot for antagonism of noradrenaline by BMY7378. Ordinate: logarithm of equieffective concentration ratio (CR) of noradrenaline minus 1. Abscissa: log concentration (M) of BMY7378. Each point is presented as mean±s.e.mean of four experiments.

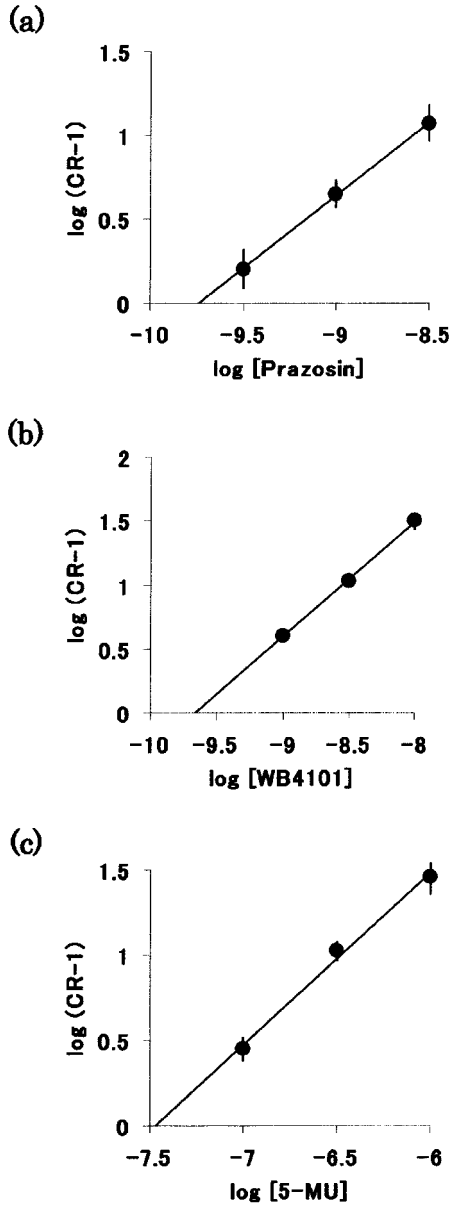

Figure 7 Schild plots for antagonism of noradrenaline by (a) prazosin, (b) WB4101 and (c) 5-methylurapidil (5-MU) in the mouse upper abdominal aorta. Ordinate: logarithm of equieffective concentration ratio (CR) of noradrenaline minus 1. Abscissa: log concentration (M) of antagonists. Each point is presented as mean±s.e.mean of four experiments.

urapidil and prazosin also inhibited the contraction for noradrenaline (Figure 7). It was obtained the good correlation for the pA_2 and pK_i values reported in rat thoracic aorta and rat cloned α_{1d}-adrenoceptors with the pA_2 values estimated in the mouse upper abdominal aorta, and regression line was close to the line of identity (Figure 10). These results suggest that noradrenaline evokes the contraction mediated through the general α_{1D}-adrenoceptor subtype in the upper site. On the other hand, in the lower site, the concentration-response curve for noradrenaline was rightward shifted by the 3–30 μM BMY7378, and the pA_2 value was 6.00, suggesting the contraction by noradrenaline mediated through the non α_{1D}-adrenoceptor subtype (Table 1, Figure 8). However, WB4101, 5-methylurapidil and prazosin indicated high affinity against the noradrenaline-induced contraction (Table 1, Figure 9). In addition, it was obtained the good correlation for the pK_i values reported in α_{1a}-adrenoceptors with the pA_2 values estimated in the mouse lower abdominal aorta, and regression line was close to the line of identity (Figure 11). These results suggest that noradrenaline evokes the contraction mediated through the α_{1A}-adrenoceptor subtype in the lower abdominal aorta. The

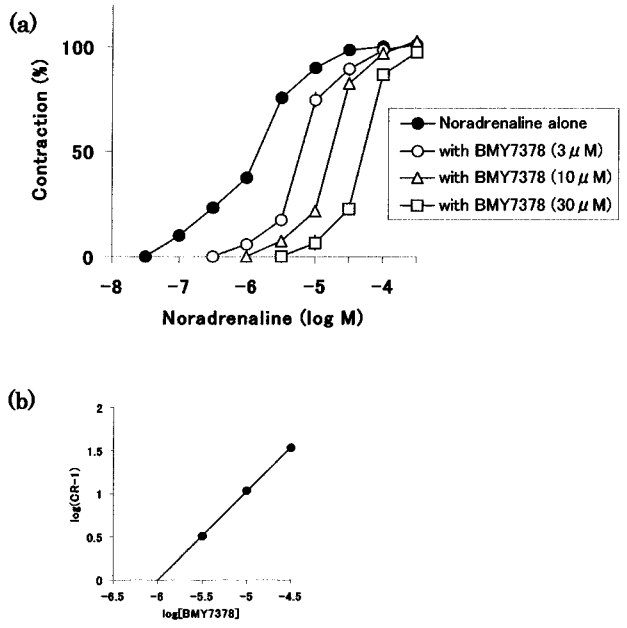

Figure 8 (a) Effects of BMY7378 on noradrenaline-induced contraction in the mouse lower abdominal aorta. Ordinate: contraction (%), expressed as a percentage of the maximum contraction induced by noradrenaline (100 μM). Abscissa: log concentration (M) of noradrenaline. (b) Schild plot for antagonism of noradrenaline by BMY7378. Ordinate: logarithm of equieffective concentration ratio (CR) of noradrenaline minus 1. Abscissa: log concentration (M) of BMY7378. Each point is presented as mean$\pm$s.e.mean of four experiments.

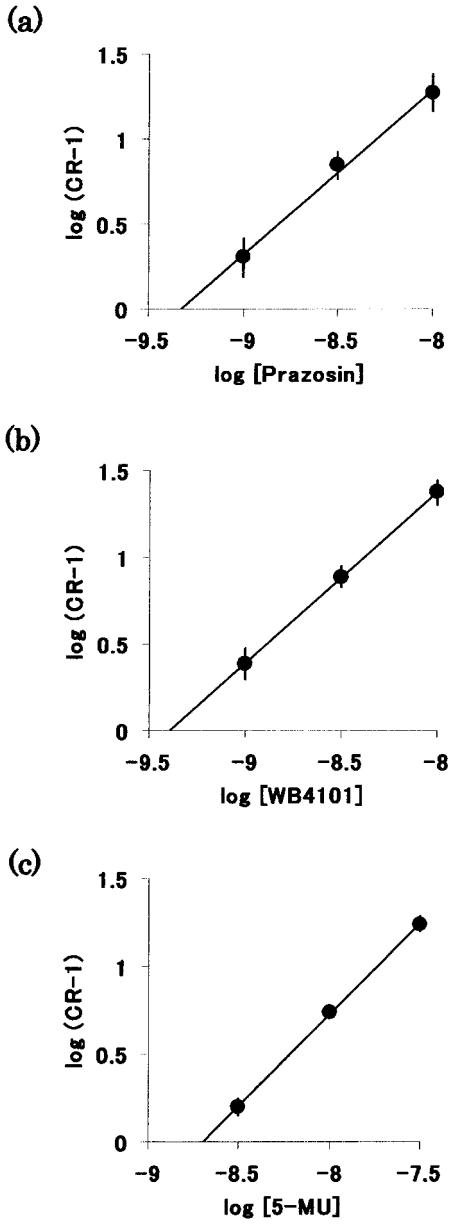

Figure 9 Schild plots for antagonism of noradrenaline by (a) prazosin, (b) WB4101 and (c) 5-methylurapidil (5-MU) in the mouse lower abdominal aorta. Ordinate: logarithm of equieffective concentration ratio (CR) of noradrenaline minus 1. Abscissa: log concentration (M) of antagonists. Each point is presented as mean$\pm$s.e.mean of four experiments.

good correlation was also obtained for the mouse lower abdominal aorta with the α_{1L}-adrenoceptor subtype, though correlation coefficient was considerably smaller than the ones obtained from the α_{1a}-adrenoceptor subtype (Figure 11). Recently, Ford *et al.* (1997) suggested that α_{1L}-adrenoceptor might be a different conformer of the α_{1A}-adrenoceptor subtype; the same α_{1A}-adrenoceptor gene product was able to display the pharmacological properties of both α_{1A}-adrenoceptors and α_{1L}-adrenoceptors. The relatively good correlation between the pA_2 values obtained in the present study and the pA_2 values against α_{1L}-adrenoceptor in the guinea-pig thoracic aorta may support this suggestion. There is not report about regional differences for characterization of α_1-adrenoceptors between upper and lower abdominal aorta and this is very interesting point. However, what do those facts mean biologically, requires further investigation.

It was obtained the good correlation for the pK_i values reported in hamster cloned α_{1b}-adrenoceptors with the pA_2 values estimated in the mouse mesenteric artery, upper and lower abdominal aorta ($R^2=0.50-073$, Figures 4, 10 and 11). These results suggested that the participation for α_{1B}-adrenoceptor to the contraction. However, considering from individual data for each antagonists, we concluded α_{1D}- like, α_{1D}- and α_{1A}-adrenoceptors were mainly participated to the contraction in the mesenteric artery, upper and lower abdominal aorta, respectively. In the present study, the concentration response curve for noradrenaline was rightward shifted by the treatment for irreversible α_{1B}-adrenoceptor alkylating agent, chloroethylclonidine (data not shown). These results also suggested that the participation for α_{1B}-adrenoceptor to the contraction. However, a number of studies have shown that this agent does inactivate the three subtypes, albeit to different degrees (Forray *et al.*, 1994; Hatano *et al.*, 1994; Laz *et al.*, 1994). Therefore, it is suggested that chloroethylclonidine inactivated not only α_{1B}-adrenoceptor but also other subtype in the present study. It is possible that α_{1B}-adrenoceptors are contributed in the mesenteric artery and both abdominal aorta from our experiments. However we believe that it is not mainly even if α_{1B}-adrenoceptor participates to the contraction.

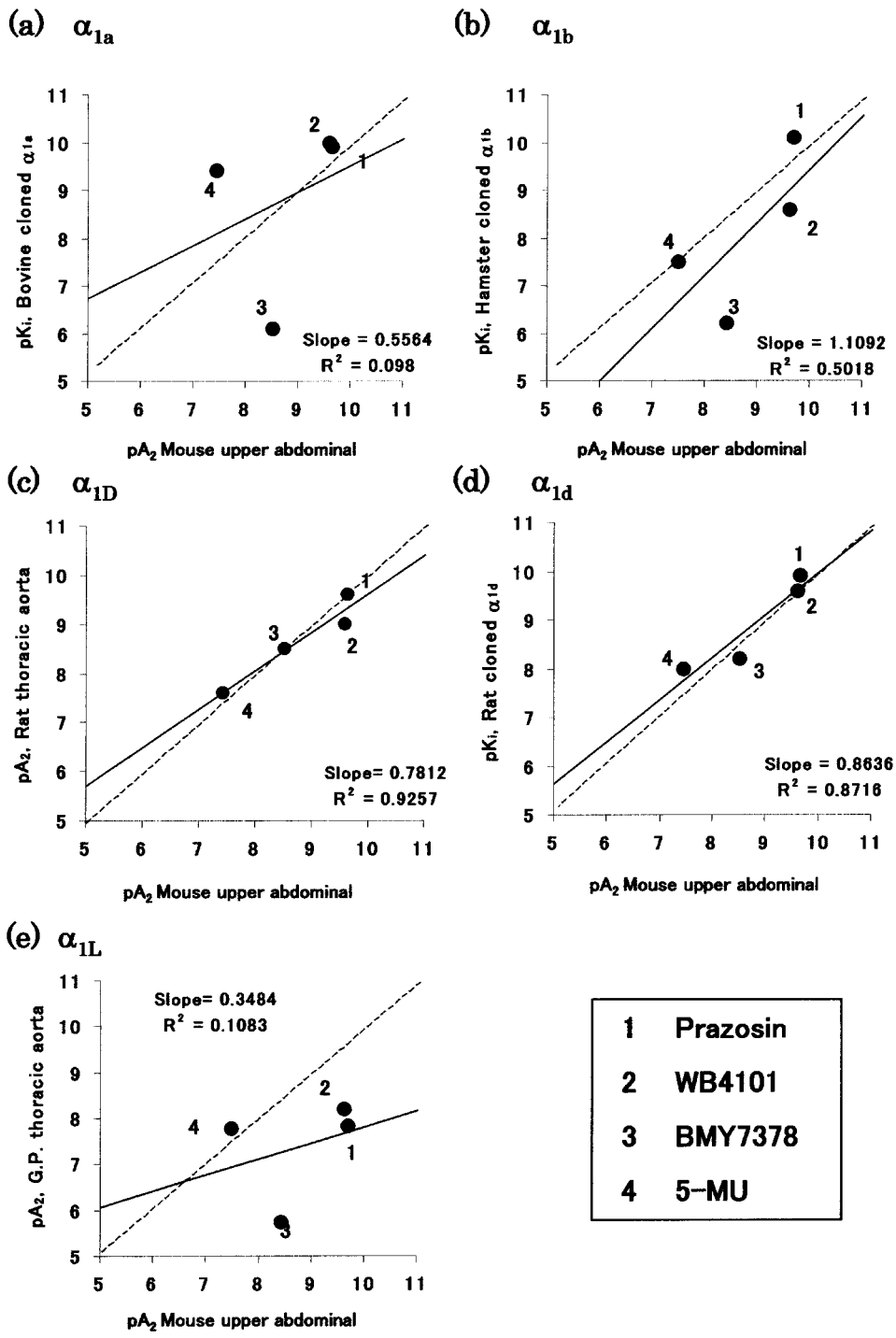

Figure 10 Correlation plots showing the relationship of affinity estimates from *in vitro* functional analysis of mouse upper abdominal aorta for some antagonists (pA_2) compared with (a) bovine cloned α_{1a}-adrenoceptor (pK_i), (b) hamster cloned α_{1b}-adrenoceptors (pK_i), (c) rat thoracic aorta (α_{1D}-adrenoceptor, pA_2), (d) rat cloned α_{1d}-adrenoceptors (Ford *et al.*, 1996) and (e) guinea-pig thoracic aorta (α_{1L}-adrenoceptor, pA_2) (Yamamoto & Koike, 1999). Cloned mammalian α_{1a}- and α_{1b}-adrenoceptors expressed in rat-1 fibroplasts (Ford *et al.*, 1996). The solid lines were obtained by linear regression, the dashed lines represent the line of identity.

In conclusion, the present data in the mouse suggest that (1) α_{1D}-like adrenoceptor exists in the mesenteric artery, (2) the different sensitivity for noradrenaline between upper and lower abdominal and (3) noradrenaline evokes the contraction mediated through α_{1D}-adrenoceptor in the upper abdominal aorta, whereas there is α_{1A}-adrenoceptor-mediated contraction in the lower abdominal aorta.

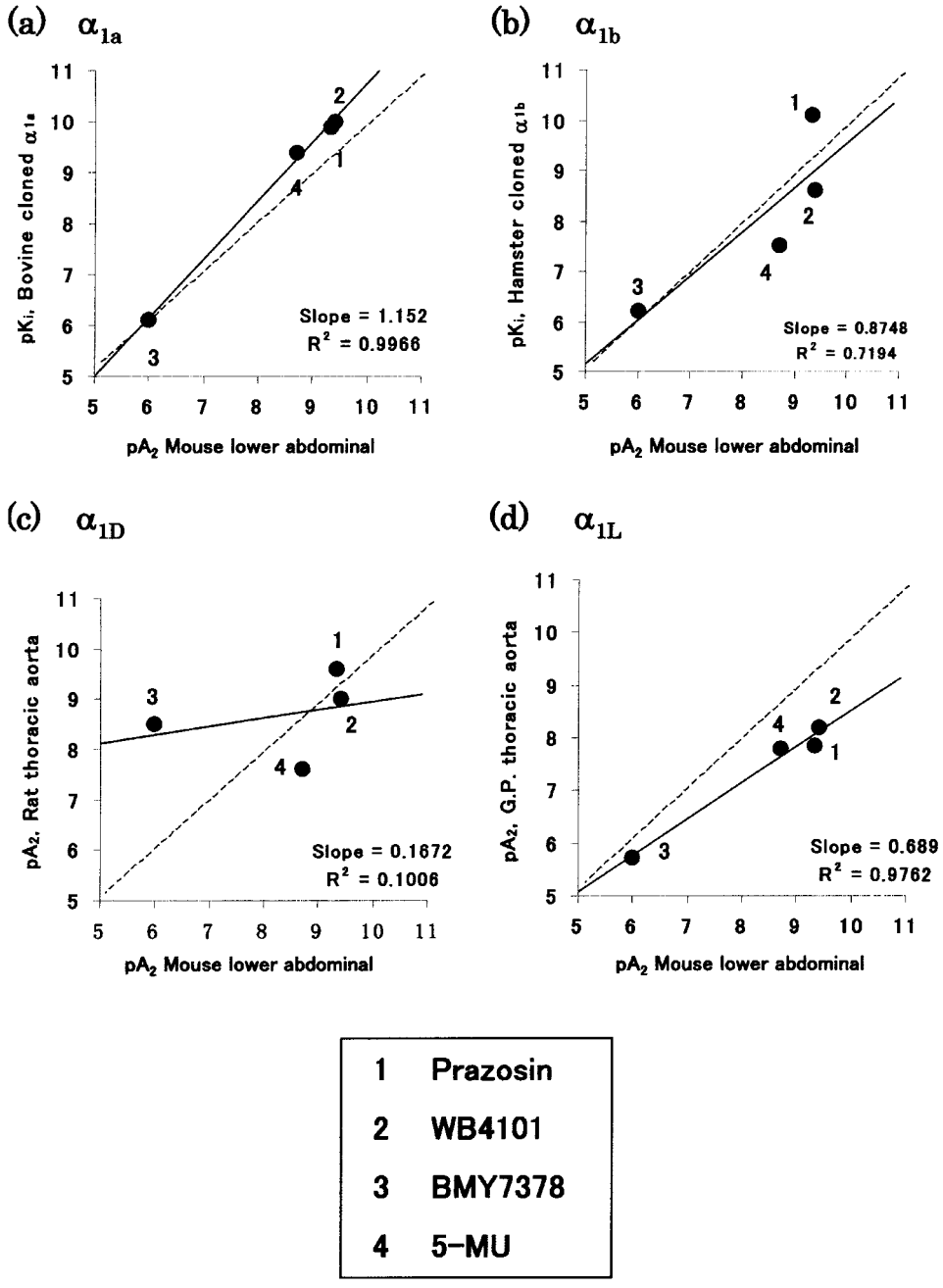

Figure 11 Correlation plots showing the relationship of affinity estimates from *in vitro* functional analysis of mouse lower abdominal aorta for some antagonists (pA_2) compared with (a) bovine cloned α_{1a}-adrenoceptor (pK_i), (b) hamster cloned α_{1b}-adrenoceptors (pK_i), (c) rat thoracic aorta (α_{1D}-adrenoceptor, pA_2) (Ford *et al.*, 1996) and (d) guinea-pig thoracic aorta (α_{1L}-adrenoceptor, pA_2) (Yamamoto & Koike, 1999). Cloned mammalian α_{1a}- and α_{1b}-adrenoceptors expressed in rat-1 fibroplasts (Ford *et al.*, 1996). The solid lines were obtained by linear regression, the dashed lines represent the line of identity.

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