In Vitro Characterization of \( \alpha \)-Adrenergic Receptor in Rabbit Detrusor Muscle

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Accepted April 8, 1987

Abstract—In the isolated detrusor smooth muscle of the rabbit urinary bladder, acetylcholine, prostaglandin (PG) \( \text{F}_{2\alpha} \), histamine and methoxamine produced dose-dependent contractions. The order of efficacy was acetylcholine > PGF\( \text{F}_{2\alpha} \) > histamine > methoxamine. Acetylcholine and oxotremorine increased tension remarkably in the rabbit detrusor muscle; and McN-A-343 also developed tension, but with weaker sensitivity and efficacy. The contractile response to acetylcholine was competitively antagonized by atropine (\( pA_2 \) 9.24) and pirenzepine (\( pA_2 \) 6.96), respectively. Histamine and 2-pyridylethylamine caused dose-dependent contractions. On the other hand, dimaprit caused no response in this tissue. Mepyramine (\( pA_2 \) 8.90) competitively antagonized the contraction induced by histamine, whereas cimetidine failed to antagonize the contraction even at a high concentration of \( 10^{-6} \) M. Norepinephrine, phentolamine and methoxamine have greater efficacies in the ability to contract than clonidine. \( R(-)\) and \( S(+)\)-YM-12617 and YM-12617 (\( pA_2 \) 10.4, 8.31 and 9.75, respectively) and prazosin (\( pA_2 \) 8.13), phentolamine (\( pA_2 \) 7.55) and yohimbine (\( pA_2 \) 6.44) competitively antagonized the contraction elicited by methoxamine. These results suggest that the contraction of rabbit detrusor muscle can be mediated by \( \alpha_1 \)-adrenergic receptors as well as \( M_2 \)-muscarinic and \( H_1 \)-histaminergic receptors and suggest that the contractile force mediated by \( \alpha_1 \)-adrenergic receptor agonist is smaller than those stimulated by the other receptor agonists.

Histochemical and pharmacological studies (1, 2) have demonstrated that the urinary bladder of various species receives a dual cholinergic and adrenergic innervation and is thought to be divided into two portions at the level of the ureter orifice: the body (detrusor muscle) and the base (trigone area). The detrusor muscle of rabbit urinary bladder is known to increase tension when stimulated by acetylcholine, histamine, prostaglandin \( E_2 \) and \( F_{2\alpha} \), barium chloride and norepinephrine, whereas isoproterenol is known to cause relaxation (3).

Recently, some receptors have been pharmacologically subdivided into two subtypes: for example, \( \alpha_1 \)- and \( \alpha_2 \)-, \( \beta_1 \)- and \( \beta_2 \)-adrenergic receptors (4, 5); \( H_1 \)- and \( H_2 \)-histaminergic receptors (6); \( D_1 \)- and \( D_2 \)-dopaminergic receptors (7); \( M_1 \)- and \( M_2 \)-muscarinic receptors (8). \( H_1 \)-histaminergic receptors (3, 9, 10) and \( M_2 \)-muscarinic receptors (11) have been reported to mediate contraction of the detrusor muscle; however, \( \alpha \)-adrenergic receptor subtype to mediate the contraction of the detrusor muscle still remains unknown.

In the present study, we have attempted to characterize the \( \alpha \)-adrenergic receptor in the detrusor muscle of the rabbit urinary bladder. First, we confirmed the contraction of rabbit detrusor muscle induced by the activation of \( H_1 \)-histaminergic and \( M_2 \)-muscarinic receptors and then determined the contraction mediated by the \( \alpha \)-adrenergic receptor subtype. The distinction between \( \alpha_1 \)- and \( \alpha_2 \)-adrenergic receptors can be made by com-
paring the target tissue responses to appropriate α-adrenergic agonists and antagonists (12). Here, the contractile responses to three different types of α-adrenergic agonists were compared. The agonists used were norepinephrine which possesses two α-adrenergic receptor sites of similar potencies, phenylephrine and methoxamine which stimulate preferentially the α₁-adrenergic receptors, and clonidine which activates preferentially the α₂-adrenergic receptors (13, 14). The subclassification of α-adrenergic receptors was also analyzed by three types of α-adrenergic receptor antagonists toward the contractile responses caused by methoxamine. Methoxamine is a suitable α-adrenergic agonist in this study due to its β-adrenergic antagonist activity. Norepinephrine and phenylephrine are both α-adrenergic agonists with α₂-adrenergic agonist activities. β₂-Adrenergic receptors are known to mediate relaxation of the detrusor muscle (15). Therefore, the contraction of the detrusor muscle induced by norepinephrine and phenylephrine was interfered by the relaxation due to their β-adrenergic receptor activation. We have selected prazosin and YM-12617 (16, 17) as selective α₁-adrenergic receptor antagonists. In addition, yohimbine was selected as an α₂-adrenergic receptor antagonist, while phentolamine served as a nonselective α-adrenergic receptor antagonist (18). The optical isomers of YM-12617 were also used in this experiment in order to study the stereoselectivity of the effects. The main part of this study was presented at the 55th General Meeting of the Japanese Pharmacological Society (19).

Materials and Methods

The lower urinary tract, urinary bladder and urethra were removed from male albino rabbits, weighing 3.0–4.0 kg, according to our previous study (17). Transverse smooth muscle strips without mucosa were prepared from the middle portion of the posterior wall of the urinary bladder body. Each segmental strip (3×15 mm) was vertically suspended in an organ bath (30 ml) at 37°C containing Krebs-Henseleit solution continuously bubbled with a gas mixture of 95% O₂ and 5% CO₂. The composition of Krebs-Henseleit solution was (in mM): NaCl, 118.4; KCl, 4.7; KH₂PO₄, 1.2; MgSO₄, 1.2; CaCl₂, 2.5; NaHCO₃, 25.0 and glucose, 11.1. The isometric contraction under a loading tension of 1 g was recorded with a force-displacement transducer (SB-1T, Nihon Kohden) on an ink-writing oscillograph (TO2N2, Fujisoku).

Concentration-response curves for agonists: After an equilibration of at least 1 hr, submaximal contractions were first elicited by each agonist. The cumulative dose-response curves for agonist were constructed by increasing bath concentrations of the agonists approximately 3-fold (20). Eₘₐₓ (the maximal effect) and ED₅₀ (the concentration causing 50% of Eₘₐₓ) of the agonists were obtained from the log dose-response curves.

Effects of antagonists: To assess the effects of antagonists, cumulative dose-response curves as described above for an agonist were constructed before and after 30 min contact with the antagonists. Each antagonist was examined at 1 to 3 different concentrations in the same preparation. In the histaminergic receptor interaction study, at least one strip without antagonist was run in parallel with the experimental strips and was used to correct for time-dependent changes in agonist sensitivity (21). The dose-ratio was obtained from the ratio of the ED₅₀ value of each agonist in the presence and absence of an antagonist. Antagonist dissociation constants (Kₐ) were determined at each concentration of the antagonist according to the method of Furchgott (21). The pA₂ values are then expressed as the negative logarithm of Kₐ. In addition, the log (dose ratio −1) was plotted against the log molar concentration of the antagonist (Schild plot), and the regression line and slope of the line were calculated (22).

Drugs: The following drugs were used: agonists: acetylcholine chloride (Daichi), prostaglandin F₂α (Ono), histamine dihydrochloride (Wako), methoxamine hydrochloride (Nippon Shinyaku), oxotremorine sesquifumarate (Sigma), McN-A-343 (4-(m-chlorophenylcarbamoyloxy)-2-butynyltrimethylammonium chloride, Yamanouchi), 2-PEA (2-(2-aminoethyl)pyridine dihydro-
chloride, Yamanouchi), dimaprit dihydrochloride (Yamanouchi), (-)-norepinephrine hydrochloride (Tokyo Kasei), (-)-phenylephrine hydrochloride (Tokyo Kasei); antagonists: atropine sulfate (Sigma), pirenzepine hydrochloride (Yamanouchi), mepyramine maleate (Sigma), cimetidine (Sigma), prazosin hydrochloride (Pfizer), phentolamine methanesulfate (Ciba-Geigy), yohimbine hydrochloride (Sigma), YM-12617 (5-[2-[[2-(o-ethoxyphenoxy)ethyl]amino]propyl]-2-methoxybenzenesulfonamide hydrochloride (Yamanouchi); others: propranolol hydrochloride (Sigma), desmethylinipramine hydrochloride (Ciba-Geigy), corticosterone (Sigma). The optical isomers of YM-12617 were also used and their physico-chemical properties were as follows: R(-)-YM-12617 (YM-12617-1): m.p. 228-230°C, [α]D -4.0° (c=0.35, MeOH); S(+)-YM-12617 (YM-12617-2): m.p. 228-230°C, [α]D +4.2° (c=0.36, MeOH).

Statistics: All data are expressed as the mean±S.E.M. or the mean with 95% confidence limits. Statistical difference between the two means was determined by the nonpaired Student's t-test. P values less than 0.05 are considered to be significant. Regression lines of the Schild plot were calculated by the least squares method.

Results

Effects of agonists: All agonists, acetylcholine, prostaglandin F2α, histamine and methoxamine increased tension dose-dependently in the rabbit detrusor muscle (Fig. 1). Since the developed tension by 3×10^{-3} M acetylcholine was lower than that by 1×10^{-3} M acetylcholine, the Emax was determined by 1×10^{-3} M acetylcholine (Fig. 1). The pattern of the dose-response curve for acetylcholine in the rabbit detrusor muscle was in agreement with that in human detrusor muscle (23). Comparison of the sensitivity (ED50) and efficacy (Emax) of the agonists indicates that prostaglandin F2α (ED50) and acetylcholine (Emax) are the most potent of the agonists used (Table 1). Oxotremorine, an M2-selective agonist (1×10^{-8}-3×10^{-5} M) (24) and acetylcholine, an M1/M2-nonselective agonist (1×10^{-8}-1×10^{-3} M) produced dose-dependent contraction, whereas McN-A-343, an M1-selective agonist, had only approximately 20% the Emax of oxotremorine and acetylcholine even at a concentration of 1×10^{-5} M (Fig. 2). Histamine, an H1/H2-nonselective agonist (3×10^{-7}-1×10^{-3} M), and 2-PEA, an H1-selective agonist (1×10^{-6}-1×10^{-3} M), elicited dose-dependent contraction, whereas dimaprit, an H2-selective agonist, failed to

![Fig. 1. Dose-response curves for acetylcholine (○), prostaglandin F2α (▲), histamine (△) and methoxamine (●) in the rabbit detrusor muscle. Each point represents the mean±S.E.M. of 10-37 experiments.](image-url)
Fig. 2. Dose-response curves for oxotremorine (○), acetylcholine (●) and McN-A-343 (△) in the rabbit detrusor muscle. Each point represents the mean±S.E.M. of 5 paired experiments. The maximal response to acetylcholine at 1×10⁻³ M was expressed as 100%.

Fig. 3. Dose-response curves for histamine (○), 2-PEA (●) and dimaprit (△) in the rabbit detrusor muscle. Each point represents the mean±S.E.M. of 5 paired experiments. The maximal response to histamine at 1×10⁻³ M was expressed as 100%.

cause a contractile response (Fig. 3). The study of α-adrenergic subtype was performed in the presence of 1×10⁻⁵ M propranolol which blocks β-adrenergic receptors, and desmethylimipramine (1×10⁻⁷ M) and corticosterone (4×10⁻⁵ M) which inhibit extra- and intra-neuronal uptakes of norepinephrine (25). Norepinephrine, an α₁/α₂-nonselective agonist (1×10⁻⁸–3×10⁻⁵ M), phenylephrine (1×10⁻⁷–1×10⁻⁴ M) and methoxamine (3×10⁻⁷–3×10⁻⁴ M), α₁-selective agonists produced dose-dependent contraction. On the other hand, clonidine, an α₂-selective agonist (3×10⁻⁷–1×10⁻⁴ M) acted as a partial agonist in the rabbit detrusor muscle (Fig. 4).

Effects of antagonists: Atropine, an M₁/M₂ nonselective antagonist (3×10⁻⁹–3×10⁻⁸ M), and pirenzepine, an M₁-selective antagonist (3×10⁻⁷–3×10⁻⁶ M), shifted the dose-contractile response curve of acetylcholine dose-dependently to the right (Fig. 5). Mepyramine, an H₁-selective antagonist (1×10⁻⁸–1×10⁻⁷ M), shifted the dose-contractile response curve of histamine to the right in a dose-dependent manner, whereas cimetidine, an H₂-selective antagonist, did not affect the dose-response curve of histamine at a high concentration of 1×10⁻⁵ M (Fig. 6). R(-)-YM-12617 (1×10⁻¹⁰–3×10⁻⁹ M), S(+) -YM-12617 (3×10⁻⁸–3×10⁻⁷ M) and YM-12617 (1×10⁻⁵–1×10⁻⁴ M) and prazosin (3×10⁻⁸–3×10⁻⁷ M), an α₁-selective antagonists; phentolamine (1×10⁻⁷–1×10⁻⁶ M), an α₁/α₂-nonselective antagonist, and yohimbine (3×10⁻⁷–3×10⁻⁶ M), an α₂-selective antagonist, shifted the dose-response curve of methoxamine dose-dependently to the right (Fig. 7). The pA₂ values and the slopes of Schild plots for the antagonists are summarized in Table 2.

R(-)- and S(+) -YM-12617 and YM-
Fig. 5. Antagonism by atropine (a) and pirenzepine (b) of the contractile responses to acetylcholine in the rabbit detrusor muscle. Maximum contractile tension developed by acetylcholine in the absence of each antagonist (○) was taken as 100%. The concentrations of atropine used were 3×10^{-9} M (○), 1×10^{-8} M (▲) and 3×10^{-8} M (△), and those of pirenzepine used were 3×10^{-7} M (○), 1×10^{-6} M (▲) and 3×10^{-6} M (△). Each point represents the mean±S.E.M. of 4 or 5 experiments.

12617 failed to antagonize the contraction induced by acetylcholine and prostaglandin F2α at a high concentration of 3×10^{-5} M, whereas α1-adrenergic receptors were completely blocked, and they weakly antagonized the contraction caused by histamine with pA2 values of 5.20, 5.04 and 4.97, respectively (Table 3).

Discussion

The present study demonstrated that there are α1-adrenergic receptors as well as H1-histaminergic and M2-muscarinic receptors mediating contractions in the urinary bladder body and that the developed tension stimulated by α1-adrenergic receptors is smaller than that by the other receptors (Fig. 1, Table 1).

By comparing the responses caused by selected agonists and antagonists, the present study confirmed that H1-histaminergic receptors (3, 9, 10) and M2-muscarinic receptors (11, 23) mediated contraction of the detrusor muscle of the urinary bladder.

It has been demonstrated that clonidine acts not only as an α2-agonist at presynaptic sites with ED50 values between 3×10^{-9} and 3×10^{-8} M in the field-stimulated rat vas deferens and guinea-pig ileum but also acts as a partial α1-agonist at postsynaptic sites with ED50 values between 1×10^{-6} and 1×10^{-5} M in the isolated rabbit aorta and rat vas deferens (14, 26). In the present study, phenylephrine and methoxamine acted as full agonists, whereas clonidine only acted as a partial agonist, since the Emax of phenylephrine and methoxamine is not significantly different from that of norepinephrine, whereas that of clonidine is significantly different from that of norepinephrine. In addition, the ED50 value of clonidine was approximately 3×10^{-6} M in the detrusor muscle. Because of these observations, clonidine was considered to act as a partial α1-agonist in the detrusor muscle of rabbits. Moreover, the pattern of contractile responses to norepinephrine, phenylephrine and clonidine in the rabbit detrusor muscle were similar to that in the

Fig. 6. Antagonism by mepyramine (a) and cimetidine (b) of the contractile responses to histamine in the rabbit detrusor muscle. Maximum contractile tension developed by histamine in the absence of each antagonist (○) was taken as 100%. The concentrations of mepyramine used were 1×10^{-8} M (○), 3×10^{-8} M (▲) and 1×10^{-7} M (△), and that of cimetidine used was 1×10^{-6} M (○). Each point represents the mean±S.E.M. of 4-12 experiments.
Fig. 7. Antagonism by R(-)-YM-12617 (a), S(+)-YM-12617 (b), YM-12617 (c), prazosin (d), phentolamine (e) and yohimbine (f) of the contractile responses to methoxamine in the rabbit detrusor muscle. The maximal response to methoxamine in the absence of each antagonist (○) was expressed as 100%. The concentrations of R(-)-YM-12617 (○: 1X10-10 M, ▲: 3X10-10 M, △: 1X10-9 M, and ■: 3X10-9 M), S(+)-YM-12617 (○: 3X10-9 M, ▲: 1X10-9 M, and △: 3X10-7 M), YM-12617 (○: 1X10-9 M, ▲: 3X10-9 M, and △: 1X10-8 M), prazosin (○: 3X10-9 M, ▲: 1X10-7 M, and △: 3X10-7 M), phentolamine (○: 1X10-7 M, ▲: 3X10-7 M, and △: 1X10-6 M) and yohimbine (○: 3X10-7 M, ▲: 1X10-6 M, and △: 3X10-6 M) were used. Each point represents the mean±S.E.M. of 4-22 experiments.

Table 2. pA2 values and slope of Schild plot for receptor antagonists

| Antagonist    | Agonist      | n  | pA2       | Slope          |
|---------------|--------------|----|-----------|----------------|
| Atropine      | Acetylcholine| 12 | 9.24±0.06 | 1.11 (0.83-1.39) |
| Pirenzepine   | Acetylcholine| 15 | 6.96±0.04 | 1.07 (0.89-1.26) |
| Mepyramine    | Histamine    | 12 | 8.80±0.02 | 0.99 (0.87-1.12) |
| Cimetidine    | Histamine    | 4  |           |                |
| R(-)-YM-12617 | Methoxamine  | 22 | 10.4±0.09 | 0.70 (0.41-1.00) |
| S(+)-YM-12617 | Methoxamine  | 15 | 8.31±0.13 | 0.64 (0.40-1.33) |
| YM-12617      | Methoxamine  | 12 | 9.75±0.09 | 0.93 (0.45-1.42) |
| Prazosin      | Methoxamine  | 12 | 8.13±0.07 | 1.04 (0.66-1.42) |
| Phentolamine  | Methoxamine  | 12 | 7.55±0.09 | 0.88 (0.37-1.39) |
| Yohimbine     | Methoxamine  | 17 | 6.44±0.07 | 0.76 (0.35-1.17) |

Data are the mean±S.E.M. (pA2) and the mean with 95% confidence limits (slope). n=number of experiments.
Table 3. Effects of YM-12617 and its optical isomers on the contractile responses to acetylcholine, prostaglandin F₂α and histamine

| Agonist       | Antagonist          | (M)         | n  | ED50 (M) | Dose ratio |
|---------------|---------------------|-------------|----|----------|------------|
| Acetylcholine | R(-)-YM-12617       | control     | 5  | 3.0±0.9×10⁻⁵ | —          |
|               |                     | (3×10⁻⁶)    | 5  | 6.3±2.1×10⁻⁵ | 2.3±0.7    |
|               | S(+) -YM-12617      | control     | 5  | 4.5±0.6×10⁻⁵ | —          |
|               |                     | (3×10⁻⁶)    | 5  | 6.8±1.3×10⁻⁵ | 1.5±0.1    |
|               | YM-12617            | control     | 5  | 1.4±0.4×10⁻⁵ | —          |
|               |                     | (3×10⁻⁶)    | 5  | 3.1±1.0×10⁻⁵ | 2.5±0.6    |
| Histamine     | R(-)-YM-12617       | control     | 5  | 1.9±0.4×10⁻⁵ | —          |
|               |                     | (3×10⁻⁶)    | 5  | 9.5±2.4×10⁻⁵ | 4.8±0.5    |
|               | S(+) -YM-12617      | control     | 6  | 2.8±0.2×10⁻⁵ | —          |
|               |                     | (3×10⁻⁶)    | 6  | 9.2±1.1×10⁻⁵ | 3.3±0.5    |
|               | YM-12617            | control     | 5  | 2.8±0.9×10⁻⁵ | —          |
|               |                     | (3×10⁻⁶)    | 5  | 7.9±2.0×10⁻⁵ | 2.8±1.1    |
| Prostaglandin F₂α | R(-)-YM-12617   | control     | 5  | 1.6±0.3×10⁻⁶ | —          |
|               |                     | (3×10⁻⁶)    | 5  | 2.3±0.4×10⁻⁶ | 1.4±0.1    |
|               | S(+) -YM-12617      | control     | 5  | 1.5±0.4×10⁻⁵ | —          |
|               |                     | (3×10⁻⁶)    | 5  | 1.7±0.5×10⁻⁵ | 1.1±0.1    |
|               | YM-12617            | control     | 3  | 1.5±0.1×10⁻⁶ | —          |
|               |                     | (3×10⁻⁵)    | 3  | 1.5±0.2×10⁻⁶ | 1.0±0.1    |

Data are the mean±S.E.M. n=number of experiments. *(P<0.05) and **(P<0.01) denote significant difference (vs. control).

rabbit trigone, urethra and prostate, which has been shown in our previous study (17) where α₁-adrenergic receptors were demonstrated to mediate contraction. Therefore, the contractile responses of the detrusor muscle as well as the trigone, urethra and prostate caused by norepinephrine, phenylephrine, methoxamine and clonidine was thought to be elicited by activation of α₁-adrenergic receptors.

To elucidate α-adrenergic receptor subtypes, the dissociation constants (Kᵦ) of the antagonists were also compared in the rabbit detrusor muscle. The comparison of Kᵦ is known to be one of the reliable techniques for differentiating receptors and receptor subtypes (21). In the present study, YM-12617 and its optical isomers, prazosin, phentolamine and yohimbine antagonized the contractions induced by methoxamine, All of these antagonists fulfilled the criteria of competitive antagonists in this tissue since the slopes of the Schild plots did not significantly differ from the theoretical value of unity. The mean pA₂ (-log Kᵦ) values for R(−)- and S(+) -YM-12617 and YM-12617, prazosin, phentolamine and yohimbine against methoxamine were 10.4, 8.31, 9.75, 8.13, 7.55 and 6.44, respectively. We previously compared the α₁- and α₂-adrenergic receptor blocking potencies of these antagonists in vitro (16, 17, 27). The mean pA₂ values for YM-12617, prazosin, phentolamine and yohimbine against norepinephrine, phenylephrine and clonidine were, respectively 9.77, 8.26, 7.67 and 6.30 in the trigone, 9.67, 8.20, 7.62 and 6.30 in the urethra and 9.73, 8.08, 7.45 and 5.94 in the prostate (17). Also, the pA₂ (-log Kᵦ) values for R(−)- and S(+) -YM-12617, YM-12617, prazosin, phentolamine and yohimbine are 10.2, 7.44, 10.1, 8.85, 8.04 and 6.35, respectively, in antagonizing α₁-adrenergic receptor mediated contraction of norepinephrine in the rabbit aorta; and they are 6.22, 6.64, 6.41, 5.16, 8.17 and 7.84, respectively, in antagonizing the α₂-adrenergic receptor mediated twitch inhibitory effect of clonidine in the field-stimulated rat vas deferens (16, 27). Furthermore, the mean pKᵦ (-log Kᵦ) values for R(−)- and S(+) -YM-12617, YM-12617, prazosin, phentolamine and yohimbine
are 10.0, 7.96, 9.64, 9.39, 8.08 and 6.40, respectively, in displacing $^3$H-WB 4101 binding ($\alpha_1$-adrenergic receptor); and they are 5.89, 6.07, 6.06, 5.63, 8.12 and 7.24, respectively, in displacing $^3$H-clonidine binding ($\alpha_2$-adrenergic receptor) in rat brain membranes (16). Thus, the actual $pA_2$ values for these antagonists against methoxamine in the rabbit detrusor muscle are comparable to those for $\alpha_1$-adrenergic receptor sites, but not to those for $\alpha_2$-adrenergic receptor sites. Accordingly, the comparison of the $pA_2$ values of these $\alpha$-adrenergic receptor antagonists suggests that the contractile responses of the rabbit detrusor muscle are due to activation of $\alpha_1$-adrenergic receptors and not by activation of $\alpha_2$-adrenergic receptors. Judging from the $pA_2$ values, YM-12617 was 42, 158 and 2,040 times more potent in antagonizing the contraction of the rabbit detrusor muscle induced by methoxamine than prazosin, phentolamine and yohimbine, respectively, and R(-)-YM-12617 was also a 120 times (=isomeric activity ratio) more potent antagonist for $\alpha_1$-adrenergic receptors than S(+)-YM-12617. The similar stereoselectivity of the optical isomers of YM-12617 was found in the study of rabbit aorta, iris dilator, prostate, urethra and trigone of urinary bladder (27, 28).

It is of interest that structurally, YM-12617 can be recognized as a derivative of catecholamines, whereas known $\alpha_1$-adrenergic receptor antagonists such as prazosin, WB 4101, BE 2254 and AR-C 239 have no apparent structural similarity to catecholamines (16) and that YM-12617 has two enantiomers which had markedly different activity towards $\alpha_1$-adrenergic receptors (this study; 27, 28). The specificity of YM-12617 and its enantiomers for $\alpha_1$-adrenergic receptors was also confirmed in the present study. YM-12617 and its enantiomers were found to have high affinities for $\alpha_1$-adrenergic receptors with little effect on the contractile responses to acetylcholine, prostaglandin F$_{2\alpha}$ and histamine (Table 3). The specificity for $\alpha_1$-adrenoceptors of YM-12617 and its optical isomers in the present study agrees with the results in another study (29). Therefore, YM-12617 and its optical isomers have also been shown to be $\alpha_1$-adrenergic receptor antagonists.

Acknowledgments: The authors would like to thank Drs. N. Inukai, M. Takeda and T. Takenaka for encouragement throughout the course of the experiments and for helpful discussions, and we thank Mrs. A. Miyata-Osawa for her excellent technical assistance.

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