In Vitro Pharmacological Profile of the Novel \( \alpha_1 \)-Adrenoceptor Antagonist HSR-175

Shigeki Hashimoto, Masafumi Oshita, Kouji Morikawa, Hideo Kato, Yasuo Ito, Shigeru Kigoshi and Ikunobu Muramatsu

Central Research Laboratories, Hokuriku Seiyaku Co., Ltd., Katsuyama, Fukui 911, Japan

Department of Pharmacology, Fukui Medical School, Matsuoka, Fukui 910-11, Japan

ABSTRACT—The pharmacological profile of HSR-175, a new \( \alpha_1 \)-adrenoceptor antagonist, was studied in vitro and compared with those of other \( \alpha_1 \)-antagonists. HSR-175, prazosin, bunazosin and yohimbine competitively antagonized the contractile responses induced by noradrenaline in the dog mesenteric arteries and the rabbit thoracic aorta. The \( pA_2 \) values for HSR-175 in the dog mesenteric arteries and the rabbit aorta were 10.38 and 9.63, respectively, which were significantly higher than those for prazosin (8.39 and 8.80), bunazosin (8.44 and 8.75) and yohimbine (7.34 and 6.10). HSR-175 also inhibited the sympathetic adrenergic contraction induced by electrical transmural stimulation in the dog mesenteric arteries, and the inhibitory effect of HSR-175 was more potent than those of prazosin and bunazosin. Although HSR-175 also possessed competitive antagonist properties at pre- and postsynaptic \( \alpha_2 \)-adrenoceptors in the rat vas deferens and the dog saphenous veins, those affinities (\( pA_2 = 6.41 \) and 7.05) were much lower than those at postsynaptic \( \alpha_1 \)-adrenoceptors. Furthermore, HSR-175 at concentration of 10\(^{-6}\)M showed no inhibition on the contractile responses to 5-HT, histamine, KCl and angiotensin II in the rabbit thoracic aorta. These results indicate that HSR-175 is a very potent and selective \( \alpha_1 \)-adrenoceptor antagonist.

Keywords: \( \alpha_1 \)-Adrenoceptor, \( \alpha_1 \)-Adrenoceptor antagonist, Blood vessel, HSR-175

Fig. 1. Chemical structure of HSR-175.

\( \alpha \)-Adrenoceptors have been pharmacologically divided into two subtypes, i.e., \( \alpha_1 \) and \( \alpha_2 \), on the basis of selective agonists and antagonists (1–3). In general, \( \alpha_1 \)-adrenoceptors are most selectively activated by phenylephrine and cirazoline and are antagonized by prazosin and bunazosin. In contrast, \( \alpha_2 \)-adrenoceptors are preferentially activated by clonidine and BHT-933 and are antagonized by yohimbine and idazoxan.

In various blood vessels \( \alpha_1 \)-adrenoceptors are located postsynaptically, mediating vasoconstriction. Postsynaptic \( \alpha_1 \)-adrenoceptors have also been demonstrated in the lower urinary tracts (4, 5). Therefore, it has now been confirmed clinically that \( \alpha_1 \)-adrenoceptor antagonists are effective for treatments of hypertension, cardiac failure and lower urinary tract disorder (6, 7).

We tried to develop a more potent and selective \( \alpha_1 \)-adrenoceptor antagonist and recently found that the newly synthesized compound \( R(-)-5-[2-[2-(5-fluoro-2-methoxyphenoxy)ethyl]amino]propyl]-2-methoxybenzenesulfonamide hydrochloride (HSR-175) (Fig. 1) had a higher affinity to \( \alpha_1 \)-adrenoceptors than prazosin and bunazosin. In this paper, we report the \( \alpha_1 \)-adrenoceptor selectivity of HSR-175, as compared with those of prazosin, bunazosin and yohimbine.

MATERIALS AND METHODS

Experiments with dog and rabbit vascular vessels

Mongrel dogs of either sex (7.5–13.0 kg) and male albino rabbits (2.1–2.8 kg) were anesthetized with sodium thiopental (20 mg/kg, i.v.) and sodium pento-
barbital (30 mg/kg, i.v.), respectively, and exsanguinated from the common carotid arteries. The dog mesenteric artery and saphenous vein and rabbit thoracic aorta were isolated and helically cut under a dissecting microscope. To avoid the possible involvement of endothelial-derived relaxing factor in the mechanical response (8), the endothelial cells of these vessels were removed by rubbing them with filter paper and the functional loss of endothelial cells was confirmed by the loss of relaxing response to acetylcholine (10⁻⁷ M) in agonist-precontracted vessels (9). Each strip was mounted vertically in an organ bath containing 10 ml of Krebs-Henseleit solution of following composition: 118 mM NaCl, 4.7 mM KCl, 2.6 mM CaCl₂, 1.2 mM MgSO₄, 1.2 mM KH₂PO₄, 24.9 mM NaHCO₃ and 11.1 mM glucose.

The bath medium was maintained at 37°C, pH 7.4, and was equilibrated with a gas mixture consisting of 95% O₂ and 5% CO₂. A resting tension of 2 g, 1 g and 0.5 g was applied to the rabbit thoracic aorta, dog mesenteric artery and saphenous vein, respectively, and the response was recorded isometrically through a force-displacement transducer (T7-30-240, Orientec, Tokyo, Japan) on a recorder (RJG-4028, Nihon Kohden, Tokyo, Japan). All preparations were equilibrated for 60 min before starting the experiments. Cumulative concentration-response curves of agonists such as noradrenaline were determined by a step-wise increase in the concentration of an agonist as soon as a steady response to the previous administration had been achieved. α-Adrenoceptor antagonists to be tested were applied 30 min before recording the concentration-response curve. Desmethylimipramine (10⁻⁷ M), deoxycorticosterone acetate (5 × 10⁻⁶ M) and propranolol (10⁻⁶ M) were added to the bath solution to block neuronal and extraneuronal uptake and β-adrenoceptors, respectively, when noradrenaline was applied as an agonist. When the responses to clonidine in the dog saphenous vein were recorded, the preparation was incubated with 10⁻⁷ M, deoxycorticosterone acetate, indomethacin, α,β-methylene ATP, and prazosin hydrochloride. In other preparations, the responses to clonidine were examined after a 30-min incubation with the antagonist. Propranolol (10⁻⁶ M) was added to the bath solution.

**Drugs**

HSR-175 (R(-)-5-[2-[[2-(5-fluoro-2-methoxyphenoxy)ethyl]amino]propyl]-2-methoxybenzenesulphonamide hydrochloride) was synthesized at Central Research Laboratories, Hokuriku Seiyaku Co., Ltd.

The following drugs were used: l-noradrenaline bitartrate, and yohimbine hydrochloride (Wako, Osaka, Japan); angiotensin II, ATP, clonidine hydrochloride, desmethyliimipramine hydrochloride, indomethacin, α,β-methylene ATP, and prazosin hydrochloride (Sigma, St. Louis, MO, USA); deoxycorticosterone acetate and histamine dihydrochloride (Nacalai, Kyoto, Japan); 5-hydroxytryptamine creatinine sulfate (5-HT) (Merck, Darmstadt, F.R.G.); propranolol hydrochloride (Ideural, Sumitomo, Osaka, Japan); guanethidine sulfate and phenoxybenzamine hydrochloride (Tokyo Kasei, Tokyo, Japan); acetylcholine hydrochloride (Ovisot, Daiichi, Tokyo, Japan); and tetrodotoxin (Sankyo, Tokyo, Japan). Bunazosin hydrochloride was prepared in our laboratory.

Deoxycorticosterone acetate, indomethacin and phenoxybenzamine were dissolved in ethanol and then diluted with distilled water. The other drugs were dissolved in distilled water.

**Statistical analysis**

Experimental values were expressed as means ± S.E. or means with 95% confidence limits. ED₅₀ values for
the concentration-response curves were calculated graphically, and the \( pA_2 \) values for \( \alpha \)-adrenoceptor antagonists were obtained according to the method of Arunlakshana and Schild (12).

**RESULTS**

**Effects on postsynaptic \( \alpha_1 \)-adrenoceptors in dog mesenteric arteries and rabbit thoracic aorta**

Noradrenaline produced concentration-dependent contractions in the dog mesenteric arteries. HSR-175 \((3 \times 10^{-10} - 3 \times 10^{-9} \text{M})\), prazosin \((10^{-8} - 10^{-7} \text{M})\), bunazosin \((10^{-8} - 10^{-7} \text{M})\) and yohimbine \((3 \times 10^{-7} - 3 \times 10^{-6} \text{M})\) produced parallel shifts to the right of the concentration-response curves for noradrenaline without a decrease in the maximal response (Fig. 2). The slope of the Schild plot for each antagonist was not different from unity (Table 1). The \( pA_2 \) value for HSR-175 \((10.38 \pm 0.16)\) was much higher than that for prazosin \((8.39 \pm 0.09)\), bunazosin \((8.44 \pm 0.10)\) and yohimbine \((7.34 \pm 0.19)\) (Table 1). None of the antagonists tested affected the resting tension of the mesenteric arteries at the concentrations used.

In the rabbit thoracic aorta, the effects of these antagonists on the contractile response to noradrenaline were similar to those in the dog mesenteric arteries. The \( pA_2 \) value for HSR-175 \((9.63 \pm 0.13)\) was higher than that for prazosin \((8.80 \pm 0.17)\), bunazosin \((8.75 \pm 0.13)\) and yohimbine \((6.10 \pm 0.07)\) (Table 1). The \( pA_2 \) values for HSR-175 and yohimbine in the dog mesenteric arteries

![Fig. 2. Effects of HSR-175 (A), prazosin (B), bunazosin (C) and yohimbine (D) on the contractile response to noradrenaline in dog mesenteric artery. Contractile responses induced by \( 10^{-4} \text{M} \) noradrenaline before drug treatment were taken as 100%. Each value is the mean ± S.E. of 6 to 9 experiments.](image-url)
Table 1. \( pA_2 \) values and slope of the Schild plot for HSR-175, prazosin, bunazosin and yohimbine at postsynaptic \( \alpha_1 \)-adrenoceptors in dog mesenteric artery and rabbit thoracic aorta

| Antagonist | Dog mesenteric artery | | | Rabbit thoracic aorta | | |
|------------|-----------------------|------------|-----------------------|-------------------------------------------------|-------------------------------------------------|
|            | \( n \) | \( pA_2 \)±S.E. | slope \( 95\% CI \) | \( n \) | \( pA_2 \)±S.E. | slope \( 95\% CI \) |
| HSR-175    | 22 | 10.38±0.16 | 0.94 (0.72–1.16) | 20 | 9.63±0.13 | 0.96 (0.72–1.20) |
| Prazosin    | 21 | 8.39±0.09  | 0.99 (0.81–1.17) | 16 | 8.80±0.17  | 0.83 (0.61–1.05) |
| Bunazosin   | 22 | 8.44±0.10  | 0.97 (0.79–1.15) | 17 | 8.75±0.13  | 0.85 (0.68–1.03) |
| Yohimbine   | 21 | 7.34±0.19  | 0.82 (0.59–1.05) | 20 | 6.10±0.07  | 0.87 (0.76–0.99) |

\( pA_2 \) values were expressed as means ± S.E. The slope of the Schild plot was expressed as means with 95\% confidence limits.

Fig. 3. Effects of HSR-175 (A), prazosin (B), bunazosin (C) and yohimbine (D) on the clonidine-induced inhibitory response to twitch contraction induced by electrical transmural stimulation (0.1 Hz) in rat vas deferens. Twitch contractile responses to electrical transmural stimulation before clonidine treatment were taken as 100\%. Each value is the mean ± S.E. of 4 to 12 experiments.
Table 2. \(pA_2\) values and slope of the Schild plot for HSR-175, prazosin, bunazosin and yohimbine at presynaptic \(\alpha_2\)-adrenoceptors in rat vas deferens and \(\alpha_1\)-adrenoceptor selectivities of these antagonists

| Antagonist | Rat Vas deferens | \(\alpha_1/\alpha_2\) Ratio |
|------------|-----------------|--------------------------|
|            | \(pA_2\)       | Slope                    | \(\alpha_1\text{(Me)}/\alpha_2\) | \(\alpha_1\text{(Ao)}/\alpha_2\) |
| HSR-175    | 6.41 ± 0.11     | 0.96 (0.73-1.19)          | 9330                            | 1660                             |
| Prazosin   | 5.38 ± 0.10     | --                       | 1020                            | 2630                             |
| Bunazosin  | 5.95 ± 0.15     | 1.15 (0.79-1.51)          | 310                             | 630                              |
| Yohimbine  | 7.68 ± 0.09     | 1.09 (0.84-1.35)          | 0.46                            | 0.026                            |

\(pA_2\) values were expressed as means ± S.E. The slope of the Schild plot was expressed as means with 95% confidence limits. \(\alpha_1\text{(Me)}/\alpha_2\): Antilogarithm of the difference between \(pA_2\) values in dog mesenteric artery and rat vas deferens. \(\alpha_1\text{(Ao)}/\alpha_2\): Antilogarithm of the difference between \(pA_2\) values in rabbit thoracic aorta and rat vas deferens. The \(pA_2\) value for prazosin was calculated as the negative logarithm of \(K_B\); therefore, the slope of the Schild plot was not determined.

Effects on presynaptic \(\alpha_2\)-adrenoceptor in rat vas deferens

In the rat vas deferens, clonidine inhibited the twitch contraction induced by electrical stimulation in a concentration-dependent manner. The concentration-inhibition curves for clonidine were shifted to the right in a parallel manner in the presence of HSR-175 (10\(^{-6}\) - 10\(^{-5}\) M), bunazosin (3 \times 10\(^{-6}\) - 3 \times 10\(^{-5}\) M) and yohimbine (3 \times 10\(^{-8}\) - 3 \times 10\(^{-7}\) M) (Fig. 3). The slopes of the Schild plot for HSR-175, bunazosin and yohimbine were not different from unity (Table 2). In the case of prazosin, only two concentration (3 \times 10\(^{-6}\) and 10\(^{-5}\) M) were tested due to the low solubility at higher concentrations (Fig. 3). Therefore, the \(pA_2\) value for prazosin was calculated as the negative logarithm of \(K_B\), where \(K_B\) is a dissociation constant (13). None of the antagonists tested affected the resting tension of the rat vas deferens.

From the \(pA_2\) values obtained in the dog mesenteric arteries, rabbit thoracic aorta and rat vas deferens, the \(\alpha_1\)- and \(\alpha_2\)-adrenoceptor selectivity of each antagonist was estimated. For this purpose, the antilogarithm of the difference between the \(pA_2\) values obtained in the dog mesenteric arteries or the rabbit aorta (postsynaptic \(\alpha_1\)-adrenoceptors) and the rat vas deferens (presynaptic \(\alpha_2\)-adrenoceptors) was calculated (Table 2). HSR-175, prazosin and bunazosin were more selective at postsynaptic \(\alpha_1\)-adrenoceptors than at presynaptic \(\alpha_2\)-adrenoceptors. The \(\alpha_1\text{(Me)}/\alpha_2\) ratio for HSR-175 was relatively greater than the \(\alpha_1\text{(Ao)}/\alpha_2\) ratio (9330 versus 1660). On the other hand, the \(\alpha_1\text{(Me)}/\alpha_2\) ratio for prazosin and bunazosin were relatively smaller than the \(\alpha_1\text{(Ao)}/\alpha_2\) ratio (1020 versus 2630 and 310 versus 630, respectively). In contrast, yohimbine was more selective at presynaptic \(\alpha_2\)-adrenoceptors.

Effects on postsynaptic \(\alpha_2\)-adrenoceptor in dog saphenous veins

Clonidine produced concentration-dependent contraction in the dog saphenous veins where the postsynaptic \(\alpha_1\)-adrenoceptors were masked by phenoxybenzamine. HSR-175 (3 \times 10\(^{-7}\) - 3 \times 10\(^{-6}\) M) and yohimbine (10\(^{-8}\) - 10\(^{-7}\) M) produced parallel shifts to the right of the concentration-response curves for clonidine without a decrease in the maximal response. The slopes of the Schild plot for HSR-175 and yohimbine were not different from unity (Table 3). The \(pA_2\) value for HSR-175 was 7.05 ± 0.16, which was much lower than those at postsynaptic \(\alpha_1\)-adrenoceptors. On the other hand, the \(pA_2\) value for yohimbine (8.88 ± 0.25) was much higher than those at postsynaptic \(\alpha_1\)-adrenoceptors (Table 3).

Effects on the responses to electrical transmural stimulation in the dog mesenteric artery

In the presence of \(\alpha,\beta\)-methylene ATP (10\(^{-5}\) M) and...
propranolol (10^{-6} M), electrical transmural stimulation at 10 Hz for 10 sec produced a transient contraction in the dog mesenteric artery. This contraction was abolished by guanethidine (3 \times 10^{-6} M) or tetrodotoxin (3 \times 10^{-7} M) (data not shown). HSR-175 (3 \times 10^{-12} - 10^{-9} M), prazosin (10^{-10} - 10^{-7} M) and bunazosin (10^{-10} - 10^{-7} M) inhibited the contraction in a concentration-dependent manner (Fig. 4). The ED_{50} value for HSR-175 (6.5 \pm 1.2 \times 10^{-11} M) was much lower than those for prazosin (1.7 \pm 0.3 \times 10^{-9} M) and bunazosin (1.4 \pm 0.4 \times 10^{-9} M).

Effects on the contractile responses to 5-HT, histamine, KCl and angiotensin II in rabbit thoracic aorta

HSR-175 (10^{-6} M) did not affect of concentration-response curves for 5-HT, histamine, KCl and angiotensin II in the rabbit thoracic aorta (Fig. 5)

DISCUSSION

Postsynaptic \( \alpha \)-adrenoceptors of the dog mesenteric artery and the rabbit thoracic aorta are characterized as the \( \alpha_1 \)-adrenoceptor subtype (10, 14, 15). Prazosin, bunazosin and yohimbine competitively inhibited the concentration-response curves of noradrenaline in both the arteries. The pA_{2} values for prazosin and bunazosin were higher than that for yohimbine (Table 1). These results confirm the previous conclusion that the contractile response to noradrenaline is mediated through postsynaptic \( \alpha_1 \)-adrenoceptors in the dog mesenteric artery and the rabbit thoracic aorta (10, 14, 15).

HSR-175 antagonized the contractile responses to noradrenaline in such preparations, and the slopes of the Schild plot were close to unity. The pA_{2} values for HSR-175 were much higher than those for prazosin and bunazosin. Furthermore, HSR-175 inhibited the sympathetic adrenergic contraction in the dog mesenteric artery and the potency for the inhibitory effect of HSR-175 was much greater than those for the inhibitory effects of prazosin and bunazosin. These results strongly indicate that HSR-175 is a very potent and competitive antagonist on postsynaptic \( \alpha_1 \)-adrenoceptors.

In addition to this, HSR-175 showed presynaptic and postsynaptic \( \alpha_2 \)-adrenoceptor blocking activities, which
were evaluated in the rat vas deferens and the dog saphenous vein, respectively. However, the potencies were markedly weaker than the postsynaptic \( \alpha_1 \)-adrenoceptor blocking activity. The ratio of the \( pA_2 \) value at postsynaptic \( \alpha_1 \)-adrenoceptors to that at presynaptic \( \alpha_2 \)-adrenoceptors was more than 1000, which was the same order as that of prazosin but significantly greater than that of bunazosin and yohimbine. Therefore, it is likely that HSR-175 is highly selective to \( \alpha_1 \)-adrenoceptors as compared with \( \alpha_2 \)-adrenoceptors.

HSR-175 at a high concentration of \( 10^{-6} \) M showed no inhibitory effects on the contractions induced by 5-HT, histamine, KCl and angiotensin II. Furthermore, HSR-175 was without effect on the responses to isoproterenol in the guinea pig atria and to acetylcholine in the guinea pig ileum (S. Hashimoto et al., unpublished observations). Therefore, it is likely that HSR-175 at the concentrations tested shows no effect on \( \beta \)-adrenoceptors, muscarinic receptors, 5-HT receptors, histamine receptors and angiotensin II receptors.

Recently, there has been increasing evidence for the existence of \( \alpha_1 \)-adrenoceptor subtypes. In functional studies with vascular smooth muscles, \( \alpha_1 \)-adrenoceptors have been divided into \( \alpha_{1N} \), \( \alpha_{1H} \) and \( \alpha_{1L} \) subtypes, which are based on their affinities to prazosin and HV-723 (16, 17). Noradrenaline-induced contraction of the dog mesenteric artery and the rabbit thoracic aorta are mediated through \( \alpha_{1N} \)- and both \( \alpha_{1L} \)- and \( \alpha_{1H} \)-adrenoceptor subtypes, respectively (16, 17). It is very interesting to note that the affinities of HSR-175 for \( \alpha_1 \)-adrenoceptors are different between these two preparations. This may suggest a possibility that HSR-175 can discriminate between different \( \alpha_1 \)-adrenoceptor subtypes. Further studies are needed to verify this point.

In conclusion, the present in vitro study shows that the newly synthesized compound HSR-175 is a potent and selective postsynaptic \( \alpha_1 \)-adrenoceptor antagonist. The extremely high affinity to postsynaptic \( \alpha_1 \)-adrenoceptors may warrant its future use for the treatment of \( \alpha_1 \)-adrenoceptor-associated diseases such as hypertension, cardiac failure and lower urinary tract disorders.

Acknowledgments

The authors thank Ms. Harumi Haba for secretarial work.

REFERENCES

1 Starke, K. and Docherty, J.R.: Recent developments in \( \alpha \)-adrenoceptor research. J. Cardiovasc. Pharmacol. 2, S269–S286 (1980)
2 McGrath, J.C.: Evidence for more than one type of postjunctional \( \alpha \)-adrenoceptor. Biochem. Pharmacol. 31, 467–484 (1982)
3 Langer, S.Z. and Hicks, P.E.: \( \alpha \)-Adrenoceptor subtypes in blood vessels: physiology and pharmacology. J. Cardiovasc. Pharmacol. 6, S547–S558 (1984)
4 Honda, K., Miyata-Osawa, A. and Takenaka, T.: \( \alpha_1 \)-Adrenoceptor subtype mediating contraction of the smooth muscle in the lower urinary tract and prostate of rabbit. Naunyn Schmiedebergs Arch. Pharmacol. 330, 16–21 (1985)
5 Kunisawa, Y., Kawabe, K., Niijima, T., Honda, K. and Takenaka, T.: A pharmacological study of \( \alpha \)-adrenergic receptor subtypes in smooth muscle of human urinary bladder base and prostate urethra. J. Urol. 134, 396–398 (1985)
6 Hoffman, B.B. and Lefkowitz, R.J.: Adrenergic receptor antagonists. In The Pharmacological Basis of Therapeutics, Edited by Gilman, A.G., Rall, T.W., Nies, A.S. and Taylor, P., 8th edition, p. 221–243, Pergamon Press, New York (1990)
7 Hedlund, H., Andersson, K.-E. and Ek, A.: Effects of prazosin in patients with benign prostatic obstruction. J. Urol. 130, 275–278 (1983)
8 Furchgott, R.F.: The requirement of endothelial cells in the relaxation of arteries by acetylcholine and some vasodilators. Trends Pharmacol. Sci. 2, 173–176 (1981)
9 Muramatsu, I.: The effect of reserpine on sympathetic, purinergic neurotransmission in the isolated mesenteric artery of the dog: a pharmacological study. Br. J. Pharmacol. 91, 467–474 (1987)
10 Oshita, M., Iwanaga, Y., Hashimoto, S., Morikawa, K. and Muramatsu, I.: Pharmacological studies on the selectivity of HV-723, a new \( \alpha_1 \)-adrenoceptor antagonist. Japan. J. Pharmacol. 47, 229–237 (1988)
11 Muramatsu, I., Ohmura, T. and Oshita, M.: Comparison between sympathetic adrenergic and purinergic transmission in the dog mesenteric artery. J. Physiol. (Lond.) 411, 227–243 (1989)
12 Arunlakshana, O. and Schild, H.O.: Some quantitative uses of drug antagonists. Br. J. Pharmacol. 14, 48–58 (1959)
13 Furchgott, R.F.: The classification of adrenoceptors (adrenergic receptors). An evaluation from the standpoint of receptor theory. In Handbook of Experimental Pharmacology, Vol. 33, Edited by Blaschko, H. and Muscholl, E., p. 283–335, Springer-Verlag, Berlin (1972)
14 Sakakibara, Y., Fujiwara, M. and Muramatsu, I.: Pharmacological characterization of the \( \alpha \)-adrenoceptors of the dog basilar artery. Naunyn Schmiedebergs Arch. Pharmacol. 319, 1–7 (1982)
15 Docherty, J.R. and Starke, K.: Postsynaptic \( \alpha \)-adrenoceptor subtypes in rabbit blood vessels and rat anococcygeal muscle studied in vitro. J. Cardiovasc. Pharmacol. 3, 854–866 (1981)
16 Muramatsu, I., Ohmura, T., Kigoshi, S., Hashimoto, S. and Oshita, M.: Pharmacological subclassification of \( \alpha_1 \)-adrenoceptors in vascular smooth muscle. Br. J. Pharmacol. 99, 197–201 (1990)
17 Muramatsu, I., Kigoshi, S. and Oshita, M.: Two distinct \( \alpha_1 \)-adrenoceptor subtypes involved in noradrenaline contraction of the rabbit thoracic aorta. Br. J. Pharmacol. 101, 662–666 (1990)