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# Selectivity and specificity for $\alpha_1$-adrenoceptor blocking activity of $R(-)$- and $S(+)$-YM-12617 orally administered to pithed, spontaneously hypertensive rats

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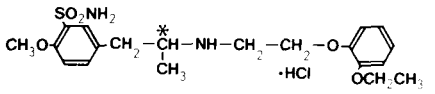
The selectivity and specificity for $\alpha_1$-adrenoceptor blocking activity of the optical isomers of YM-12617 have been examined in pithed, spontaneously hypertensive rats. $R(-)$-YM-12617 and prazosin (1 mg kg$^{-1}$ p.o.) produced 360- and 88-fold rightward shifts, respectively, of the dose-response curve of control to phenylephrine, whereas $S(+)$-YM-12617 (1 mg kg$^{-1}$ p.o.) failed to cause a shift. Based on dose ratio, $R(-)$-YM-12617 was 320 times more potent as an $\alpha_1$-adrenoceptor antagonist than $S(+)$-YM-12617. This potency ratio corresponded to that formed in an in-vitro study. Both $R(-)$- and $S(+)$-YM-12617 hardly affected the UK-14304, angiotensin II, vasopressin and isoprenaline dose-response curves. These results suggest that $R(-)$-YM-12617 exerted selective $\alpha_1$-adrenoceptor blocking activity and its activity was specific for $\alpha_1$-adrenoceptors.

YM-12617, 5-[2-[[2-(*o*-ethoxyphenoxy)ethyl]amino]-propyl]-2-methoxybenzenesulphonamide hydrochloride, is a structurally new type of potent and highly selective $\alpha_1$-adrenoceptor antagonist (Honda et al 1985a). The $\alpha_1$-adrenoceptor antagonist activity of YM-12617 was found to be approximately 10 times more potent than that of prazosin in the rabbit isolated aorta, urinary bladder base, urethra and prostate (Honda et al 1985a,b) using pharmacological techniques, and in the guinea-pig isolated mesenteric and pulmonary arteries using an electrophysiological technique (Fujii & Kuriyama 1985), and in the rat brain membrane using a binding technique (Honda et al 1985a). From its chemical structure (I), YM-12617 can




I

be recognized as a I. Chemical structure of YM-12617. Asterisk denotes the asymmetric centre.

catecholamine derivative whereas known $\alpha_1$-adrenoceptor antagonists such as prazosin, WB 4101, BE 2254 and AR-C 239 have no apparent structural similarity to catecholamines.

An asymmetric centre exists at the $\alpha$-carbon atom in the phenethylamine of YM-12617, therefore two optical isomers are possible: $R(-)$- and $S(+)$-YM-12617. In the rabbit isolated aorta, urinary bladder base, urethra and prostate, $R(-)$-YM-12617 is 50–580 times more potent as an antagonist than $S(+)$-YM-12617 for the $\alpha_1$-adrenoceptor (Honda & Nakagawa 1986; Takayanagi et al 1986). The effects of oral administration of $R(-)$- and $S(+)$-YM-12617 have not been investigated.

In the present study, the selectivity and specificity for the $\alpha_1$-adrenoceptor antagonist effect of the orally administered optical isomers of YM-12617, was examined in pithed, spontaneously hypertensive rats.

## *Materials and methods*

Male spontaneously hypertensive rats (SHR) of Okamoto-Aoki strain (Hoshino, Saitama, Japan), 320–390 g, were given an oral dose of test drug or vehicle (0·5% methylcellulose solution, 5 mL kg$^{-1}$) via a stomach tube. According to the method described previously (Honda et al 1985c), animals were anaesthetized with ether and pithed by inserting a steel rod into the spinal cord via the orbit 1 h after dosing. Immediately after pithing, SHR were bilaterally vagotomized at the neck and ventilated artificially with room air in a tidal volume of 1 mL/100 g at a rate of 50 breaths min$^{-1}$ using a rodent respirator (SN-480-7, Shinano, Tokyo, Japan). The carotid artery and femoral vein were cannulated for blood pressure recording and intravenous injections of agonists, respectively. Systemic blood pressure was measured with a transducer (MPU-0·5, Nihon Kohden, Tokyo, Japan) and heart rate was measured with a cardiotachometer (RT-5, Nihon Kohden) triggered by the pulse wave of blood pressure. After a 15 min stabilization period, increasing doses of phenylephrine, UK-14 304, angiotensin II, vasopressin and isoprenaline were injected intravenously.

Drugs: $R(-)$- and $S(+)$-YM-12617 were prepared by Dr Fujikara in Chemistry Department, Yamanouchi Pharmaceutical Co. Ltd. Physicochemical properties of the optical isomers were as follows: $R(-)$-YM-12617(YM-12617-1): m.p. 228–230 °C, $[\alpha]_D^{24}$ −4·0° (c = 0·35, MeOH), optical purity 99·9%; $S(+)$-YM-12617(YM-12617-2): m.p. 228–230 °C, $[\alpha]_D^{24}$ +4·2° (c = 0·36, MeOH), optical purity 99·5%.

Angiotensin II (Protein Research Foundation, Osaka, Japan), (−)-isoprenaline HCl (Tokyo Kasei,

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Tokyo, Japan), (−)-phenylephrine (Tokyo Kasei) and vasopressin (Sankyo, Tokyo, Japan) were obtained commercially. UK-14 304 tartrate (2-(8-bromoquinoxalyl-7-imino)imidazolidine tartrate) and prazosin HCl were kindly donated by Pfizer (Sandwich, UK and New York, USA). Ascorbic acid (0·01%) was added to isoprenaline-containing intravenous solution to retard oxidation. Doses are expressed in terms of the salts.

*Statistics.* All results were expressed as the mean ± s.e.m. or the mean with 95% confidence limits and the statistical significance was assessed by non-paired Student *t*-test ($P < 0.05$). In the case of *R*(−)-YM-12617 for $\alpha_1$-adrenoceptors, the slope of Schild regression was quantified by the method of Arunlakshana & Schild (1959).

*Results*

Base line diastolic blood pressure (DBP) and heart rate (HR) of pithed rats treated with *R*(−)-YM-12617 (DBP 67 ± 5 mmHg, HR 299 ± 10 beats $min^{-1}$; n = 5), *S*(+)-YM-12617 (DBP 67 ± 5 mmHg, HR 255 ± 12 beats $min^{-1}$; n = 5) and prazosin (DBP 56 ± 3 mmHg, HR 290 ± 7 beats $min^{-1}$; n = 7) were not significantly different from those of rats treated with vehicle (DBP 56 ± 3 mmHg, HR 275 ± 9 beats $min^{-1}$; n = 5).

All vasopressors, phenylephrine (0·3–10 μg $kg^{-1}$ i.v.), UK-14304 (0·3–30 μg $kg^{-1}$ i.v.), angiotensin II (1–300 ng $kg^{-1}$ i.v.) and vasopressin (3–100 m iu $kg^{-1}$ i.v.) dose-dependently increased DBP, and isoprenaline (1–100 ng $kg^{-1}$ i.v.) dose-dependently increased HR of rats pretreated orally with vehicle (0·5% methylcellulose solution) (control). The phenylephrine dose-response curve of control was shifted 360-fold to the right in animals receiving *R*(−)-YM-12617 (1 mg $kg^{-1}$ p.o.), whereas it was not modified in those receiving *S*(+)-YM-12617 (1 mg $kg^{-1}$ p.o.) (Fig. 1). *R*(−)-YM-12617 produced a 3-fold rightward shift of the dose-response curves to UK-14304 whereas *S*(+)-YM-12617 did not affect the response to UK-14304 (Fig. 1). In contrast, *R*(−)- and *S*(+)-YM-12617 failed to affect the angiotensin II, vasopressin and isoprenaline dose-response curves of control (Fig. 1, Table 1). Prazosin (1 mg $kg^{-1}$ p.o.) exerted an 88-fold rightward shift of the dose-response curves to phenylephrine, but had hardly any effects on the responses to UK-14304, angiotensin II, vasopressin or isoprenaline.

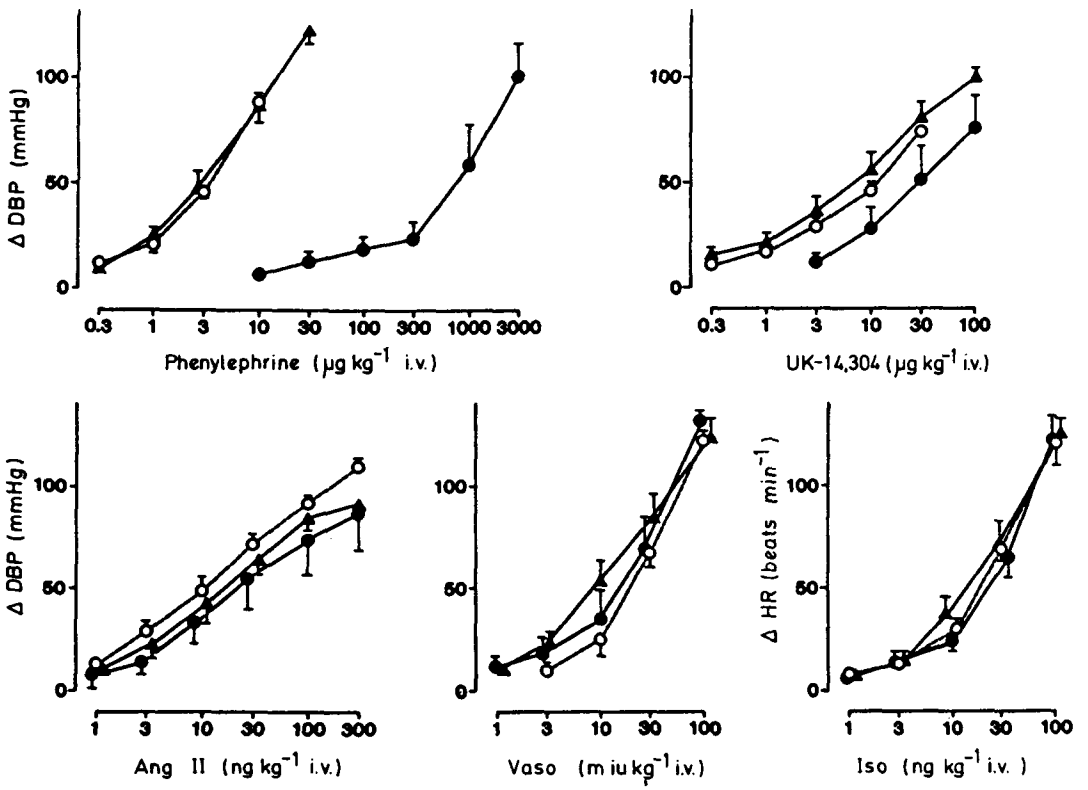


FIG. 1. Effects of *R*(−)-YM-12617 (●; 1 mg $kg^{-1}$ p.o.) and *S*(+)-YM-12617 (○; 1 mg $kg^{-1}$ p.o.) on increases in diastolic blood pressure (BDP) induced by phenylephrine, UK-14304, angiotension II (Aug II) and vasopressin (Vaso) and increase in heart rate (HR) induced by isoprenaline (ISO) or vehicle (▲; 0·5% methylcellulose solution 5 mL $kg^{-1}$ p.o.) in pithed, spontaneously hypertensive rats. The results are the mean ± s.e.m. of 4 or 5 animals.

Table 1. Effects of $R(-)$- and $S(+)$-YM-12617 on vasopressor and tachycardia in pithed, spontaneously hypertensive rats.

| | Dose (mg kg$^{-1}$ p.o.) | ED50 value: Phenylephrine (μg kg$^{-1}$) | UK-14304 (μg kg$^{-1}$) | Vasopressin (m iu kg$^{-1}$) | Isoprenaline (ng kg$^{-1}$) | Angiotensin II (ng kg$^{-1}$) |
|---|---|---|---|---|---|---|
| Control | | 3·0 ± 0·3 | 10 ± 2 | 19 ± 3 | 19 ± 4 | 12 ± 4 |
| $R(-)$-YM-12617 | 0·1 | 46 ± 22 (15) | 10 ± 6 (1) | 18 ± 6 (0·9) | | 22 ± 6 (2) |
| | 0·3 | 109 ± 36* (36) | 5 ± 1* (0·5) | 14 ± 5 (0·7) | 31 ± 6 (2) | 12 ± 5 (1) |
| | 1 | 1080 ± 450* (360) | 24 ± 6 (2) | 20 ± 7 (1) | 23 ± 5 (1) | 18 ± 6 (2) |
| $S(+)$-YM-12617 | 1 | 3·4 ± 1 (1) | 7 ± 2 (0·7) | 11 ± 4 (0·6) | 17 ± 6 (0·9) | 20 ± 5 (2) |
| Prazosin | 1 | 264 ± 115* (88) | 28 ± 12 (3) | 10 ± 2* (0·5) | 16 ± 3 (0·8) | 36 ± 4* (3) |

Data are the mean ± s.e.m. of 4 to 7 animals.
ED50: Intravenous dose required to increase diastolic blood pressure by 50 mmHg or heart rate by 50 beats min$^{-1}$.
Dose ratio represents figure in parentheses; ED50 (drug)/ED50 (control).
* $P < 0.05$ (drug vs control).

Smaller doses of $R(-)$-YM-12617 (0·1 and 0·3 mg kg$^{-1}$ p.o.) also caused the dose-response curves to phenylephrine to shift to the right dose-dependently with dose ratios of 15 and 36, respectively (Table 1). The slope of Schild plot for $R(-)$-YM-12617 at doses of 0·1, 0·3 and 1 mg kg$^{-1}$ was 1·61 (0·91–2·30, 95% confidence limits; n = 15), and its slope was greater than unity, but not significant.

*Discussion*

Some vascular smooth muscle contains postsynaptic $\alpha_2$-adrenoceptors as well as $\alpha_1$-adrenoceptors (for review see Timmermans & van Zwieten 1982, Langer & Shepperson 1982). To study postsynaptic $\alpha_1$- and $\alpha_2$-adrenoceptors, pithed animals were often used as an in-vivo model.

Oral administration of $R(-)$- and $S(+)$-YM-12617 and prazosin did not reduce the base line DBP showing that they did not have direct vasodilator activities. Oral $R(-)$-YM-12617 produced a marked rightward shift of the dose-response curve to phenylephrine ($\alpha_1$-adrenoceptor blocking effect) and marginal rightward shift of the dose-response curve to UK-14304 ($\alpha_2$-adrenoceptor blocking effect) at the dose of 1 mg kg$^{-1}$. This result suggests $R(-)$-YM-12617 is a selective $\alpha_1$-adrenoceptor antagonist. At an oral dose of 1 mg kg$^{-1}$, $R(-)$-YM-12617 was 320 times more potent than $S(+)$-YM-12617 in $\alpha_1$-adrenoceptor antagonist activity. This isomeric activity ratio corresponds to that found in-vitro (Honda & Nakagawa 1986) and in an intravenous study in pithed rats (unpublished data). Inasmuch as the $\alpha_1$-adrenoceptor blocking activity of the optical isomers of YM-12617 showed a constant ratio after oral administration, metabolic transformations of these compounds administered orally might not occur. The specificity of $R(-)$-YM-12617 for $\alpha_1$-adrenoceptors is high, since $R(-)$-YM-12617 did not produce any effects on the dose-response to angiotensin II, vasopressin and isoprenaline.

In summary, $R(-)$-YM-12617 exerted selective $\alpha_1$-adrenoceptor blocking activity and its activity was specific for $\alpha_1$-adrenoceptors.

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