Adrenoceptor Blocking and Cardiovascular Effects of the Optical Isomers of Amosulalol (YM-09538), a Combined $\alpha$- and $\beta$-Adrenoceptor Blocking Agent, and the Corresponding Desoxy Derivative (YM-11133) in Rats

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Abstract—The pharmacological activities of the enantiomers of amosulalol (YM-09538), a combined $\alpha$- and $\beta$-adrenoceptor antagonist, and the corresponding desoxy derivative (YM-11133) were investigated in the cardiovascular system of rats. The optical isomers of amosulalol and YM-11133 antagonized the vasopressor effect of phenylephrine and the positive chronotropic effect of isoproterenol in normotensive pithed rats. Based on $DR_2$ values ($\mu g/kg$, i.v.) obtained from Schild plots, (+)-amosulalol and YM-11133 ($DR_2=30$) were approximately 10 times more potent than (-)-amosulalol ($DR_2=324$) in blocking $\alpha_1$-adrenoceptors. For $\beta_1$-adrenoceptors, in contrast, (-)-amosulalol ($DR_2=107$) was approximately 60 times more potent than (+)-amosulalol ($DR_2=6460$), which was almost equipotent with YM-11133 ($DR_2=3250$). The results indicate that the optical isomers of amosulalol interact differently with $\alpha_1$- and $\beta_1$-adrenoceptors. The effects of these phenethylamines on blood pressure and heart rate were studied in urethane-anesthetized rats (i.v.). The rank order of hypotensive potency in anesthetized rats ((+)-desoxy>(-)-form) was consistent with the rank order of $\alpha_1$-adrenoceptor antagonism in pithed rats. In contrast, (-)-amosulalol having a more potent $\beta_1$-adrenoceptor antagonist activity than (+)-amosulalol and YM-11133 only produced dose-dependent bradycardia at the hypotensive doses. The results indicate that the vascular $\alpha_1$- and cardiac $\beta_1$-adrenoceptor blocking activities of the optical isomers of amosulalol contribute to their hypotensive and bradycardia, respectively. Thus, the racemate of amosulalol appears to exert an overall activity reflecting the activities of the individual isomers.

Amosulalol (YM-09538), a sulfamoylphenethanolamine derivative, is a newly developed antihypertensive agent with combined $\alpha$- and $\beta$-adrenoceptor blocking activities (1, 2). In conscious spontaneously hypertensive rats (SHR), renal hypertensive rats and DOCA/salt hypertensive rats, a single oral administration of amosulalol (3–30 mg/kg) lowered acutely systolic blood pressure with a duration of over 6 hr. Repeated oral administration of amosulalol 50 mg/kg, b.i.d., for 12 weeks produced not only an antihypertensive effect without evidence of tolerance, but also reductions in plasma renin activity and heart rate in SHR with established hypertension (3). In adrenoceptor blocking studies in isolated tissues of rats and guinea pigs (2, 4) and in radioligand binding studies (5), amosulalol displayed a two orders of magnitude greater selective antagonism of $\alpha_1$-adrenoceptors than $\alpha_2$-adrenoceptors but amosulalol showed no selectivity towards $\beta_1$- or $\beta_2$-adrenoceptors. In guinea pig vascular tissues, amosulalol blocked the actions of norepinephrine and isoproterenol at pre- and post-junctional
membranes without changing in the membrane properties of the smooth muscle cells. The inhibitory effects of amosulalol may be due to inhibition of $\alpha_1$- and $\beta_1$-adrenoceptors. High concentrations of amosulalol had only weak inhibitory actions on $\alpha_2$-adrenoceptors located in perivascular adrenergic nerve endings and in the smooth muscle membrane of the mesenteric vein (6). Amosulalol has one asymmetric center at the $\beta_1$-carbon (Fig. 1), so two enantiomers of this compound can exist. $\alpha_1$- and $\beta_1$-Adrenoceptor subtype blocking activities of the optical isomers of amosulalol and the corresponding desoxy derivative (YM-11133) have been investigated in anesthetized rats (7), preliminarily, and in isolated tissues (8). (+)-Amosulalol and YM-11133 were one log unit order more potent and less potent than (−)-amosulalol in blocking $\alpha_1$- and $\beta_1$-adrenoceptors, respectively, in both the anesthetized rat and the isolated tissue.

In this paper, postsynaptic vascular $\alpha_1$-adrenoceptor and cardiac $\beta_1$-adrenoceptor antagonist activities and cardiovascular effects of the enantiomers of amosulalol and YM-11133 were investigated in rats in vivo.

Materials and Methods

Male normotensive Wistar rats (Shizuoka Agriculture Coop. Assoc., Shizuoka, Japan) weighing 280–330 g were used for evaluating the postsynaptic vascular $\alpha_1$- and cardiac $\beta_1$-adrenoceptor antagonist activities and cardiovascular functions. The postsynaptic vascular $\alpha_1$- and cardiac $\beta_1$-adrenoceptor blocking activities in pithed normotensive rats were assessed by antagonizing the $\alpha_1$-adrenoceptor mediated pressor effect of phenylephrine and the $\beta_1$-adrenoceptor mediated positive chronotropic effect of isoproterenol, respectively. Cardiovascular functions were investigated in urethane-anesthetized rats (i.v.).

Adrenoceptor blocking activity: Wistar rats were anesthetized with ether and pithed by inserting a steel rod (1.5 mm in diameter) through the orbit and foremen magnum down into the spinal canal. Immediately after pithing, the animals were ventilated artificially with room air in a tidal volume of 1 ml/100 g body weight at a rate of 50 breaths/min using a rodent respirator (SN-480-7, Shinano, Tokyo, Japan). After bilateral vagotomy at the neck level, systemic arterial blood pressure was measured at the left carotid artery via a pressure transducer (MPU-0.5, Nihon Kohden, Tokyo, Japan) and recorded on a Nihon Kohden recorder (RJG-3004). Heart rate was measured with a cardiographs (RT-5, Nihon Kohden) triggered by pulse pressure. In the first series of experiments, the postsynaptic vascular $\alpha_1$-adrenoceptor antagonist activity was studied after a 15 min period when cardiovascular parameters were allowed to stabilize. Phenylephrine was injected into the right femoral vein through a cannula at intervals of approximately 5 to 10 min until an increase in diastolic blood pressure of 80 to 120 mmHg. The dose-response curves for phenylephrine were constructed before and 15 min after i.v. treatment with each dose of antagonists. Three dose levels of antagonists given at an interval of approximately 1 hr were examined in the same animal. In a second series of experiments, the cardiac $\beta_1$-adrenoceptor antagonist activity was investigated in the other pithed rats. Dose-response curves for isoproterenol which was injected at an interval of approximately 5 to 15 min until an increase in heart rate of 80 to 100 beats/min were obtained before and 15 min after i.v. treatment with each dose of antagonists, and then three dose levels of antagonists were examined in the same animal as described above. The doses of antagonists were given at an interval of approximately 90 min. In
the study on both α₁- and β₁-adrenoceptor antagonist activities, both phenylephrine and isoproterenol administered in saline-treated rats (control study) repeatedly gave in 4 trials dose-response curves whose ED50 values were not significantly different from each other (data not shown). The ED50 values, doses of phenylephrine required to elicit a 50 mmHg increase in diastolic blood pressure and those of isoproterenol required to elicit a 50 beats/min increase in heart rate, were calculated from the log dose-response curves, and then the dose-ratio was calculated (3). The adrenoceptor antagonist activities were quantified by the method of Arunlakshana and Schild (9). The dose of antagonist required to produce an agonist dose-ratio of 2 (DR₂) and the slope of the regression line were calculated.

Study in anesthetized rats: Rats were anesthetized with urethane (1.2 g/kg, s.c.), and the vagal nerves were bilaterally cut at the neck level. The tracheas were cannulated to facilitate breathing, but the animals were permitted to respire spontaneously. Systemic arterial blood pressure and heart rate were measured as described above. Mean arterial pressure was calculated as the diastolic blood pressure plus one-third of the pulse pressure (mmHg). The test drugs were non-cumulatively injected into the right femoral vein through a cannula at an interval of 20 min and in a volume of 1 ml/kg.

Drugs: Amosulalol hydrochloride (YM-09538), its optical isomers and the corresponding desoxy derivative (YM-11133) were prepared by Dr. Fujikura in the Chemistry Department of Yamanouchi Pharmaceutical Co. The optical isomers were resolved into (−) and (+) tartaric acid salts of the enantiomers which were recrystallized to constant rotation in order to determine the absolute configuration and subsequently converted to hydrochloride salts. Physicochemical properties of the optical isomers were as follows:

R·(−)-Amosulalol: m.p. 158–160,
[α]₂³⁰iang -30.4 (c=1, MeOH)
S·(+)-Amosulalol: m.p. 158–160,
[α]₂³⁰iang +30.7 (c=1, MeOH)
(−)-Phenylephrine hydrochloride and (−)-isoproterenol hydrochloride (Tokyo Kasei, Tokyo, Japan), phentolamine methanesulfonate (Ciba-Geigy, Takarazuka, Japan), propranolol hydrochloride (Sigma Chemical Co., U.S.A.) were obtained commercially. Prazosin hydrochloride (Pfizer Inc., U.S.A.) was kindly donated by its manufacture. The enantiomers and racemate of amosulalol and the other drugs were dissolved in physiological saline (0.9 % w/v) but YM-11133 and prazosin were dissolved in a few drops of 1N HCl and distilled water, and then saline or 0.5% methylcellulose solution was added to them up to the appropriate volume. Ascorbic acid (0.01%, Takeda Chemical Industry, Japan) was added to the isoproterenol-containing solution to retard oxidation. Doses are expressed in terms of the salts, except for YM-11133, which was expressed as the base.

Data analysis: All results in the text are expressed as the mean±S.E.M. or the mean and 95% confidence limits with the number of experiments. Comparisons of values before and after the drug in the same group of pithed and anesthetized rats, and those of the vehicle and drug-treated group in conscious SHR were made by Student’s paired and non-paired t-test, respectively. P values less than 0.05 are considered to be significant. Regression equations were calculated by the method of least squares.

Results

Adrenoceptor blocking effects
The basal diastolic blood pressure and heart rate were 55±2 mmHg and 305±5 beats/min (n=32), respectively, in pithed rats. ED50 values for phenylephrine and isoproterenol, doses of phenylephrine required to elicit a 50 mmHg increase in diastolic blood pressure and those of isoproterenol required to elicit a 50 beats/min increase in heart rate, were 2.7±0.2 μg/kg and 9.2±0.4 ng/kg (n=16), respectively, before treatment with antagonist. (+)-, (−)- and (±)-Amosulalol did not significantly (P>0.05) decrease basal blood pressure and heart rate.

Postsynaptic vascular α₁-adrenoceptor antagonistic activity: The log dose-response curves with respect to the increase in diastolic pressure elicited by phenylephrine, before and after pretreatment with (+)-amosulalol
(100, 300 and 1000 μg/kg, i.v.), (-)amosulalol (300, 1000 and 3000 μg/kg, i.v.), (+)-amosulalol and YM-11133 (30, 100, 300 and 1000 μg/kg, i.v.) are shown in Fig. 2. (+)-, (-)- and (+)-Amosulalol and YM-11133 caused a parallel shift of the log dose-response curves for phenylephrine to the right. Based on DR2 values (Table 1), (+)-amosulalol and YM-11133 were 10.7 and 10.9 times more potent than (-)-amosulalol in antagonizing phenylephrine-induced vasoressor response, respectively. In the same experimental condition, prazosin and phentolamine, α-adrenoceptor antagonists, also antagonized the phenylephrine-induced vasopressor effects with DR2 values of 1.66 (n=12) and 128 (n=16) μg/kg, i.v., respectively, whereas propranolol hardly affected the log dose-response curves for phenylephrine up to 1 mg/kg, i.v. Both (+)-

![Alpha-1 blockade](image1)

![Beta-1 blockade](image2)

**Fig. 2.** Antagonism by (+)-, (-)- and (+)-amosulalol and the corresponding derivative (YM-11133) of phenylephrine-induced vasopressor effects (Left panel) and isoproterenol-induced tachycardiac effects (Right panel) in pithed rats. The results are the mean±S.E.M. of 4 animals.
Table 1. Alpha-1 and beta-1 adrenoceptor blocking activities of amosulalol, its optical isomers and the corresponding desoxy derivative (YM-11133) in pithed rats

|               | Alpha-1 blockade | Beta-1 blockade |
|---------------|------------------|-----------------|
|               | n    | DR₂c  | Relative potency | Slope | n    | DR₂  | Relative potency | Slope  |
| (±)-Amosulalol| 16   | 49.0  | 1/1.62         | 0.608 | 16   | 135  | 1/1.28          | 1.20   |
|  (             |      | (25.1–97.7) |                      | (0.299–0.913) | (110–166) |                      | (1.01–1.31) |                      |
| (-)-Amosulalol| 12   | 324   | 1/10.7         | 0.621 | 16   | 107  | 1.00          | 1.41   |
|  (             |      | (263–398) |                      | (0.476–0.766) | (77.6–145) |                      | (1.26–1.56) |                      |
| (+)-Amosulalol| 16   | 30.2  | 1.00           | 0.967 | 8    | 6460 | 1/60.4        | 1.24   |
|  (             |      | (21.4–42.7) |                      | (0.805–1.13) | (3020–13800) |                      | (0.496–1.98) |                      |
| YM-11133      | 16   | 29.6  | 1.02           | 1.18  | 8    | 3250 | 1/30.4        | 1.64   |
|  (             |      | (24.1–37.3) |                      | (1.08–1.28) | (1960–5270) |                      | (0.994–2.29) |                      |

a : Antagonism of phenylephrine-induced vasopressor effect.  b : Antagonism of isoproterenol-induced tachycardiac effect.  c : DR₂ values (μg/kg, i.v.) and slope of the Schild plot are the mean with 95% confidence limits in parentheses.  n : Number of experiments.

amosulalol and YM-11133 were 18 times less but 4 times more potent than prazosin and phentolamine, respectively, in blocking vascular α₁-adrenoceptors; however, (-)-amosulalol was a weaker antagonist for α₁-adrenoceptors.

Cardiac β₁-adrenoceptor antagonistic activity: Figure 2 also illustrates the log dose-response curves for isoproterenol, before and after pretreatment with (-)- and (±)-amosulalol (100, 300, 1000 and 3000 μg/kg, i.v.), (+)-amosulalol (3000, 10000 and 30000 μg/kg, i.v.) and YM-11133 (1000, 3000 and 10000 μg/kg, i.v.). (-)- and (±)-Amosulalol dose-dependently produced a parallel shift of the log dose-response to isoproterenol to the right, but (+)-amosulalol and YM-11133 did not significantly cause a parallel shift to the right except the highest dose of 10000 μg/kg. Based on DR₂ values (Table 1), (-)-amosulalol, in contrast to its α₁-adrenoceptors, was 60.4 and 30.4 times more potent than (+)-amosulalol and YM-11133, respectively, in antagonizing isoproterenol-induced positive chronotropic response. Propranolol, a β-adrenoceptor antagonist, also antagonized isoproterenol-induced positive chronotropic effects with a DR₂ value of 28.2 μg/kg, i.v. (n=12), whereas prazosin did not cause any changes in the response to isoproterenol up to 1 mg/kg, i.v. (+)-Amosulalol, (-)-amosulalol and YM-11133 were 182, 3.8 and 94 times less potent, respectively than propranolol in antagonizing cardiac β₁-adrenoceptors.

Study in anesthetized rats

Resting mean arterial pressure and heart rate of urethane-anesthetized rats were 114 ±4 mmHg and 459±9 beats/min (n=28),
respectively. (+), (-) and (±)-Amosulalol and YM-11133 (0.001–0.3 mg/kg, i.v.) dose-dependently decreased mean arterial pressure. The reductions in mean arterial pressure elicited by (-) and (±)-amosulalol were associated with bradycardia, whereas (+)-amosulalol and YM-11133 did not significantly affect heart rate (Fig. 3). The ED20 values (i.e., dose required to reduce mean arterial pressure by 20%) for (+), (-), (±)-amosulalol and YM-11133 were 2.6, 47.3, 7.9 and 21.0 μg/kg, i.v., respectively. Based on ED20 values, (+)-amosulalol was 18 times more potent in hypotensive activity than (-)-amosulalol. Prazosin also lowered mean arterial pressure with an ED20 value of 2.5 μg/kg, i.v. (n=6), but it did not affect heart rate. In contrast, propranolol did not significantly (P>0.05) reduce blood pressure, but dose-dependently lowered heart rate. (-) and (±)-Amosulalol dose-dependently reduced heart rate, whereas (+)-amosulalol and YM-11133 hardly influenced heart rate at their hypotensive doses (Fig. 3).

Discussion

Amosulalol, its optical isomers and the corresponding desoxy derivative (YM-11133) have been evaluated for their adrenoceptor blocking activities in vivo. Normotensive pithed rats were used for estimating antagonistic properties of (+), (-) and (±)-amosulalol at the α, and β, adrenoceptor subtypes. These phene-thanolamines dose-dependently antagonized the α, -adrenoceptor-mediated vasopressor response to phenylephrine and the β, -adrenoceptor-mediated positive chronotropic response to isoproterenol in pithed rats. In this experimental procedure, prazosin exerted a dose-dependent shift to the right of the dose-response curves for phenylephrine with a DR2 value of 1.66 μg/kg, i.v., without affecting the dose-response curves for isoproterenol, in contrast to propranolol which did not affect the α, -adrenoceptor-mediated vasopressor responses but caused dose-dependent inhibition of the β, -adrenoceptor mediated positive chronotropic effects with a DR2 value of 28.2 μg/kg, i.v. Based on DR2 values, (+)-amosulalol was found to be 11 times more potent than (-)-amosulalol in blocking vascular α1-adrenoceptors. The α1-adrenoceptor blocking activity of YM-11133 was almost equipotent with (+)- but not (-)-amosulalol. This result in pithed rats is consistent with that of our previous studies in anesthetized rats (7) and in the isolated rabbit aorta (8). (+)-Amosulalol was, in contrast to its α1-adrenoceptor blocking activity, 60 times less potent than (-)-amosulalol in blocking cardiac β1-adrenoceptors. The β1-adrenoceptor blocking activity of YM-11133 was less potent than that of (-)-amosulalol, but nearly equipotent with that of (+)-amosulalol, similar to the findings for the blockade of α1-adrenoceptors. This result with respect to β1-adrenoceptor blocking potency in this pithed rat is consistent with that of our previous reports (7, 8). These results indicate that stereochemical requirements of α1- and β1-adrenoceptors differ for the optical isomers of amosulalol, with the α1-adrenoceptor subtype favoring the (+)-isomer and the desoxy form and the β1-adrenoceptor favoring the (-)-isomer.

The rank order of potency for β1-adrenoceptors in this study ((−)>desoxy>(+)-forms of amosulalol) is in agreement with the order predicted by the Easson-Stedman hypothesis, a theory governing the adrenoceptor mediated activity of the optically active phenethanolamines possessing an asymmetric β-carbon atom (10–12). In contrast, the potency order for α1-adrenoceptors in this study ((+)=desoxy>(−)) is different from that predicted by the Easson-Stedman hypothesis. Phenethanolamines have been previously studied on activation of α- and β-adrenoceptors and on blockade of β-adrenoceptors (10, 12), but not on blockade of α-adrenoceptors. Stereospecificity in α-adrenoceptor blocking agents has been a relatively limited area of research due to the fact that most α-adrenoceptor antagonists do not possess the phenethylamine. Recent studies on the stereoisomers of labetalol (13) and medroxalol (14), which also display combined α- and β-adrenoceptor blocking activities, have indicated that the α- and β-adrenoceptor blocking properties are not distributed uniformly among the individual
isomers. The results of the present study are consistent with those reported for labetalol and medroxalol. However, the studies of the stereochemical requirements for blockade of adrenoceptors by labetalol and medroxalol are complicated by the fact that both of these compounds possess two asymmetric centers, resulting in four possible isomers. In contrast to labetalol and medroxalol, amosulalol possesses only one asymmetric center and then just two isomers exist. It appears, therefore that amosulalol, its enantiomers and the corresponding desoxy derivative are useful pharmacological tools for studying stereochemical requirements for \( \alpha \)- and \( \beta \)-adrenoceptor antagonists of the phenethanolamine class (8).

In anesthetized rats, the hypotensive potency order was: prazosin = (+)-amosulalol > YM-11133 > (-)-amosulalol >> propranolol. Based on ED20 values, (+)-amosulalol was 18 times more potent in hypotensive activity than (-)-amosulalol. This isomeric activity ratio was consistent with that of a vascular \( \alpha_1 \)-adrenoceptor, but not consistent with that of cardiac \( \beta_1 \)-adrenoceptor antagonism. (-)- and (±)-Amosulalol produced bradycardic activity, but (+)-amosulalol and YM-11133 did not at the hypotensive dose-range. This result may be caused by the cardiac \( \beta_1 \)-adrenoceptor blocking property.

The adrenoceptor blocking effects of (±)-amosulalol was approximately half that of (+)-amosulalol for vascular \( \alpha_1 \)-adrenoceptors and half that of (-)-amosulalol for cardiac \( \beta_1 \)-adrenoceptors. The hypotensive and bradycardic effects of (±)-amosulalol were intermediate between those of (+) and (-)-amosulalol in anesthetized rats (i.v.). Thus, (±)-amosulalol is a racemic mixture with equal proportions of the two enantiomers. and as such, the overall activity may be due to the sum of the activities of the individual enantiomers.

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