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New sulfamoylphenethylamines, potent α_1-adrenoceptor antagonists

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The (+)-isomer of amosulalol, a combined α- and β-adrenoceptor antagonist, was one log unit order more potent and less potent than the (−)-isomer in blocking α_1- and β_1-adrenoceptors, respectively, in anaesthetized rats. Nine newly synthesized desoxy compounds derived from amosulalol and its analogues were found to possess potent α_1-adrenoceptor blocking activity and to be practically devoid of β_1-adrenoceptor blocking activity. Among the desoxy derivatives, YM-12617 was more potent than prazosin in blocking α_1-adrenoceptors in anaesthetized rats and in reducing blood pressure, total peripheral resistance and left ventricular work in anaesthetized dogs.

It has been shown that substitution of aralkyl groups at nitrogen atom of phenethanolamines lead to β-adrenoceptor antagonists with additional α-adrenoceptor blocking activity (Brittain & Levy 1976; Grisar et al 1981; Clifton et al 1982). For example, labetalol has been shown to exert a non-selective β-adrenoceptor- and a selective α_1-adrenoceptor-blockade (Brittain & Levy 1976; Blakeley & Summers 1977; Drew 1978). We also found that a series of arylethanolamines derived from benzenesulfonamide possessed both α- and β-adrenoceptor blocking activities (Takenaka et al 1982b; Fujikura et al 1982). However, our analogues such as amosulalol (YM-09538), YM-09586 and YM-09649 differ from labetalol in the ratio of their α- to β-adrenoceptor blocking effect, with the YM-compounds being more potent at α_1-adrenoceptors and labetalol being more potent at β_1-adrenoceptors (Takenaka et al 1982a, b; Asano et al 1983). More recently, we have synthesized the optical isomers of amosulalol and found the (+)-isomer to be one log unit order more potent and less potent than the (−)-isomer in blocking α_1- and β_1-adrenoceptors, respectively. The finding stimulated us to synthesize the desoxy derivatives of amosulalol and its analogues to obtain more potent α_1-adrenoceptor antagonists devoid of β_1-adrenoceptor blocking activity, since prazosin, a selective α_1-adrenoceptor antagonist, is useful for the treatment of congestive heart failure (Awan et al 1978) in which β-adrenoceptor blockade is considered to be contra-indicated (Prichard & Gillam 1969). This paper describes α_1- and β_1-adrenoceptor blocking activities of the optical isomers of amosulalol and nine newly synthesized desoxy compounds derived from amosulalol and its analogues. The sulfamoylphenethylamines reported here were found to be a structurally new type of extremely potent α_1-adrenoceptor antagonists.

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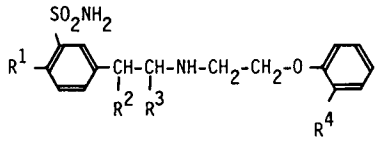
Methods and materials

α_1- and β_1-Adrenoceptor blocking effects in anaesthetized rats. Male Wistar rats, 250–350 g were used. α_1-Adrenoceptor blocking activity was assessed by antagonism of the increase in mean blood pressure induced by (−)-phenylephrine (10 μg kg^{-1} i.v.) in pentolinium (5 mg kg^{-1} i.v.)-treated rats anaesthetized with urethane (1 g kg^{-1} i.p.) (Takenaka et al 1982b). β_1-Adrenoceptor blocking activity was assessed by antagonism of the increase in heart rate induced by (−)-isoprenaline (0·1 μg kg^{-1} i.v.) in reserpinized (8 mg kg^{-1} i.p., 18 h before experiments) rats anaesthetized with pentobarbitone sodium (55 mg kg^{-1} i.p.) (Tachikawa & Takenaka (1973). In all rats bilateral vagotomy was performed at the neck. The calculations of ED50 values were described previously (Tachikawa & Takenaka 1973).

Cardiovascular effects in anaesthetized dogs. Mongrel dogs of either sex weighing 9–16 kg were anaesthetized with pentobarbitone sodium (30 mg kg^{-1} i.v.). Subsequent anaesthesia was maintained by i.v. infusion of the same anaesthetic at a rate of 3–5 mg kg^{-1} h^{-1}. The animals were artificially ventilated with room air. The chest was opened at the 4th intercostal space and cardiac output was determined by an electromagnetic flowmeter (MF-27, Nihon Kohden, Tokyo, Japan) with a probe positioned around the pulmonary artery (Imai et al 1977). Arterial blood pressure was measured with a pressure transducer (MPU-0·5, Nihon Kohden) connected to a catheter inserted into the right femoral artery. Heart rate was measured with a cardiotachometer (AT-600G, Nihon Kohden) triggered by the blood pressure pulse. Left ventricular pressure was obtained by inserting a catheter tip manometer (PC-350A, Millar Instruments, Inc., Texas, USA) into the left ventricle through the left common carotid artery. A ventricular pressure signal was continuously differentiated electronically by a resistance-capacitance circuit (EQ-600G, Nihon Kohden) to give dLVP dt^{-1}. The calculations of total peripheral resistance and left ventricular cardiac work were described previously (Takenaka et al 1982a). The cardiovascular parameters were monitored continuously for 1 h after i.v. administration of test drugs.

Drugs used were: (±)-amosulalol HCl (Yamanouchi Pharmaceutical, Tokyo, Japan), (−)-isoprenaline HCl (Sigma Chemical, St Louis, Mo, USA), (−)-phenylephrine HCl (Tokyo Kasei), phentolamine methanesulfonate (Ciba-Geigy, Takarazuka, Japan), prazosin HCl (Pfizer, New York, NY, USA) and

Table 1. α- and β-Adrenoceptor blocking activities (measured as ED50 values ± s.e.m.) of new sulfamoylphenethylamines and other reference compounds in anaesthetized rats.



Compound	Structure R¹	R²	R³	R⁴	ED50 (mg kg⁻¹ i.v.) α₁-Blockade	β₁-Blockade
YM-09686[a]	OH	OH	H	OCH_3	0·0027 ± 0·0005 (6)	2·58 ± 0·26 (6)
YM-09649[a]	OCH_3	OH	H	OCH_3	0·0079 ± 0·0007 (6)	1·19 ± 0·13 (5)
(±)-Amosulalol[a]	CH_3	OH	H	OCH_3	0·032 ± 0·004 (6)	0·22 ± 0·03 (8)
(−)-Amosulalol					0·33 ± 0·03 (7)	0·20 ± 0·05 (7)
(+)-Amosulalol					0·012 ± 0·002 (6)	8·5 ± 1·1 (6)
YM-12044	OH	H	H	OCH_3	0·0013 ± 0·0003 (4)	10< (3)
YM-12040	OCH_3	H	H	OCH_3	0·0059 ± 0·0008 (4)	6·1 ± 3·4 (2)
YM-11133[b]	CH_3	H	H	OCH_3	0·011 ± 0·002 (4)	5·8 ± 0·2 (3)
YM-12688	OH	H	CH_3	OCH_3	0·00050 ± 0·00006 (3)	10< (2)
YM-12045	OCH_3	H	CH_3	OCH_3	0·00080 ± 0·00007 (6)	5·5 ± 0·9 (4)
YM-12263	CH_3	H	CH_3	OCH_3	0·0012 ± 0·0001 (4)	4·5 ± 0·3 (4)
YM-12689	OH	H	CH_3	OC_2H_5	0·00071 ± 0·00006 (6)	10< (3)
YM-12617	OCH_3	H	CH_3	OC_2H_5	0·00064 ± 0·00007 (5)	10< (6)
YM-13118	CH_3	H	CH_3	OC_2H_5	0·00050 ± 0·00003 (3)	7·7 ± 3 (2)
Phentolamine[a,c]					0·054 ± 0·005 (6)	10< (4)
Prazosin[a]					0·0014 ± 0·0001 (6)	10< (3)
Propranolol[a]					10< (4)	0·063 ± 0·004 (6)

[a] Data from Takenaka et al (1982b).
[b] and [c] were base and methanesulfonate salt respectively and others hydrochloride salts.
Figure in parentheses indicates the number of animals used.

propranolol HCl (Sigma Chemical). All YM-compounds were prepared in our laboratories as hydrochloride salts except YM-11133 which was prepared as base. Physicochemical properties of the optical isomers of amosulalol were as follows: (−)-isomer, $[\alpha]_D^{20}$ − 30·4 (c = 1, MeOH), mp 158–160 °C; (+)-isomer, $[\alpha]_D^{20}$ + 30·7 (c = 1, MeOH), mp 158–160 °C. All doses of drugs are expressed in terms of the salts.

Results

α_1- and β_1-Adrenoceptor blocking activities in anaesthetized rats. The resting mean blood pressure of pentolinium-treated rats anaesthetized with urethane was 55 ± 2 mmHg (n = 86) and the resting heart rate of reserpinized rats anaesthetized with pentobarbitone was 270 ± 8 beats min^{-1} (n = 74). Phenylephrine (10 μg kg^{-1} i.v.) and isoprenaline (0·1 μg kg^{-1} i.v.) caused increases in mean blood pressure of 66 ± 1 mmHg (n = 86) and heart rate of 132 ± 3 beats min^{-1} (n = 74), respectively.

Table 1 summarized the stringent structural requirements in a series of sulfamoylphenethylamines for antagonisms of the α_1-adrenoceptor-mediated vasopressor response to phenylephrine and the β_1-adrenoceptor-mediated positive chronotropic response to isoprenaline in anaesthetized rats. As previously demonstrated (Takenaka et al 1982b), three phenethanolamines such as YM-09686, YM-09649 and (±)-amosulalol antagonized both α_1- and β_1-adrenoceptor-mediated responses. The optical isomers of amosulalol exhibited substantial differences from each other in their adrenoceptor blocking potencies. For α_1-adrenoceptor antagonism, the (+)-isomer was 28 times more potent than the (−)-isomer. In contrast, for β_1-adrenoceptor antagonism, the (−)-isomer was 43 times more potent than the (+)-isomer. Removal of a hydroxy group at the β-carbon of the phenethanolamine side chain (R^2 = H) increased α_1-adrenoceptor blocking activity slightly less than 3-fold but reduced β_1-adrenoceptor blocking activity considerably more than 5-fold (YM-12044, YM-12040, YM-11133 vs YM-09686, YM-09649, amosulalol). YM-11133, a desoxy derivative of amosulalol, was approximately as active as (+)-amosulalol at both receptors. Introduction of a methyl group at the α-carbon of the phenethylamines (R^3 = CH_3) increased α_1-adrenoceptor blocking potency markedly more than 3-fold but no longer decreased β_1-adrenoceptor blocking potency (YM-12688, YM-12045, YM-12263 vs YM-12044, YM-12040, YM-11133). Regarding *o*-alkoxy substituents in phe-

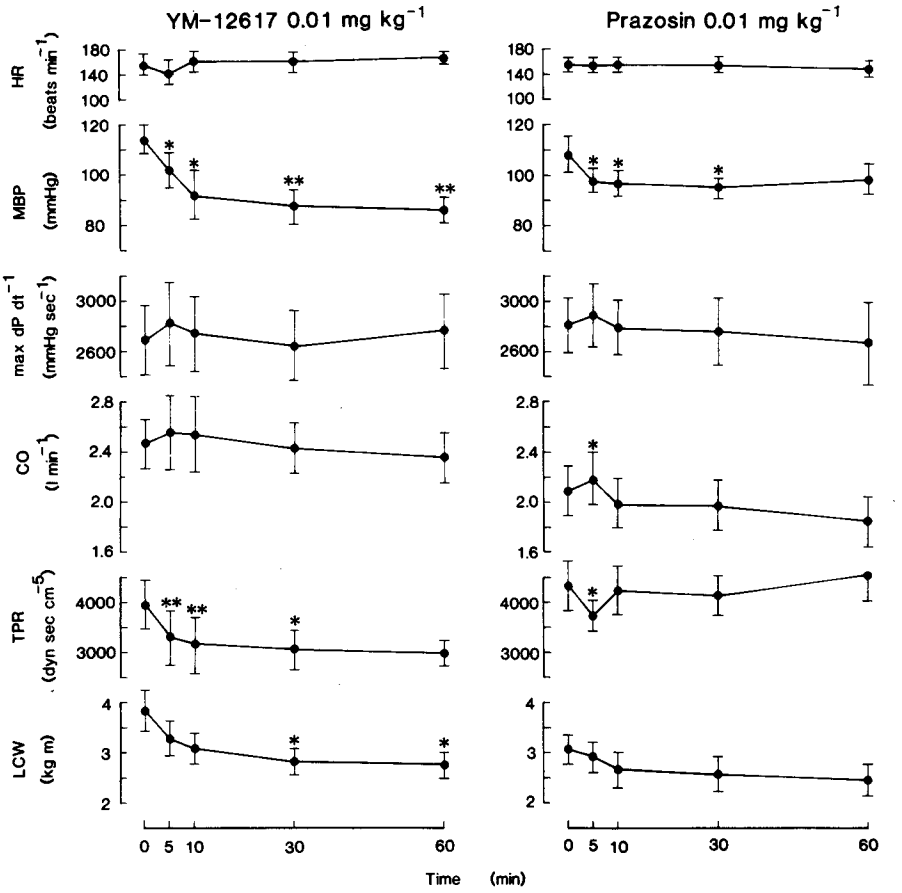


FIG. 1. Changes in heart rate (HR), mean blood pressure (MBP), left ventricular pressure (LVP), maximal dLVP dt^{-1} (max dP dt^{-1}), cardiac output (CO), total peripheral resistance (TPR) and left ventricular cardiac work (LCW) after single i.v. injection of YM-12617 and prazosin in anaesthetized and open-chest dogs. Each point represents the mean ± s.e.m. of 5 animals. Asterisk indicate values significantly different from the corresponding pretreatment values. $*P < 0.05$, $**P < 0.01$.

noxyethylamine moiety, substitution of an ethoxy group ($R^4 = OC_2H_5$) instead of a methoxy group increased α_1-blocking activity and decreased β_1-blocking activity slightly (YM-12689, YM-12617, YM-13118 vs YM-12688, YM-12045, YM-12263). Among the desoxy derivatives, YM-12688, YM-12689 and YM-12617 were more potent than prazosin in blocking α_1-adrenoceptors. Prazosin, phentolamine, YM-12688, YM-12689 and YM-12617 attenuated the positive chronotropic response to isoprenaline by less than 20% even at 10 mg kg^{-1} i.v., indicating that these compounds are practically devoid of β_1-adrenoceptor blocking activity.

Cardiovascular effects in anaesthetized dogs. Cardiovascular effects of YM-12617, one of the desoxy derivatives with potent α_1-adrenoceptor blocking activity, were compared with those of prazosin in anaesthetized dogs (Fig. 1). YM-12617 (0·01 mg kg^{-1} i.v.) acted on cardiovascular parameters in a manner similar to prazosin (0·01 mg kg^{-1} i.v.); it reduced mean blood pressure, total peripheral resistance and left ventricular cardiac work with almost no effects on heart rate, max. dLVP dt^{-1} and cardiac output. Changes in mean blood pressure, total peripheral resistance and left ventricular work after YM-12617 appeared to be greater than those after prazosin.

Discussion

The present experiments in anaesthetized rats clearly demonstrate that the optical isomers of amosulalol and its desoxy derivative (YM-11133) differ markedly in α_1- and β_1-adrenoceptor blocking activity. It is not surprising to find that β_1-adrenoceptor blocking potency of (−)-amosulalol is greater than that of the (+)-isomer which is approximately equipotent with the desoxy derivative (YM-11133). The result is consistent with earlier reports pertaining to β-adrenoceptor agonist or antagonist activities of optically active phenethanolamines such as adrenaline, noradrenaline, isoprenaline, INPEA or sotalol and the corresponding desoxy deriva-

tives (Patil 1968; Patil et al 1970, 1974). For α_1-adrenoceptor antagonism, in contrast, (+)-amosulalol and the corresponding desoxy derivative (YM-11133) were found to be one log unit order more potent than the (−)-isomer, with the former compounds being equipotent to each other. This is unexpected, since it has been reported that the rank order of α-agonist potencies of optically active adrenaline or noradrenaline and the corresponding desoxy derivatives are (−)- > (+)-desoxy (Patil et al 1970, 1974) and that (−)- and (+)-isomers of INPEA are identical in blocking α_1-adrenoceptors (Gulati et al 1969, 1973). Thus, the stereochemical requirements of α_1- and β_1-adrenoceptors are opposite for the optical isomers of amosulalol with the α_1-receptor favouring the (+)-isomer and the β_1-receptor favouring the (−)-isomer. At present, we have not yet established the absolute configuration of the optical isomers of amosulalol about the asymmetric centre (i.e. *R* or *S*). When this is done, the enantiomers may be useful tools for studying the Easson-Stedman hypothesis, a theory governing the adrenoceptor-mediated activity of optically active phenethylamines possessing an assymmetric β-carbon atom (Easson & Stedman 1933; Patil et al 1970, 1974).

Our findings with amosulalol have led us to structurally new potent α_1-adrenoceptor antagonists. The desoxy derivatives of YM-09686, YM-09649 and amosulalol and their related derivatives possess potent α_1-adrenoceptor blocking activity and are practically devoid of β_1-adrenoceptor blocking activity. It is of interest that α-methylphenethylamines are more potent than phenethylamines in blocking α_1-adrenoceptors. Among them, we selected YM-12617 and tested for its cardiovascular effect in anaesthetized dogs. YM-12617 reduced blood pressure, total peripheral resistance and left ventricular work with almost no effects on heart rate and max. dLVP dt^{-1} in a manner similar to that observed for prazosin. As regards heart rate and max. dLVP dt^{-1}, the effects of YM-121617 and prazosin were different from those reported for the combined α- and β-antagonists, amosulalol and labetalol, which reduced these parameters markedly in anaesthetized dogs (Takenaka et al 1982a). These observations suggest that YM-12617 would not cause any β_1-adrenoceptor blockade and act solely as an α_1-adrenoceptor antagonist on the cardiovascular system of anaesthetized dogs. Prazosin is reported to improve the haemodynamic status of congestive heart failure patients (Awan et al 1978) but β-adrenoceptor antagonists are contraindicated in these patients due to their cardiac depressant effect (Prichard & Gillam 1969). Thus, the present haemodynamic data suggest that YM-12617 may be of benefit in the treatment of congestive heart failure. In preliminary in-vitro studies (Honda et al 1981), YM-12617 competively antagonized the noradrenaline-induced contraction of the rabbit aorta with a pA_2 value of 10·11 and the clonidine-induced twitch inhibitory effect of the electrically stimulated rat vas deferens with a pA_2 value of 6·41, indicating that YM-12617 has a 5000 times higher affinity for α_1-adrenoceptors than for α_2-adrenoceptors in-vitro. Accordingly, YM-12617 and its related compounds may be useful for characterizing α-adrenoceptors.

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