Structure–Activity Relationship of Yohimbine and Its Related Analogs in Blocking Alpha-1 and Alpha-2 Adrenoceptors: A Comparative Study of Cardiovascular Activities

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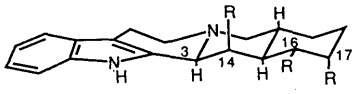
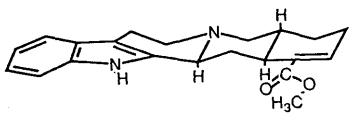
We investigated the selectivities and structure requirements for alpha-1 and alpha-2 adrenoceptor blocking activities of yohimbine (YO) and its 12 related analogs, such as β-yohimbine (β-YO), dihydrocorynantheine (DHC) and (−)indoloquinolizidine ((−)IQ). The affinity of YO analogs to alpha-adrenoceptor was assessed by measuring their blockade of pressor responses to epinephrine in pithed rats. Among YO structure groups, the potency order was YO > DHC = β-YO > geissoschizine methylether > 14β-hydroxy YO > 14β-benzoyloxy YO (inactive). (−)IQ was slightly less potent than YO, but much stronger than (+)IQ. Among (±)IQ structure groups, the potency order was (±)IQ > (±)1,12b-*trans*-1-hydroxy IQ ≫ (±)1,12b-*cis*-1-hydroxy IQ (inactive). (±)Borrerine was active, but (±)desmethylborrerine was inactive. The alpha-1 blocking activities of the four compounds YO, β-YO, DHC and (−)IQ, were assessed in experiments of pressor responses to methoxamine in pithed rats and contractile responses to methoxamine in the rat *vas deferens*. The potency order was (−)IQ > YO > DHC > β-YO. Furthermore, the alpha-2 blocking activities of the four analogs were assessed in experiments of pressor responses to clonidine and inhibition of electrically driven cardioacceleration by clonidine, in pithed rats. The potency order was YO > β-YO > (−)IQ > DHC. Based on the potency ratio between alpha-1 and alpha-2 blocking activities, DHC or YO was most selective for alpha-1 or alpha-2 subtype, respectively, among the four YO analogs. These results suggest that the A, B, C and D rings of YO analogs and their planarity are necessary for the affinity to alpha-adrenoceptors and that the predominant conformation of the carboxymethyl or hydroxy group on the E ring of YO structure determines the selectivity for alpha-1 and alpha-2 blocking activities.

Keywords yohimbine; dihydrocorynantheine; indoloquinolizidine; adrenoceptor blocking activity; blood pressure; heart rate; methoxamine; clonidine; structure–activity relationship; rat

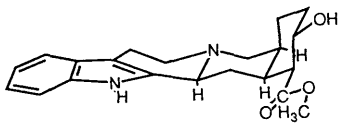
Since alpha adrenoceptors were classified into two subtypes of alpha-1 and alpha-2,[1] it has been extensively investigated as to which subtype is most closely involved in specific pharmacological actions. Yohimbine (YO) is now regarded as a potent alpha-2 adrenoceptor blocker in both *in vivo*[2] and *in vitro*[3] studies. Furthermore, it is known that stereoisomers of YO possess different selectivities to the adrenoceptor subtypes; corynanthine is potent in blocking alpha-1, rauwolscine is potent in blocking alpha-2, and apoyohimbine is equipotent in blocking alpha-1 and alpha-2.[4] On the basis of structural similarities among apoyohimbine and other typical adrenoceptor blockers,



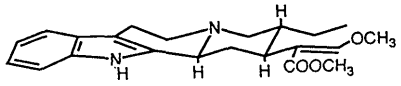
yohimbine (YO) analogs	R 14β	16	17
YO	H	$COOCH_3$ (α)	OH (α)
14β-hydroxy YO	OH	$COOCH_3$ (α)	OH (α)
14β-benzoyloxy YO	C_6H_5COO	$COOCH_3$ (α)	OH (α)
β-YO	H	$COOCH_3$ (α)	OH (β)
corynanthine[a]	H	$COOCH_3$ (β)	OH (α)
yohimbol[a]	H	H	OH (α)



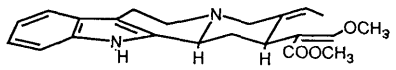
apoyohimbine[a]



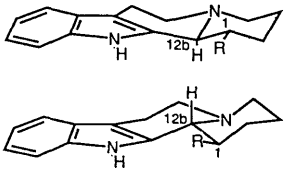
rauwolscine[a]



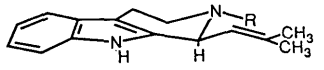
dihydrocorynantheine



geissoschizine methylether



indoloquinolizidine (IQ) analogs	R
(±) IQ	H
(±) 1, 12b-*cis*-1-hydroxy IQ	OH
(±) 1, 12b-*trans*-1-hydroxy IQ	OH



	R
(±) borrerine	CH_3
(±) desmethylborrerine	H

Chart 1. Chemical Structures of Yohimbine and Its Related Compounds

a) These are depicted as reference drugs.

McGrath has claimed the importance of binding sites of apoyohimbine at alpha adrenoceptors, and has presumed some structural requirements of YO analogs for selectivity between alpha-1 and alpha-2 adrenoceptors.[5]

The purpose of the present study was to investigate alpha-adrenoceptor blocking effects of YO analogs such as β-yohimbine (β-YO), dihydrocorynantheine (DHC) and (−)indoloquinolizidine ((−)IQ) (Chart 1) on cardiovascular responses to alpha-adrenoceptor agonists in association with structural features of these compounds. Some parts of the data obtained in this study have been preliminarily reported elsewhere.[6]

Materials and Methods

Effects of YO Analogs on Pressor Response to Epinephrine in Pithed Rats According to Shipley and Tilden's method,[7] experimental procedures were done as follows. Male Wistar rats (250—350 g of body weight) were anesthetized with pentobarbital sodium at 50 mg/kg, i.p. After the trachea was cannulated, the animals were artificially ventilated with room air using a respiration pump (Takahashi B-34; 60 stroke/min and 1 ml air/100 g of body weight). Polyethylene cannulas were inserted into the right femoral vein for i.v. injection of drugs and into the left carotid artery for measurement of blood pressure. Arterial blood pressure was recorded by means of a pressure transducer (Toyo Baldwin TMY-MPU-0.5-290-0-III) and heart rate was recorded with a heart rate meter (San-ei Type 2140 N2507) by counting triggers derived from the pulse pressure. Bilateral vagotomy and ligation of the right carotid artery were performed. After treatment with *d*-tubocurarine (1 mg/kg, i.v.), the animals were pithed by introducing a steel rod into the spinal canal *via* the orbit. Rectal temperature was maintained at approx. 37 °C using a heating pad. The animal preparation was left for at least 20 min to equilibrate. Pressor responses to epinephrine (3 μg/kg, i.v.) were first examined. Then, one of YO analogs was i.v. injected, and 3 min later, the pressor responses to epinephrine were again examined. Inhibition of the pressor responses by YO analogs (% control response) was evaluated by measuring the peak diastolic blood pressure. The potency ratio of a YO analog to YO was calculated using the 2 × 2 point assay.

Effects of YO Analogs on Pressor Responses to Methoxamine or Clonidine in Pithed Rats The animal preparations were made according to the method described above. The rat was pretreated with propanolol (1 mg/kg, i.v.) to exclude beta-adrenoceptor stimulating effects on the heart. After 10 min the vehicle solution (0.1 ml/100 g of body weight) was injected. Five min later, pressor responses to methoxamine (30 or 90 μg/kg) or clonidine (3 or 10 μg/kg) were measured; two doses were tested for each adrenergic agonist. Following a control response test, a YO analog (1 mg/kg, i.v.) was injected, and 3 min later, the pressor responses to methoxamine or clonidine were examined. The potency of each YO analog to depress pressor responses to agonists was evaluated on the basis of the ratio of agonist doses to produce the same pressor response after vehicle or YO analog administration (2 × 2 point assay). These evaluations were made for values of the peak diastolic blood pressure.

Effect of YO Analogs on Clonidine-Induced Inhibition of Electrically Driven Cardioacceleration in Pithed Rats Male Wistar rats were pithed as described above. The pithing rod was removed and a trocar was inserted in the spinal canal. A concentric bipolar electrode was placed in the C6-Th1 level through the trocar. Thereafter, *d*-tubocurarine was i.v. injected at a dose of 1 mg/kg. For continuous stimulation of the cardiac accelerator nerve, square wave pulses (30 V, 1 ms and 1 Hz) were delivered to the electrode from an electric stimulator (San-ei, 3F31). Clonidine (100 μg/kg, i.v.) was injected 10 min after the onset of stimulation; the drug caused inhibition of the electrically driven cardioacceleration, and its maximal response lasted mostly for more than 30 min. Administration by stepwise increases in the doses of a YO analog was made 5—7 min after clonidine treatment. The prejunctional alpha-2 blocking effects of YO analogs were assessed as percent reversal of the inhibitory response to clonidine.

Effects of YO Analogs on Contractile Responses to Methoxamine in the Rat Isolated *Vas Deferens* Male Wistar rats were killed by a blow at the head, and epididymal sections about 1 cm away from the *vasa deferentia* were removed. They were placed in a 5 ml organ bath containing Krebs solution of the following compositions (mM); NaCl 120, KCl 6.0, $CaCl_2$ 2.2, $MgCl_2$ 1.2, $NaHCO_3$ 25.0, and glucose 14.0. The Krebs solution was gassed with 95% O_2 and 5% CO_2 and kept at 37 °C. The contractile responses of the tissue were measured with an isotonic transducer (Natume KN-259) under a loaded condition of 0.5 g. After equilibrating the tissue for 30 min, a cumulative dose–response curve for methoxamine was determined; the methoxamine response test was started 5 min after vehicle or a YO analog, and an interval between tests was about 60 min. The blocking effects of YO analogs were analyzed from the dose–response curves.

Drugs Pentobarbital sodium (Tokyo Kasei), *d*-tubocurarine chloride (Yoshitomi), epinephrine hydrochloride (Daiichi), methoxamine hydrochloride (Nihon Shinyaku), clonidine hydrochloride (Sankyo), propranolol hydrochloride (I.C.I.) and yohimbine hydrochloride (YO) (Tokyo Kasei) were commercially purchased. YO analogs such as β-YO, 14β-hydroxy yohimbine (14β-OHY), 14β-benzoyloxy yohimbine (14β-BOY), DHC, geissoschizine methylether (GME), (−), (+) or (±)IQ, respectively, (±)1,12-*cis*-1- or *trans*-1-hydroxy indoloquinolizidine ((±)*cis*-1- or *trans*-1-OHI, respectively), (±) borrerine ((±)BR) and (±)desmethyl borrerine ((±)DMB) were prepared either by isolation from their originating plants or by chemical synthesis, if necessary, from natural alkaloids in our laboratories.[8] Of these compounds, the base compounds were dissolved in distilled water and free base compounds were dissolved in 0.1 M sodium phosphate, then diluted in saline. Drug doses were expressed as the free base form. Sodium phosphate solution adjusted to pH 5.2 was used for control injections.

Statistical Analysis For evaluation of statistical significance, the paired or non-paired Student's *t* test or Tukey's multiple range test was used.[9]

Results

Effects of YO Analogs on Pressor Responses to Epinephrine in Pithed Rats Inhibition of pressor responses to epinephrine by YO analogs was examined in pithed rats. Diastolic blood pressure and heart rate in the pithed rats averaged about 40 mmHg and 340 beat/min, respectively, before drug administration. Injection of epinephrine in a dose of 3 μg/kg produced an increase in the peak diastolic blood pressure by 79.5 ± 1.3 mmHg ($n=4$). After pretreatment with YO at 1 mg/kg, this increase was reduced to 59.6 ± 3.3% ($n=4$) of control (Fig. 1). The potencies of all YO analogs were listed in Table I. β-YO was half as potent as YO, and 14β-OHY was only 0.13 times as potent as YO. DHC and GME, which are characterized by cleavage of the E ring of YO structure, possessed the potency ratios of 0.54 and 0.38, respectively. (−)IQ, which is lacking the E ring of YO structure, showed a strong blocking activity (potency ratio of 0.84), while (+)IQ exerted a weak blocking activity (potency ratio of 0.14). When compared among (±)IQ compounds, the order of the potency ratios was

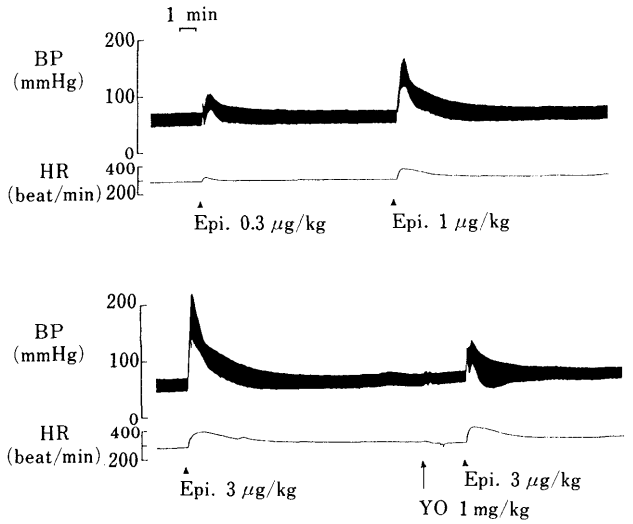


Fig. 1. Typical Recordings of Pressor and Tachycardia Responses to Epinephrine and Their Inhibition by YO in a Pithed Rat

BP, blood pressure; HR, heart rate; Epi., epinephrine. Drugs were i.v. administered.

TABLE I. Potencies of Inhibitory Effect of YO Analogs on the Peak Diastolic Pressor Responses to Epinephrine in Pithed Rats

Test drug[a]	Potency ratio[b] (95% confidence limits; $n=4$)
YO	1.00[c]
β-YO	0.50 (0.36—0.69)
14β-OHY	0.13 (0.09—0.17)
14β-BOY	Inactive
DHC	0.54 (0.37—0.80)
GME	0.38 (0.27—0.56)
(−)IQ	0.84 (0.62—1.15)
(+)IQ	0.14 (0.09—0.21)
(±)IQ	0.58 (0.37—0.92)
(±)IQ	1.00[d]
(±)*trans*-1-OHI	0.62 (0.39—0.98)
(±)*cis*-1-OHI	Inactive
(±)BR	0.49 (0.28—0.87)
(±)DMB	Inactive

a) Test drugs were i.v. administered 3 min before epinephrine (3 μg/kg, i.v.). *b*) The potency ratio was analyzed by the 2×2 point assay. *c*) The potency ratio to YO was calculated. *d*) The potency ratio to (±)IQ was calculated.

TABLE II. Effect of YO Analogs on Heart Rate Increased by Epinephrine in Pithed Rats

Test drug[a]	Dose (mg/kg, i.v.)	Change (%) in heart rate[b]
YO	1.0	9.5±3.5[c]
β-YO	1.0	−1.8±8.9
14β-OHY	3.0	−1.0±10.6
14β-BOY	3.0	−1.2±8.4
DHC	1.0	−3.6±4.0
GME	1.0	1.1±4.0
(−)IQ	1.0	11.4±11.0
(+)IQ	3.0	3.9±4.6
(±)IQ	1.0	4.1±11.0
(±)*trans*-1-OHI	1.0	−6.2±5.5
(±)*cis*-1-OHI	1.0	−8.2±3.6
(±)BR	1.0	−0.6±5.5
(±)DMB	1.0	−0.8±4.7

a) Test drugs were i.v. administered 3 min before epinephrine (3 μg/kg, i.v.). *b*) Net increase in heart rate after epinephrine (3 μg/kg, i.v.) was regarded as 100%. *c*) Each value represents the mean±S.E. ($n=4$). No significant change was observed, as compared with the control value seen before drug administration.

(±)IQ>(±)*trans*-1-OHI>(±)*cis*-1-OHI. (±)BR,which is a (±)IQ derivative lacking the D ring, was almost half as potent as (±)IQ, and (±)DMB, which is a desmethyl derivative of (±)BR, had no blocking activity.

In this experiment, some of YO analogs produced transient changes in blood pressure or heart rate immediately after administration in pithed rats, but these changes returned to the original blood pressure level in a few minutes. On the other hand, injection of epinephrine in a dose of 3 μg/kg produced an increase in heart rate by 105±3 beat/min ($n=4$). Pretreatment with YO analogs did not appreciably change the tachycardia induced by epinephrine (Table II).

Effect of YO Analogs on Pressor Response to Methoxamine or Clonidine in Pithed Rats Inhibition of pressor responses to methoxamine or clonidine by four YO analogs YO, β-YO, (−)IQ and DHC was examined in pithed rats. Diastolic blood pressure and heart rate in these animal preparations was about 40 mmHg and 340 beat/min, respectively, before drug administration. Typical recordings of inhibitory effects of DHC and YO on pressor responses

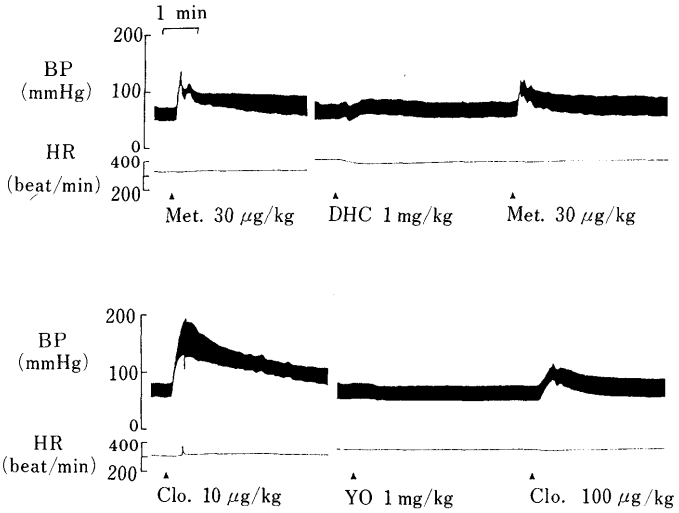


Fig. 2. Typical Recordings of Inhibitory Effects of DHC and YO on Pressor Responses to Methoxamine and Clonidine, Respectively, in Pithed Rats

BP, blood pressure; HR, heart rate; Met., methoxamine; Clo., clonidine. Drugs were i.v. administered.

TABLE III. Potencies of Inhibitory Effect of YO Analogs on the Peak Diastolic Pressor Responses to Methoxamine and Clonidine in Pithed Rats

Test drug[a]	Dose ratio[b] (95% confidence limits; $n=4$)		Relative selectivity[c]
	Methoxamine	Clonidine	
YO	1.90 (1.55—2.34)	6.15 (4.06—9.34)	0.31
β-YO	1.60 (1.29—1.98)	4.28 (2.83—6.49)	0.37
DHC	1.73 (1.42—2.12)	1.72 (1.18—2.49)	1.00
(−)IQ	2.10 (1.54−2.84)	3.11 (2.02—4.80)	0.68

a) Test drugs were i.v. administered at 1 mg/kg. *b*) The ratio of the agonist doses to produce the same pressor response after administration of vehicle or a YO analog. The greater the dose ratio is, the more potent the blocking activity is. *c*) The ratio of values between methoxamine and clonidine. The greater the ratio is, the more selective the alpha-1 blocking activity is, and *vice versa*.

to methoxamine and clonidine, respectively, were presented in Fig. 2 Methoxamine, a selective alpha-1 adrenoceptor agonist, increased the diastolic pressure dose-dependently with a steep curve between doses of 30 and 90 μg/kg. Pretreatment with (−)IQ caused the most potent inhibition of the pressor response to methoxamine among the four YO analogs; the order of the potencies of the YO analogs was (−)IQ>YO>DHC>β-YO (Table III). Clonidine, a selective alpha-2 adrenoceptor agonist, also showed a dose-related increase in the peak diastolic pressure, steeply in doses ranging 3 and 10 μg/kg. YO exhibited the most potent inhibition of the pressor responses to clonidine. The order of the potencies of the YO analogs was YO>β-YO>(−)IQ>DHC (Table III). The differences in adrenoceptor blocking activity among YO analogs were much greater in pressor responses to clonidine than in the pressor responses to methoxamine.

Effects of YO Analogs on Clonidine Induced Inhibition of Electrically Driven Cardioacceleration in Pithed Rats In this experiment, basal heart rate was about 330 beat/min

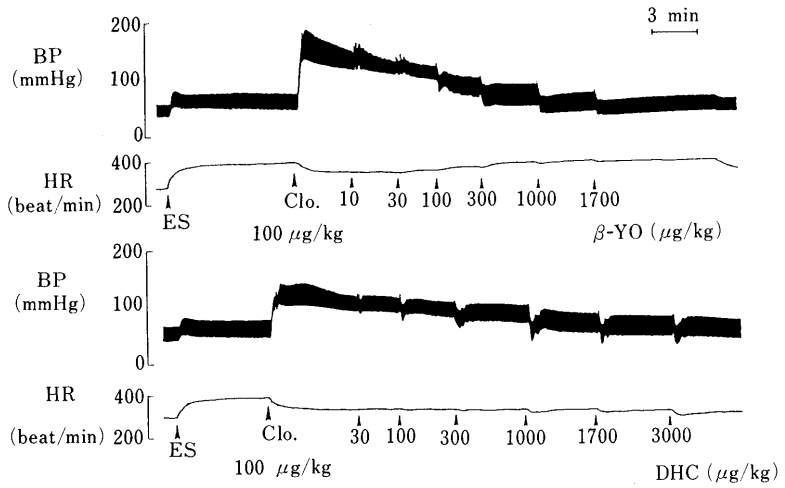


Fig. 3. Typical Recordings of Reversing Effects of β-YO and DHC on Clonidine Induced Inhibition of Electrically Driven Cardioacceleration in Pithed Rats

BP, blood pressure; HR, heart rate; ES, electrical stimulation; Clo., clonidine. Drugs were i.v. administered.

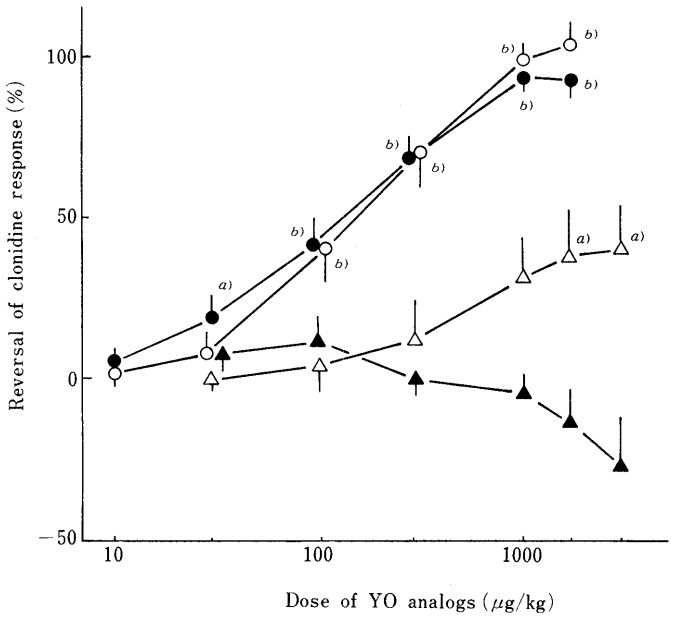


Fig. 4. Reversing Effects of YO Analogs on Clonidine Induced Inhibition of Electrically Driven Cardioacceleration in Pithed Rats

Clonidine (100 μg/kg) and YO analogs were i.v. administered. ○, YO ($n=6$); ●, β-YO ($n=6$); △, (−) IQ ($n=5$); ▲, DHC ($n=3$). Each point represents the mean±S.E. *a*) $p<0.05$, *b*) $p<0.01$ *vs.* control heart rate seen before administration of YO analogs.

and net increase in the heart rate by electric stimulation was about 145 beat/min. Clonidine, at an i.v. dose of 100 μg/kg, produced about 70% inhibition of the increased heart rate (Fig. 3). Administration of YO, β-YO or (−)IQ reversed the clonidine-induced inhibition (Figs. 3 and 4). The effect of β-YO was as potent as that of YO and a complete reversal was seen at a cumulative dose of 1 mg/kg of YO or β-YO. (−)IQ produced about 40% reversal of the heart rate inhibition at a cumulative dose of 3 mg/kg. In contrast, DHC did not affect the inhibition induced by clonidine. Accordingly, the order of the potencies of the YO analogs was YO=β-YO>(−)IQ≫DHC (inactive).

Effects of YO Analogs on Contractile Responses to Methoxamine in the Rat Isolated *Vas Deferens* Methoxamine produced a dose-dependent contraction of the *vas deferens*

TABLE IV. pA_2 Values of YO Analogs in Blocking Contractions Induced by Methoxamine in the Isolated Rat *Vas Deferens*

Test drug	pA_2 value[a)]
YO	6.56±0.11
β-YO	5.89±0.12
DHC	6.42±0.07
(−)IQ	6.65±0.12

a) Each value represents the mean±S.E. ($n=4$). The pA_2 value of β-YO was significantly different from those of the other YO analogs at $p<0.01$.

in doses between 10^{-7} and 10^{-5} M. The inhibitory effects of YO analogs on the methoxamine-induced contraction were compared by determining pA_2 values (Table IV). The order of the potencies of the YO analogs was (−)IQ=YO>DHC>β-YO, although there were small differences among potencies of the former three YO analogs.

Discussion

In the present study, several pharmacological tests were carried out to assess alpha-adrenergic blocking activities of YO and its 12 related analogs. Pithed rats were used to measure blood pressure and heart rate with minimal nerve reflex following drug administration. In such experimental conditions, pressor responses, but not depressor responses, to epinephrine appeared *via* stimulation of both alpha-1 and alpha-2 adrenoceptors. Likewise, methoxamine-induced pressor responses would be mediated predominantly by alpha-1 receptors, while clonidine-induced ones would be due largely to alpha-2 receptors. However, it is known that discrimination of adrenoceptor subtypes by measuring pressor responses to agonists is not always valid because available pressor agonists are not fully selective for alpha-1 or alpha-2 adrenoceptors. Thus, selectivities of the four chosen YO analogs for alpha-1 and alpha-2 adrenoceptors were further confirmed by measuring methoxamine-induced contraction of the rat *vas deferens* and clonidine-induced inhibition of electrically driven cardioacceleration, respectively.

The potency of YO and its related analogs in inhibiting epinephrine-induced pressor responses in pithed rats is

thought to reflex the affinity to alpha-adrenoceptors. According to this assumption, YO, (−)IQ, DHC and β-YO may well be considered to possess high affinity for the alpha-adrenoceptor. Since (−)IQ has no E ring unlike YO, and DHC looks like YO whose E ring is cleaved, it appears that the E ring is not essential for exerting alpha-adrenergic blocking activities. In contrast, (±)BR, a compound without a D ring, was very weak in blocking the activities. On the other hand, IQ analogs showed stereospecificity for their activities; the (−)isomer was much stronger than the (+)isomer. As is seen in 14β-OHY, introduction of hydroxy substituent at C-14 on the D ring of YO greatly reduced the blocking activities. Similar results were obtained for IQ related compounds, especially in the case of the *cis* formed analogs. The introduction of a *p*-nitrobenzoyloxy group instead of the hydroxy group reduced the affinity greatly and increased calcium channel blocking activities prominently.[10] Accordingly, it is postulated that the presence of substituents at C-14 of YO or at C-1 of IQ (see Chart 1) is closely associated with reduction of the affinity to alpha-adrenoceptors. On the other hand, YO analogs did not significantly affect the tachycardia induced by epinephrine (Table II), suggesting that they had no beta-adrenoceptor blocking activities.

From results obtained in the experiments of methoxamine-induced pressor responses and of contractile responses in the isolated *vas deferens*, the order of potencies of the four analogs for alpha-1 adrenoceptor blocking activity was assessed as (−)IQ > YO > DHC > β-YO. On the other hand, the order of potencies of these compounds for alpha-2 adrenoceptor blocking activity was assessed as YO > β-YO > (−)IQ > DHC in the experiments of the clonidine induced inhibition of electrically driven cardioacceleration. The potency order was also almost the same as that assessed in the experiments of pressor responses. If the relative selectivity between alpha-1 and alpha-2 is calculated (Table III), DHC or YO would be most selective for the alpha-1 or alpha-2 subtype, respectively, among these four analogs.

McGrath has surveyed much work on alpha-adrenergic responses to agonists and antagonists including YO analogs and presumed alpha-adrenoceptor binding sites and drug sensitivities for alpha subtypes.[5] Based on the fact that apoyohimbine has equipotent antagonistic effects on alpha-1 and alpha-2 adrenoceptors,[11] he thought that its chemical structure could be regarded as a template for alpha-adrenoceptors; the A, B and C rings contain the binding sites for the alpha-2 adrenoceptor and the C, D and E ring for the alpha-1 adrenoceptor. This hypothesis has fairly well been accepted to explain alpha-1 and alpha-2 adrenoceptor selectivities, especially to YO analogs. However, the hypothesis was contradictory to the present finding that (−)IQ produced the blocking activities on alpha-1 adrenoceptors more potently than on alpha-2 adrenoceptors, although the drug is thought to possess the affinity to alpha-2 adrenoceptors according to his prediction. Thus, it could not be justified to predict the specific binding sites for alpha-1 and alpha-2 subtypes on the YO rings.

It is also claimed by McGrath[5] that corynanthine, a YO isomer known to be a selective alpha-1 antagonist, possesses no affinity for the alpha-2 adrenoceptor because of inability to place its ring E carboxymethyl substituent (C-16 position) below the plane of the rest of the rather flat molecule. Thus, he concluded that the binding sites will be below in alpha-1 but be above or on the plane in alpha-2. This postulation seems to be valid among YO analogs with the carboxymethyl group at the C-16 position (YO, apoyohimbine, rauwolscine and corynanthine). Actually, DHC, whose carboxymethyl group is oriented above the plane of the rest molecule like corynanthine in the structure model, exhibited the high selectivity for alpha-1 adrenoceptor in the present study. However, if the carboxymethyl group is deleted as in yohimbol[5] or as in (−)IQ, a compound without an E ring, the affinity to the alpha-2 adrenoceptor is markedly decreased, as compared with the affinity to the alpha-1 site. Thus, it is assumed that the carboxymethyl group is indispensable for the affinity to alpha-2 adrenoceptor and its conformation determines the potencies of alpha-2 adrenoceptor blocking activities.

Presence of the hydroxy group at the C-17 position of YO structure would not be prerequisite for alpha-1 adrenoceptor affinity, because apoyohimbine exerts the alpha-1 blocking activities.[4a] On the other hand, β-YO is a diastereomer of YO with β-orientation of the hydroxy group and its alpha-1 adrenoceptor blocking activities were weak as compared with those of YO. From the present findings together with previous reports,[4a,5] it is suggested, among YO analogs with the hydroxy group at the C-17 position, that the order of potencies in blocking alpha-1 adrenoceptors is; compounds with the hydroxy group below the molecule plane (YO or corynanthine) > compounds with the hydroxy group on the molecule plane (β-YO) > compounds with the hydroxy group above the molecule plane (rauwolscine), in the case of their predominant conformation.

In conclusion, it is suggested that the A, B, C and D rings of YO analogs and their planarity are necessary for the affinity to alpha-adrenoceptors; the predominant conformation of the carboxymethyl group or hydroxy group on the E ring of YO structure determines the selectivity for alpha-1 and alpha-2 adrenoceptor blocking activities.

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