ANTIARRHYTHMIC ACTIVITY OF 1-(7-INDENYLOXY)-3-ISOPROPYLAMINOPROPANE-2-OL HYDROCHLORIDE (YB-2) AND ITS OPTICAL ISOMERS

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Abstract—The antiarrhythmic activities of YB-2 and its optical isomers were investigated in experimentally induced arrhythmias in anesthetized guinea pigs and dogs, and compared with those of propranolol. The local anesthetic and negative inotropic properties of these agents were also examined because of their possible contribution to the antiarrhythmic profile. In anesthetized guinea pigs, these agents showed a significant protecting effect against ouabain-induced arrhythmias; the order of the potency was as follows, 1-YB-2=dl-YB-2>propranolol>d-YB-2. The similar tendency was also observed in anesthetized dogs. YB-2 and its l-isomer, 0.1–0.4 mg/kg i.v., were equipotent with propranolol with respect to their protecting effects against methylchloroform-epinephrine-induced ventricular fibrillation in dogs, while the d-isomer, 4 mg/kg i.v., failed to inhibit the arrhythmias. YB-2 and its optical isomers and propranolol were found to have significant local anesthetic activities in guinea pig cornea and dorsal skin and negative inotropic activities in isolated guinea pig atria. There was no significant difference among these agents in each activity. The results suggest that YB-2 and its optical isomers appear to have a similar potency ratio for antiarrhythmic activity as is the case with propranolol and its optical isomers, and that YB-2 may prove to be a useful antiarrhythmic agent in clinical situations.

It is now well established that beta-adrenergic receptor blocking agents effectively antagonize a variety of experimentally induced and clinically occurring cardiac arrhythmias. On the basis of their effectiveness against catecholamine-induced and digitalis-induced cardiac arrhythmias, it has been proposed that some agents having a specific beta-adrenergic blocking activity are more selective in suppressing adrenergically induced arrhythmias, whereas other agents suppress both types of arrhythmias (1–6). The latter action is involved in a non-specific mechanism which has been referred to as a quinine-like or a local anesthetic activity.

Recently, 1-(7-indenyloxy)-3-isopropylaminopropane-2-ol hydrochloride (YB-2) has been found to possess a potent beta-adrenergic receptor blocking activity with a local anesthetic effect and to be effective against epinephrine-induced and digitalis-induced arrhythmias (7–9).

In our previous studies on the cardiovascular beta-adrenergic receptor blocking activities of YB-2 and its optical isomers, the l-isomer was 1.7–2 times as active as the racemate and 50–100 times as active as the d-isomer (10). The results are similar to those with propranolol reported by Howe and Shanks (11) and Levy and Richards (12).

The present study was undertaken to evaluate the antiarrhythmic activities of YB-2 and its optical isomers in some experimentally induced arrhythmias, and compare them with those of propranolol. The local anesthetic and negative inotropic properties of these agents were also examined because of their possible contribution to the antiarrhythmic profile.

MATERIALS AND METHODS

Ouabain-induced arrhythmias in anesthetized guinea pigs

The experiments were performed according to the method of Sekiya and Vaughan Williams (13). Male guinea pigs weighing 350 to 500 g were anesthetized with urethane, 1.5 g/kg i.p., and were artificially ventilated by a positive-pressure respirator (Natsume, KN-58) with room air. Lead II electrocardiograms and blood pressure via a pressure transducer (Nihon Kohden, MPU-0.5) connected with the cannulated common carotid artery were recorded on a polygraph (Nihon Kohden, RM-150). Pretreatment with procainamide or beta-adrenergic blocking agent (i.v.) was performed and 10 min later followed by ouabain-infusion (9 μ g/kg/min in saline) into the subclavian vein from a motor-driven syringe (Natsume, KN-202). The mean doses of ouabain at which 1) extrasystoles, 2) ventricular fibrillation appeared and 3) cardiac arrest occurred were calculated for each group and compared with those of the control group pretreated with saline.

Ouabain-induced arrhythmias in anesthetized dogs

Male mongrel dogs weighing 8 to 12 kg were anesthetized with sodium pentobarbital, 35 mg/kg i.v. Femoral blood pressure was monitored with a pressure transducer and electrocardiograms were taken from Lead II. Recordings were made on a polygraph. The procedure used as well as the criteria employed to determine antiarrhythmic activity was the same as described by Moran *et al.* (14). The animals were given ouabain (5 μ g/kg/min in saline) into the cephalic vein from a motor-driven syringe. The agents studied were administered i.v. to the animals 10 min prior to ouabain-infusion. The mean doses of ouabain at which 1) arrhythmias first appeared and 2) cardiac arrest occurred were obtained for each agent and compared with those of the control group pretreated with saline.

Methylchloroform-epinephrine-induced arrhythmias in anesthetized dogs

Male mongrel dogs weighing 8 to 12 kg were anesthetized with sodium pentobarbital, 35 mg/kg i.v. The experiment was performed according to the method of Somani and Lum (2). Femoral blood pressure was monitored via a pressure transducer, and electrocardiograms were taken from Lead II. The trachea was cannulated with a glass "T" tube and all drugs with the exception of methylchloroform were administered via the catheterized cephalic vein. Methylchloroform, 0.1 ml/kg, was instilled intratracheally via the "T" cannula and 20 sec later epinephrine, 10 μ g/kg i.v., was given rapidly. The procedure caused ventricular fibrillation in all of the control animals pretreated with saline. Other animals were pretreated with each beta-adrenergic blocking agent 10 min

prior to the methylchloroform-epinephrine challenge. Dogs which were protected by the agents were rechallenged at 60-min intervals over a period of 2 hr.

Local anesthetic activity

Local anesthetic activity was investigated by means of two methods. Surface anesthetic activity of the agents on the cornea was determined according to the method of Chance and Lobstein (15) using male guinea pigs weighing 350 to 500 g. The drug solutions, 0.1 ml, were instilled in the conjunctival sac in different concentrations and left there for 30 sec. Five min later, corneal anesthesia was measured by applying pressure by means of a test hair, 6 times at 5-sec intervals. The trial was performed every 5 min for 30 min.

Infiltration anesthetic activity on the guinea pig dorsal skin was determined according to the method of Büllbring and Wajda (16). On the day preceding the experiment the hair on the back was shaved. The drug solutions, 0.25 ml, were injected intracutaneously into 6 points on the back. The skin responses to pain prick were tested 5 min after the injection. Six pricks were applied to each injected area at 5-sec intervals. The trial was performed every 5 min for 30 min.

In both methods, the number which failed to respond to the test during 30-min exposure to a given agent was compared with the response seen with procaine. The results were plotted graphically against the log concentrations of the agents used and the concentration to cause a 50% reduction in the responses was calculated according to Litchfield and Wilcoxon (17).

Negative inotropic activity

Direct negative inotropic effects were determined on electrically driven guinea pig left atria. Male guinea pigs weighing 250 to 300 g were stunned by a blow on the head and the hearts were quickly removed. The left atrium was suspended in a 25-ml organ bath containing Krebs-Henseleit solution gassed with a mixture of 95% O₂ and 5% CO₂ at 31°C. Supramaximal stimuli, 3 msec in duration and 0.5 Hz in frequency, were continuously applied to the atria using a square-wave stimulator (Nihon Kohden, MSE-20). The force of resulting contractions of the atria was isometrically measured via a force displacement transducer (Nihon Kohden, ST-1) and recorded on a polygraph (Nihon Kohden, RM-150). The atria were maintained at a diastolic tension of 0.7 g and equilibrated for 60 min prior to drug administration. Changes in the force of contraction by the drug solution were expressed as percent of the force measured at the end of 60-min equilibration period and compared with those of control atria.

Drugs used

The following drugs were used: 1-(7-indenyl-oxy)-3-isopropylaminopropane-2-ol hydrochloride (YB-2) and its 1- and d-isomers (Yamanouchi Pharmaceutical Co.), dl-propranolol hydrochloride (Sumitomo Chemical Co.), procainamide hydrochloride (Dai-ichi Seiyaku Co.), procaine hydrochloride (Sankyo Co.), 1-epinephrine hydrochloride (Sankyo Co.), ouabain (E. Merck AG.) and methylchloroform (Tokyo Kasei Organic Chemicals Co.). The drugs except methylchloroform were freshly dissolved in 0.9%

saline and ascorbic acid, 0.01%, as a preservative, was added to l-epinephrine solution. All doses of the drugs are expressed in terms of the salt.

RESULTS

Effect on ouabain-induced arrhythmias

The effects of dl-, l- and d-YB-2 on ouabain-induced arrhythmias in anesthetized guinea pigs and dogs were examined and compared with those of propranolol or procainamide.

In 27 control guinea pigs anesthetized with urethane the infusion of ouabain (9 μ g/kg/min i.v.) consistently resulted in extrasystoles, ventricular fibrillation and cardiac arrest and the mean total doses of ouabain required to cause these cardiac changes were 77.2 ± 4.1 , 89.3 ± 5.4 and 137.5 ± 6.9 (S.E.M.) μ g/kg, respectively. The tracings from a typical experiment on dl-YB-2 are shown in Fig. 1. The doses of ouabain required to induce extrasystoles, ventricular fibrillation and cardiac arrest are shown in Table 1. Pretreatments with procainamide, 40 mg/kg i.v., propranolol, dl-YB-2 and l-YB-2, 0.125, 0.25 and 0.5 mg/kg i.v., and d-YB-2, 0.5 and 1.0 mg/kg i.v., significantly increased the doses of ouabain to cause the cardiac changes, which developed dose-dependently. In contrast, no significant increase in the doses of ouabain after the treatments with procainamide, 20 mg/kg i.v., and d-YB-2, 0.25 mg/kg i.v., were observed. The order of

FIG. 1. Effect of dl-YB-2, 0.5 mg/kg i.v., on ouabain-induced extrasystoles, ventricular fibrillation and cardiac arrest in an anesthetized guinea pig.

The upper part of each panel shows Lead II electrocardiograms and the lower part arterial blood pressure. A: extrasystoles (17 min after the onset of ouabain-infusion), B: ventricular fibrillation (23 min) and C: cardiac arrest (27 min),

TABLE 1. Effects of procainamide, propranolol, dl-YB-2, l-YB-2 and d-YB-2 on ouabain-induced arrhythmias in anesthetized guinea pigs.

Drug	No. of Animals	Dose of Ouabain ($\mu\text{g/kg}$)		
		Extrasystoles	Ventricular Fibrillation	Cardiac Arrest
Control	27	77.2 $\pm$ 4.1	89.3 $\pm$ 5.4	137.5 $\pm$ 6.9
Procainamide 20 mg/kg	9	76.0 $\pm$ 4.9	88.3 $\pm$ 5.4	133.3 $\pm$ 5.7
	9	93.5 $\pm$ 5.8*	112.6 $\pm$ 10.2*	165.7 $\pm$ 10.2*
Propranolol	0.125	119.1 $\pm$ 7.5**	142.6 $\pm$ 9.9**	169.9 $\pm$ 9.8*
	0.25	120.9 $\pm$ 3.7**	154.9 $\pm$ 5.0**	184.5 $\pm$ 4.7**
	0.5	137.9 $\pm$ 7.3**	170.2 $\pm$ 12.5**	211.4 $\pm$ 13.2**
dl-YB-2	0.125	107.5 $\pm$ 7.6**	137.7 $\pm$ 6.5**	177.7 $\pm$ 11.2*
	0.25	146.1 $\pm$ 8.0**	168.9 $\pm$ 7.4**	197.7 $\pm$ 14.8**
	0.5	157.5 $\pm$ 5.6**	203.7 $\pm$ 12.7**	244.4 $\pm$ 13.2**
l-YB-2	0.125	134.8 $\pm$ 5.8**	154.9 $\pm$ 7.7**	205.6 $\pm$ 11.1**
	0.25	131.2 $\pm$ 7.6**	169.5 $\pm$ 8.7**	212.7 $\pm$ 8.2**
	0.5	158.7 $\pm$ 10.3**	202.0 $\pm$ 13.1**	240.2 $\pm$ 13.2**
d-YB-2	0.25	93.3 $\pm$ 5.9	109.9 $\pm$ 9.8	162.1 $\pm$ 15.9
	0.5	96.5 $\pm$ 4.6**	110.8 $\pm$ 6.5*	163.2 $\pm$ 6.6*
	1	116.8 $\pm$ 7.2**	145.8 $\pm$ 5.7**	185.4 $\pm$ 7.3**

The doses of ouabain required to induce extrasystoles, ventricular fibrillation and cardiac arrest are presented as the mean value $\pm$ S.E.M. ($\mu\text{g/kg}$).

* significantly different from control value ($p < 0.05$) and ** highly significant from control value ($p < 0.01$).

FIG. 2. Effect of dl-YB-2, 4 mg/kg i.v., on ouabain-induced first arrhythmias and cardiac arrest in an anesthetized dog.

A : Lead II electrocardiograms and arterial blood pressure before the onset of ouabain-infusion, B : first arrhythmias (18 min after the onset of the perfusion) and C : ventricular tachycardia and cardiac arrest (34 min).

TABLE 2. Effects of propranolol, dl-YB-2, l-YB-2 and d-YB-2 on ouabain-induced arrhythmias in anesthetized dogs.

Drug	No. of animals	Dose of ouabain ($\mu\text{g/kg}$)	
		First Arrhythmias	Ventricular Fibrillation
Control	4	78.1 $\pm$ 3.9	121.0 $\pm$ 4.9
Propranolol 2 mg/kg	3	82.8 $\pm$ 8.2	124.6 $\pm$ 11.0
4	3	99.1 $\pm$ 16.8	140.9 $\pm$ 14.1
dl-YB-2 2	3	72.3 $\pm$ 7.3	141.9 $\pm$ 13.2
4	4	91.7 $\pm$ 8.0	147.6 $\pm$ 10.4
l-YB-2 2	3	74.9 $\pm$ 5.8	138.9 $\pm$ 6.8
4	4	94.0 $\pm$ 3.6	139.3 $\pm$ 8.0
d-YB-2 2	3	73.0 $\pm$ 8.6	118.2 $\pm$ 7.0
4	4	100.9 $\pm$ 11.0	142.3 $\pm$ 10.9

The doses of ouabain required to induce first arrhythmias and ventricular fibrillation are presented as the mean value $\pm$ S.E.M. ($\mu\text{g/kg}$).

antiarrhythmic potency was as follows; l-YB-2 $\approx$ dl-YB-2 $>$ propranolol $>$ d-YB-2 $>$ procainamide. The antiarrhythmic activities of d-YB-2, 0.25 and 0.5 mg/kg i.v., with the exception of 0.25 mg/kg for cardiac arrest, were significantly less potent than those of dl-YB-2 in the same dose level ($p < 0.01$).

In dogs anesthetized with pentobarbital, ouabain-infusion, 5 $\mu\text{g/kg/min}$ i.v., invariably caused cardiac changes: ventricular ectopic beats first appeared and were followed by ventricular tachycardia and cardiac arrest. The mean total doses of ouabain required to induce arrhythmias and cardiac arrest were 78.1 $\pm$ 3.9 and 121.0 $\pm$ 4.9 (S.E.M.) $\mu\text{g/kg}$ ($N=4$), respectively. The tracings from a typical experiment on dl-YB-2 are shown in Fig. 2. dl-YB-2, l-YB-2, d-YB-2 and propranolol, 2 and 4 mg/kg i.v., showed a tendency to protect against the ouabain-induced arrhythmias. However, no significant differences from the control group were obtained, as shown in Table 2. The beta-adrenergic blocking agents studied caused a fall in heart rate in the stage of first arrhythmias dose-dependently. Ventricular tachycardia just before cardiac arrest and a rise in blood pressure caused by ouabain were not significantly influenced by the treatments with beta-adrenergic blocking agents.

Effect on methylchloroform-epinephrine-induced ventricular fibrillation

In 5 control dogs myocardial sensitization with the intratracheal administration of methylchloroform, 0.1 ml/kg, followed by a rapid injection of epinephrine, 10 $\mu\text{g/kg}$ i.v., consistently induced ventricular fibrillation as shown in Fig. 3A. In the dogs challenged with methylchloroform-epinephrine 10 min after the administration of dl-YB-2, l-YB-2 or propranolol, 0.1, 0.2 or 0.4 mg/kg i.v., ventricular fibrillation did not develop. The tracings from a typical experiment on dl-YB-2 are shown in Figs. 3B and 3C. The protecting effect of the highest dose of each blocking agent, 0.4 mg/kg i.v., against ventricular fibrillation persisted for 120 min. In some animals on lower doses of the agents, ventricular fibrillation developed 60 or 120 min after the treatment. In

FIG. 3. Effect of dl-YB-2, 0.1 mg/kg i.v., on methylchloroform-epinephrine-induced ventricular fibrillation in anesthetized dogs.

A : control showing ventricular fibrillation 10 min after the treatment with saline, B : protection against ventricular fibrillation 10 min after dl-YB-2 and C : ventricular fibrillation 60 min after dl-YB-2 in the same dog which is shown in B.

TABLE 3. Protection against methylchloroform-epinephrine-induced arrhythmias in anesthetized dogs by propranolol, dl-YB-2, l-YB-2 and d-YB-2.

Drug	No. of Animals (Fibrillated/Tested)			
	10 min	60 min	120 min	Total
Control	5/5			5/5
Propranolol 0.1 mg/kg	0/3	2/3	0/1	2/3
0.2	0/3	0/3	0/3	0/3
0.4	0/3	0/3	0/3	0/3
dl-YB-2 0.1	0/5	3/5	1/2	4/5
0.2	0/5	0/5	2/5	2/5
0.4	0/3	0/3	0/3	0/3
l-YB-2 0.1	0/3	1/3	0/2	1/3
0.2	0/3	1/3	0/2	1/3
0.4	0/3	0/3	0/3	0/3
d-YB-2 0.5	3/3			3/3
1.0	1/4	1/3	0/2	2/4
2.0	2/5	1/3	0/2	3/5
4.0	0/5	4/5	0/1	4/5

The time in minutes indicates the interval between the administration of a given agent and the methylchloroform-epinephrine challenge.

contrast, d-YB-2, even in the highest dose, 4 mg/kg i.v., could not protect against methylchloroform-epinephrine-induced ventricular fibrillation. In all of the groups treated with the beta-adrenergic blocking agents the duration of the protecting effect against the challenge was prolonged dose-dependently. These results are summarized in Table 3.

Local anesthetic activity

In surface anesthetic activities of dl-YB-2, l-YB-2, d-YB-2 and propranolol performed in guinea pig cornea, no significant difference was obtained; the EC 50s of these agents being 0.39–0.60%, while procaine (EC 50–6.7%) was very weak as is well known (18). Relative to procaine, the beta-adrenergic blocking agents studied showed a significant local anesthetic activity.

TABLE 4. Fifty percent inhibitory concentrations (EC 50) of procaine, propranolol, dl-YB-2, l-YB-2 and d-YB-2 in the corneal responses (surface anesthesia) and the dorsal skin responses (infiltration anesthesia) in guinea pigs.

Drug	Surface Anesthesia	Infiltration Anesthesia
	EC 50(% conc.)	EC 50 (% conc.)
Procaine	6.7 (6.2–7.2)	0.23 (0.21–0.25)
Propranolol	0.56 (0.50–0.63)	0.14 (0.12–0.15)
dl-YB-2	0.40 (0.38–0.43)	0.14 (0.13–0.16)
l-YB-2	0.39 (0.35–0.43)	0.12 (0.11–0.13)
d-YB-2	0.60 (0.54–0.63)	0.27 (0.24–0.30)

Each value was obtained from 6 experiments. Figures in parentheses represent 95% confidential limits of EC 50.

FIG. 4. Changes in contractile force produced by dl-YB-2, l-YB-2, d-YB-2 and propranolol in electrically driven guinea pig left atria.

A: incubated with 4×10^{-6} M of each agent, B: incubated with 4×10^{-5} M. Each point represents the mean value $\pm$ S.E.M. from 6 experiments.

In infiltration anesthetic activities performed in guinea pig dorsal skin, the beta-adrenergic blocking agents studied were found to be equipotent to procaine; the EC 50s of the agents being 0.12–0.27%. These results are summarized in Table 4.

Negative inotropic activity

The effects of equimolar concentrations of dl-YB-2, l-YB-2, d-YB-2 and propranolol on the contractile force of electrically driven guinea pig left atria are shown in Fig. 4. The contractile force of untreated atria declined at a rate of about 25% per 30 min. YB-2 and its isomers and propranolol, 4×10^{-6} M, did not cause a significant decline in contractile force from the controls over a 45-min experimental period. In the presence of these agents, 4×10^{-5} M, marked negative inotropic effects were observed and the decline in contractile force was significantly greater than in the controls. There was no significant difference in the negative inotropic effect among these agents.

DISCUSSION

A number of beta-adrenergic blocking drugs have been shown to differ in their potencies as beta-receptor antagonists and in the other properties not directly related to beta-receptor blockade, i.e. quinidine-like action, local anesthetic action or non-specific membrane stabilizing action.

A potent local anesthetic activity which is a property common to pronethalol, propranolol or alprenolol, but not to sotalol or practolol, may have a causative relationship to be effective against ouabain-induced arrhythmias (1, 3, 4, 19–22). In addition, the d-isomers of pronethalol, propranolol and alprenolol, and the diethylmethyl analogue of propranolol (ICI 46037), which have insignificant beta-receptor blocking activities, retain their potent local anesthetic activities and are also effective against ouabain-induced arrhythmias (1, 4, 19, 23).

The cardiovascular beta-adrenergic blocking activity of l-YB-2 was found to be 1.7 to 2 times as potent as the racemate and 50 to 100 times as potent as the d-isomer (10). The results are similar to those obtained from the experiments with propranolol (11, 12).

In the present studies, YB-2 and its optical isomers and propranolol showed a significant local anesthetic activity in guinea pig cornea and dorsal skin and a negative inotropic activity in isolated guinea pig atria. There was, however, no significant difference among these agents in each activity. In anesthetized guinea pigs, these agents showed a significant protecting effect against ouabain-induced arrhythmias; the order of antiarrhythmic potency was as follows, l-YB-2 > dl-YB-2 > propranolol > d-YB-2. The antiarrhythmic activity of the l-isomer and the racemate was significantly more potent than that of the d-isomer. The result appears to be consistent with the findings on propranolol reported by Barrett and Cullum (20).

Recently the association between antiarrhythmic activity against ouabain-induced cardiac disturbances and local anesthetic activity, and the dissociation between the former property and beta-receptor blockade have been questioned by several investigators (20, 24, 25). Burrett and Cullum (20) suggested that local anesthetic property is essen-

tial for non-specific antiarrhythmic activity and that beta-adrenergic blocking activity may potentiate this effect. Dohadwalla *et al.* (26) also obtained a similar result. A possible explanation related to their suggestion is that the capacity of an agent to protect against digitalis-induced arrhythmias would be related, at least in part, to action on the adrenergic nerve terminals. Some procedures, including reserpination, sympathectomy and adrenalectomy, have been found to reduce the incidence or degree of digitalis-induced arrhythmias (27-31). Gillis (32) demonstrated an increased activity in the preganglionic sympathetic nerves to the heart following administration of arrhythmic doses of ouabain to decerebrated cats, and suggested that the sympathetic hyperreactivity may contribute importantly to the genesis of ouabain-induced arrhythmias. It has been also reported that an increased release of catecholamines from the heart and adrenal glands by the administration of ouabain may be an important factor in this type of arrhythmia (33, 34).

It is of interest to note that ambonestyl was equipotent with procainamide with respect to its antiarrhythmic activity but was lacking in local anesthetic activity (35), and that UM-272, a quaternary analogue of propranolol, was lacking in local anesthetic activity but was effective against digitalis-induced arrhythmias as well as cardiac rhythm disturbances associated with acute myocardial ischemia or infarction (35).

Howe and Shanks (11) found that propranolol and its 1-isomer were equally effective in preventing halothane-epinephrine-induced arrhythmias and were at least 10 times as active as the d-isomer. In the present studies, YB-2 and its 1-isomer were equipotent with propranolol with respect to preventing methylchloroform-epinephrine-induced ventricular fibrillation in dogs, while the d-isomer, even in a dose as high as 4 mg/kg i.v., failed to demonstrate antiarrhythmic activity. These results appear to be related to beta-adrenergic blocking activities, which were reported in the previous paper (10).

Thus, YB-2 and its optical isomers appear to have a similar potency ratio for antiarrhythmic activity as is the case with propranolol and its optical isomers (5, 11, 20, 37). Furthermore, in clinical situations, a mild intrinsic sympathomimetic activity of YB-2 (7, 9) would reduce the risk of aggravating heart failure and the degree of bronchospasm in susceptible patients, as suggested by several investigators (38-40).

REFERENCES

- 1) LUCCHESI, B.R.: *J. Pharmacol. exp. Ther.* **148**, 94 (1965)
- 2) SOMANI, P. AND LUM, B.K.B.: *J. Pharmacol. exp. Ther.* **147**, 194 (1965)
- 3) SOMANI, P., FLEMING, J.G., CHAN, G.K. AND LUM, B.K.B.: *J. Pharmacol. exp. Ther.* **151**, 32 (1966)
- 4) LUCCHESI, B.R., WHITSITT, L.S. AND STICKNEY, L.J.: *Ann. N.Y. Acad. Sci.* **139**, 940 (1967)
- 5) PARMALEY, W.W. AND BRAUNWALD, E.: *J. Pharmacol. exp. Ther.* **158**, 11 (1967)
- 6) LADDU, A.R. AND SOMANI, P.: *Europ. J. Pharmacol.* **8**, 167 (1969)
- 7) TAKENAKA, T. AND TACHIKAWA, S.: *Arzneim.-Forsch.* **22**, 1864 (1972)
- 8) TAKENAKA, T. AND TACHIKAWA, S.: *Pharmacometrics*, **6**, 1233 (1972) (in Japanese)
- 9) TACHIKAWA, S. AND TAKENAKA, T.: *Archs int. Pharmacodyn. Théor.* **202**, 79 (1973)
- 10) KATO, H., NOGUCHI, Y., NAKAO, K. AND TAKAGI, K.: *Japan. J. Pharmacol.* **24**, 261 (1974)
- 11) HOWE, R. AND SHANKS, R.G.: *Nature*, **210**, 1336 (1966)
- 12) LEVY, J.V. AND RICHARDS, V.: *Proc. Soc. exp. Biol. Med.* **122**, 373 (1966)
- 13) SEKIYA, A. AND VAUGHAN WILLIAMS, E.M.: *Br. J. Pharmacol. Chemother.* **21**, 462 (1963)

- 14) MORAN, N.C., MOORE, J.L., HOLCOMB, A.K. AND MUSCHET, G.: *J. Pharmacol. exp. Ther.* **136**, 327 (1962)
- 15) CHANCE, M.R.A. AND LOBSTEIN, H.: *J. Pharmacol. exp. Ther.* **82**, 203 (1944)
- 16) BÜLBRING, E. AND WAJADA, I.: *J. Pharmacol. exp. Ther.* **85**, 78 (1945)
- 17) LITCHFIELD, J.T. AND WILCOXON, F.: *J. Pharmacol. exp. Ther.* **96**, 99 (1949)
- 18) HERR, F.: *Arzneim.-Forsch.* **8**, 137 (1958)
- 19) DUCE, B.R., GARBERG, L. AND JOHANSSON, B.: *Acta pharmacol. tox.* **25**, Suppl. 2, 41 (1967)
- 20) BARRETT, A.M. AND CULLUM, V.A.: *Br. J. Pharmacol. Chemother.* **34**, 43 (1968)
- 21) SOMANI, P. AND WATSON, D.L.: *J. Pharmacol. exp. Ther.* **164**, 317 (1968)
- 22) DUNLOP, D. AND SHANKS, R.G.: *Br. J. Pharmacol. Chemother.* **32**, 201 (1968)
- 23) LUCCHESI, B.R. AND IWAMI, T.: *J. Pharmacol. exp. Ther.* **162**, 49 (1968)
- 24) BAUM, T., ECKFELD, D.K., SHROPSHIRE, A.T., ROWLES, G. AND VARNER, L.L.: *Archs int. Pharmacodyn. Thé.* **193**, 149 (1971)
- 25) GLYNN, I.M. AND WARNER, A.E.: *Br. J. Pharmacol. Chemother.* **44**, 271 (1972)
- 26) DOHADWALLA, A.N., FREEDBERG, A.S. AND VAUGHAN WILLIAMS, E.M.: *Br. J. Pharmacol. Chemother.* **36**, 257 (1969)
- 27) MENDEZ, C., ACEVES, J. AND MENDEZ, R.: *J. Pharmacol. exp. Ther.* **131**, 191 (1961)
- 28) CAIROLI, V., REILLY, J., ITO, R. AND ROBERTS, J.: *Fedn Proc.* **21**, 127 (1962)
- 29) LEVITT, B. AND ROBERTS, J.: *Circulation Res.* **19**, 622 (1966)
- 30) KATZ, R.L., LORD, C.O. AND EAKINS, K.E.: *J. Pharmacol. exp. Ther.* **158**, 40 (1967)
- 31) HERMANSEN, K.: *Acta pharmacol. tox.* **28**, 57 (1970)
- 32) GILLIS, R.A.: *Science*, **166**, 508 (1969)
- 33) SAITO, H., OTANI, T., SHUDO, I., MONMA, Y. AND TANABE, T.: *Japan. J. Pharmacol.* **23**, Suppl. 7 (1973)
- 34) HASHIMOTO, K., KIMURA, T. AND KUBOTA, K.: *Japan. J. Pharmacol.* **23**, Suppl. 10 (1973)
- 35) LANZONI, V. AND CLARK, B.B.: *Circulation Res.* **3**, 335 (1955)
- 36) SCHISTER, D.P., LUCCHESI, B.R., NOBEL, N.L., MIMNAUGH, M.N., COUNSELL, R.E. AND KNIFFEN, F.J.: *J. Pharmacol. exp. Ther.* **184**, 312 (1973)
- 37) LUCCHESI, B.R., WHITSITT, L.S. AND IWAMI, T.: *Cardiovascular Beta Adrenergic Responses*, Edited by KATTUS, A.A., ROSS, G. AND HALL, V.E., p. 21, University of California Press, Berkeley (1970)
- 38) ÅBLAD, B.: *Acta pharmacol. tox.* **25**, Suppl. 2, 1 (1967)
- 39) HERMANSEN, K.: *Acta pharmacol. tox.* **26**, 343 (1968)
- 40) BAUM, T., ROWLES, G., SHROPSHIRE, A.T. AND GLUCKMAN, M. I.: *J. Pharmacol. exp. Ther.* **176**, 339 (1971)