

Vasodilating Effect of Diphenylalkanolamines in Anesthetized Dogs

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The effects of five diphenylalkanolamine derivatives, including YS 3635, YS 3636, YS 3632, YS 3623 and YS 3423, on the coronary and hindquarter vascular beds in anesthetized dogs were studied and compared with those of glyceryl trinitrate and papaverine.

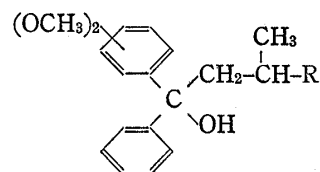
These five derivatives in doses of 62.5 to 1000 μg *i.a.* reduced coronary and hindquarter vascular resistances, and the effects were in the following order: YS 3423 > YS 3623 > papaverine > YS 3632 > YS 3635 > YS 3636 in the coronary, and YS 3423 > papaverine > YS 3623 > YS 3635 > YS 3632 > YS 3636 in the hindquarter vascular beds.

Three derivatives, YS 3423, YS 3623 and YS 3635 having a relatively potent vasodilating effect were further examined. These compounds, 1 mg/kg *i.v.*, also showed an increase in coronary and hindquarter blood flows, concomitantly with a transient hypotension, sustained decrease in heart rate and increase in cardiac output.

The vasodilating effect of the diphenylalkanolamine derivatives studied appears to show a direct and non-specific effects on the peripheral blood vessels as is the case of glyceryl trinitrate or papaverine.

Since the discovery of a potent spasmolytic activity of a series of propanolamine derivatives,²⁾ such alcohol-type spasmolytics have attracted much attention. Several investigators have reported a diphenylalkanolamine derivative, 1,1-diphenyl-3-piperidinobutanol hydrochloride (Aspaminol), to have a potent anti-acetylcholine and anti-barium effects in the isolated guinea pig ileum.³⁾ In the clinical studies, Aspaminol showed a more potent spasmolytic and less untoward effects than those of atropine and papaverine, and was effective on spasmogenic pain in acute gastro-intestinal diseases after oral or intravenous administration.⁴⁾

The pharmacological properties of several newly synthesized diphenylalkanolamine derivatives have been studied and their spasmolytic, local anesthetic and hypotensive effects, and cocaine-like sensitizing action to catecholamines were found.⁵⁾ Some of them having coronary








YS 3635	2, 5-di OCH ₃	R = -N 
YS 3636	2, 5-di OCH ₃	R = -N 
YS 3632	2, 5-di OCH ₃	R = -N 
YS 3623	2, 5-di OCH ₃	R = -NH-CH 
YS 3423	3, 4-di OCH ₃	R = -NH-CH 

Fig. 1. Chemical Structures of Diphenyl-alkanolamines

- 1) Location: *Hongo, Bunkyo-ku, Tokyo.*
- 2) J.J. Denton, R.J. Turner, W.B. Neier, V.A. Lawson and H.P. Schedl, *J. Am. Chem. Soc.*, **71**, 2048 (1949); A.W. Ruddy and J.S. Buckley, Jr., *J. Am. Chem. Soc.*, **72**, 718 (1950).
- 3) K. Takagi, Y. Kasuya and K. Hattori, *Yakugaku Zasshi*, **71**, 1328 (1951); K. Takagi, Y. Kasuya and Y. Ota, *Yakugaku Zasshi*, **73**, 541 (1953); K. Takagi, Y. Kasuya, H. Fukuda and Y. Ota, *Yakugaku Zasshi*, **75**, 566 (1954); K. Yamamoto and S. Chuma, *J. Osaka City Med. Col.*, **4**, 127 (1955); Y. Kasuya, *Yakugaku Zasshi*, **78**, 509 (1958).
- 4) G. Koguchi, H. Kurita, K. Maruyama and T. Kojima, *Shinyaku To Rinsho*, **8**, 507 (1959); K. Yamada, S. Ogawa, N. Sakamoto and H. Hayakawa, *Rinsho Naika Shonika*, **14**, 1043 (1959); K. Kobayashi, T. Kusabuka and M. Endo, *Rinsho Shokakibyogaku*, **8**, 46 (1960).
- 5) Y. Kasuya and M. Watanabe, *Arzneim.-Forsch.*, **15**, 1279 (1965); M. Watanabe, *Arzneim.-Forsch.*, **15**, 1284 (1965).

vasodilating effect, which is comparable to that of papaverine in the isolated rabbit hearts, have also been reported.⁶⁾

In the present studies, some hemodynamic effects of five diphenylalkanolamine derivatives, as shown in Fig. 1, including vasodilating effects on the coronary and hindquarter vascular beds in anesthetized dogs, were investigated and compared with those of glyceryl trinitrate and papaverine.

Experimental

Methods—1. **Coronary and Hindquarter Vascular Resistances in Anesthetized Dogs:** Adult male mongrel dogs weighing 10 to 16 kg were anesthetized with sodium pentobarbital, 35 mg/kg *i.v.* The trachea was intubated, and ventilation was maintained by a positive pressure respirator (Natsume, KN-50) with room air. The left chest was opened at the fourth intercostal space, and the pericardium was opened. After heparinization, 500 unit/kg *i.v.*, the left anterior descending coronary artery was proximally ligated, distally cannulated and perfused with the blood derived from the left common carotid artery through polyvinyl tubing and an electromagnetic flowmeter (Nihon Kohden, MF-2). Femoral arterial blood pressure was obtained *via* a pressure transducer (Nihon Kohden, MPU-0.5) and recorded together with coronary blood flow on a polygraph (Nihon Kohden, RM-150).

For the measurement of femoral blood flow, pentobarbitalized and heparinized dogs as mentioned above were also utilized. The left femoral artery was exposed and cannulated in its proximal portion, the blood derived from the cannula was streamed into another cannula inserted into the distal portion of the artery through polyvinyl tubing and an electromagnetic flowmeter.

The following parameters were calculated: coronary vascular resistance = mean blood pressure (mmHg) / mean coronary blood flow (ml/min), and hindquarter vascular resistance = mean blood pressure (mmHg) / mean femoral blood flow (ml/min).

Each drug solution having no influence on systemic blood pressure was injected close to the perfusing artery in a volume of 0.4 ml in 10 sec.

2. **Coronary or Femoral Blood Flow, Cardiac Output, Heart Rate and Arterial Blood Pressure in Anesthetized Dogs:** In pentobarbitalized dogs, the chest was opened at the left fourth intercostal space the pericardium was opened, and approximately 20 mm of the ascending aorta was cleared of fat. The blood flow through the ascending aorta was measured with a flow probe (internal diameter: 11 to 12 mm, Nihon Kohden) positioned around the vessel. The flow probe signals were fed into an electromagnetic flowmeter (Nihon Kohden, MF-5), and recorded together with femoral arterial blood pressure, heart rate obtained *via* a cardiometer (Nihon Kohden, RT-2) triggered by femoral arterial pulse, and coronary or femoral blood flow on a polygraph. Each drug solution was injected into the left cephalic vein through an inserted catheter, and was flushed with 1 ml of physiological saline.

Materials—The drugs used were as follows: the diphenylalkanolamine derivatives, 1-phenyl-1-(2',5'-dimethoxyphenyl)-3-piperidinobutanol hydrochloride (YS 3635), 1-phenyl-1-(2',5'-dimethoxyphenyl)-3-morpholinobutanol hydrochloride (YS 3636), 1-phenyl-1-(2',5'-dimethoxyphenyl)-3-(dimethylamino)butanol hydrochloride (YS 3632), 1-phenyl-1-(2',5'-dimethoxyphenyl)-3-(isopropylamino)butanol hydrochloride (YS 3623) and 1-phenyl-1-(3',4'-dimethoxyphenyl)-3-(isopropylamino)butanol hydrochloride (YS 3423), which were synthesized and supplied by Nihon Kayaku Company Ltd., glyceryl trinitrate (Nihon Kayaku Co.), papaverine hydrochloride (Iwaki Seiyaku Co.), isoproterenol hydrochloride (Kaken Chemical Co.), histamine dihydrochloride (Wako Pure Chemicals Co.), acetylcholine chloride (Daiichi Seiyaku Co.), atropine sulfate (Wako Pure Chemicals Co.), diphenhydramine hydrochloride (Tokyo Kasei Co.) and propranolol hydrochloride (Sumitomo Chemical Co.). These drugs were freshly dissolved in 0.9% saline at the required concentrations. All doses of the drugs were expressed in terms of the salt.

Result

1. Effect on Coronary Vascular Bed

The effects of five diphenylalkanolamine derivatives in doses of 62.5, 125 and 250 μg *i.a.* on the coronary vascular bed were examined comparing with those of glyceryl trinitrate, 2 to 8 μg *i.a.*, and papaverine, 100 and 200 μg *i.a.* All these agents exerted a dose-dependent vasodilating effect on the coronary vascular bed. Some typical data are shown in the upper

6) K. Takagi, Y. Kasuya and S. Kayaoka, The 84th Annual Meeting of Pharmaceutical Society of Japan, Tokyo, April 1964.

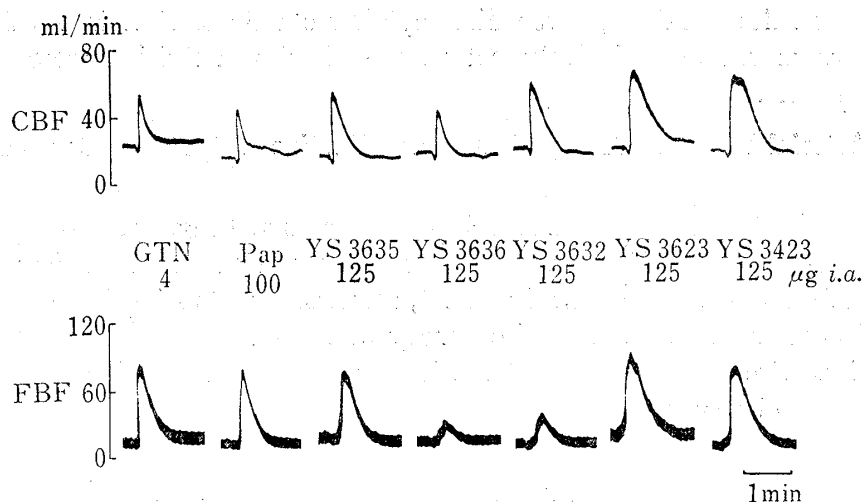


Fig. 2. Effects of Intra-arterially Administered Diphenylalkanolamines on Coronary and Femoral Blood Flows in Anesthetized Dogs
 CBF: coronary blood flow; FBF: femoral blood flow; GTN; glyceryl trinitrate; Pap: papaverine

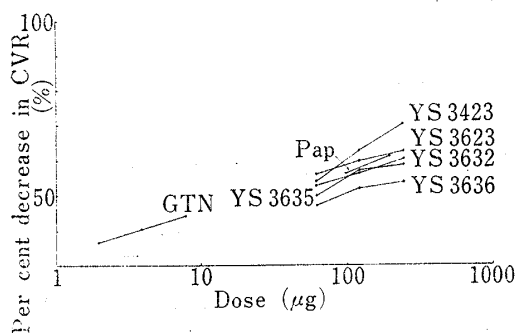


Fig. 3. Effects of Intra-arterially Administered Diphenylalkanolamines, Glyceryl Trinitrate and Papaverine on Coronary Vascular Resistance in Anesthetized Dogs
 GTN: glyceryl trinitrate; Pap: papaverine
 abscissa: doses of the agents in $\mu\text{g i.a.}$; ordinate: per cent decrease in coronary vascular resistance. Each point represents the mean value obtained from five separate experiments performed on different dogs.

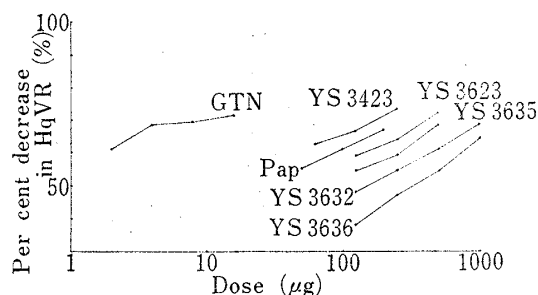


Fig. 4. Effects of Intra-arterially Administered Diphenylalkanolamines, Glyceryl Trinitrate and Papaverine on Hindquarter Vascular Resistance in Anesthetized Dogs
 GTN: glyceryl trinitrate; Pap: papaverine
 abscissa: doses of the agents in $\mu\text{g i.a.}$; ordinate: per cent decrease in hindquarter vascular resistance. Each point represents the mean value obtained from six separate experiments performed on different dogs.

part of Fig. 2, and per cent decreases in vascular resistance for each agent are shown in Fig. 3. Five diphenylalkanolamines decreased coronary vascular resistance, which were almost the same degree as those of papaverine, and an approximate order of their potencies was as follows: YS 3423 > YS 3623 > papaverine > YS 3632 > YS 3635 > YS 3636. The potency of glyceryl trinitrate could not be compared with these agents, as only a low concentration had been prepared.

2. Effect on Hindquarter Vascular Bed

The effects of five diphenylalkanolamine derivatives in doses of 62.5, 125, 250 and 1000 $\mu\text{g i.a.}$ on the hindquarter vascular bed were examined comparing with those of glyceryl trinitrate, 2 to 16 $\mu\text{g i.a.}$, and papaverine, 50 to 200 $\mu\text{g i.a.}$ These agents showed a dose-dependent vasodilating effect on the hindquarter vascular bed. Some typical data are shown in the lower part of Fig. 2, and per cent decreases in vascular resistance for each agent, as shown in Fig. 4, was in the following order: YS 3423 > papaverine > YS 3623 > YS 3635 > YS 3632 > YS 3636.

From these results obtained, three diphenylalkanolamines, that is YS 3635, YS 3623 and YS 3423, which exerted relatively potent vasodilating activities, were chosen for the following experiments.

3. Effect on Arterial Blood Pressure, Heart Rate, Cardiac Output and Coronary or Femoral Blood Flow

The effects of YS 3635, YS 3623 and YS 3423 in doses of 1 mg/kg *i.v.* on systemic arterial blood pressure, heart rate, cardiac output and coronary or femoral blood flow were observed in three anesthetized dogs. As shown in Fig. 5, all these agents slightly reduced blood pressure, decreased heart rate and increased coronary blood flow and cardiac output. YS 3635 showed a sustained rise following a slight fall in blood pressure. Similar changes in femoral blood flow were also observed.

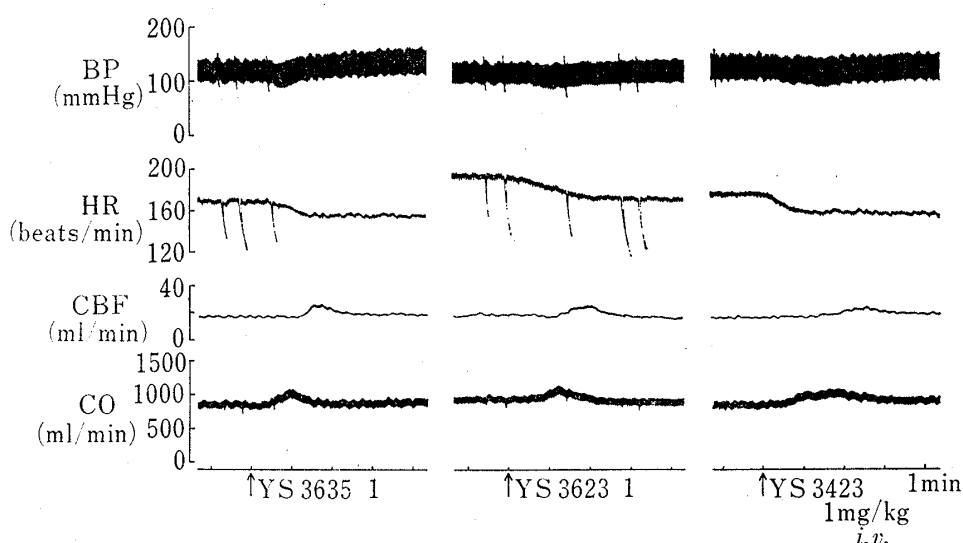


Fig. 5. Effects of Intravenously Administered Diphenylalkanolamines on Arterial Blood Pressure (BP), Heart Rate (HR), Coronary Blood Flow (CBF) and Cardiac Output (CO) in An Anesthetized Dog

4. Studies on The Mechanism of Vasodilating Effect

To examine the mechanism involved in the vasodilating effects of three diphenylalkanolamine derivatives on the coronary and hindquarter vascular beds, the following experiments were performed.

The influences of some blocking agents, including propranolol, 0.5 mg/kg, diphenhydramine, 3 mg/kg, and atropine, 2 mg/kg *i.v.*, on the vasodilating effects of YS 3635, YS 3623, YS 3423 and glyceryl trinitrate in doses producing the responses to approximately the same degree, were observed. Each corresponding blocking effect of these blocking agents was verified by the administration of isoproterenol, 0.1 μ g, histamine, 0.1 μ g, or acetylcholine, 0.1 μ g *i.a.*, respectively. YS 3635, 250 μ g, YS 3623, 125 μ g, YS 3423, 125 μ g, and glyceryl trinitrate, 4 μ g *i.a.*, induced 50 to 60% increases in coronary vascular resistance in five dogs, and no significant change after treatment with each blocking agent was observed, as shown in Fig. 6. Similar results were obtained from the experiments on hindquarter vascular resistance in five dogs, as shown in Fig. 7.

Discussion

1,1-Diphenyl-3-piperidinobutanol (Aspaminol) has been used as a potent and useful spasmolytic drug.⁴⁾ The chemical structures of diphenylalkanolamine derivatives used in the present studies are closely related to that of Aspaminol, and each compound is substituted

by two dimethoxy groups in one phenyl ring. The compounds having piperidino, morpholino, dimethylamino or isopropylamino group at the end of an alkyl chain, as shown in Fig. 1, were chosen because of a relatively potent coronary vasodilating effect in the isolated guinea pig heart utilized Langendorff's method.⁶⁾

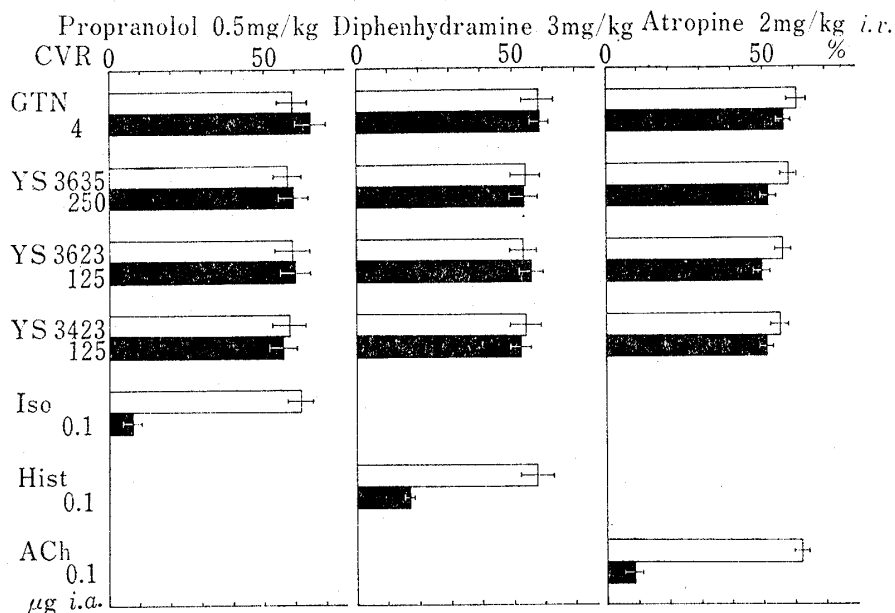


Fig. 6. Influences of Propranolol, Diphenhydramine and Atropine on the Changes in Coronary Vascular Resistance Induced by Intra-arterially Administered Diphenylalkanolamines in Anesthetized Dogs

GTN: glyceryl trinitrate; Iso: isoproterenol; Hist: histamine; ACh: acetylcholine
 abscissa: per cent change in coronary vascular resistance. White column: before the treatment with each blocking agent; black column: after the treatment. Each horizontal bar represents the standard error of mean value obtained from five separate experiments performed on different dogs.

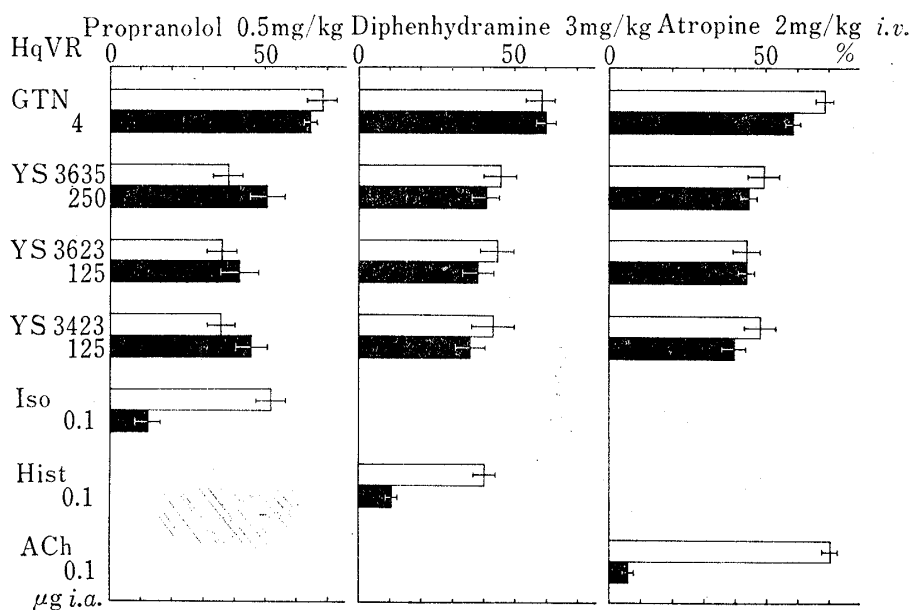


Fig. 7. Influences of Propranolol, Diphenhydramine and Atropine on the Changes in Hindquarter Vascular Resistance Induced by Intra-arterially Administered Diphenylalkanolamines in Anesthetized Dogs

abscissa: per cent change in coronary vascular resistance For details see Fig. 6.

All diphenylalkanolamine derivatives used showed a vasodilating effect on the coronary and hindquarter vascular beds autoperfused in pentobarbitalized dogs, when administered close-arterially. From the results of per cent decreases in both peripheral vascular resistances, 2',5'-dimethoxyphenyl-3-isopropylamino (YS 3423) and 3',4'-dimethoxyphenyl-3-isopropylamino (YS 3623) derivatives were the most potent, and their potencies were comparable to or superior to that of papaverine. 2',5'-Dimethoxyphenyl-3-piperidino derivative (YS 3635) was ranked next. These results were consistent with those observed in the isolated guinea pig heart.⁶⁾ Furthermore, YS 3423, YS 3623 and YS 3635 clearly showed increases in coronary and femoral blood flows even when administered intravenously, concomitantly with a transient hypotension, sustained decrease in heart rate and increase in cardiac output. The sustained rise in blood pressure produced by the administration of YS 3635 might be related to its potentiating activity to catecholamines observed by Kasuya and Watanabe.⁵⁾

Although experiments on the vascular beds other than the coronary and hindquarter vessels have not been carried out, the diphenylalkanolamine derivatives used appear to have no specific vasodilating effect in particular area, since the compounds showed similar activity in the coronary and hindquarter vascular beds.

The determination of a peripheral vasodilating mechanism of the diphenylalkanolamines was attempted utilizing some blocking agents, including propranolol, diphenhydramine and atropine. Since there was no influence by these blocking agents on the responses induced by the derivatives, that is YS 3423, YS 3623 and YS 3635, the mechanism through beta-adrenergic, histamine-like or muscarinic effect may be ruled out from their vasodilating activities. Although more detailed experiments on the mechanisms involved in the vasodilating effect are required, the diphenylalkanolamine derivatives used in the present studies appear to have a direct vasodilating activity on the blood vessels as in the case of glyceryl trinitrate or papaverine.

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