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Coronary Vasodilating Effect of Some Chromanone Derivatives

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The effects of benzylidene chromanones and its related compounds on coronary and femoral blood flow were examined in anesthetized dogs. They exhibited vasodilating activity in both vascular beds, but less active than that of papaverine. Intravenous administration of 3-(4′-β-diethylaminoethoxy)-benzylidene chromanone HCl (CDY-902) caused an increase in coronary blood flow as well as a transient hypotension and persistent negative chronotropic action. No significant effect of CDY-902 on myocardial oxygen consumption of the dog *in situ* was observed. On oxygen uptake of the rat heart slices CDY-902 elicited a decrease similar to papaverine. As the results were compared with those of papaverine, GTN and dipyridamole, CDY-902 appears to have a direct and non-selective effects on coronary vascular bed.

Coronary vasodilating activity of chromone derivatives has been reported.[2] It is worth examining if chromanone derivatives have a coronary vasodilating effect, since they are chemically related to chromone.

In the present study the effects of some benzylidene chromanones and its related compounds on coronary blood flow and myocardial oxygen consumption in anesthetized dogs and also on the oxygen uptake of isolated rat heart muscle were investigated. Results were discussed comparing with those of such coronary vasodilators as papaverine, glyceryl trinitrate and dipyridamole.

Experimental

Method

1. Coronary and Femoral Blood Flow——Male mongrel dogs weighing 11 to 16 kg were anesthetized with 35 mg/kg of intravenously administered sodium pentobarbital. The trachea was intubated, and ventilation was maintained by positive pressure respirator (Natsume KN-50). The left chest was opened at the fourth intercostal space, and the heart was exposed. After heparinization (300 units/kg), the left anterior descending coronary artery was proximally ligated, distally cannulated and perfused with the blood led from the left common carotid artery through an electromagnetic flowmeter (Nihon Koden MF-2). Femoral arterial pressure was obtained *via* a pressure transducer (Nihon Koden MP-4T) and recorded together with coronary flow on a multipurpose polygraph (Nihon Koden RM-150).

For the measurement of the fremoral 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 led from the cannula was streamed into another cannula inserted into the distal portion of the artery through polyvinyl tubings and an electromagnetic flowmeter.

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

2. Myocardial Oxygen Consumption——Dogs were anesthetized in the same manner as mentioned above and the chest was opened along the midline under artificial respiration. The femoral artery cannula was connected to a special coronary artery cannula after the method described by Yago.[3] The latter cannula was passed down the left common carotid artery into the aortic bulb and its cone-shaped tip was wedged into the orifice of the main left coronary artery. This cannula carried the blood from the left femoral artery to the left coronary artery *via* an electromagnetic flowmeter which was interposed to measure total left

1) Location: *Hongo, Bunkyo-ku, Tokyo.*

2) G. Jogebrem, *Arch. Intern. Pharmacodyn.*, **90**, 348 (1952); D.S. Bariana, *J. Med. Chem.*, **12**, 927 (1969); J. Klosa, *J. Prakt. Chem.*, **311**, 183 (1969).

3) C. Yago, *Folia pharmacol. Japon.*, **57**, 380 (1961).

coronary inflow. A Morawitz type glass cannula was inserted into the coronary sinus through the right auricle and the blood was led into the right external jugular vein *via* a polyvinyl tubing. Blood samples were taken from the left common carotid artery as well as from the circuit of coronary sinus outflow in order to determine oxygen contents by van Slyke and Neil's method.[4] Myocardial oxygen consumption was calculated by multiplying left coronary inflow by arteriovenous oxygen difference (the difference in oxygen content between the carotid artery and coronary sinus blood). Coronary vascular resistance was calculated by dividing mean femoral arterial pressure by coronary blood flow per 100 g heart weight per min.

Femoral arterial pressure measured *via* a pressure transducer and heart rate by a cardiotachography triggered by the arterial pulse were recorded as well as coronary blood flow onto a multipurpose polygraph.

Each drug solution was injected into the right brachial vein through a catheter. Blood coagulation was further prevented by additional heparin, 300 units/kg *i.v.*, every one hr.

3. Oxygen Uptake of Myocardial Slices——Male rats (Donryu strain, 300—350 g) were killed by a blow on the head and their hearts were quickly removed. The myocardial slices of 0.5 mm thickness were prepared by free hand with a thin razor blade. The oxygen uptake (qO_2) of the slices was measured by the Warburg method described by Nakamura, *et al.*[5] Approximately 50 mg wet weight of the rat's myocardium was used. The flasks contained 2.2 ml of a Krebs–Ringer phosphate buffer (pH 7.4) dissolving 5.5 mM glucose as a substrate. Drug effects were studied by adding appropriate amount of the drug to the stock buffer solution in order to yield the desired final molar concentration in the flask. The buffer solution was gassed with 100% O_2 before placing it in the flask. The centre well contained 0.2 ml of 20% KOH. The tissues were incubated for 60 minutes at 37°. The qO_2 was expressed as μl per mg dry weight per hr.

Materials

The drugs used were as follows: the chromanone derivatives and its related compounds, that is 4-diethylaminoethoxycalcone citrate (CDY-811), 3-(4′-β-diethylaminoethoxy)benzylidenechromanone hydrochloride (CDY-902), 3-(2′-β-piperidinoethoxy)benzylidenechromanone citrate (CDY-916), 3-(2′-β-diethylaminoethoxy)-benzylidenechromanone citrate (CDY-917), and 2-(2′-β-diethylaminoethoxy)benzylidenecoumaranone citrate (CDY-1010), were synthetized by Yoshitomi Pharmaceutical Industries, Ltd. These chemical structures are shown in Fig. 1. Glyceryl trinitrate (GTN, Nihon Kayaku), papaverine hydrochloride (Iwaki Seiyaku) and dipyridamole (Boehringer Sohn, Ingelheim) were also used.

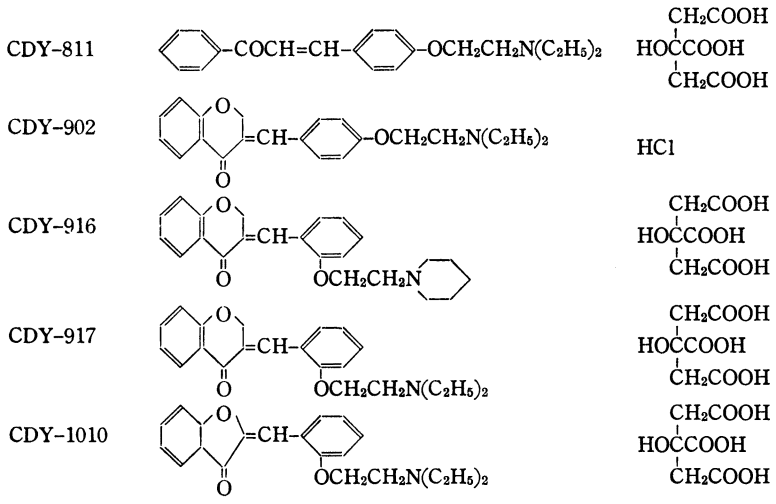

Fig. 1. Chemical Stractures of CDY-902 and Its Related Compounds

Result

Effects on Coronary and Femoral Blood Flow

The effects of the chromanone derivatives on coronary and femoral blood flow were examined after intra-arterial administration comparing with those of papaverine. As shown in Fig. 2, the chromanones exerted both coronary and femoral vasodilating activity. However,

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5) M. Nakamura, T. Miyazaki, T. Sata, and Y. Ishihara, *Arzneimittel-Forsch.*, **15**, 1382 (1965).

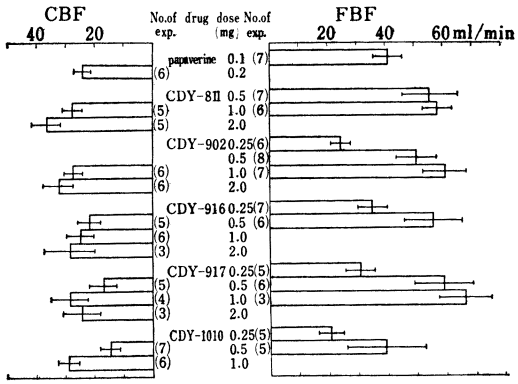

Fig. 2. Effects of Intra-arterial Injection of the Compounds and Papaverine on the Coronary (CBF) and Femoral Blood Flow (FBF) in Anesthetized Dogs

The horizontal scale shows the maximal increase in blood flow after the administration of drugs. Each column represents the mean value and each horizontal bar standard error.

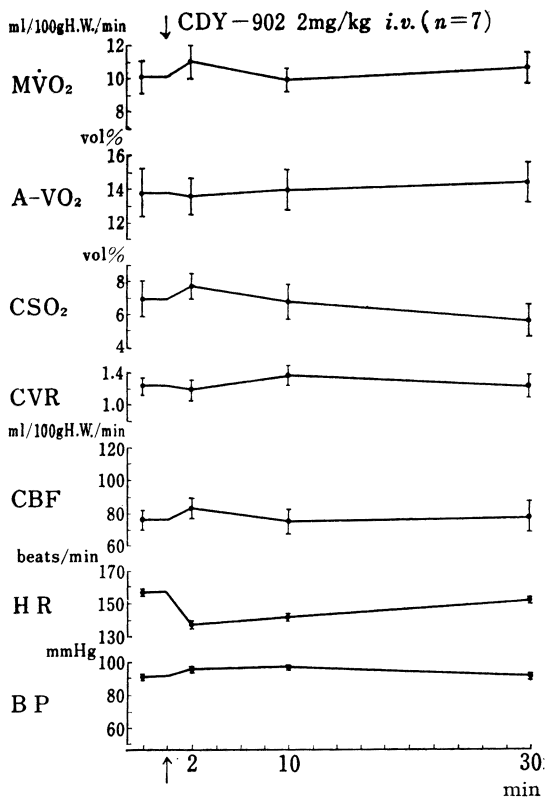

Fig. 3. Effects of CDY-902 on Coronary and Myocardial Oxygen Consumption in Open Chest Dogs

The values are means ± standard errors of seven experiments. MVO_2: myocardial oxygen consumption, $A\text{-}VO_2$: arteriovenous oxygen difference, CSO_2: O_2 content in coronary sinus blood, CVR: coronary vascular resistance (presented as mmHg ml/100 g heart weight/min), CBF: coronary blood flow, HR: heart rate, BP: blood pressure.

they were less active than papaverine and their duration of action was about 90 sec which was similar to that of papaverine. Potency differences among five chromanones and related compounds were small, but CDY-902 showed slightly longer duration of action when compared with others.

Coronary and Myocardial Oxygen Consumption

Effects of CDY-902, GTN and dipyridamole, which were administered intravenously, on coronary blood flow and myocardial oxygen consumption were investigated.

CDY-902 caused a transient hypotension which returned within two minutes. As shown in Fig. 3, CDY-902 (2 mg/kg) exerted a significant increase in coronary inflow, with which O_2 content in the coronary venous blood increased and coronary vascular resistance decreased. On the other hand, myocardial oxygen consumption slightly increased, but not statistically significant. Ten minutes after injection of the compound coronary blood flow returned to control value. However, a negative chronotropic action still persisted.

As exhibited in Fig. 4, 10 μg/kg of GTN caused a marked decrease in systemic blood pressure. Coronary blood flow and O_2 content of coronary venous blood declined and coronary vascular resistance decreased. Myocardial oxygen consumption also decreased at the time when blood pressure lowered.

As shown in Fig. 5, dipyridamole (0.2 mg/kg) exerted a hypotension and negative chronotropic action. Coronary venous O_2 content increased markedly with an increase in coronary blood flow. Coronary vascular resistance decreased significantly. Myocardial oxygen consumption was not affected when an increase in coronary blood flow was not affected when an increase in coronary blood flow was maximum, and decreased when blood pressure lowered and coronary blood flow almost recovered.

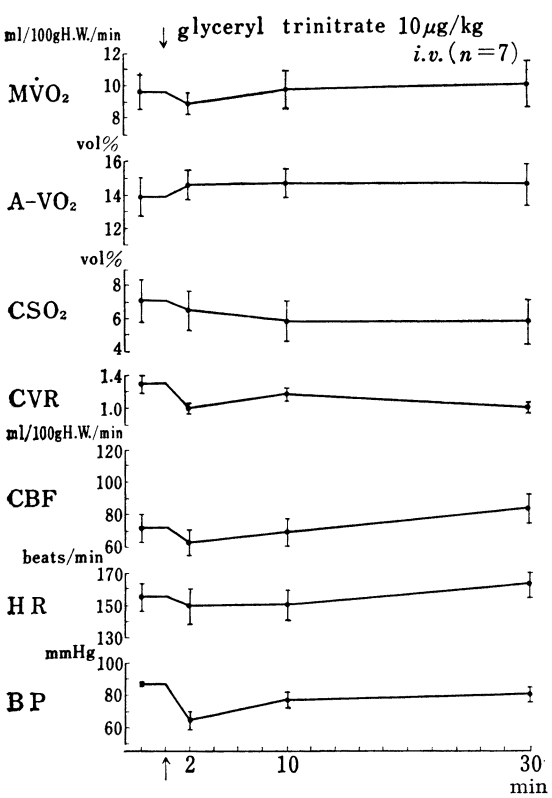

Fig. 4. Effects of Glyceryl Trinitrate on Coronary and Myocardial Oxygen Consumption

The same parameters were studied and the notion used as in Fig. 3.

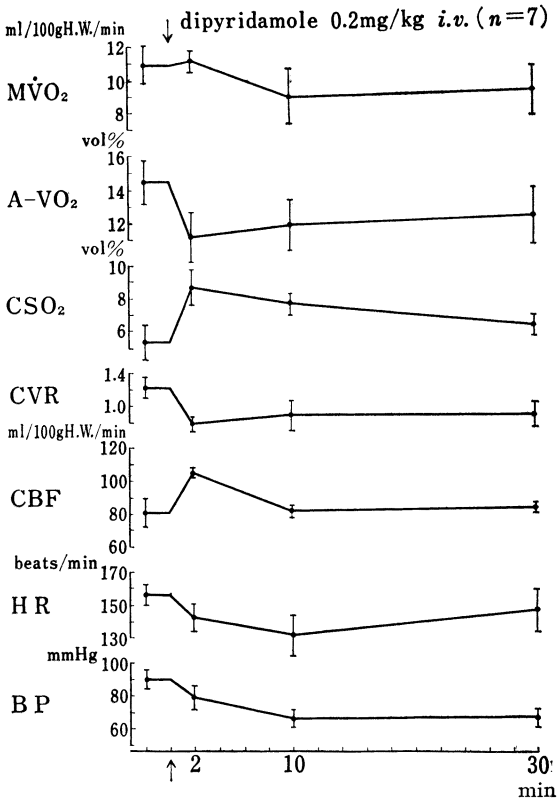

Fig. 5. Effects of Dipyridamole on Coronary and Myocardial Oxygen Consumption

The same parameters were studied and the notion used as in Fig. 3.

TABLE I. Effects of CDY-902 and Some Coronary Vasodilating Drugs on Oxygen Uptake of Rat Myocardial Slices

Compound	Conc. (M)	qO_2 μl/mg dry wt. per hr	
		Control	Test
CDY-902	2.0×10^{-4}	4.06 ± 0.76[a]	3.06 ± 0.71
	2.0×10^{-3}	4.06 ± 0.76	2.86 ± 0.43
Glyceryl trinitrate	2.0×10^{-5}	4.38 ± 0.30	4.25 ± 0.45
Dipyridamole	1.7×10^{-4}	4.38 ± 0.30	4.45 ± 0.63
Papaverine	2.3×10^{-4}	5.37 ± 0.21	3.26 ± 0.43[b]

a) Each value is mean ± standard error of six experiments.
b) $p<0.05$

Oxygen Uptake of Rat Ventricular Slices

Table I summarizes the effects of CDY-902 and other vasodilators on qO_2 of myocardial slices in a glucose-fortified Krebs–Ringer buffer. A decrease in O_2 uptake was observed at 2.0×10^{-4} and 2.0×10^{-3}M of CDY-902. In a similar concentration papaverine produced a significant ($p<0.05$) decrease in O_2 uptake. On the other hand, GTN and dipyridamole in the concentrations used elicited no marked effect.

Discussion

In the present study, total left coronary inflow was measured as coronary flow in open-chest dogs, and simultaneously the blood of the coronary sinus was returned into the right external jugular vein. Thus, the measurements of A-V O_2 difference and of coronary blood flow were simultaneously engaged. The total left coronary inflow was 70—80 ml per 100 g heart weight per min, which was comparable with the value obtained by Yago.[3] The calculated myocardial oxygen consumption was 10.2 ml per 100 g heart weight per min and the oxygen extraction (A-V O_2/A $O_2 \times 100$) was 70%. These values are consistent with those described by Gregg, *et al.*[6]

The chromanone derivatives which were chemically similar to chromones also exerted coronary vasodilating effect. Non chromanone derivatives, CDY-811 and CDY-1010, also showed vasodilating activity. Among the compounds examined, diethylaminoethoxybenzylidene moiety appears to be more essential to exert vasodilation than chromanone moiety. Potencies of the compounds relative to paraverine were almost in an identical degree in the two vascular beds studied. Therefore, vasodilating effect of chromanone derivatives on coronary vascular bed seems to be non-selective one. Intraveous administration of CDY-902 caused an increase in coronary blood flow accompanied with a slight increase in myocardial oxygen consumption. However, in this expeiment, coronary vasodilating effect of CDY-902 is due to direct vascular effect or indirect one is not clear.

Melville, *et al.*[7] reported that intravenously administered GTN induced a transient increase followed by a decrease in coronary flow. However, in the present study an increase in coronary flow induced by GTN was not observed. As GTN decreases coronary vascular resistance in spite of a decrease in coronary blood flow, coronary vasidilation might occur. Hypotensive action of GTN may contribute at least in part to the decrease in myocardial oxygen consumption.[8]

Coronary vasodilating action of dipyridamole was considered to be a direct one to vascular bed, because myocardial oxygen consumption was not affected at the time when an increase in coronary blood flow was maximum.[9] In addition, Bretschneider, *et al.*[10] reported that dipyridamole was rather selective to coronary artery.

These three drugs decreased coronary vascular resistance and caused hypotension. However, they had no consistent effect on coronary and myocardial oxygen consumption *in situ*. Therefore, the direct effects on myocardial oxygen consumption were studied. CDY-902 decreased qO_2 of rat ventricular slices as did papaverine. Levy[11] reported GTN, 442 μM, decreased oxygen uptake in the isolated rabbit atrial tissue. In the present study GTN, 20 μM, in which concentration it caused a significant relaxation of isolated coronary artery of the dog,[12] exerted a slight decrease in qO_2. Isosorbide dinitrate was found to have no effect on qO_2 in rabbit atrial tissue[11] and in cattle heart slices.[5] Dipyridamole had no significant effect on qO_2 of rat myocardium. The result was consistent with those obtained by Kadaz in the mouse heart[13] and by Nakamura, *et al.* in the cattle heart.[5] GTN and dipyridamole showed no significant effects on qO_2 *in vitro*. On the other hand, CDY-902 and

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papaverine decreased the qO_2. In addition, CDY-902 caused a slight relaxation of the isolated coronary smooth muscle.[12] Therefore, CDY-902 seems to have a direct and non-selective effects on coronary vascular bed.

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