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Effects of Some Anti-Anginal Drugs on Ergonovine-Induced Contractions of Isolated Dog Coronary Arteries

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Key Words : Dog coronary artery, Ergonovine, Contraction, Alpha adrenoceptor, Anti-anginal drug

Abstract

Effects of some anti-anginal drugs on dog coronary arterial contractions induced by ergonovine were investigated in vitro under potassium-contracture. Administrations of phentolamine (10^{-6}g/ml) or phenoxybenzamine (3×10^{-6}g/ml) did not affect potassium-contracture and ergonovine (10^{-6}g/ml)-induced contractions of coronary arterial strips, but phentolamine at a higher dose (10^{-5}g/ml) depressed both of them. Dihydroergotamine (10^{-7}-10^{-6}g/ml) produced further contractions of the strips under potassium-contracture and dose-dependently depressed ergonovine-induced contractions. Contractile responses to ergonovine (10^{-6}g/ml) were depressed by prior administrations of nitroglycerin (10^{-7}-10^{-6}g/ml), nifedipine (10^{-8}-10^{-7}g/ml), diltiazem (10^{-6}-10^{-5}g/ml) and SG-75 (10^{-6}-10^{-5}g/ml) in a dose-dependent fashion. Results indicate that ergonovine-induced contractions of isolated dog coronary arteries under potassium-contracture are not mediated mainly through an activation of alpha adrenoceptors and that some anti-anginal drugs such as nitroglycerin, nifedipine, diltiazem and SG-75 have a depressant action on these contractions.

Introduction

Ergonovine has been known to produce coronary vasospasm in man[1-3], and hence the drug is utilized for a provocative diagnosis of angina pectoris with spasm[4)5)]. Recently, it was reported that the action of ergonovine on coronary artery would be mediated through an activation of serotonergic receptors[6)7)]. However, possible participation of an activation of alpha adrenoceptors in the action of ergonovine is also proposed[6)8)9)].

According to the view that pharmacological properties of ergonovine will be related to genesis of vasospastic angina pectoris[10)], it must be meaningful to estimate whether the so-called anti-anginal drugs have the spasmolytic action against ergonovine-induced coronary arterial spasm.

The present study was undertaken to investigate participation of alpha adrenoceptors in the action of ergonovine and effects of some anti-anginal drugs on ergonovine-induced coro-

nary vasoconstriction by means of isolated dog coronary arterial strips under potassium-contracture.

Methods

Experiments were carried out using mongrel dogs of either sex weighing 6−13kg. Animals were anesthetized with sodium pentobarbital 30 mg/kg i.v. After the chest was opened by the fourth intercostal thoracotomy, the heart with both lungs was isolated. Spiral strips, 2 mm wide and 20 mm long, were prepared from the left circumflex coronary artery (1.5−2.0 mm in diameter), and placed in a 20−ml muscle bath filled with Krebs-Ringer bicarbonate solution of the following millimolar.composition : NaCl 117.7, KCl 4.7, $CaCl_2$ 2.5, $MgSO_4$ 1.2, KH_2PO_4 1.2, $NaHCO_3$ 24.4 and glucose 10.0 . The solution was maintained at 37°C and continuously aerated with a gas mixture of 95 % O_2 and 5 % CO_2 . When measured by means of a blood-gas analyzer (Instrumentation Laboratory, Micro-13), the oxygen tension of the solution was 600 mmHg and the pH was 7.40 . The strips were connected to a force-displacement transducer (Nihonkohden, TB-611T), and force developments of the strips were isometrically measured and recorded on an ink-writing recticorder (Nihonkohden, RJG-4004). Resting tension was adjusted to an optimal tension, about 1.0 g, and the strips were allowed to equilibrate for 2 hrs before any experiments were begun. In order to give the active tone to coronary arteries, all the strips were contracted with potassium 30 mM in this experiment.

The drugs used in the present study were as follows: ergonovine maleate (Sandoz), phentolamine mesylate (Ciba-Geigy), phenoxybenzamine hydrochloride (Nakarai), dihydroergotamine methanesulfonate (Sandoz), nitroglycerin (Nihon-kayaku), nifedipine (Bayer), diltiazem hydrochloride (Tanabe) and 2-nicotinamidoethyl nitrate (SG-75, nicorandil, Chugai). Ergonovine and dihydroergotamine were dissolved in 0.5 % tartaric acid, and diluted with physiological saline solution (PSS). Nifedipine was dissolved in acetone, and diluted with PSS. Other drugs were dissolved in PSS. The drug solution was added to the bath in a volume of 0.2 ml. All solvents had no effect on potassium-contracture of the strips. The doses of drugs corresponded to final bath concentrations of the salts in ergonovine, phentolamine, phenoxybenzamine, dihydroergotamine and diltiazem and of free forms in nitroglycerin, nifedipine and SG-75. In the text, the doses were expressed in terms of g/ml except potassium. Statistical analysis of the date was done by Student's t -test.

Results

1. Effects of cumulative administrations of ergonovine on coronary arterial strips

In 11 dog coronary arterial strips under potassium 30 mM-contracture, the effects of cumulative administrations of ergonovine were examined. Eight out of 11 strips did not respond to ergonovine $10^{-11}-10^{-7}$ g/ml (Fig. 1). When potassium 30 mM−induced contracture was defined as 100% (mean ± SE=885 ± 158 mg, n=8), force developments of the strips

reached 94 ± 4 % with ergonovine 10^{-6} g/ml and 85 ± 6 % with 10^{-5} g/ml, respectively (Fig. 1). In remaining 3 coronary arterial strips under potassium−contracture (100 % = 983 ± 262 mg), ergonovine 10^{-11} 10^{-5} g/ml produced contractile responses as shown in Fig. 2 : force of the strips was increased to 101 ± 1 % with ergonovine 10^{-10} g/ml, to 102 ± 2 % with 10^{-9} g/ml, to 111 ± 1 % with 10^{-8} g/ml, to 118 ± 1 % with 10^{-7} g/ml, to 118 ± 1 % with 10^{-6} g/ml and to 111 ± 2 % with 10^{-5} g/ml, respectively.

2. Effects on coronary arterial strips under potassium-contracture

In other 12 coronary arterial strips under potassium 30 mM-contracture (mean ± SE= 1415 ± 229 mg), phentolamine 10^{-6} g/ml did not affect potassium-contracture of the strips but 10^{-5} g/ml lowered it by 18 ± 9 %. Phenoxybenzamine 3 × 10^{-6}g/ml had no effect on the strips under potassium -contracture. Dihydroergotamine 10^{-7} g/ml and 10^{-6} g/ml produced further contractions of the strips by the same degree (8 ± 5 % in both doses). Nitroglycerin dose-dependently decreased potassium-contracture by 68 ± 10 % with a concentration of 10^{-7} g/ml and by 87 ± 13 % with 10^{-6} g/ml. Nifedipine 10^{-8} g/ml decreased coronary arterial contracture by 87 ± 4 %, and 10^{-7} g/ml by 100 %. Diltiazem also showed the similar effect on potassium-contracture of the strips to nifedipine : the drug decreased it by 76 ± 21 % with a concentration of 10^{-6} g/ml and by 100 % over with 10^{-5} g/ml. With SG-75 10^{-6} g/ml, potassium 30 mM-induced contracture was lowered by 57 ± 13 %, and with SG-75 10^{-5} g/ml by 72 ± 11 %.

3. Effects on ergonovine-induced contractions of coronary arterial strips

In 12 coronary arterial strips under potassium-contracture, single administrations of ergonovine 10^{-6} g/ml produced further increases in contractile force, which were reproducible by second administrations of the drug after 1 hr-washing. When the increased force was defined as 100 % (= 206 ± 35 mg, n=12), ergonovine-induced contractions were depressed to 56 ± 28 % by administration of phentolamine 10^{-5} g/ml (Fig. 3). Phentolamine 10^{-6} g/ml and phenoxybenzamine 3 × 10^{-6} g/ml did not induce any change in ergonovine-induced contractions (Fig. 3). Dihydroergotamine 10^{-7} g/ml depressed the contractions to 38 ± 12 % of the control, and 10^{-6} g/ml abolished them (Fig. 3). Ergonovine-induced contractions were decreased to 38 ± 24 % of the control with nitroglycerin 10^{-7} g/ml, to 67 ± 16 % with nifedipine 10^{-8} g/ml, to 25 ± 14 % with diltiazem 10^{-6} g/ml and to 50 ± 25 % with SG-75 10^{-6} g/ml, respectively (Fig. 4). These contractions disappered when nitroglycerin 10^{-6} g/ml, nifedipine 10^{-7} g/ml, diltiazem 10^{-5} g/ml or SG-75 10^{-5} g/ml was applied prior to ergonovine (Fig. 4).

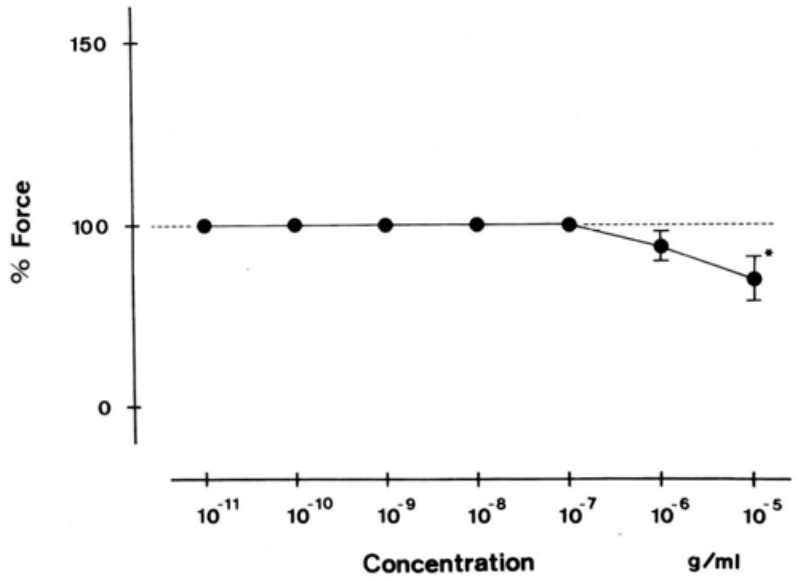

Fig. 1 Effect of cumulative administrations of ergonovine on potassium 30 mM-contracture of isolated dog coronary arterial strips : Cases in which relaxations alone were obtained.
100 % =885 ± 158 mg (mean ± SE, n=8). *P<0.05 vs 100 %.

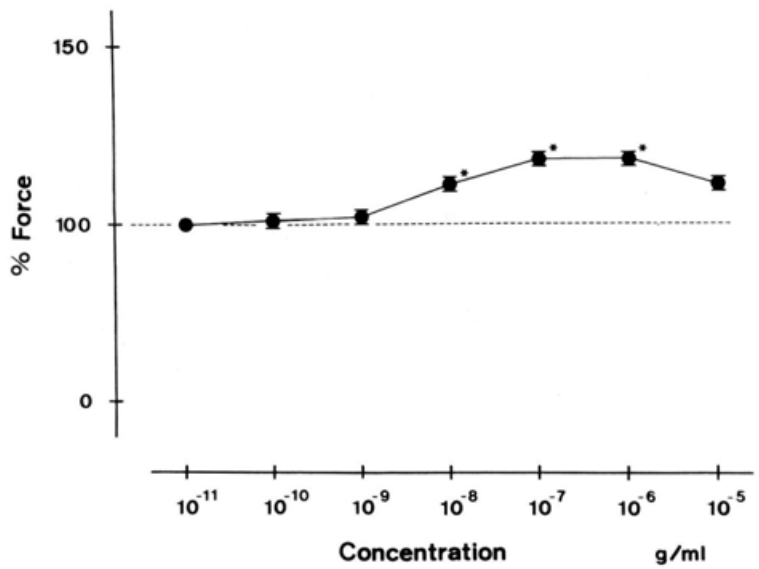

Fig.2 Effect of cumulative administrations of ergonovine on potassium 30 mM-contracture of isolated dog coronary arterial strips : Cases in which contractions alone were obtained.
100 % = 983 ± 262 mg (n=3). *P<0.05 vs 100 %.
The value at ergonovine 10^{-5} g/ml was obtained in 2 strips.

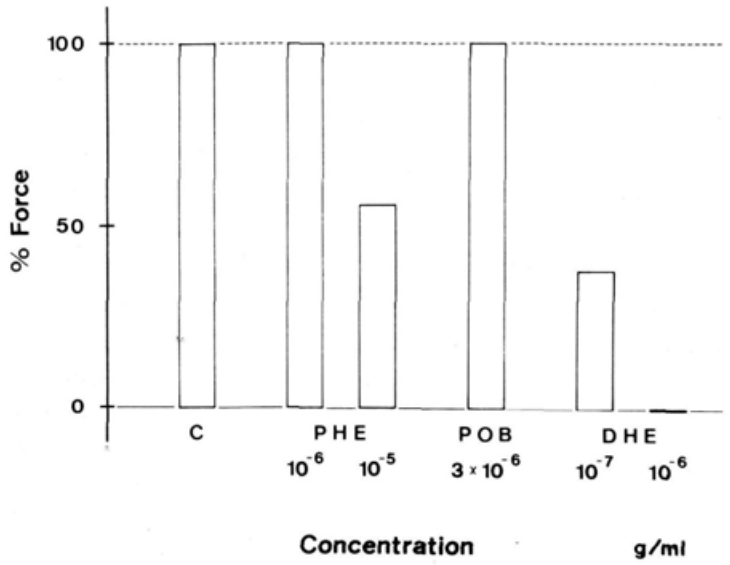

Fig. 3 Effect of phentolamine (PHE), phenoxybenzamine (POB) and dihydroergotamine (DHE) on ergonovine 10^{-6} g/ml-induced contractions of isolated dog coronary arterial strips under potassium 30 mM-contracture.

C : control contraction obtained by ergonovine 10^{-6} g/ml

100 % = 206 ± 35 mg (n=12).

Each bar shows mean values in 3 strips.

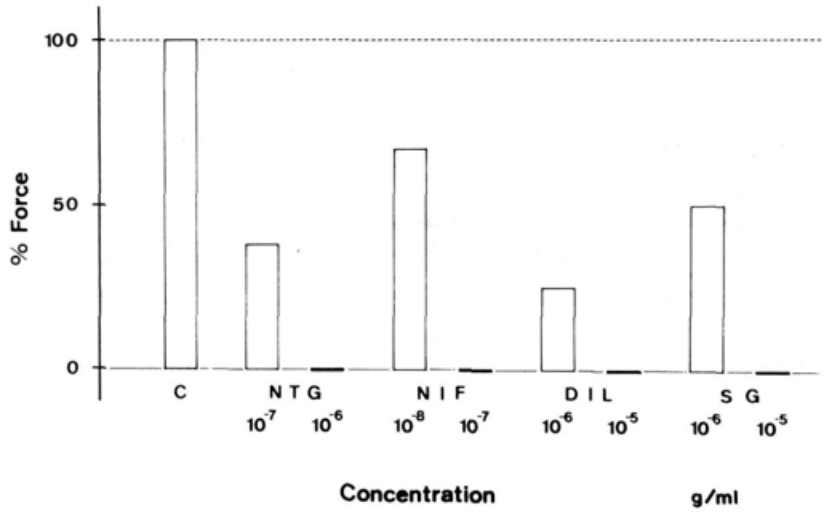

Fig. 4 Effect of nitroglycerin (NTG), nifedipine (NIF), diltiazem (DIL) and SG-75 (SG) on ergonovine 10^{-6} g/ml -induced contractions of isolated dog coronary arterial strips under potassium 30 mM-contracture.

C : control contraction obtained by ergonovine 10^{-6} g/ml

100 % = 206 ± 35 mg (n=12).

Each bar shows mean values in 3 strips.

Discussion

Blood vessels, which are innervated by sympathetic nerves, have a vascular tone caused by spontaneous sympathetic discharges[11]. In the present study, therefore, coronary arteries were contracted with potassium 30 mM in order to give the active tone to coronary arterial strips.

In this study, only 3 out of 11 coronary arterial strips under potassium-contracture showed contractile responses to cumulative administrations of ergonovine. Since ergonovine is considered to act on vascular tissues as "partial agonist"[8], ergonovine may display the antagonistic action rather than the agonistic action when administered cumulatively, resulting in no contraction as observed in 8 out of 11 coronary arterial strips.

The present results showed that single administrations of ergonovine (10^{-6} g/ml) further increased contractile force of all isolated dog coronary arteries under potassium-contracture, which was reproducible. Phentolamine (10^{-6} g/ml) or phenoxybenzamine (3×10^{-6} g/ml) at a dose enough to inhibit alpha adrenoceptor activity[12] could not influence the ergonovine-induced contractions of coronary arteries, meaning that ergonovine does not mainly act on dog coronary arteries through an activation of alpha adrenoceptors. This result coincides with our previous observations[6)9)]. The depression of ergonovine-induced contractions by dihydroergotamine or a higher dose of phentolamine (10^{-5} g/ml) will be resulted from an anti-serotonergic activity of both drugs rather than an alpha adrenoceptor blocking activity[6)9)]. In fact, both dihydroergotamine and phentolamine have been confirmed to have the depressant action on serotonergic receptors[13-15]. Maybe, ergonovine mainly acts on serotonergic receptors resulting in further contractions of isolated dog coronary arteries.

Nitroglycerin is a typical anti-anginal drug of which mechanisms of action have not fully been clarified up to this time. Nifedipine and diltiazem are the so-called calcium-antagonists which inhibit the calcium iuflux in cell membrane[16-19]. SG-75 is a new nitro-ester which has been reported to increase the potassium conductance in myocardial cell membrane[20] and/or enhance the prostacyclin formation in aortic tissues[21]. Thus, in spite of different mode of action, these four drugs relaxed the isolated dog coronary arteries under potassium-contracture and depressed the ergonovine-induced contractions of the arteries as shown in this study. From the results it is suggested that nitroglycerin, nifedipine, diltiazem and SG-75 have a possibility to be effective on coronary vasospasm, if pharmacological properties of ergonovine are certainly related to pathogenesis of variant angina[10].

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