Enhancement of coronary vasodilating action of adenosine by dilazep and dipyridamole in the dog

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Abstract—The mechanism of the augmentation of adenosine action by 1, 4-bis-[3-(3, 4, 5-trimethoxybenzoyl-oxy)-propyl] perhydro-1, 4-diazepine (dilazep, N, N,) and dipyridamole on the coronary vessel was examined in the dog. Coronary blood flow was measured by applying a Morawitz cannula to the in vivo heart. It was found that the ratio of coronary vasodilating activity of adenosine administered into saphenous vein, right atrium, and left atrium was 1: 1.5: 30, and that coronary vasodilating actions of adenosine administered into saphenous vein, right atrium, and left atrium after dilazep (10 μg/kg, i.v.) were 15.6, 10.8, and 3.3 times greater than those without dilazep, respectively. After dipyridamole coronary vasodilating actions of adenosine administered into saphenous vein, right atrium, and left atrium were 17.5, 14.3, and 5.4 times greater. These results indicate that augmentation of coronary vasodilating action of intravenously administered adenosine by dilazep or dipyridamole was mainly exerted at the lung and myocardium, and slightly in the blood, and was due to inhibition of the disappearance of adenosine.

It is well known that there is a close relationship between coronary blood flow and myocardial metabolism (1); either an augmentation of the myocardial metabolism or hypoxia of the myocardium results in an increased coronary blood flow.

Berne (2) has hypothesized that the metabolic regulation of coronary circulation is mediated by adenosine, which produces a powerful coronary vasodilation. Adenosine is always released in a small amount from the myocardium, and the amount of this adenosine release is increased in a hypoxic condition (3, 4).

Several long-acting coronary vasodilators (5, 6, 7, 8, 9, 10, 11) have been reported to enhance the coronary vascular response to adenosine, and the possible mechanism has been considered to be an inhibition of adenosine deaminase in the tissue (12), a blockade of the permeation of adenosine into erythrocytes (13) and vascular smooth muscle cells (14), and/or an inhibition of adenosine degradation in the lung (15).

The objective of this study was to clarify the mechanism of the potentiation of adenosine by certain long-acting vasodilators.

Materials and Methods

Forty-six male dogs, weighing 10 to 13 kg, were used. One hr after s.c. administration of 3 mg/kg of morphine and 1 g/kg of urethane, these animals were anesthetized with 20 mg/kg i.v. of sodium pentobarbital. An endotracheal tube was applied to each animal and
artificial ventilation was performed with a Harvard respirator (Model 607). After the chest was opened by the midsternal incision, a Morawitz cannula was introduced into the coronary sinus through the apex of the right auricle. The coronary sinus outflow was measured continuously with an electromagnetic flowmeter (Nihon-Kohden MF-2), and blood was returned to the right atrium. The blood pressure was measured with an electromanometer (San-ei 1206) in the femoral artery. The heart rate was recorded with a cardiotachometer (San-ei 2130) triggered by the arterial pulse pressure. These measurements were recorded on an ink-writing recorder (San-ei 142-8).

Sodium heparin (500 U/kg) was injected into the femoral vein before the experiment, and 200 U/kg was additionally given at 1 hour intervals. Adenosine was administered into the saphenous vein or right or left atrium, through a polyethylene cannula. Dilazep or dipyridamole, long-acting coronary vasodilators, were administered into the saphenous vein. The routes of injection are schematically shown in Fig. 1.

The change in coronary blood flow produced by adenosine was expressed by the product of the maximum increase in coronary blood flow multiplied by the half period of duration of vasodilation. The magnitude of the augmentation of the effect of adenosine by dilazep or dipyridamole was represented by a quotient obtained by dividing the dose of adenosine alone necessary to produce the same effect of adenosine after dilazep or dipyridamole by the dose of adenosine given after dilazep or dipyridamole.

RESULTS

1) Coronary vasodilator action of adenosine injected into the saphenous vein, or right or left atria.

When adenosine was injected into the saphenous vein in various doses, the coronary vasodilating action began to appear with a dose of 10 or 30 μg/kg. With a dose of 100 or 200 μg/kg, the coronary blood flow increased markedly and, with 300 μg/kg, the blood pressure and heart rate produced variable effects on the coronary flow. In the case of right atrial administration, the coronary blood flow increased slightly with 10 or 30 μg/kg.
and there was further increase with higher doses. With 300 μg/kg into the right atrium, the blood pressure and heart rate decreased so markedly that the coronary blood flow was equal to or a little greater than that after 200 μg/kg. When administered into the left atrium, the coronary blood flow began to increase with 1 μg/kg and gradually increased as the dosage was increased. Dose-response curves of adenosine obtained by the three ways of administration mentioned are shown in Fig. 2 (N=12). The potency of coronary vasodilator action of i.v. adenosine was 2/3 or 1/30 as effective as adenosine injected into the right atrium or the left atrium, respectively. This result indicated that 33.5% of i.v. adenosine disappeared or was inactivated during the passage of blood from the saphenous vein to the right atrium, and 64% of adenosine (i.v.) disappeared or was inactivated between the right and left atrium, i.e. within pulmonary circulation.

2) Potentiation of adenosine-induced coronary vasodilation by dipyridamole

After dipyridamole had been injected i.v. in a dose of 30 μg/kg, a subthreshold dose for its coronary vasodilator action, adenosine was administered into the saphenous vein, or right or left atrium, at 10-min intervals. When adenosine was injected i.v. in a dose of 10 μg/kg 10-min after the administration of dipyridamole, the coronary blood flow was augmented to the same level produced by 175 μg/kg of adenosine alone. This potentiation decreased gradually and vanished 60 to 90 min after dipyridamole administration (Fig. 3). When 10 μg/kg of adenosine was administered into the right atrium 10 min after dipyridamole, the coronary blood flow was augmented to the same level as that produced by 143 μg/kg of adenosine alone. This effect disappeared 60 to 90 min after dipyridamole (Fig. 4). On administration of 1 μg/kg of adenosine into the left atrium 10 min after dipyridamole, the increase in coronary blood flow was the same degree as that produced by 5.4 μg/kg of adenosine alone, and this effect was no longer observed after 30 to 60 min (Fig. 5). Time course of potentiating action of dipyridamole is shown in Fig. 6.
FIG. 3. Potentiation of the coronary vascular response to adenosine (i.v.) by 30 μg/kg dipyridamole.

P.B.P., phasic blood pressure; M.B.P., mean blood pressure; M.B.P., mean blood pressure; H.R., heart rate; C.F., coronary blood flow.

FIG. 4. Potentiation of the coronary vascular response to adenosine (r.a.) by 30 μg/kg dipyridamole.

FIG. 5. Potentiation of the coronary vascular response to adenosine (l.a.) by 30 μg/kg dipyridamole.
FIG. 6. Time-course of potentiating action of dipyridamole on adenosine-induced coronary vasodilation.

Magnitude of the augmentation of the effect of adenosine by dipyridamole is represented by a quotient obtained by dividing the dose of adenosine alone necessary to produce the same effect of adenosine after dipyridamole by the dose of adenosine given after dipyridamole.

It may be concluded that the potentiation of the effect of adenosine given i.v. by dipyridamole was 1.2 times as strong as that of the effect of adenosine given into the right atrium, while the potentiation for adenosine administered into the right atrium was 2.7 times stronger than that for adenosine into left atrium.

The effect of adenosine given into the left atrium after dipyridamole was 5.4 times as strong as that of adenosine given alone.

3) Potentiation of adenosine-induced coronary vasodilation by dilazep

After administration of dilazep in a dose of 10 μg/kg i.v. which is a subthreshold dose for its coronary vasodilation, adenosine was administered into saphenous vein, or right or left atrium at 10-min intervals. When 10 μg/kg of adenosine was injected intravenously 10 min after administration of dilazep, the coronary blood flow increased to the same magnitude as that produced by 156 μg/kg of adenosine alone. This augmentation gradually decreased and disappeared after 2 hr. When 10 μg/kg of adenosine was administered into the right atrium 10 min after dilazep administration, the coronary blood flow was augmented to the same level as that produced by 108 μg/kg of adenosine alone. On administration of 1 μg/kg of adenosine into the left atrium 10 min after dilazep administration, increase in the coronary flow was found to be the same degree as shown by 3.3 μg/kg of adenosine alone. This potentiation of adenosine effect by dilazep dis-
appeared 90 min after administration. The time course of the potentiating action of dilazep is shown in Fig. 7.

It may be concluded that the potentiation of the effect of adenosine given into saphenous vein by dilazep was 1.45 times as strong as that of the effect of adenosine given into the right atrium, while the potentiation for adenosine administered into the right atrium was 3.3 times stronger than that for adenosine administered into the left atrium.

The effect of adenosine given into left atrium after dilazep was 3.3 times as strong as that of adenosine given alone.

Fig. 7. Time-course of potentiating action of dilazep on adenosine-induced coronary vasodilation.

Table 1. Effect of dilazep and dipyridamole on the coronary vasodilating action of adenosine.

<table>
<thead>
<tr>
<th>Route of adenosine administration</th>
<th>Time after coronary vasodilator</th>
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<tbody>
<tr>
<td></td>
<td>10 min</td>
</tr>
<tr>
<td>Dilazep 10 μg/kg (i.v.)</td>
<td></td>
</tr>
<tr>
<td>i.v.</td>
<td>15.6±2.2</td>
</tr>
<tr>
<td>r.a.</td>
<td>10.8±1.5</td>
</tr>
<tr>
<td>l.a.</td>
<td>3.3±0.7</td>
</tr>
<tr>
<td>Dipyridamole 30 μg/kg (i.v.)</td>
<td></td>
</tr>
<tr>
<td>i.v.</td>
<td>17.5±3.4</td>
</tr>
<tr>
<td>r.a.</td>
<td>14.3±1.6</td>
</tr>
<tr>
<td>l.a.</td>
<td>5.4±0.6</td>
</tr>
</tbody>
</table>

Each value represents the degree of potentiation expressed by a quotient obtained by dividing the dose of adenosine alone necessary to produce the same effect of adenosine after dilazep or dipyridamole by the dose of adenosine given after dilazep or dipyridamole. Each value is mean ± S.E. (N=6).
DISCUSSION

Berne (2) postulated that the substance playing a regulating role in coronary vessels is adenosine, as a powerful coronary vasodilation is produced and it is continuously released from normal myocardium. As to the mechanism of disappearance or inactivation of exogenous adenosine, it has been postulated by other investigators that 1) decomposition of adenosine by adenosine deaminase occurs in erythrocytes or tissues (12), 2) adenosine may be taken up into the myocardium and into the smooth muscle of the blood vessel (13, 14), and 3) it may disappear in the pulmonary circulation (15).

In the present experiments the coronary vasodilating efficacy of intravenously administered adenosine was slightly less than that of right atrially administered adenosine (2/3), which may be taken to indicate that the adenosine uptake by erythrocytes and platelets is low. Van Belle (17) has shown that adenosine uptake by the blood varies according to animal species; the uptake is highest in the chicken and rabbit, less in humans and pig, and much less in the dog. Coronary vasodilator action of adenosine injected into the left atrium was 20 times as potent as that into the right atrium. This indicates that 95% of adenosine injected into the right atrium disappeared within the pulmonary circulation. Rubio et al. (3) reported that only 5% of the adenosine infused into the left circumflex branch of the coronary artery was recovered from the coronary sinus blood. Kolassa (16) reported, from his study with the isolated heart preparation, that when 0.004 µmol of adenosine was added to the perfusion fluid, 30% of adenosine was taken up as such and 18% as inosine into the heart. This fact demonstrates that as little as 1/600 part or less of adenosine arrives at the coronary sinus when adenosine is administered intravenously, even when distribution from the aorta to the systemic circulation is lacking and all of intravenously administered adenosine passes through the coronary artery.

It has generally been recognized that the augmentation of the adenosine-induced coronary vasodilation by long-acting coronary vasodilators is due to the decreased disappearance of adenosine from blood. The results obtained in the present series of experiments show that the degree of augmentation of adenosine-induced coronary vasodilators varied according to the site of adenosine injection. After administration of dilazep the augmentation of adenosine action was mainly due to the decreased take up into the lung and myocardium, and slightly due to the decreased breakdown in the blood (3.3: 3.3: 1.45). In the case of dipyridamole, suppression of the uptake of adenosine was highest in myocardium, less in pulmonary circulation, and much less in the blood (5.4: 2.7: 1.2). The suppressing effect of dipyridamole was greater than that of dilazep in the myocardium, but less in the pulmonary circulation. The uptake of dipyridamole was greater in the myocardium than in other areas.

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