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EFFECT OF PHENTOLAMINE ON CORONARY VASCULAR RESISTANCE AND HEART RATE

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Several mechanisms of the cardiostimulating and vasodilator effects of phentolamine have been discussed in the literature. In particular, it has been suggested that the preparation possesses β-adrenomimetic activity. The β-adrenomimetic mechanism of the cardiostimulating [1, 4, 6] and vasodilator [6] actions of phentolamine has been confirmed by a number of investigations. However, some workers [1] found no effect of β-adrenoreceptor blockade on the vasodilator effect of phentolamine. The mechanisms of the effect of phentolamine on coronary vascular resistance have not so far been studied.

The aim of this investigation was to study the action of phentolamine on coronary vascular resistance and on the heart rate and also the effect of β_1-adrenoreceptor blockade on the effects of phentolamine.

EXPERIMENTAL METHOD

Experiments were carried out on 23 isolated hearts of cats anesthetized with pentobarbital (30-40 mg/kg), perfused with donor's blood under constant pressure (80-100 mm Hg). The inflow of blood into the coronary arteries was recorded by means of an electromagnetic flowmetric transducer (type MF-46 flowmeter, from Nihan Kohden Kogyo, Japan). The pressure in the right atrium and left ventricle and the perfusion pressure were recorded by means of electromanometric transducers (EMT-746, Siemens-Elema, Sweden). The parameters were recorded on a Mingograf-82 apparatus (Siemens-Elema). Coronary blood flowing out into the left compartment of the heart was drained through a catheter into the apex of the left ventricle, ensuring

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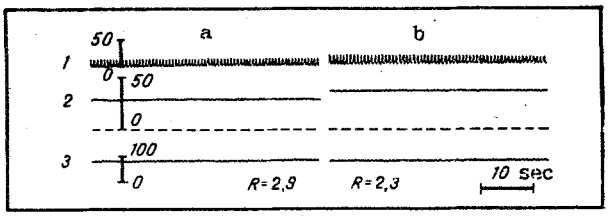

Fig. 1. Changes in coronary resistance and activity of isolated heart in response to phentolamine. 1) Pressure in left ventricle (in mm Hg); 2) inflow into coronary arteries (in ml/min); 3) perfusion pressure (in mm Hg). Broken line represents zero value of coronary blood flow. R) Values of coronary resistance. a) Initial data, b) after injection of phentolamine.

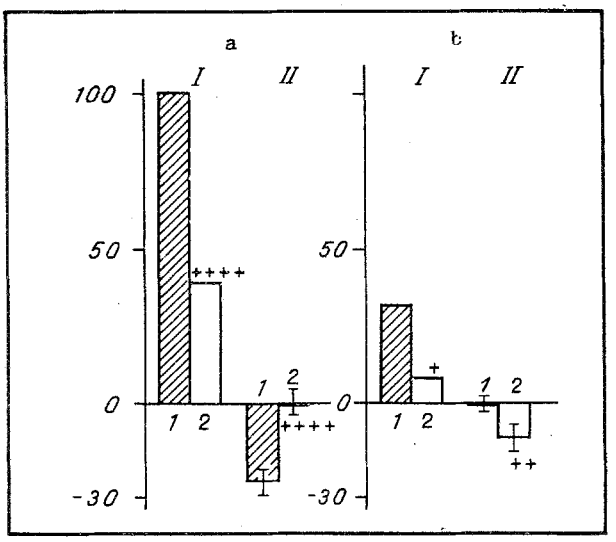

Fig. 2. Changes in coronary resistance (a) and HR (b) in response to injection of phentolamine without (1) and after (2) β_1-adrenoreceptor blockade by Cordanum. a: I) Frequency (in %) of responses of a fall in resistance, II) mean data (M ± m) on changes in resistance; b: I) frequency (in %) of positive chronotropic reactions, II) mean data (M ± m) on changes in HR. *p < 0.05, **p < 0.02, ***p < 0.001.

low values of the intraventricular pressure. The coronary resistance was calculated as the ratio of the difference in perfusion pressure and pressure in the right atrium to the volume velocity of the coronary blood flow (in mm Hg/ml/min). Coronary vascular tone was estimated from the value of reactive hyperemia in response to ischemia for 10 sec. Phentolamine (1-2.5 mg) was injected in 1 ml of blood into the end of the perfusion system nearest to the heart. Control injection of 1 ml of blood showed that injection of this volume itself caused no changes in the parameters recorded. The β_1-adrenoblocker Cordanum* (0.7×10^{-5}-1.0×10^{-5} g/ml) was injected through the perfusion stabilizing vessel. The results were subjected to statistical analysis by Student's t test.

EXPERIMENTAL RESULTS

Injection of phentolamine (one typical curve is shown in Fig. 1) reduced the coronary resistance in 100% of cases by 25.9 ± 4.4% ($p < 0.001$) compared with the initial values (Fig. 2a). HR was increased in only 31.6% of cases by 9.1 ± 1.4%, and on average for the whole series of observations, the change was not significant ($p > 0.1$; Fig. 2b).

*Alternative name: talindol.

After injection of phentolamine, preceded by β_1-adrenoreceptor blockade by Cordanum, the frequency of coronary dilator responses was significantly reduced (from 100 to 38.5%, $p < 0.001$, Fig. 2a: I). On average for all cases, the coronary resistance did not change significantly ($p > 0.1$, Fig. 2a: II). The frequency of positive chronotropic reactions also fell significantly (from 31.6 to 7.7%, $p < 0.05$; Fig. 2b: I). On average HR decreased compared with its initial values (—11.6 ± 4.0%, $p < 0.02$; Fig. 2b: II).

Thus in individual cases phentolamine caused a small increase in HR, which was significantly ($p < 0.05$) blocked by Cordanum and, consequently, was due to the β_1-adrenomimetic action of phentolamine.

Phentolamine caused the coronary resistance to fall by 25.9 ± 4.4% from its initial values, in agreement with the quantitative data obtained by other workers (22.1 ± 6.0% [2]). This fall of the coronary resistance was significantly ($p < 0.001$) blocked by Cordanum.

The magnitude of dilator responses is known to depend on the initial vascular tone. It can be tentatively suggested that the presence and absence of dilator responses, respectively, to phentolamine, and when given together with Cordanum, is connected with differences in the initial tone of the coronary vessels. However, comparison of the initial values of resistance and tone of the coronary vessels in response to injection of phentolamine, either with or after β_1-adrenoreceptor blockade caused no significant differences (resistance: 5.7 ± 0.5 and 4.6 ± 0.4 mm Hg/ml/min, $p > 0.1$; reactive hyperemia: 61.0 ± 10.0 and 55.0 ± 7.7%, $p > 0.1$).

Consequently the marked reduction of coronary resistance in response to injection of phentolamine is due to the β_1-adrenomimetic activity of the drug. The lowering of the coronary resistance under these circumstances may take place due to both the primary action of phentolamine on the coronary vessels and to metabolic vasodilatation, which is secondary relative to the cardiostimulating effect of the drug. In the present investigation changes in coronary vascular resistance did not correlate with changes in HR: the coronary resistance fell significantly more often than HR rose ($p < 0.001$); on average the coronary resistance fell significantly ($p < 0.001$) whereas changes in HR were not significant ($p > 0.1$). However, after injection of phentolamine alone, the pressure in the left ventricle of the isolated heart increased in virtually every case (92.9%) (on average from 16.0 ± 3.2 to 31.0 ± 5.6 mm Hg, $p < 0.05$), whereas when phentolamine was injected together with Cordanum, the pressure in the left ventricle was unchanged ($p > 0.1$). Changes in left ventricular pressure of the isolated heart, as may be seen, correlated with changes in coronary resistance. On the basis of these results the fall of coronary resistance can be attributed to secondary metabolic vasodilatation, due to the β_1-adrenomimetic potentiation of the activity of the isolated heart in response to injection of phentolamine. The possibility of a primary β_1-adrenomimetic coronary dilator action of phentolamine likewise cannot be ruled out, more especially because it has recently been suggested that β_1-adrenomimetic dilatation of the coronary vessels is possible in principle [3, 5].

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