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DUAL EFFECTS OF A NEW CORONARY VASODILATOR, DILTIAZEM, ON THE CONTRACTILE FORCE OF THE BLOOD-PERFUSED PAPILLARY MUSCLE OF THE DOG

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Nifedipine, prenylamine and verapamil are coronary vasodilators the mechanism of action of which is attributed mainly to calcium antagonism (1, 2). Pronounced negative inotropic effects of these drugs were reported for prenylamine by Linder (3), for verapamil by Haas et al. (4), and for nifedipine by Vater et al. (5), Hashimoto et al. (6), and Fleckenstein et al. (1, 2). A coronary vasodilator, d-cis-isomer of 3-acetoxy-2,3-dihydro-5-[2-(dimethylamino)ethyl]-2-(p-methoxyphenyl)-1, 5-benzothiazepin-4(5H)-one hydrochloride (Diltiazem), developed recently by Sato et al. (7) and Nagao et al. (8), appears to belong to the calcium antagonistic coronary vasodilators, because it was found to exert a negative inotropic effect on the guinea-pig ventricular muscle and this was overcome by an increase in calcium ion concentration in the bathing media (Nakajima, personal communication).

The present experiments were performed in an attempt to examine how diltiazem affects the contractile force of the heart and coronary blood flow. The isolated blood-perfused papillary muscle was utilized.

Experiments were carried out on 10 anterior papillary muscles of the right ventricle of the dog heart. The procedures were essentially the same as those of Endoh and Hashimoto (9). The preparations were placed in a water-jacket at about 38°C and were cross-circulated through the anterior septal artery with arterial blood of the supporting dog. The supporting animals were anesthetized with sodium pentobarbital (30 mg/kg, i.v.) and heparinized (500 U/kg, i.v.). Constant pressure perfusion was performed at about 100 mm Hg by use of a peristaltic pump and a Starling pneumatic resistance. The preparations were driven with rectangular pulses of 0.6-1.5 V (about twice threshold) and 5-msec duration at a frequency of 120/min delivered through bipolar silver electrodes sutured at the base of the papillary muscle. The isometric tension of the papillary muscle with a load of 1.5 g was picked up with a strain gauge transducer. The blood flow rate was measured by an electromagnetic flowmeter.

Diltiazem hydrochloride (Tanabe Pharmaceutical Co.), l-norepinephrine bitartrate (Merck) and dl-propranolol hydrochloride (Sumitomo Chemicals) were dissolved in 0.9% saline. Drug solutions were injected using a microsyringe in a constant volume of 30 μl for 4 sec into the blood-conducting rubber tubing close to the preparation. Doses are expressed in terms of their bases.
The basal developed tension of the papillary muscle and the basal blood flow rate through the preparation were $5.9 \pm 0.5 \text{ g}$ and $5.4 \pm 0.4 \text{ ml/min}$ (mean $\pm$ S.E.; n=10), respectively. Single injections of diltiazem ($0.1-300 \mu\text{g}$) into the artery produced a dose-related increase in flow rate. With $100 \mu\text{g}$ of diltiazem there was an increase which amounted to about 135% of the basal blood flow rate. Fig. 1 is typical of such experiments. The action of diltiazem on the contractile force was dual depending upon the dose. Diltiazem in doses of $0.3-3 \mu\text{g}$ caused a slight but dose-related increase in contractile force in all 10 preparations and this positive inotropic effect was reproducible. Percent increases in developed tension caused by $0.3$, $1$, and $3 \mu\text{g}$ of diltiazem were $1.8 \pm 0.6$, $6.7 \pm 0.8$, and $13.6 \pm 1.4\%$ (mean $\pm$ S.E.; n=10), respectively. However large doses of diltiazem, 30 to $300 \mu\text{g}$, produced a dose-related negative inotropic effect, reaching about 70% of the basal contractile force with $300 \mu\text{g}$. An intermediate dose of $10 \mu\text{g}$ produced only a positive inotropic response in 6 of 10 preparations and a positive response preceded by a transient negative one in the remaining 4 preparations.

To examine whether or not the positive inotropic effect observed in small doses of diltiazem is mediated through an adrenergic mechanism, $3 \mu\text{g}$ of diltiazem was injected 2 min after administration of $10 \mu\text{g}$ of propranolol. As shown in Fig. 1, this dose of propranolol exerted no blocking action on the positive inotropic effect of diltiazem, although it effectively suppressed the positive inotropic effect of $0.03 \mu\text{g}$ of norepinephrine.

The present results clearly demonstrate that diltiazem in large doses ($30-300 \mu\text{g}$) produces a negative inotropic effect on the blood-perfused papillary muscle preparation of the dog heart. This is along the same line as the results obtained by Nakajima (personal communication) in the guinea-pig ventricular muscle and the finding by Sato et al. (7).

![Fig. 1. Effects of increasing doses of diltiazem (0.3 to 300 μg) on the blood flow rate and developed tension of the isolated, blood-perfused papillary muscle and the lack of the blocking effect of propranolol (10 μg) on the positive inotropic action of diltiazem (3 μg). The responses to 3 μg of diltiazem in the upper panel served as control for those after propranolol. Dilt: diltiazem. Prop: dl-propranolol. NE: l-norepinephrine.](image-url)
that diltiazem elevated the right atrial pressure in the dog heart-lung preparation, which reflected the decreased contractile force. However, diltiazem in small doses (0.3–3 μg) produced a definite positive inotropic effect. Since this positive inotropic effect was not affected by the beta-adrenoceptor blocking action of propranolol, a possible involvement of adrenergic mechanism can be ruled out. It is feasible that an increase in blood flow rate might exert a positive inotropic effect which was masked by the negative inotropic action of a large dose of a diltiazem. Without neglecting such a possibility, a likely explanation worth considering is that diltiazem in small doses may raise the free myoplasmic calcium ion concentration needed for papillary muscle contraction by increasing the influx of calcium ions or causing the release of calcium ions from the sarcoplasmic reticulum or inhibition of their uptake.

REFERENCES


A NEW PIPERAZINOBIGUANIDE SERIES EFFECTIVE AGAINST SYPHACIA OBVELATA IN MICE

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Brown et al (1) and Harfenist et al (2) have evaluated a large number of piperazine derivatives against Syphacia obvelata in mice. It was thought worthwhile to extend this study by screening more of these derivatives. The laboratory exposure method described by Chan (3) was used to obtain relatively uniform infection in mice. The infected mice were fasted for one day prior to drug treatment. Drugs were administered in doses of 100, 200 and 500 mg/kg body weight. Each dose was suspended in 0.5 ml of distilled water together with gum acacia and administered orally. The mice were allowed food on the day of treatment and were fasted again the next day. Autopsy was carried on the day following the treatment. Contents of caecum and rectum were brushed out gently into a petri dish containing water and worm count was done against a black background.