EFFECT OF ATP AND SODIUM NUCLEINATE ON COLLATERAL CIRCULATION AND OXYGEN TENSION IN THE MYOCARDIUM AFTER LIGATION OF THE CORONARY ARTERY

A. V. Sapozhkov

UDC 615.272:547.963.32].015.45:
616.127-005.5

In acute experiments on dogs injection of the disodium salt of adenosinetriphosphoric acid (0.1 and 0.5 mg/kg) and sodium nucleinate (5 and 20 mg/kg) increased the retrograde blood flow and lowered the pressure in the distal segment of the ligated anterior descending branch of the left coronary artery, increasing the oxygen tension in different parts of the ischemic myocardium.

* * *

Phosphorylated derivatives of adenosine are known to be powerful vasodilators. It has been shown experimentally that they can also dilate the coronary vessels [8]. The effect of the nucleic acids on the coronary circulation remains virtually unstudied.

EXPERIMENTAL METHOD

Experiments were carried out on mongrel dogs of both sexes weighing 7-24 kg, anesthetized with pentobarbital sodium (40-45 mg/kg body weight intraperitoneally).

To study the action of ATP and sodium nucleinate on the collateral coronary circulation the retrograde blood flow from the peripheral end of the ligated anterior descending branch of the left coronary artery was recorded by means of a photographic drop-counter, automatically recording on the drum of a kymograph the number of drops of blood escaping, and the total outflow during various time intervals was determined [2]. The collateral inflow of blood was recorded for 35-40 sec at intervals of 5 min. The pressure in the ligated vessel was measured in the intervals between recording the retrograde outflow.

The systemic arterial pressure was recorded in the left carotid artery by a mercury manometer. The ECG was recorded in chest (V4) and epicardial leads (in the marginal zone of ischemia). To prevent the blood from clotting the animals received heparin (1500 units/kg intravenously).

The oxygen tension in the myocardium was determined by a polarometric method using a copper amalgam — iron pair of electrodes [4]. The active electrodes were fixed in the assumed zone of ischemia, in an intact part of the myocardium, and at the border between helathy and ischemic areas of the heart determined visually and also by means of displacement of the epicardial electrode.

ATP was injected intravenously in single doses of 0.1 (9 experiments) and 0.5 mg/kg (11 experiments), sodium nucleinate in doses of 5 (10 experiments) and 20 mg/kg (9 experiments).

Changes in the studied indices were expressed as percentages of their initial level in each experiment. The mean values for 39 animals in the control series were: retrograde blood flow 1.7 ± 0.2 ml/min, retrograde pressure 36 ± 4 mm Hg, systemic arterial pressure 118 ± 9 mm Hg.

The numerical results were subjected to statistical analysis [3].

EXPERIMENTAL RESULTS AND DISCUSSION

ATP, in a dose of 0.1 mg/kg, within the first 5 min after its administration, caused a slight decrease in the retrograde blood flow in most experiments against the background of a small decrease in arterial

Department of Pharmacology, Kemerovo Medical Institute. (Presented by Academician V. V. Parin).
Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 68, No. 9, pp. 61-63, September, 1969. Original article submitted November 14, 1967.

pressure. Later an increase in the collateral blood flow was observed (after 15 min by 33 ± 3.7%; $P < 0.001$), persisting for 30 min or more. The changes in arterial pressure and heart rate during this time interval were not significant.

Injection of ATP in a dose of 0.5 mg/kg was followed by lowering of the systemic arterial pressure, to a particularly marked degree during the first 5 min of investigation (13.3 ± 2.1%; $P < 0.001$). Against this background the retrograde blood flow in some experiments was reduced. Later, in all experiments a sharp increase in the collateral blood flow was observed (after 10 min by 34.9 ± 3.9%; $P < 0.001$), persisting until 35 min. A significant decrease in the retrograde pressure was observed only during the first 5 min after injection of the preparation, after which it returned to normal.

Sodium nucleinate in a dose of 5 mg/kg caused a sharp increase in the collateral blood flow (after 10 min by 49.2 ± 7.4%; $P < 0.001$) persisting for 55 min of the investigation and associated with a very slight decrease in the systemic arterial pressure. Lowering of the arterial pressure was more marked, especially toward the end of the experiment (after 55 min by 25.6 ± 6.6%; $P < 0.02$).

The increase in the collateral blood flow after injection of sodium nucleinate in a dose of 20 mg/kg was less marked (after 15 min by 19.4 ± 7.9%; $P < 0.05$) and shorter in duration (20 min). The fall of arterial pressure developing after injection of this compound increased in degree toward the end of the experiments. The decrease in retrograde pressure was more marked (after 10 min by 28.6 ± 6.4%; $P < 0.01$), and also increased with time. In neither group of experiments were the changes in heart rate significant.

Ligation of the anterior descending branch of the left coronary artery lowered the oxygen tension in the ischemic myocardium by 30-81% of its initial level. Fluctuations in the oxygen tension in the intact heart were slight in degree and varied in direction.

After a transient decrease in the oxygen tension in the zone of ischemia which was not statistically significant (7.6 ± 3.6%; $P < 0.1$), injection of ATP in a dose of 0.1 mg/kg increased the oxygen tension (38.1 ± 8.9%; $P < 0.01$) for 40 min of the investigation. The change in oxygen tension in the marginal zone of ischemia was less marked (23.7 ± 9.3%; $P < 0.05$) and shorter in duration (20 min). The increase in oxygen tension in the intact myocardium was shorter still (15 min).

Sodium nucleinate in a dose of 5 mg/kg increased the oxygen tension in the center of the ischemic zone (59.2 ± 11.4%; $P < 0.001$) throughout the 60 min of investigation. This increase in the marginal zone of ischemia (49.7 ± 14.8%; $P < 0.01$) was shorter in duration (45 min). In areas of the myocardium outside the zone supplied by the ligated artery, sodium nucleinate increased the oxygen tension (34.7 ± 5.9%; $P < 0.001$) only during the first 30 min of the experiments.

Changes in the ECG after ligation of the coronary artery were characteristic of acute coronary insufficiency: increased amplitude of the T wave, a sharp upward deviation of the S—T interval from the isoelectric line, and disturbance of the rhythm. Injection of ATP in some experiments increased or precipitated ventricular extrasystoles. Except in a few experiments, the action of ATP did not prevent intensification of the pathological changes in the ECG following acute occlusion of the coronary artery. Sodium nucleinate lowered the S—T segment slightly toward the isoelectric line in the epicardial lead and did not prevent changes in its position in the chest lead (V4). In some experiments, the extrasystoles were abolished or reduced in severity under its influence.

Three main factors determining the level of inflow of blood into the ischemic myocardium can now be identified: the level of the systemic arterial pressure, the tone of the interarterial anastomoses [1,2], and the pressure in the territory of distribution of the ligated blood vessel. The last of these is determined principally by the resistance of the blood vessels in the territory of the ligated artery, for not more than 5-10% of the inflowing blood enters through the anastomoses [7]. It is natural to assume that such an inflow of blood cannot have any significant effect on the value of the retrograde pressure, the level of which was fairly high (35-40 mm Hg). The absence of significance changes in the systemic arterial pressure and pressure in the vessels of the ischemic myocardium in the experiments in which ATP was injected suggests that the positive action of this substance was due to its dilator effect on the lumen of the interarterial anastomoses. It is interesting to note than an increase in the dose of ATP did not increase the level of the retrograde blood flow. A possible explanation of this fact may be that ATP, in large doses, lowers the systemic arterial pressure considerably. The possibility likewise is not ruled out that an in-

crease in the dose of the compound leads to its intensive dephosphorylation and, in consequence of this, to a reduction in its dilator action on the coronary vessels [9].

Sodium nucleinate also increased the inflow of blood into the ischemic myocardium without any significant changes in the systemic arterial pressure. However, in this series of experiments a marked lowering of the retrograde pressure was observed. This evidently led to an increase in the pressure gradient between the intact and affected arteries and helped to increase the collateral blood flow. Injection of a large dose of the preparation caused a marked decrease of the systemic arterial pressure, and this was evidently responsible for the smaller positive effect of sodium nucleinate in this group of experiments.

Fluctuations in the oxygen tension in the myocardium were synchronized with changes in the collateral blood flow and corresponded to them in intensity. This fact is evidence of the close link between the oxygen tension in the ischemic myocardium and its collateral blood supply. The differences in duration of changes in the oxygen tension in different parts of the ischemic zone are interesting. They were presumably due to differences in the degree of disturbance of enzymic reactions in the various parts of the ischemic myocardium [5].

It should be emphasized that the most powerful stimulus for opening of the anastomoses at activation of the collateral circulation in the myocardium is anoxia [6]. The ability of the tested compounds to increase the retrograde coronary blood flow without any significant changes in the hemodynamics suggests the existence of a "vasodilator reserve of anastomoses" and gives good hopes that pharmacological regulation of the collateral circulation in the myocardium will eventually become possible.

LITERATURE CITED

1. V. V. Gatsura, in: Problems in Experimental and Clinical Cardiology [in Russian], Kursk (1966), p. 5.
2. A. I. Oivin, Pat. Fiziol., No. 4, 76 (1960).
3. A. V. Sapozhkov, Farmakol. i Toksikol., No. 1, 48 (1965).
4. R. A. Frol'kis, in: Essential Hypertension, Atherosclerosis, Coronary Insufficiency [in Russian], Kiev (1966), p. 208.
5. I. M. Epshtein, Byull. Éksperim. Biol. i Med., No. 12, 104 (1960).
6. R. W. Eckstein, Circulat. Res., 3, 306 (1955).
7. F. R. Mautz and D. E. Gregg, Proc. Soc. Exp. Biol. (N. Y.), 36, 797 (1937).
8. G. G. Rowe, S. Afonso, et al., Am. Heart J., 64, 228 (1962).
9. M. Winbury et al., J. Pharmacol. Exp. Ther., 109, 255 (1953).