EFFECT OF MALABEN ON CATECHOLAMINE CONTENT IN ORGANS OF ANIMALS WITH EXPERIMENTAL MYOCARDIAL INFARCTION

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The content of adrenalin and noradrenalin was determined in tissues of the heart, adrenals, spleen, and brain of rats with experimental myocardial infarction. A considerable fall in the tissue catecholamine level was found. Malaben restores the normal catecholamine content in the tissues in myocardial infarction, possibly as a result of the antihistamine properties of the compound.

KEY WORDS: *catecholamines; myocardial infarction; histamine; malaben.*

Previous investigations have shown that the compound malaben (sodium N_1,N_1-malonylbis-paraaminobenzoate), synthesized by Professor L. B. Dashkevich in the Department of Organic Chemistry, Leningrad Institute of Pharmaceutical Chemistry, is an active remedy for the treatment of coronary insufficiency. The compound has a beneficial action on histamine and serotonin metabolism in experimental myocardial infarction and possesses antihistamine activity [6, 7, 10]. Meanwhile, an important role in the pathogenesis of myocardial infarction is ascribed to the functional state of the sympathico-adrenal system [4, 5, 8, 9].

The object of this investigation was to study the catecholamine content in tissues of various organs in experimental myocardial infarction before and after administration of malaben.

EXPERIMENTAL METHOD

Experiments were carried out on 336 albino rats weighing 180-220 g. The content of adrenalin (A) and noradrenalin (NA) was determined [5] in the tissues of intact animals, of rats with experimental myocardial infarction (caused by ligation of the left coronary artery), and of rats with experimental myocardial infarction treated with malaben. Tissues were studied from the heart, brain, spleen, and adrenals.

EXPERIMENTAL RESULTS

The hearts of the intact animals contained significantly more NA (0.98 ± 0.08 μg/g) than A (0.14 ± 0.03 μg/g). The adrenals contained more A (940 ± 117 μg/g); the NA level in the adrenals was much lower (243 ± 37.5 μg/g). The spleen contained more NA (0.56 ± 0.01 μg/g) than A (0.03 ± 0.005 μg/g). This was also true of brain tissue (NA 0.42 ± 0.04 μg/g; A 0.047 ± 0.003 μg/g).

A marked decrease in the NA content (by 40%) was found in the hearts of the animals 6 h after ligation of the coronary artery; a smaller decrease was found in the A content. After 24 h the NA level in the heart also was sharply reduced, but later (on the 3rd, 5th, and 10th days) it increased a little, although on the 10th day it was still 15-20% below the initial level. By the 15th day the NA level was again lowered, but it increased approximately to the initial level on the 17th day. Later the NA content remained constant (on the 20th, 25th, and 30th days). The A content in the heart fell to a minimum on the 5th day after the operation, but by the 15th day it was 50% higher than initially. Toward the end of the period of observation the A content in the heart returned to its initial level.

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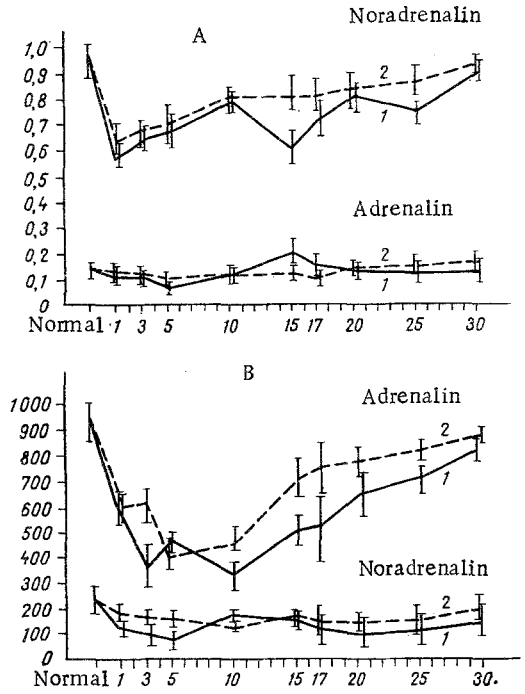

Fig. 1. Catecholamine content in heart (A) and adrenals (B) of rats with experimental myocardial infarction (1) and in similar rats treated with malaben (2) (M ± m). Here and in Fig. 2: abscissa, period of observation (in days); ordinate, concentration of catecholamines (in μg/g).

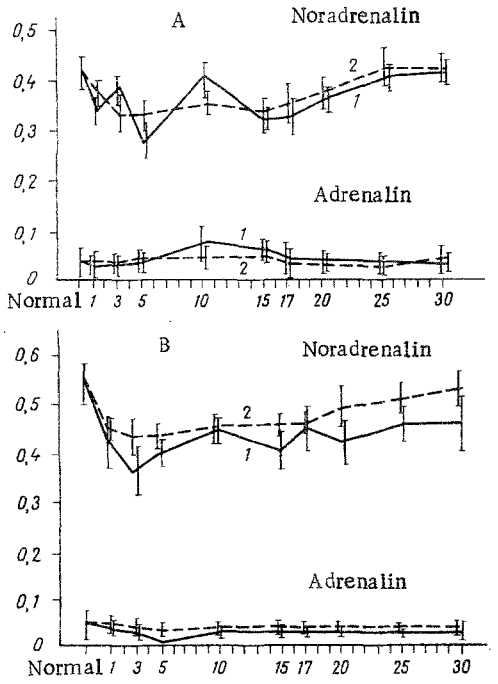

Fig. 2. Catecholamine content in brain (A) and spleen (B) of rats with experimental myocardial infarction (1) and in similar rats treated with malaben (2) (M ± m).

The A content in the adrenals fell on the first day after the operation by 40-45% and remained at its lowest level on the 3rd and 10th days of observation, after which it returned gradually to its initial value by the end of the period of observation. The NA content also fell somewhat during the first few days; it was considerably reduced on the 5th day, and it gradually returned to its initial level by the end of the period of observation.

The NA content in the brain of animals with experimental myocardial infarction was lowered on the 1st and 5th days; it rose to its initial level by the 10th day, then fell again on the 15th day. By the 20th-30th day the NA content in the brain tissue was back to normal. The A content was above normal on the 10th and 15th days of observation, but at all other times it was close to its initial level.

The NA content in the spleen during the two weeks after the production of myocardial infarction was below normal, to which it returned by the 17th day; it fell again on the 20th day, and did not return to normal until the 25th-30th day. The A level fell during the first days of observation and by the 5th day virtually no A could be detected in the spleen. By the 17th day the A content in the spleen was back to normal again.

In the animals with experimental myocardial infarction treated with malaben (in a daily dose of 20 mg/kg) the changes in the catecholamine content in the heart and other organs (Figs. 1 and 2) were less marked than in the untreated rats. Malaben prevented the sharp changes in the catecholamine content in the organs.

In experimental myocardial infarction, for instance, the catecholamine content in the tissues of the heart, adrenals, spleen, and brain of the experimental animals was reduced, possibly evidence of increased activity of the sympathico-adrenal system. The decrease in the catecholamine content in the heart muscle on the first day was also attributable to the operation itself [3]. Changes observed in the NA content in the heart were similar to those discovered previously in neurogenic myocardial degeneration [1, 2].

Increased activity of the sympathico-adrenal system in myocardial infarction is known to lead to hypercatecholaminemia and hypercatecholaminuria [4, 5, 7, 9, 13-15]. Despite the positive inotropic and chronotropic action of the catecholamines, the increase in their blood levels in myocardial infarction is an unfavorable factor, for they simultaneously increase the oxygen demand of the heart and, in addition, by promoting the shunting of blood, they aggravate the myocardial hypoxia still more. The disturbance of the cardiac rhythm is also linked with hypercatecholaminemia, especially with the raised blood level of NA. Abolition of the undesirable effect of the catecholamines by adrenolytics or sympatholytics does not appear to be possible because of their negative inotropic action. Malaben has neither adrenolytic nor sympatholytic properties, but it has a coronary-dilator and anithistamine action [6, 7, 10]. This may explain its effects on the catecholamine content in the organs in myocardial infarction. The excretion of catecholamines of the tissue reserves has been shown [11, 12] to take place through the medium of histamine.

The possibility cannot therefore be ruled out that changes in the functional state of the sympathico-adrenal system in myocardial infarction are somehow linked with a disturbance of histamine metabolism. The antihistamine action of malaben not only restores the disturbed histamine metabolim in myocardial infarction to normal, but also ensures the more rapid normalization of the functional state of the sympathico-adrenal system.

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