EFFECT OF CHANGES IN MEDIATOR METABOLISM ON THE DEVELOPMENT OF CARDIAC HYPERTROPHY

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Cardiac hypertrophy, which regularly develops as a result of hyperfunction of the organ in diseases of the circulatory system, of systematic physical effort, or of high-altitude anoxia, enables prolonged adaptation of the myocardium to take place to a high level of functional activity. The important role of the autonomic division of the nervous system in the process of adaptation of tissues to their functional level is well known. In the present investigation the effect of pharmacologically induced changes in mediator metabolism on the development of compensatory hypertrophy of the heart was studied in animals with experimental coarctation of the aorta.

EXPERIMENTAL METHODS

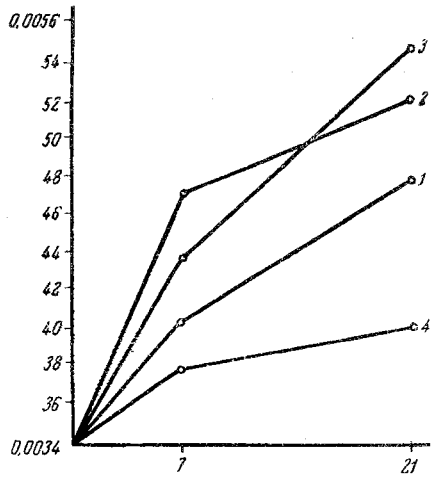
Experiments were conducted on 300 male albino rats weighing 140-180 g. Experimental coarctation of the aorta was produced by constricting the aorta with a metal sprinc clip; as a result of the operation the lumen of the aorta was constricted to 40-33% of its normal area. Hypertrophy of the heart was judged by changed in the cardiac index (ratio between weight of the heart and the body weight).

As factors providing for predominance of the acetylcholine system over the system of the catecholamines, the anticholinesterase drug proserine was used (0.01 mg of 1 ml physiological saline per injection), and also reserpine, which causes an intensive elimination of catecholamines from the tissues (0.22 mg in 1 ml physiological saline per injection daily for 1 week or 0.05 mg injected daily for 3 weeks). To stimulate the action of the system of the catecholamines, the monoamine oxidase inhibitor iprazid (Iproniazid) was given, causing catecholamines to accumulate in the tissues (3.5 mg in 0.5 ml solution per injection). All the substances were injected 24 h before formation of the experimental coarctation of the aorta, and thereafter daily throughout the period of investigation.

In order to study each drug, the experimental animals were divided into 4 groups: the 1st group consisted of normal animals (controls), the 2nd – normal animals receiving the substances mentioned, the 3rd – animals with coarctation of the aorta, and the 4th – animals with coarctation of the aorta and receiving the drugs. Groups 2, 3, and 4 were divided into 2 subgroups: the animals of one subgroup were sacrificed 5-7 days after the creation of experimental coarctation of the aorta, and the animals of the other subgroup 3 weeks after. Investigations previously conducted in the laboratory showed that these times correspond to the emergency stage of cardiac hyperfunction and to the stage of permanent compensation [1].

EXPERIMENTAL RESULTS

Injection of the drugs listed above into healthy animals caused little if any effect on their state, and by comparison with the controls the only feature observed was some delay in gaining weight. Iprazid inhibited the gain in weight by the animals only during the first few days of the experiment. The effect on weight of factors leading to a direct (proserine) or indirect (reserpine) predominance of parasympathetic influences appeared only after 3 weeks had elapsed from the beginning of the injections, and the effect of these drugs was similar in direction to that of iprazid. Prolonged administration of proserine and reserpine to animals not subjected to operation also caused a small increase in the relative weight of the heart (from a normal value of 0.0034 to 0.0036-0.00385).



Changes in the relative weight of the heart after production of experimental coarctation in normal rats (1) and in animals receiving proserine (2), reserpine (3), and iprazid (4).

It can be seen from the figure that after production of coarctation of the aorta the relative weight of the heart of the control animals increased during the first 7 days under the influence of hyperfunction from 0.0034 to 0.0040, i.e., by 0.0006. After 21 days it reached 0.0047, i.e., an increase of 0.0013 on the normal value. If the values of 0.0006 and 0.0013, characterizing the degree of hypertrophy of the myocardium, are taken as 100%, it appears that the factors used differed in their effect on the degree of hypertrophy. During the first 7 days reserpine increased the degree of hypertrophy by 56%, and during 21 days by 49%, and the corresponding figures for proserine were 100 and 29%. Iprazid inhibited the development of hypertrophy and depressed its degree over the first 7 days by 37.5%, and 21 days by 55.7%.

Hence, reserpine and proserine – factors leading to predominance of the acetylcholine system – considerably increased the degree of cardiac hypertrophy. Iprazid – a factor causing predominance of the system of the catecholamines – conversely lessened the degree of hypertrophy of the heart and inhibited its development.

The main part of the catecholamines of heart muscle consists of noradrenalin, which in physiological conditions has a positive inotropic action and plays an essential role on the adaptation of the myocardium to an increased level of functional activity. Reserpine, in the doses which we used, removed the greater part of the noradrenalin and thereby led to a lowering of the level of maximal tension which could be developed by the myocardial fibers [2]. Acetylcholine, in physiological conditions, possesses a negative inotropic effect, and accumulation of this compound under the influence of proserine naturally depressed the contractile powers of the myocardium. Iprazid, which inhibits monoamine oxidase, increased the noradrenalin concentration in the myocardium and, in contrast to reserpine and proserine, increased the contractile powers of the myocardium.

Since in our experiments reserpine and proserine increased, but iprazid diminished the degree of cardiac hypertrophy, it may be concluded that the factor increasing the contractile function of the myocardium inhibits its hypertrophy, and that factors stimulating the contractile function of the myocardium promote its development.

Hypertrophy begins before hypertrophy and is characterized primarily by the fact that the ratio between the function of the myocardium and its mass rises sharply: the function performed per unit mass of myocardium, which we call the intensity of functioning of structures, increases. Hypertrophy of the myocardium subsequently develops and the increased function is distributed among its increasing mass: the intensity of functioning of the structures returns to a subnormal or normal level, and the increasing function of the heart as a whole is maintained by an increase in its mass. Hence it is clear that whereas during the development of hypertrophy a factor depressing the contractile power of the structures of the myocardium acts upon the heart, the maintenance of a high level of cardiac function as a whole demands a high degree of hypertrophy. Conversely, whereas the factor increasing the contractile power of the structures of the myocardium acts on the heart throughout this time, a lesser degree of hypertrophy is sufficient to attain the same functional level. In our experiments stimulation or depression of the contractile powers of the structures of the myocardium was brought about by a deliberate change in mediator metabolism. The depression of the functional level of the myocardial structures caused by a deficiency of catecholamines and by predominance of the acetylcholine system was compensated during hyperfunction by the additional increase in the mass of the myocardium, and the increase in the intensity of function of the structures, caused by predominance of the system of the catecholamines, leads to the result that a lesser degree of hypertrophy is adequate for maintaining the heart at a high functional level.

This hypothesis also concurs with the fact that reserpine and proserine, when administered for long periods to normal (not undergoing operation) animals, cause a slight increase in the relative weight of the heart. A deficiency of noradrenalin and a predominance of the acetylcholine system evidently lead to a lowering of the intensity of function of the myocardial structures, as a result of which the heart must increase its mass in order to maintain its normal, or even a depressed function.

The results demonstrate the important role of the nervous system in determining the intensity of function of the structures of heart muscle and the development of hypertrophy of the heart, and they help to explain the discrepancy often observed in cardiopathology between the degree of hypertrophy of the myocardium and the size of the load carried by the heart.

SUMMARY

Substances creating prevalence of the catecholamine system (iprazid) or of the acetylcholine system (proserine, reserpine) were administered to rats with experimental coarctation of aorta. The evidence proved that proserine and reserpine increase the degree of hypertrophy. The results thus obtained are examined in the light of interrelations between the contractile function level of the myocardium and its hypertrophy.

LITERATURE CITED

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2. W. Lee and F. Shideman, Science, Vol. 129 (1959), p. 967.
