ACTION OF CARDIAC GLYCOSIDES ON SOME INDICES OF MEDIATOR METABOLISM OF THE MYOCARDIUM IN EXPERIMENTAL CARDIOVASCULAR PATHOLOGY

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Experiments on rats showed that constriction of the abdominal aorta (cardiac failure of hemodynamic type) is accompanied by a decrease in the catecholamine level in the myocardium and adrenals. The decrease in the catecholamine concentration in the myocardium was more marked 90 min after the operation, when the level was 52% of its initial value. Administration of the cardiac glycosides strophanthin and convallatoxin under these conditions (in doses of 0.1 mg/100 g and 0.07 mg/100 g respectively) helps to restore the normal catecholamine level in the myocardium without changing the adrenalin and noradrenalin levels in the adrenals.

It has been concluded from various investigations [5, 6, 11] that the decrease in contractile power of the myocardium in heart failure is based on a decrease in the catecholamine concentration in the myocardium.

Administration of glycosides is the most effective method of pharmacotherapy at present available in cardiovascular failure. However, the character of changes in the mediator metabolism of the myocardium and, in particular, of the sympathetic component, during the treatment of heart failure by cardiac glycosides has not yet been explained.

The object of the investigation described below was to examine this problem in animals with experimental heart disease.

EXPERIMENTAL METHOD

Experiments were carried out on rats weighing 180-210 g. The total catecholamine concentration was determined in the myocardium and the concentrations of adrenalin and noradrenalin were determined separately in the adrenals [4]. Cardiovascular failure of hemodynamic type was produced by Beznak's method [10] in Kogan's modification [3]. The animals were sacrificed 90 min (acute cardiovascular failure) and 7-8 days (subacute failure) after the operation. These times were chosen on the basis of earlier investigations in the writers' laboratory [1, 7, 8] of the action of cardiac glycosides on carbohydrate-phosphorus, protein, and electrolyte metabolism of the myocardium in this pathology. Changes indicating reduced contractile power of the myocardium were observed in the ECG at these times after the operation. Strophanthin (0.1 mg/100 g body weight) and convallatoxin (0.07 mg/100 g body weight) were injected intraperitoneally as a single dose 30 min after constriction of the abdominal aorta; the animals were sacrificed 60 min after injection of the drugs. In subacute hemodynamic failure the same drugs were injected starting on the second day after the operation in doses of 0.05 mg/100 g (strophanthin) and 0.035 mg/100 g (convallatoxin) once a day.

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TABLE 1. Effect of Cardiac Glycosides on Catecholamine Concentration in Myocardium and Adrenals of Rats with Experimental Myocardial Insufficiency of Hemodynamic Type

	Experimental conditions and preparation	Total catecholamine concentration in myocardium (in μg noradrenalin/g fresh tissue)	Catecholamine concentration in adrenals (in μg adrenalin or noradrenalin/g weight of gland)	
			adrenalin	noradrenalin
1	Control	1,79±0,08 n=35	19,75±1,5 n=22	3,3±0,73 n=16
2	Hemodynamic failure (90 min)	0,86±0,077 n=16 $P_{1-2}<0,001$	11,34±1,37 n=14 $P_{1-2}<0,001$	1,87±0,5 n=14 $0,25<P_{1-2}<0,1$
3	Hemodynamic failure + strophanthin (80 min)	1,43±0,14 n=10 $P_{2-3}<0,001$	8,94±0,74 n=10 $P_{2-3}>0,5$	1,62±0,55 n=10 $P_{2-3}>0,5$
4	Hemodynamic failure + convallatoxin (90 min)	1,34±0,06 n=8 $P_{2-4}<0,001$	12,8±1,48 n=8 $P_{2-4}>0,5$	1,49±0,35 n=8 $P_{2-4}>0,5$
5	Hemodynamic failure (7-8 days)	1,31±0,09 n=8 $P_{1-5}<0,01$	11,2±1,61 n=8 $P_{1-5}<0,01$	2,61±0,68 n=8 $P_{1-5}>0,5$
6	Hemodynamic failure + strophanthin (7-8 days)	1,17±0,068 n=8 $P_{6-5}>0,5$	12,49±1,15 n=8 $P_{6-5}>0,5$	2,26±0,5 n=8 $P_{6-5}>0,5$
7	Hemodynamic failure + convallatoxin (7-8 days)	1,25±0,11 n=7 $P_{7-5}>0,5$	13,43±0,4 n=10 $P_{7-5}>0,5$	2,22±0,14 n=10 $P_{7-5}>0,5$

EXPERIMENTAL RESULTS AND DISCUSSION

In the animals with experimental stenosis of the abdominal aorta, 90 min after the operation there was a marked decrease in the catecholamine concentration in the myocardium (by 52%) and in the adrenalin concentration in the adrenals (by 42.5%) with a clear tendency toward a decrease in the noradrenalin concentration in the adrenals by comparison with the control. In animals undergoing a mock operation (laparotomy without stenosis of the abdominal aorta) no significant changes were observed in these indices. The results agree with those obtained by Meerson et al. [5], who found a decrease in the catecholamine level in the myocardium of rabbits in the crisis stage of compensatory hyperfunction of the heart.

Injection of strophanthin and convallatoxin after the production of acute hemodynamic failure largely restored the normal catecholamine level in the myocardium. This level rose by 66 and 55% respectively, although it did not reach the control. The levels of adrenalin and noradrenalin in the adrenals remained within the same limits as during cardiovascular failure.

In the next series of experiments on rats in the later stage of cardiovascular failure (7-9 days) the experiments showed that the catecholamine concentration in the myocardium was still a little below the control level (by 20%), but it was higher than in animals with acute failure. The adrenalin concentration in the adrenals was lowered within the same limits as in acute failure.

Repeated administration of cardiac glycosides under these conditions did not restore the normal catecholamine level in the myocardium and adrenals. The results of these experiments are given in Table 1.

The results support the view of Manukhin [4] that the noradrenalin concentration falls rapidly in experimental situations leading to severe disturbances of normal physiological functions, and by a lesser degree during a gradual change in the state of the cardiac function. The partial restoration of the lowered catecholamine level on the 7th-8th day after production of cardiovascular failure is evidence of the development of compensatory mechanisms; biosynthesis and inactivation of catecholamines probably reach equilibrium.

The ability of cardiac glycosides to restore the normal catecholamine level in the myocardium in acute failure, when this level is considerably reduced, is a manifestation of their "economizing" effect [2, 9] which, under these same conditions, extends also to other aspects of cardiac metabolism (normalization of glycolytic enzyme activity, intensity of respiration and phosphorylation, electrolyte balance of the myocardial cell, its protein composition, and so on). The increase in the catecholamine concentration in the myocardium under the influence of strophanthin and convallatoxin during failure is evidence of involvement of the adrenergic component in the mechanism of the positive trophic action of the cardiac glycosides

on the myocardium. This may to some degree explain the mechanism of the therapeutic effect of strophanthin and closely related glycosides in acute myocardial insufficiency.

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