EFFECT OF CARDIAC GLYCOSIDES ON CONTENT OF CATECHOLAMINES IN THE RAT MYOCARDIUM AND ADRENALS

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Experiments on rats have shown that the catecholamine concentration in the myocardium falls 1, 3, and 6 h after a single injection of strophanthin, and also after repeated injections for 7 days. The catecholamine level in the myocardium is almost completely normal again 20 h after a single injection of strophanthin. Injection of strophanthin causes a slight decrease in the adrenalin concentration in the adrenals after 1 and 20 h. Like strophanthin, convallatoxin reduces the catecholamine reserves in the myocardium. Strophanthin, if injected 24 h after reserpine, causes a further decrease in the catecholamine concentration in the myocardium. This effect of strophanthin is not exhibited 4 h after injection of reserpine. These results indicate that strophanthin acts on the labile fraction of the catecholamine depots.

The mechanism of the positive inotropic action of cardiac glycosides is still largely unexplained. During recent years attention has been drawn to work indicating the role of the functional state of adrenergic structures in the cardiotonic action of cardiac glycosides. It is postulated that the liberation of endogenous noradrenalin from tissue depots in the myocardium plays an important role in the development of the positive inotropic reaction to cardiac glycosides [10, 13-15].

Accordingly, the study of the direct effect of cardiac glycosides (strophanthin, convallatoxin) on the content of mediators of the sympathetic nervous system (catecholamines) in the myocardium and adrenals of rats is of considerable interest, and it formed the suject of the present investigation.

EXPERIMENTAL METHOD

Experiments were carried out on rats weighing 160-200 g. The content of catecholamines in the myocardium and adrenals was determined by fluorescence analysis by Osinskaya's method [3] with modifications [5, 9].

Strophanthin was injected intraperitoneally in low (0.1 mg/100 g) and high (0.5-1 mg/100 g) doses. The rats were killed by decapitation 1, 3, 6, and 20 h after injection of the drug. Convallatoxin was injected in a low dose (0.07 mg/100 g body weight) and the animals were sacrificed 1 h after injection. In the experiments with repeated injection of strophanthin, daily subcutaneous injections were given for 7 days in doses of 0.05 mg/100 g body weight; the animals were sacrificed 24 h after the last injection of the drug. Reserpine was injected intramuscularly in a dose of 5 mg/kg, 4 and 24 h before injection of strophanthin; strophanthin was injected after reserpine in a dose of 0.1 mg/100 g body weight intraperitoneally, and the rats were sacrificed 1 h after the injection. The doses and time intervals after injection of the drugs were based on data in the literature and previous investigations by A. I. Cherkes and co-workers.

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TABLE 1. Effect of Cardiac Glycosides on Catecholamine Content in Myocardium and Adrenalin Content in Adrenals of Rats (M ± m)

Drug	Dose of drug, mg/100 g	Time (in h) after injection of drug	Total content of catecholamines in myocardium (in μg noradrenalin/g fresh tissue)	P	Content of adrenalin in adrenals (in μg adrenalin per weight of 2 adrenals)	P
Control	—	—	1,82±0,1 (1,64÷2,0) n=34	—	19,66±1,98 (15,54÷23,78) n=21	—
Strophanthin	0,5	1	0,92±0,08 (0,74÷1,1) n=12	<0,001	16,66±1,52 (13,16÷20,16) n=9	>0,05
»	0,1	1	1,08±0,1 (0,86÷1,3) n=10	<0,001	14,28±1,14 (11,68÷16,88) n=9	<0,05
»	0,1	3	1,02±0,112 (0,76÷1,28) n=9	<0,001	18,72±1,24 (15,86÷21,58) n=9	>0,05
»	0,1	6	0,96±0,1 (0,74÷1,18) n=8	<0,001	—	
»	0,1	20	1,52±0,112 (1,26÷,78) n=9	>0,05<0,1	14,24±1,22 (10,24÷16,24) n=7	<0,05
»	0,05 daily for 7 days	24	1,14±0,058 (1,04÷1,24) n=12	<0,001	—	—
Convallatoxin	0,07	1	0,62±0,046 (0,52÷0,72) n=13	<0,001	18,6±1,30 (15,68÷21,52) n=10	>0,05

RESULTS AND DISCUSSION

Strophanthin, when injected in a high dose, reduced the catecholamine content in the myocardium 1 h after injection by 49.4% compared with the control and showed a tendency to reduce the adrenalin content in the adrenals. After a single injection of a low dose of strophanthin, and after repeated injections, the changes took place in the same direction. The catecholamine content in the myocardium after 1, 3, and 6 h was lowered by 40.6, 48.9, and 47.2%, respectively, compared with the control level, and after repeated injections the decrease amounted to 37.3% of the initial level. The catecholamine content in the myocardium was almost completely back to normal 20 h after injection of this dose of strophanthin (Table 1). The adrenalin concentration in the adrenals showed a slight decrease (about 27%) 1 and 20 h after injection of strophanthin. Like strophanthin, convallatoxin lowered the catecholamine concentration in the myocardium (by 65.9%). After injection of the specified dose of convallatoxin, the adrenalin content in the adrenals was unchanged (Table 1).

To analyze the action of strophanthin reserpine was used; this was based on the report by Zakusov and co-workers [1, 4, 6] that the dynamics of the liberating action of reserpine on the catecholamine reserves is such that 4-6 h after a single injection of reserpine, only the labile fraction of noradrenalin is exhausted. After 24 h this labile, functionally important fraction of catecholamines is partly restored, and the stable reserves of firmly bound amine are depleted. Strophanthin, injected 24 h after reserpine, caused a further, statistically significant decrease in the level of myocardial catecholamines. This further decrease amounted to 42.3% of the catecholamine content observed 24 h after injection of reserpine. Strophanthin, given 4 h after injection of reserpine, caused no further depletion of the myocardial catecholamine depots (Fig. 1).

These results suggest that the action of strophanthin in lowering the catecholamine level is due to its effect on the labile, functionally important fraction of catecholamines. The question of the mechanism of action of cardiac glycosides on the catecholamine level in the tissue depots naturally arises. The following suggestion can be put forward.

Work in Brodie's laboratory [7] has shown that catecholamines are stored in the tissue depots with the the aid of an active transport system (ATS), playing the role of a biological "pump" and functioning at the

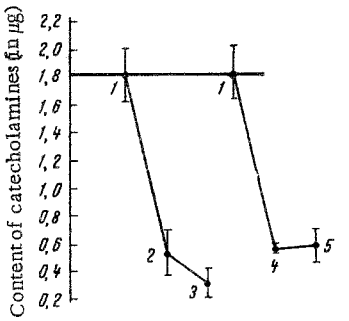

Fig. 1. Effect of strophanthin on catecholamine content in myocardium of reserpinized rats: 1) control; 2) 24 h after injection of reserpine; 3) reserpine (24 h) + strophanthin; 4) 4 h after injection of reserpine; 5) reserpine (4 h) + strophanthin.

expense of energy provided by high-energy phosphate fractions. The present writers consider that there are definite features of similarity between the ATS and the system of transport of K^+ and Na^+ (the potassium–sodium pump) across membranes, and, in particular, that the common source of energy for both systems is ATP. The potassium–sodium pump is known to be inhibited by cardiac glycosides [2]. It can accordingly be postulated that cardiac glycosides also inhibit the activity of the catecholamine transport system. As a result, the departure of catecholamines from tissue depots, uncompensated by active transport, is observed.

The second question is: what is the role of catecholamines in the mechanism of the cardiotonic effect of cardiac glycosides. The work of Stam and Honig [11, 12] has shown that noradrenalin interacts with the so-called soluble system of myocardial relaxation and inhibits its activity. As a result of this inhibition, noradrenalin exerts its positive inotropic action on the myocardium. In the light of this description, the hypothesis can be put forward that, together with other mechanisms, a mechanism illustrated in the following scheme may also participate in the inotropic effect of the cardiac glycosides.

Cardiac glycoside → Block of active transport system of catecholamines
→ Decrease in content of catecholamines in tissue depots
↓
Creation of active concentration of mediator outside depot
↓
Inhibition of soluble system of myocardial relaxation
↓
Realization of inotropic effect of catacholamines

It is also probable that the inhibition of uptake of catecholamines produced by cardiac glycosides may also contribute to the creation of an active concentration of mediator [8].

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