this may also give rise to changes in the conformation of the protein phase, as shown by changes in the parameters of fluorescence of the tryptophanyl residues of the membrane proteins. Direct interaction between gangliosides and membrane proteins also is possible.

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CARDIOTOXICITY OF STROPHANTHIN AND ITS CORRECTION BY ANAPRILIN IN RATS WITH MYOCARDIAL LESIONS OF CORONARY AND NONCORONARY GENESIS AND WITH ACUTE HEART FAILURE

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A pathological state of the myocardium is one of the important factors which predisposes to glycoside poisoning [1, 7]. The experimental study of changes in sensitivity to the cardiotoxic action of strophanthin in animals with lesions of the myocardium of coronary and noncoronary genesis, during exercise evoking acute heart failure, and investigation of the effectiveness of anaprilin to correct the cardiotoxocity of strophanthin in these conditions, are of great interest.

EXPERIMENTAL METHOD

Experiments were carried out on 177 mature female Wistar rats weighing 160-180 g, anesthetized with thiopental sodium (40mg/kg, intraperitoneally). Sensitivity of the animals to the toxic action of strophanthin K was judged from the minimal arrhythmogenic dose (AD), causing the appearance of the first grouped ventricular extrasystoles or of bigeminy on the ECG, and the lethal dose (LD) leading to cardiac arrest. These doses were established by biological titration, a solution of strophanthin in a concentration of 0.4 mg/ml being injected into the rat's femoral vein from a microburet at the rate of 0.5 ml/min under ECG control in standard lead II. The duration of infusion of the solution in control experiments averaged 12.1 ± 0.4 min.

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TABLE 1. Tolerance of Rats with Myocardial Lesions of Coronary and Noncoronary Genesis, and during Physical Exertion, to Strophanthin

Experimental conditions	Number of experiments	Duration of swimming		Relative weight of myocardium		Dose of strophanthin			
						arrhythmogenic		lethal	
		min	In % of control	mg/100 g	In % of control	mg/kg	In % of control	mg/kg	In % of control
Control	16			338,6±5,3	100,0	7,6±0,11	100,0	14,6±0,20	100,0
24 h after CAO	12			346,8±6,2*	102,4	6,1±0,18	80,3	13,2±0,16	90,4
48 h after CAO	15			366,5±8,2	108,2	5,5±0,19	72,4	11,6±0,32	79,5
After MDI	10			389,5±5,0	115,0	5,0±0,22	65,8	11,7±0,58	80,1
Intact rats after MTPE	25	74,5±3,1	100			5,0±0,10	65,8	11,4±0,14	78,1
Intact rats after 30% of MTPE	24	22	30			6,9±0,12	90,8	13,5±0,33	92,5
24 h after CAO and MTPE	12	29,8±5,9	40			5,2±0,20	68,4	10,7±0,26	73,3
48 h after CAO and MTPE	13	31,8±4,6	42			4,4±0,12	57,9	9,4±0,29	64,4
After MID and MTPE	7	16,3±2,2	21			4,9±0,26	64,5	9,6±0,53	65,8

Legend. CAO) Coronary artery occlusion; MDI) myocardial damage caused by isoproterenol; MTPE) maximal tolerable physical exertion. * $P > 0.05$; in all other cases $P < 0.05$.

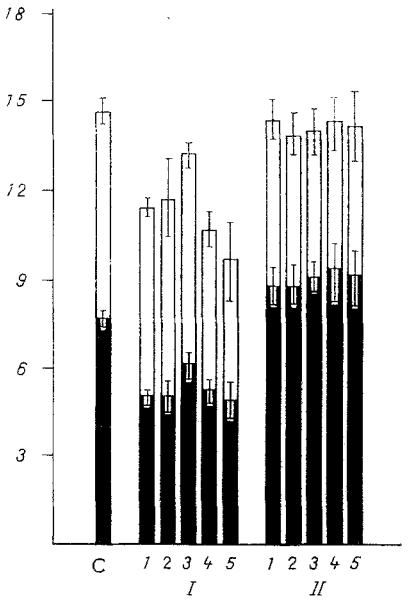

Fig. 1. Effect of anaprilin (5 mg/kg) on tolerance to strophanthin of rats with myocardial damage of coronary and noncoronary genesis and during physical overexertion. Abscissa, experimental conditions: I) animals without premedication; II) after premedication with the β-adrenoblocker anaprilin; C) control; 1) after MTPE; 2) after MDI; 3) 24 h after CAO; 4) 24 h after CAO and MTPE; 5) after MDI and MTPE. Ordinate, dose of strophanthin K (in mg/kg). Black columns denote AD, white columns – LD. Confidence limits given at $P = 0.05$.

A lesion of the myocardium of coronary genesis was produced by thoracotomy followed by electrocoagulation of the descending branch of the left coronary artery at the level of the edge of the auricle of the left atrium. The wound was then sutured in layers. Artificial respiration was not used during the operation. A myocardial lesion of noncoronary genesis was produced by daily subcutaneous injections of isoproterenol in a dose of 80 mg/kg for 5 days. Acute heart failure was induced by physical overexertion: by making the rats swim in water at a temperature of 28-30°C carrying a load equal to 7.5% of body weight, until total fatigue.

The character and degree of myocardial damage were judged from the ECG, the ability of the rats to tolerate physical exertion, the relative weight of the myocardium, and the results of anatomical and histological investigation. The material was processed in the usual way and stained with hematoxylin–eosin.

Tolerance to strophanthin was determined in intact animals (control), 24 and 48 h after coronary artery occlusion (CAO), and 3 days after damage to the myocardium by isoproterenol (MDI); after maximal tolerable physical exertion (MTPE) in intact animals, and 24 and 48 h after CAO and MDI, under the same experimental conditions, but after premedication with anaprilin (5 mg/kg, intravenously).

EXPERIMENTAL RESULTS AND DISCUSSION

It will be clear from Table 1 that the myocardial lesion of coronary genesis reduced the tolerance of the rats to the arrhythmogenic and general toxic action of strophanthin; there was a definite time course of hypersensitivity to strophanthin depending on the time after CAO. For instance, 24 h after CAO, AD and LD of strophanthin were reduced compared with the control by 19.7 and 9.6% respectively, and 48 h after CAO by 27.6 and 20.5% respectively.

Similar results were obtained previously in experiments on cats. On that occasion pharmacologic analyzers were used to show that hypersensitivity to strophanthin in experimental myocardial infarction is an integral state, which is determined successively by mobilization of the sympathicoadrenal system, increased permeability of cell membranes and, finally, electrolyte imbalance in the heart muscle [2, 3].

The developing heart failure also evidently plays a definite role in the genesis of hypersensitivity to strophanthin after CAO, as is shown by the reduction by more than half in the physical endurance of the animals, and the significant (48 h after CAO) increase in relative weight of the myocardium.

The myocardial lesion of noncoronary genesis, produced by repeated injections of large doses of the β-adrenomimetic isoproterenol, led to the same decrease in tolerance to the general toxic action of strophanthin as 48 h after CAO, and increased sensitivity to the arrhythmogenic action of strophanthin rather more strongly (AD was reduced by 34.2%).

This effect was evidently the result of the histotoxic action of large doses of isoproterenol, causing diffuse damage to the myocardium. This was shown by the sharp decrease (by 4.5 times) in the exercise tolerance of the animals and the appreciable (by 15%) increase in the relative weight of the myocardium.

The results were indirect evidence that compensatory hyperfunction of the myocardium arising in connection with lesions of coronary or noncoronary genesis, and realized through potentiation of adrenergic mediation and electrolyte shifts in the myocardium [4, 5], may evidently also be a factor reducing tolerance to strophanthin.

To test the validity of this hypothesis special experiments were conducted on intact animals, which were made to exercise at the maximal tolerable level, namely swimming until total fatigue. Their tolerance to strophanthin was then determined. It was found (Table 1) that AD and LD of strophanthin were reduced to the same degree as after myocardial damage of noncoronary genesis, by isoproterenol.

At autopsy on these animals dilatation of the heart, marked thinning of the walls of both ventricles, and pulmonary edema were observed. Foci of edema of the interstitial tissue with loosening of the structure of the myocardium, and marked congestion of the vessels were detected histologically in different parts of the heart; swelling of the muscle fibers and disappearance of their cross striation were found.

Consequently, physical overexertion by intact animals in the form of swimming until total fatigue and also, evidently, the onset of acute heart failure, formed against the background of mobilization of the sympathicoadrenal system [4, 6], thus reduce tolerance to the cardiotoxic action of strophanthin to the same degree as severe myocardial damage of noncoronary genesis by isoproterenol.

Incidentally, after measured physical exertion (30% of MTPE) the rats' tolerance to strophanthin was reduced by a much smaller degree (AD by only 9.2%, LD by 7.5%; $P < 0.05$).

Participation of an adrenergic mechanism in the realization of hypersensitivity to strophanthin is confirmed, in particular, by the fact that premedication of intact animals already subjected to MTPE, by the β-adrenoblocker anapralin, just as of animals after MDI, completely restored their tolerance to the cardiotoxic action of strophanthin (Fig. 1).

To determine the importance of physical overexertion as a factor contributing to hypersensitivity to strophanthin in myocardial lesions of different genesis, experiments were carried out in which rats were subjected to MTPE after sustaining myocardial damage of coronary or noncoronary genesis. The results showed that 24 h after CAO, MTPE caused a further decrease in AD and LD of strophanthin by 14.8 and 18.9% respectively (Table 1), and 48 h after CAO, by 20 and 19% ($P < 0.05$), whereas after damage induced by isoproterenol, physical overexertion no longer potentiated hypersensitivity to the arrhythmogenic action of strophanthin.

This state of affairs shows that myocardial damage of noncoronary genesis (diffuse), caused by isoproterenol, reduces tolerance to the cardiotoxic action of strophanthin by a greater degree than damage of coronary genesis (local disturbance of the blood supply to the myocardium).

Meanwhile (Fig. 1) MTPE reduces tolerance of intact animals to strophanthin and after CAO to virtually the same minimal level, which was observed in rats after MDI alone. This fact confirms that the adrenergic mechanisms mobilized during physical overexertion behave as a factor determining the maximal decrease in tolerance to strophanthin. It was also shown that premedication of animals of all groups subjected previously to MTPE with anapralin had a protective effect of practically identical degree, completely restoring their tolerance to strophanthin.

Physical overexertion by intact animals (or myocardial damage by isoproterenol) can thus be used as a model of acute heart failure, characterized by a sharp decrease in tolerance to the cardiotoxic action of strophanthin. This hypersensitivity to the cardiac glycoside is effectively corrected by the β-adrenoblocker anaprilin.

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