PHARMACOPROPHYLAXIS OF CHANGES IN SENSITIVITY TO STROPHANTHIN DUE TO SENSITIZATION BY TISSUE ANTIGENS

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Recent investigations have shown that tissue antigens (TAG) liberated in the course of various inflammatory and destructive processes can affect the immunologic status of the organism and its sensitivity to drugs [1, 3-5]. However, the mechanisms of changes in immunologic reactivity and tolerance to drugs during sensitization by TAG still remain largely unexplained.

The effect of TAG was studied on specific and nonspecific mechanisms of immunity and on tolerance to strophanthin, and methods of pharmacoprophylaxis and correction of changes in sensitivity to the cardiac glycoside arising during sensitization by homocardiac antigen (HCA) also were investigated.

EXPERIMENTAL METHOD

Experiments were carried out on 110 cats of both sexes weighing 2-3.1 kg. Pentobarbital sodium (30 mg/kg) was used for anesthesia. The animals were sensitized by homologous (cardiac, renal, pulmonary) and heterologous (human myocardium) tissue antigens by intramuscular injection of saline extracts of the corresponding tissues in a dose titrated relative to protein content (3 mg/kg).

Immunologic reactivity was assessed by the phagocytic test, and by determining the bactericidal, complementary, and lysozyme activity of the blood serum (BACL), blast transformation of lymphocytes, spontaneous and under the influence of phytohemagglutinin and TAG, and the level of specific antibodies in the complement fixation test. Morphological changes were judged by examination of myocardial sections stained with hematoxylin-eosin.

Sensitivity to strophanthin was assessed by the minimal arrhythmia-inducing dose (MAD) and the lethal dose causing cardiac arrest, which were determined by biological titration under ECG (lead II) control, a solution of strophanthin in a concentration of $8 \cdot 10^{-6}$ g/ml being injected intravenously at the rate of 1 ml/min.

To rule out the effect of the experimental conditions, animals kept for 10 days in the animal house were used as the control (experiments of series I). Animals in the experiments of series II-V were sensitized with HCA for 5-20 days, animals of series VI-VIII were synsitized with renal, pulmonary, and heterocardiac antigens, animals of series IX-XII were sensitized with HCA against a background of daily administration of methyluracil (30 mg/kg by mouth), diphenhydramine, hydrocortisone, and the β-adrenoblocker, alprenolol (in doses of 4, 3, and 2 mg/kg intramuscularly, respectively). The animals of series XIII-XV, after sensitization for 10 days with HCA, were given diphenhydramine (4 mg/kg), alprenolol (5 mg/kg), and trimecaine (40 mg/kg), intravenously, 10 days before the beginning of determination of MAD and LD of strophanthin.

EXPERIMENTAL RESULTS

Changes in tolerance to strophanthin, as will be clear from Table 1, depended on the duration of action of HCA and were biphasic in character. During the first phase an in-

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TABLE 1. Pharmacoprophylaxis and Correction of Changes in Tolerance of Cats to Strophanthin Arising during Sensitization with TAG

Series of experiments	TAG, therapeutic agent	Number of animals	Duration of administration of TAG, days	Preparation		Dose of strophanthin, μg/kg	
				dose (in mg/kg)	duration of administration, days	MAD	LD
I (control)	—	12	—	—	—	66±2,4	117±3,6
II	HCA	8	5	—	—	59±3,4	100±2,3
III	HCA	8	10	—	—	49±3,2	77±5,7
IV	HCA	9	15	—	—	66±2,1	99±3,2
V	HCA	8	20	—	—	77±1,7	130±3,2
VI	Antigen from kidney	7	10	—	—	56±2,8	93±3,7
VII	from lung	5	10	—	—	67±4,7	107±4,2
VIII	Heterocardiac antigen	5	10	—	—	78±3,3	114±4,6
IX	HCA + diphenhydramine	10	10	4	10	76±3,5	120±4,0
X	HCA + methyluracil	6	10	30	10	80±3,4	118±4,7
	The same	3	10	30	10	52±1,0	86±3,8
XI	HCA + hydrocortisone	7	10	3	8	81±2,0	120±3,0
XII	HCA + alprenolol	5	10	2	8	71±2,3	124±2,7
XIII	HCA + diphenhydramine	6	10	4	1	49±1,7	87±3,7
XIV	HCA + alprenolol	5	10	5	1	93±4,7	133±5,0
XV	HCA + trimecaine	6	10	40	1	107±3,0	144±2,6

crease in sensitivity to the cardiotoxic action of strophanthin was observed, reaching a maximum by the 10th day of sensitization with HCA. Further administration of HCA was followed by gradual recovery of tolerance to strophanthin (phase of adaptation), and on the 20th day of the experiment it was a little higher than in the control.

All subsequent series of experiments were therefore set up on animals sensitized with TAG for 10 days. The results of the experiments of series III and VI-VIII showed that the effect of TAG on tolerance to strophanthin depends on the organ- and species-specificity of the antigen and is most marked in the case of administration of HCA (series III).

The study of immunologic reactivity during sensitization with HCA showed that during the first 10 days of the experiment (the phase of lowering of tolerance to strophanthin) divergent changes took place in the indices of specific and natural immunity (Fig. 1). An increase in the titer of anticardiac antibodies and in the number of blast-transformed lymphocytes under the influence of HCA took place against the background of inhibition of the phagocytic response (the efficiency of phagocytosis was reduced by two-thirds) and a significant decrease in BACL.

The appearance of anticardiac antibodies provided a basis for the formation of an immune complex (IC) which, in this case, was formed in the presence of an excess of antigen, i.e., when IC becomes particularly active and can be fixed on the endothelium of the myocardial vessels [9], for its neutralization and elimination are delayed through depression of the nonspecific factors of immunity. This was confirmed by the results of morphological studies which revealed scattered punctate hemorrhages in the myocardium of the experimental animals, marked congestion of the vessels, and an increase in their permeability.

It must also be remembered that IC formation is accompanied by liberation of histamine and serotonin [8], which, as the present writers have found [2], can potentiate the cardiotoxicity of strophanthin.

By the 15th-20th days of sensitization with HCA (when tolerance to strophanthin was gradually restored) the immunologic changes became different in character. Against the backgound of a continuing increase in the specific indices of immunity, the mechanisms of nonspecific resistance (BACL and the efficiency of phagocytosis increased to their initial levels) were appreciably activated, i.e., the dissociation between the indices of specific and natural immunity disappeared (Fig. 1). In this phase of the immune response IC was formed in the presence of an excess of antibodies, which reduced its toxicity, and the increasing activity of mechanisms of natural resistance led to the development of a perfect immune response, with elimination of the IC.

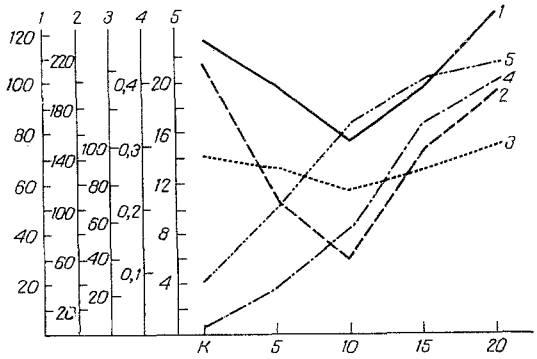

Fig. 1

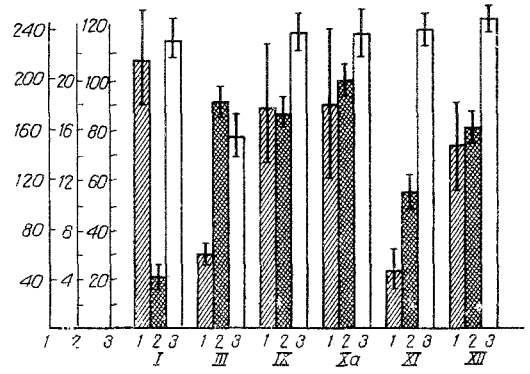

Fig. 2

Fig. 1. Dynamics of changes in specific and nonspecific indices of immunity and sensitivity to strophanthin in cats during sensitization with HCA. Abscissa, duration of administration of antigen (in days). C) Control; ordinate: 1) LD of strophanthin (in μg/g; 2) efficiency of phagocytosis; 3) BACL (in %); 4) titer of anticardiac antibodies (in units); 5) blast-transformation of lymphocytes in presence of cardiac antigen (in %).

Fig. 2. Effect of diphenhydramine, methyluracil, hydrocortisone, and alprenolol on efficiency of phagocytosis, blast-transformation of lymphocytes, and sensitivity to strophanthin in cats sensitized by HCA. Abscissa: 1) efficiency of phagocytosis; 2) blast transformation of lymphocytes in presence of cardiac antigen (in %); 3) LD of strophanthin (in μg/kg). Roman numerals denote series of experiments.

Several drugs affecting different components of immunologic reactivity were used for pharmacoprophylaxis of the lowering of tolerance to strophanthin due to sensitization with HCA.

Diphenhydramine and methyluracil (the former in all experiments, the latter in most) prevented the increase in sensitivity to strophanthin and depression of the nonspecific mechanisms of immunity, although they did not affect the specific immune response (Fig. 2). In three experiments methyluracil had no protective action on tolerance to strophanthin and a fall in the indices of nonspecific resistance was observed.

Hydrocortisone and the β-adrenoblocker alprenolol also prevented the lowering of tolerance to strophanthin. These drugs were injected during the first 8 days of sensitization with HCA, so that they could not directly affect the results of determination of toxic doses of strophanthin. Hydrocortisone had a typical immunodepressive action, while causing a parallel decrease in the indices of specific and nonspecific immunity. Alprenolol also affected immunologic reactivity, abolishing depression of the nonspecific indices and weakening the intensity of the specific immune response a little. These results confirmed the well-known fact that the sympathetic nervous system plays a role in the mechanism of the immune response of the organism [6, 7].

In the experiments of series XIII-XV an attempt was made to correct tolerance to strophanthin when already lowered as a result of sensitization with HCA, through premedication with a single dose of diphenhydramine, alprenolol, and trimecaine.

In this case diphenhydramine was ineffective, whereas alprenolol and trimecaine increased resistance to the cardiac glycoside to a higher level than in the control.

The experimental results thus indicate that in the first phase of sensitization with HCA sensitivity to the cardiotoxic action of strophanthin is increased, evidently due to dissociation of the mechanisms of specific and natural immunity. This decrease in tolerance to the cardiac glycoside can be prevented by the use of drugs which affect different components of the immune response and which reduce dissociation between the mechanisms of specific immunity and the natural resistance of the organism.

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