EXPERIMENTAL RESULTS

Data on induction of postural asymmetry by enkephalin analogs are given in Table 1. Compounds 1, 2, 3, and 4 caused the development of postural asymmetry of the hind limbs, which decreased in the order 1, 2, 3, and 4. Compounds 5 and 6, which are not structural analogs of opioid peptides, did not change the number of animals with postural asymmetry. The magnitude of postural asymmetry in rats of the control group (receiving water) averaged 3 mm, whereas in the experimental animals (receiving peptides) it averaged 5-7 mm (from 3 to 15 mm). Analog 1, which has been studied more thoroughly than the rest, induced flexion of the left and right hind limbs in an about equal percentage of cases (Table 1).

Nalorphine, an analog of morphine with the properties of an opiate antagonist, if injected 24 h after Arg^6-Leu^5-enkephalin (analog 1), considerably reduced the number of animals with postural asymmetry (Table 2); consequently, opiate receptors were involved in the formation of postural asymmetry. It has been shown that opiate receptors participate in the regulation of motor reflexes at the spinal level [2, 3]. The ability of enkephalin analogs to induce postural asymmetry is perhaps due to differences in the sensitivity of the system regulating activity of symmetrical spinal effector neurons to these analogs. In other words, enkephalin analogs can bring to light the asymmetry of the CNS.

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ROLE OF INFLAMMATION MEDIATORS IN HYPERSENSITIVITY TO STROPHANTHIN ARISING IN SOME TYPES OF EXPERIMENTAL MYOCARDIAL PATHOLOGY

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In acute myocardial ischemia, in inflammation of the heart muscle, and during sensitization by homocardial antigen a decrease in tolerance to cardiac glycosides is observed and may provoke glycoside poisoning [3, 4, 14]. These pathological states are usually accompanied by the accumulation of inflammation mediators in the myocardium [2, 12].

It was accordingly interesting to study the effect of some pharmacological agents which are inflammation mediators on the cardiotoxicity of strophanthin in intact animals, and also to study the effect of antiinflammatory and desensitizing agents on tolerance to strophanthin against the background of the action of these inflammation mediators and after experimental occlusion of the coronary artery.

EXPERIMENTAL METHOD

Experiments were carried out on 312 cats of both sexes weighing 1.9-3.1 kg, anesthetized with pentobarbital sodium (30 mg/kg, intraperitoneally) or thiopental sodium (30 mg/kg, intravenously). The method of estimating the animals' tolerance to strophanthin, based on the values of the minimal arrhythmogenic dose (MAD) and the lethal dose (LD), and also the method

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TABLE 1. Changes in ECG Intervals and Tolerance to Strophanthin in Cats under the Influence of Some Inflammation Mediators and Antiinflammatory and Desensitizing Agents

Substances tested	Mode of administration	Dose	ECG interval		Dose of strophanthin, μg/kg	
			P—P	Q-T	arrhythmogenic	lethal
Control	—	—	0,30±0,09	0,16±0,006	81,8±3,0 (75,0—88,6)	125,6±2,2 (120,6—130,6)
Histamine	B/B	90 μg/kg	0,20±0,01	0,12±0,004	69,7±1,6 (65,8±73,6)	99,4±1,4 (97,3—101,5)
Serotonin	"	30 μg/kg	0,21±0,009	0,10±0,008	64,0±2,5 (58,1—69,9)	98,8±2,9 (82,2—105,4)
Histamine + alprenolol	B/B	90 μg/kg + 4 mg/kg	0,35±0,018	0,15±0,010	80±2,7 (73,4±86,6)	118,0±2,9 (110,9—125,1)
Serotonin + diphenhydramine	B/B	30 μg/kg 4 mg/kg	0,34±0,018	0,15±0,012	84,8±2,0 (80,1±89,5)	120,0±2,1 (114,0—126,0)
Histamine + diphenhydramine	B/B	90 μg/kg + 4 mg/kg	0,32±0,009	0,16±0,012	79,8±1,5 (75,6±84,0)	111,7±1,5 (107,5±115,9)
Serotonin + diphenhydramine	B/B	30 μg/kg + 4 mg/kg	0,29±0,012	0,15±0,005	87,1±2,3 (81,5±92,7)	118,7±2,2 (113,2±124,2)
Amidopyrine	"	15 mg/kg	0,29±0,016	0,16±0,06	77,6±2,7 (71,0±84,2)	117,1±2,5 (111,0±123,2)
Histamine + amidopyrine	"	90 μg/kg + 15 mg/kg	0,30±0,007	0,15±0,04	97,6±2,0 (92,9±102,3)	141,0±3,1 (130,6—151,4)
Serotonin + amidopyrine	B/B B/B	30 μg/kg + 15 mg/kg	0,30±0,014	0,16±0,006	81,5±1,5 (77,8±85,2)	113,5±2,2 (108,1—118,9)
Hydrocortisone	"	25 mg/kg	0,30±0,012	0,15±0,006	83,5±1,5 (77,8±85,2)	113,5±2,2 (108,1—118,9)
Hydrocortisol	"	+10 mg/kg	—	—	56,6±1,5 (52,4—260,8)	83,9±1,0 (81,1±86,7)
Hydrocortisone	"	+10 mg/kg	0,20±0,009	0,11±0,003	67,8±1,5 (63,8—71,8)	103,3±2,1 (98,3—108,3)
Histamine the same	"	90 μg/kg +	0,29±0,013	0,15±0,004	85,4±2,1 (80,3±90,5)	120,0±1,7 (115,8±124,2)
Hydrocortisone	"	+10 mg/kg	0,31±0,008	0,15±0,006	79,1±3,1 (70,5—87,7)	117,7±1,7 (112,9—122,3)
Serotonin	"	30 μg/kg	0,31±0,006	0,16±0,009	84,7±2,0 (80,1—89,3)	122,3±2,0 (117,7—126,9)

Legend. Confidence interval at P = 0.05 level given in parentheses.

of producing experimental myocardial infarction by ligating the coronary artery, were described previously [3, 5].

The ECG (standard lead II) was recorded throughout the experiment. Doses of the drugs and methods of their administration are shown in Table 1. Their concentrations in the myocardium were determined on a BIAN-140 photometer [8] and the concentrations of adrenalin and noradrenalin in the blood and myocardium were measured on the BIAN-130 fluorometer [1], with a yield of 75%.

EXPERIMENTAL RESULTS

The writers showed previously that histamine and serotonin significantly potentiate the cardiotoxicity of strophanthin [5]. The study of the mechanism of this potentiating effect of histamine and serotonin showed that it is evidently connected with the sympathomimetic action of biogenic amines on the myocardium. As the data in Table 1 show, the two biogenic amines cause quickening of the heart rate and shortening of electrical ventricular systole. Premedication with the β-adrenoblocker alprenolol prevented these sympathomimetic effects of histamine and serotonin on the heart and abolished their potentiating action on the cardiotoxicity of strophanthin.

Consequently, the lowering of the animals' tolerance to strophanthin under the influence of inflammation mediators took place largely through an adrenergic mechanism. Histamine, which itself activates adenylate cyclase [6], and serotonin, which liberates catecholamines from nerve endings in the adrenal glands [7], potentiate adrenergic effects on the myocardium and increase the intensity of catecholamine utilization. This is shown, in particular, by the results indicating a decrease in the adrenalin and noradrenalin concentrations in the myocardium and a small increase in their concentrations in the blood under the influence of histamine and serotonin (Fig. 1). Potentiation of sympathetic influences on the heart leads to the accumulation of cyclic AMP in the myocardial cells; cyclic AMP inhibits activity of K^+, Na^+-ATPase and, consequently, reduces the potassium ion concentration in the myocardium [16, 15]. It was these changes in the electrolyte composition of the myocardium that were observed after injection of serotonin into the animals (Fig. 1).

It will be clear from Fig. 1 that toxic (arrhythmogenic) doses of strophanthin caused similar shifts of the myocardial electrolyte balance and to a certain extent, of their catecholamine concentrations which, as is supposed [11], also take place through the participation of an adrenergic component. The fact that the effects of strophanthin and inflammation

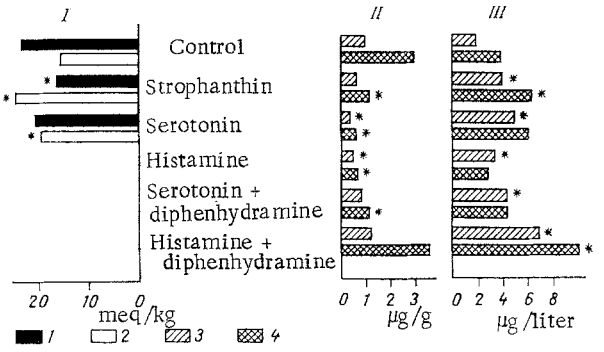

Fig. 1

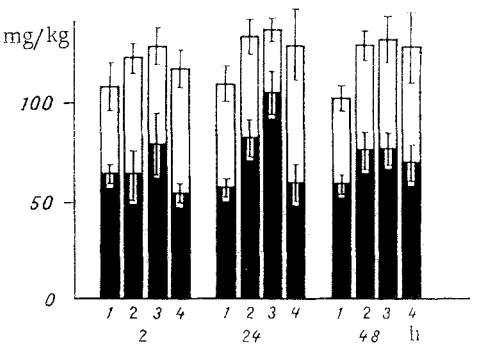

Fig. 2

Fig. 1. Effect of some pharmacologic agents on concentrations of electrolytes and catecholamines in the myocardium (I, II) and blood (III). 1) Potassium, 2) sodium, 3) adrenalin, 4) noradrenalin. *) Differences from control significant at P = 0.05 level.

Fig. 2. Effect of amidopyrine, diphenhydramine, and hydrocortisone on tolerance to strophanthin in experimental myocardial infarction: 1) control after premedication, 2) amidopyrine, 3) diphenhydramine, 4) hydrocortisone. Abscissa, time after ligation of coronary artery (in h); ordinate, dose of strophanthin (in mg/kg). Black columns represent MAD, white columns lethal dose LD. Confidence interval at P = 0.05 level.

mediators are realized by common mechanisms is the reason why these mediators potentiate the cardiotoxicity of cardiac glycosides.

This effect, as was pointed out above, is amenable to pharmacologic correction by the β-adrenoblocker alprenolol. However, it was interesting to study other possible means of pharmacologic correction of the tolerance of the animals to strophanthin depressed through the action of inflammation mediators, by the use of desensitizing and antiinflammatory agents.

The results (Table 1) showed that different desensitizing and antiinflammatory agents had dissimilar actions on the cardiotoxicity of strophanthin. Amidopyrine, for instance, appreciably increased MAD and LD of the cardiac glycoside, probably because of its membrane-stabilizing action [10]. Diphenhydramine, on the other hand, increased the cardiotoxicity of strophanthin a little, evidently because of its ability to block phosphodiesterase and to raise the cyclic AMP concentration in the myocardium [13]. Hydrocortisone significantly reduced the resistance of the animals to the cardiac glycoside, and the degree of its potentiating action was directly dependent on dose. This was evidently a result of the permissive action of hydrocortisone, i.e., its ability to sensitize the myocardium to catecholamines [9]. This hypothesis is supported by the sympathicomimetic effects of hydrocortisone on the heart observed in the present experiments, and the fact that the β-adrenoblocker alprenolol completely abolished its potentiating action on the cardiotoxicity of strophanthin.

Premedication with amidopyrine, diphenhydramine, and hydrocortisone prevented the adrenomimetic effects of histamine and serotonin on the heart and also the lowering of the animals' tolerance to strophanthin against the background of the action of inflammation mediators (Table 1). This protective action of diphenhydramine, amidopyrine, and hydrocortisone is evidently the result of multilateral antagonism with inflammation mediators [10]. Diphenhydramine, in particular, according to our own data, prevents the increased utilization of catecholamines induced by histamine in the myocardium (Fig. 1).

Having discovered experimentally that antiinflammatory and desensitizing agents abolish the potentiating action of histamine and serotonin on the cardiotoxicity of strophanthin the next step was to use these drugs to correct the tolerance of animals to strophanthin when depressed at different times after the production of experimental myocardial infarction, on the grounds that in this pathology the concentrations of inflammation mediators in the heart muscle are increased [2].

The antiinflammatory and desensitizing agents, tested at different times after occlusion of the coronary artery, had a dissimilar protective effect (Fig. 2). Diphenhydramine had the

clearest protective action, for 24 h after ligation it increased MAD of strophanthin by 81.0% and LD by 27.5%, and amidopyrine had a rather weaker effect. Hydrocortisone was virtually ineffective 2 h after ligation of the coronary artery, 24 h after ligation it increased LD of strophanthin a little but did not affect its MAD. The protective action of diphenhydramine, amidopyrine, and hydrocortisone 48 h after ligation of the coronary artery was appreciable and about equal.

The experiments thus showed that the potentiating effect of histamine and serotonin on the cardiotoxicity of strophanthin, brought about through the participation of adrenergic mechanisms, can be prevented not only by a β-adrenoblocker (alprenolol), but also by certain antiinflammatory and densitizing agents. It was also shown that inflammation mediators participate in the genesis of hypersensitivity to strophanthin observed in acute myocardial ischemia. This state of affairs justifies the use of antiinflammatory and desensitizing agents for the pharmacoprophylaxis of glycoside poisoning at certain times after the onset of a myocardial infarct.

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