EFFECT OF THE β-ADRENOBLOCKER ALPRENOLOL AND THE α-ADRENOLYTIC TROPAPHEN ON TOLERANCE TO STROPHANTHIN IN EXPERIMENTAL MYOCARDIAL INFARCTION

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KEY WORDS: strophanthin; myocardial infarction; alprenolol; tropaphen.

The recently discovered role of an adrenergic component in the realization of the effects of cardiac glycosides [1, 7, 8, 10] has evidently opened up new prospects for the therapeutic regulation of increased sensitivity to these cardiotonics due to disturbance of the myocardial blood supply.

The object of this investigation was to study changes in the sensitivity of cats to strophanthin after disturbance of their coronary blood flow and also to examine the degree of the corrective influence on tolerance to strophanthin of pharmacological β- and α-adrenoreceptor blockades at different stages after experimental occlusion of a branch of the coronary artery.

EXPERIMENTAL METHOD

Experiments were carried out on 76 cats of both sexes weighing 2-3.1 kg. The animals were anesthetized with thiopental sodium (30 mg/kg, intravenously). In animals maintained on controlled respiration thoracotomy was performed, the pericardium opened, and the descending branch of the left coronary artery ligated at the level of the lower border of the auricle in one stage. The wound was closed in layers, air was aspirated from the thorax, and the animal was returned to natural breathing.

Tolerance of the cat to strophanthin (ouabain) was judged relative to the two most objective parameters: the minimal arrhythmia-producing dose (MAD), leading to the appearance of the first grouped ventricular extrasystoles, and the lethal dose (LD), leading to cardiac arrest. Both these doses of strophanthin were established by biological titration, a solution of the cardiac glycoside in a concentration of $8 \cdot 10^{-6}$ g/ml in 0.9% sodium chloride solution being injected intravenously at the rate of 1 ml/min.

There were six series of experiments: MAD and LD of strophanthin was determined on intact animals (control), after premedication of the intact animals with the α-adrenoblocker alprenolol (5 mg/kg, intravenously) and with the α-adrenolytic tropaphen* (5 mg/kg, intravenously), 2, 24, and 48 h after ligation of the coronary artery, and also at the same times after occlusion in animals premedicated with alprenolol and tropaphen, respectively.

EXPERIMENTAL RESULTS

The results given in Table 1 show that tolerance to strophanthin after occlusion of the coronary artery depends on certain conditions. When the animals remained under thiopental anesthesia (initial dose 30 mg/kg, then 15 mg/kg every 40 min up to a total dose of 75 mg/kg) for 2 h after ligation of the coronary artery, tolerance of the cats to strophanthin was virtually indistinguishable from that in the control experiments. However, in animals which remained awake for 2 h after application of the ligature and which gave a painful response to operative trauma (the cats were reanesthetized only immediately before the beginning of strophanthin infusion), a considerable increase was observed in sensitivity to the arrhythmia-

*Tropine ester of β-acetoxyphenyl-α-phenylpropionic acid.

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TABLE 1. Effect of Alprenolol and Tropaphen on Tolerance of Cats to Strophanthin after Experimental Occlusion of the Coronary Artery

Experimental conditions	Number of experiments	Dose of strophanthin, mg/kg	
		minimal arrhythmia-inducing dose (MAD)	lethal dose (LD)
Intact animals (control)	9	87±4,3 (78—97)	125±4,7 (114—136)
After occlusion of coronary artery			
2 h (anesthesia)	6	86±2,5 (79—93)	135±7,7 (115—155)
2 h (awake)	7	64±1,8 (59—69)	108±7,5 (90—126)
24 h	6	56±2,0 (51—61)	117±6,4 (101—133)
48 h	5	59±1,8 (54—64)	102±1,2 (99—105)
Intact animals, after administration of alprenolol (5 mg/kg)	8	115±5 (103—127)	153±5 (141—165)
Occlusion of coronary artery after premedication with alprenolol:			
2 h (awake)	8	122±4,7 (111—133)	167±8,6 (147—187)
24 h	5	77±2,8 (69—85)	137±5,5 (122—153)
48 h	7	87±5,2 (74—100)	130±5,7 (117—143)
Intact animals receiving tropaphen (5 mg/kg)	5	90±3,1 (81—99)	136±7,5 (116—156)
After occlusion of coronary artery and premedication with tropaphen			
2 h (awake)	5	87±2,7 (79—95)	137±6,5 (119—15[illegible])
48 h	5	72±3,4 (63—81)	109±3,6 (99—11[illegible])

Note. Confidence intervals at P = 0.05 given in parentheses.

inducing action of strophanthin (MAD was reduced by 36%) and there was a tendency for LD of strophanthin to decrease.

Sensitivity to the bathmotropic action of strophanthin was increased even more 24 h after occlusion; after 48 h MAD of strophanthin was reduced by 32% and LD by 18% compared with the control ($P < 0.05$).

The cardiotonic effect of cardiac glycosides is due, besides to inhibition of sarcolemmal Na,K-ATPase [6], to a certain degree also to liberation of catecholamines in the myocardium [8,10], with subsequent activation of adenylate cyclase and accumulation of cyclic AMP in the cells [3]. Acute myocardial ischemia causes mobilization of the sympathicoadrenal system [5] and a substantial increase in the cyclic AMP level in the myocardium [3], and this is evidently a factor which potentiates the arrhythmia-inducing effect of strophanthin. This is shown, in particular, by the results of experiments on animals awake for 2 h after occlusion of the coronary artery.

The decrease in tolerance to strophanthin observed 24 and 48 h after occlusion was also the result of changes arising in the electrolyte balance of the myocardium [9].

Premedication of intact animals with the β-adrenoblocker alprenolol [2], inducing sinus bradycardia, significantly increased their resistance to strophanthin (MAD was increased by 32% and LD by 22%). This effect was even more marked when cats treated with alprenolol were awake 2 h after occlusion of the coronary artery (MAD was increased by 90% and LD by 55%). The fall in tolerance to the cardiac glycoside 24 and 48 h after disturbance of the coronary blood flow could be completely abolished by premedication with alprenolol. Consequently, pharmacologic blockade of β-adrenergic structures enabled the potentiating effects of acute myocardial ischemia on the toxicity of strophanthin to be reliably prevented.

In the next series of experiments the effect of the α-adrenolytic tropaphen on tolerance to strophanthin was studied [4]. In intact animals trophaphen did not change the heart rate and caused only a slight tendency for resistance to the cardiotonic to rise. Premedication of the animals with tropaphen had no corrective effect on the increased sensitivity to the cardiac glycoside after disturbance of the myocardial circulation.

It can thus be concluded from these results that experimental myocardial infarction is accompanied by increased sensitivity to the toxic action of strophanthin. This fall in tolerance to the cardiac glycoside can be successfully corrected by the β-adrenoblocker alprenolol, whereas the α-adrenolytic tropaphen is virtually ineffective in this situation. The experimental results in particular confirm the known concept that mainly β-adrenergic structures are represented in the myocardium and it is these which participate in the mechanism of the effects of cardiac glycosides.

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EFFECT OF TETRODOTOXIN AND ETHMOZINE ON ARRHYTHMIAS OF THE DOG'S HEART ISOLATED IN THE LATE STAGE OF EXPERIMENTAL MYOCARDIAL INFARCTION

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Intravenous injection of tetrodotoxin (TTX), a specific blocker of sodium channels, abolishes cardiac arrhythmias arising in dogs 24 h after occlusion of the coronary artery [1]. TTX potentiates antiarrhythmic activity of ethmozine and mexetil (mexiletine) [2], which effectively suppress arrhythmias in this period of experimental myocardial infarction [3, 4]. These results enabled the antiarrhythmic action of these preparations in the late stage of infarction to be explained by their ability to affect the fast inward sodium current. However, the sensitivity of nerve cells to TTX is known to be much higher than that of myocardial cells [5]. During intravenous injection of TTX and antiarrhythmic agents, suppression of arrhythmias may take place as a result of both the direct action of the drugs on the myocardium and their action on the nervous system, activity of which plays a definite role in the development and abolition of arrhythmias in myocardial infarction [6].

The object of the present investigation was to study the action of TTX and ethmozine on cardiac arrhythmias in a dog isolated 24 h after occlusion of the coronary artery. By conducting the experiments in this way, the possible participation of the nervous system in the mechanism of the antiarrhythmic action of the drugs tested could be eliminated.

EXPERIMENTAL METHOD

In experiments on mongrel dogs weighing 10-15 kg, under pentobarbital anesthesia (35 mg/kg, intravenously) and with artificial respiration, the thorax was opened under sterile conditions through the 4th left intercostal space. A myocardial infarct was induced by two-stage occlusion of the left descending coronary artery by Harris' method [8]. When marked ventricular extrasystoles were present 24 h after the operation, the coronary vessels of the infarcted recipient's heart were perfused with blood from a donor dog. Animals weighing 25-40 kg served as donors. Recipient and donor were anesthetized with a mixture of 600 mg/kg urethane and

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