EFFECT OF THE β-ADRENOBLOCKER ATENOLOL ON AREA OF MYOCARDIAL NECROSIS IN TRANSIENT AND PERMANENT CORONARY OCCLUSION

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KEY WORDS: coronary occlusion; myocardial infarction; atenolol; area of zone of necrosis; anti-ischemic action.

Propranolol and other nonselective β-adrenoblockers exert an anti-ischemic action and reduce the area of myocardial necrosis in acute coronary occlusion [1, 4, 7-9, 12-15, 17]. The effect of cardioselective β-adrenoblockers on the course of acute coronary occlusion has received little study. Only in one paper [7] is the effect of atenolol on the area of myocardial necrosis described in dogs with transient coronary occlusion, and in another paper [5] the effect of metoprolol on changes in the ST interval and increased CPK activity in acute coronary occlusion in rats is described.

The aim of the present investigation was to study the effect of the cardioselective β-adrenoblocker atenolol on the area of myocardial necrosis and cross-section of the left ventricle in permanent (24 h) and transient (30 min) coronary occlusion.

EXPERIMENTAL METHOD

Experiments were carried out on 120 male rats weighing 180-200 g. Permanent (24 h) and transient (30 min) coronary occlusion followed by reperfusion (23 h 30 min) were induced by ligation of the left coronary artery 2-3 mm below the level at which it crosses the left border of the infundibulum of the heart at its base [2-4]. Operations were carried out under endotracheal ether anesthesia. For the model of transient ischemia a special plastic device ("tube") was used, enabling the coronary-occluding ligature to be removed at the necessary time without further damage to the myocardium. The animals were killed 24 h after the beginning of coronary occlusion. To measure the area of myocardial necrosis the reaction with nitro-BT was used; this is based on the fact that normal cardiomyocytes, containing dehydrogenases, stain a deep blue color on incubation with nitro-BT, whereas necrotic tissues do not stain in this way [7, 16]. To perform the nitro-BT reaction the heart was removed from the chest and washed free from blood, the left ventricle was separated from the right, and cut (starting from the apex) into four or five equal transverse segments 2 mm in height (the last segment could be less high than the others). These segments were incubated with 0.1% nitro-BT solution in phosphate buffer, pH 7.4, for 15 min at 37°C. Morphometry was carried out with the MBS-1 stereoscopic microscope and the "Biolam" ordinary microscope, equipped with ocular rule and objective-micrometer. The total area of the zone of necrosis was calculated by adding together the areas of necrosis of all the segments. The absolute area of the zone of necrosis thus obtained was converted into a relative percentage of the total area of myocardium of the left ventricle. In addition, the weight of the zone of myocardial necrosis (absolute and relative) and the cross-section of the left ventricle (the mean cross section of all segments studied morphometrically) were determined. The experimental results were subjected to statistical analysis by Student's t test and the index of significance (P) was calculated. Atenolol was injected intravenously: in animals with transient occlusion in a single dose of 1 or 10 mg/kg 5 min before occlusion, and in animals with permanent occlusion twice in a dose of 10 mg/kg, once before occlusion and again 6-8 h after coronary occlusion.

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TABLE 1. Effect of Atenolol on Area and Weight of Zone of Myocardial Necrosis and on Cross Section of Left Ventricle in Transient and Permanent Coronary Occlusion

Parameter studied	Transient ischemia				Permanent ischemia	
	control	1 mg/kg	control	10 mg/kg	control	10 mg/kg
Area of zone of myocardial necrosis, % of total area of left ventricle	35,5±0,78	32±2,3	36±0,7	17±1,62*	35±0,95	22±1,02*
Weight of zone of myocardial necrosis, % of total weight of left ventricle	35±2,04	35±1,78	35±1,78	35±1,8*	33±1,34	23±0,96*
Area of cross section of left ventricle, mm^2	5,6±0,2	5,0±0,2	5,6±0,24	2,4±0,23*	5,6±0,32	2,7±0,28*

Legend. *P < 0.001. Effect of atenolol in a dose of 1 mg/kg in permanent coronary occlusion was not studied because this dose was ineffective in transient coronary occlusion.

EXPERIMENTAL RESULTS

In transient occlusion atenolol in a dose of 1 mg/kg did not affect the area or weight of the zone of myocardial necrosis or the area of cross section of the left ventricle (Table 1). In a dose of 10 mg/kg atenolol caused a decrease in the relative area of the zone of myocardial necrosis from 36 ± 0.7% in the control to 17 ± 1.6% (by 2.1 times), in the relative weight of the zone of myocardial necrosis from 35 ± 1.8 to 15 ± 1.8% respectively (by 2.3 times), and in the area of cross section of the left ventricle from 5.6 ± 0.24 to 2.4 ± 0.24 mm^2 (by 2.3 times). During permanent occlusion atenolol in a dose of 10 mg/kg led to a reduction in the relative area of the zone of myocardial necrosis from 35 ± 0.95% in the control to 22 ± 1.02% (by 1.59 times), in the relative weight of the zone of myocardial necrosis from 33 ± 1.34 to 23 ± 0.96% respectively (by 1.4 times), and in the area of cross section of the left ventricle from 5.6 ± 0.32 to 2.7 ± 0.28 mm^2 (by 2.1 times).

Atenolol thus limits the area and weight of the zone of myocardial necrosis in both transient and permanent coronary occlusion. Comparison of the anti-ischemic action of atenolol in transient and permanent coronary occlusion shows that it is more effective in transient ischemia. For instance, under the influence of atenolol the area of the zone of myocardial necrosis was reduced by 2.1 times in transient occlusion but only by 1.59 times in permanent occlusion, and the relative weight of the zone of myocardial necrosis was reduced by 2.3 and 1.4 times respectively. In our own experiments on rats atenolol in a dose of 1 mg/kg was ineffective in transient occlusion, unlike in similar experiments on dogs [7], in which in a dose of 0.3 mg/kg it had an anti-ischemic action. The probable reason for these differences is that different models of myocardial infarction were used. The model of myocardial infarction in rats, with an insufficiency of collaterals and with the development of spontaneous aneurysm [2, 3, 11], resembles more closely myocardial infarction in man than does the model of infarction in dogs [10, 11]. Another possible cause is the relatively larger size of the infarct (control) in the present experiments compared with those in [7]. In our experiments the area of necrosis amounted to 35-36% of the total area of the left ventricle, compared with only 23% in the experiments in [7]. Finally, another possibility is that stability of the area of infarction in rats may be of definite significance [10, 11].

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ROLE OF DOPAMINE RECEPTORS IN THE MECHANISM OF STRESS INJURIES OF THE STOMACH

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The writers showed previously that the protective effect of metoclopramide (MC) against stress injuries of the gastric mucosa (GM) in rats is not due to its ability to stimulate the motor-evacuatory function of the stomach, for it is exhibited against a background of atropine and in rats with a ligature applied to the pyloric sphincter [2]. Attention is directed to the specificity of the gastroprotective action of MC, which gave the best protection of GM against massive hemorrhages. In the light of modern views on the mechanism of action of MC, to which the properties of a selective blocker of dopamine receptors (DR) are ascribed [7, 8, 10], it has been suggested that one cause of stress injury to GM in rats is excitation of DR. Since MC blocks DR both centrally and peripherally, the site of dopamine excitation has not been identified.

The aim of the present investigation was to test this hypothesis and to clarify the role of excitation of DR in the CNS and at the periphery in ulcerogenesis.

EXPERIMENTAL METHOD

The investigation was carried out on 300 albino rats of both sexes weighing 150-200 g, which were deprived of food for 24 h before the experiment, but allowed water ad lib. Two models of combined immobilization ulcer were used: immobilization + generalized electrization (GE) [3] and immobilization + the action of "social stress" (SS) [1], i.e., keeping the immobilized animals in a colony of unrestrained rats. For pharmacologic stimulation of DR the rats were given an intraperitoneal injection 30 min before exposure to stress of the dopamine agonist apomorphine, in doses of 2-17 mg/kg, dopamine in doses of 3.125-50.0 mg/kg, and the dopamine precursor L-dopa in doses of 30-240 mg/kg. Some experiments were carried out on vagotomized animals; the rats were used in the experiments 7 days after bilateral subdiaphragmatic vagotomy. The animals were killed 24 h after exposure to stress, the stomach was removed, and by means of a transillumination gastroscope and magnifying glass, the presence of ulcers and hemorrhagic lesions was determined on the surface of GM; the lesions were differentiated into ulcers, erosions, and massive hemorrhages, in accordance with the principle adopted previously [1]. The number of lesions in each animal and the number of animals with stomach lesions were counted.

EXPERIMENTAL RESULTS

Injection of L-dopa and apomorphine into the rats in doses of 60 and 16 mg/kg respectively without exposure to stress had no effect on the state of GM (Table 1). Apomorphine,

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