PHARMACOLOGY AND TOXICOLOGY

Antiarrhythmic Activity of *n*-Tyrosol during Acute Myocardial Ischemia and Reperfusion

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Antiarrhythmic activity of *n*-tyrosol was demonstrated on the model of early occlusion and reperfusion arrhythmia. The preparation reduces the incidence of ventricular tachycardia and fibrillation, increases the percent of animals without ventricular arrhythmia, and moderates the severity of developing ventricular arrhythmias.

Key Words: *n-tyrosol; ventricular arrhythmias; ischemia; reperfusion*

One of the most important aspects of coronary reperfusion syndrome is cardiac arrhythmia, which in many cases leads to sudden death due to fatal hemodynamic disturbance [3]. There are published reports that *n*-tyrosol moderates arrhythmias caused by the toxic doses of epinephrine, but not by aconitine [2,4].

We studied antiarrhythmic activity of *n*-tyrosol on the model of acute myocardial ischemia and reperfusion.

MATERIALS AND METHODS

Experiments were carried out on Wistar rats (*n*=38) weighing 230-250 g intraperitoneally narcotized with sodium etaminal (60 mg/kg). Acute myocardial ischemia was modeled by a 10 min occlusion of the left coronary artery between the base of *conus pulmonalis* and the lower edge of *auricular sinistra* under conditions of artificial ventilation provided by AID-2 apparatus. During ischemia and following 10-min reperfusion, ECG was recorded in standard lead II.

Taking into account the pharmacokinetic data [7], *n*-tyrosol was injected to experimental rats (*n*=19) intravenously (20 mg/kg, 0.8 ml) 10 min before coronary occlusion. The control rats (*n*=19) received the same volume of physiological saline.

Activity of *n*-tyrosol was assessed by its effect on the incidence of cardiac rhythm disturbances and their severity. We recorded only the incidence of ventricular arrhythmias (VA): single ventricular extrasystole (VEx, <16 over 10 min interval), multiple VEx (>16 over 10 min interval), ventricular tachycardia (VT), and ventricular fibrillation (VF). The animals without rhythm disturbances comprised the VA-free group.

Taking into consideration the criteria published in Methodical Directives on Testing Antiarrhythmic Activity of Pharmacological Substances [1] and other reports [5], we modified the scale of VA severity: 0 point (0-6 VEx without VT and VF); 1 point (6-16 VEx without VT and VF); 2 points (more than 16 VEx or up to 5 sequential ectopic ventricular excitations without VT and VF); 3 points (unstable ventricular ectopic activity with

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more than 5 cycles, one or more episodes with spontaneous reversion and total duration of less than 30 sec); 4 points — stable VT (one or more episodes of spontaneous ectopic ventricular activity with spontaneous reversion lasting in total for more than 30 sec) or VF.

The data were processed statistically using Student's t test and χ^2 test.

RESULTS

In control group, acute coronary occlusion and subsequent reperfusion provoked rhythm abnormalities in 84 and 89% rats, which agrees with other reports [5]. Ischemia or reperfusion induced the life-threatening VA (stable or unstable) in 58% and 74% rats, respectively.

Preliminary injection of *n*-tyrosol affected the distribution of rats by the types of arrhythmia in comparison with the control: the percent of VA-free rats increased, and the percent of rats with VA decreased (Table 1).

The severity scores of ischemic arrhythmias were different in the control and experimental (*n*-tyrosol-treated) groups (Fig. 1). Preliminary injection of *n*-tyrosol to experimental rats prevented the development of most grave form of VA (4 points) during ischemic period and elevated the percent of rats with 0-point arrhythmia. *n*-Tyrosol significantly decreased the mean severity of VA from 2.5±0.3 (control) to 1.1±0.3.

The effect of *n*-tyrosol on the structure of reperfusion arrhythmias was less pronounced: the preparation decreased the percent of rats with VF and multiple VEx. At the same time, the distribution of rats by arrhythmia types significantly differed in the control and experimental groups (Table 1).

The severity of reperfusion arrhythmias did not significantly differ in the control and experimental groups (Fig. 1), but a trend to an increase in the number of rats with minimal-score arrhythmias and to a decrease in percent of rats with most grave rhythm abnormalities was noted. *n*-Tyrosol significantly decreased the mean severity score of reperfusion arrhythmias from 3.0±0.3 (control) to 1.8±0.4.

Probably, antiarrhythmic activity of *n*-tyrosol is based on its membrane-stabilizing effects. This agent is an active antioxidant: it 4-5-fold surpasses natural quinols by antioxidant activity, but is less potent than quercetin or dibunol [6]. *n*-Tyrosol is highly soluble in polar and non-polar solvents, so it can rapidly cross the tissue-blood barriers [4,7]. The membrane-stabilizing effect of *n*-tyrosol in cardiomyocytes was confirmed by a decrease in accumulation of labeled pyrophos-

TABLE 1. Effect of n-Tyrosol on Heart Resistance to Arrhythmogenic Action of Acute Ischemia and Reperfusion

Group	Ischemia (10 min)					Reperfusion (10 min)				
	VA-free	Single VEx	Multiple VEx	VT	VF	VA-free	Single VEx	Multiple VEx	VT	VF
Control	3	2 (16)	8 (11)	11 (42)	3 (58)(16)	2 (11)	1 (5)	6 (32)	12 (63)	4 (21)
n-Tyrosol	12*	1 (63)	4 (5)	5** (21)	0* (26)	7*	4 (37)	1** (21)	9 (5)	0** (47)

Note. Percents are shown in brackets. *$p<0.01$, **$p<0.05$ compared to the control.

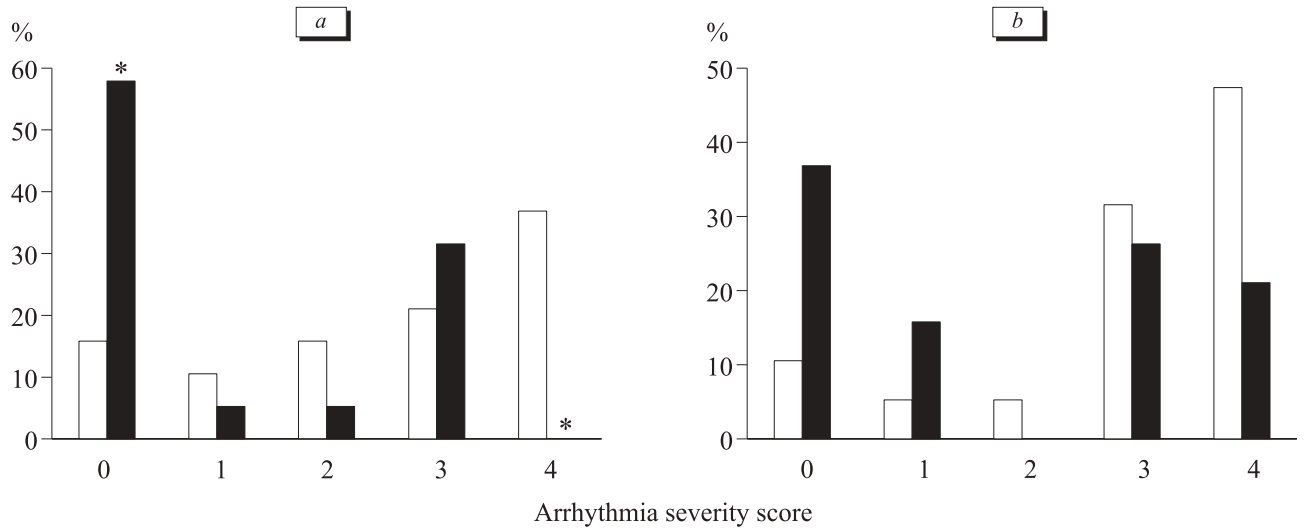

Fig. 1. Effect of *n*-tyrosol on the percent of rats with VA during ischemia (*a*) and reperfusion (*b*). Open and closed bars show the data for control and experimental (treated with *n*-tyrosol) rats. **p*<0.05 compared to the control.

phate on the model of stress-induced damage to the myocardium [4].

During myocardial ischemia, the ameliorating effect of *n*-tyrosol is probably potentiated by its antihypoxic activity most markedly manifested on the model of histotoxic hypoxia caused by sodium nitroprusside [4].

Hemorheological activity of *n*-tyrosol can also moderate the pathological effects of myocardial ischemia. Blood supply to ischemized regions is maintained by two major sources: the collateral blood flow and retrograde venous perfusion with the dominant role of the former [3]. *n*-Tyrosol-induced drop in blood viscosity and decrease in aggregation capacity of erythrocytes can moderate the deleterious effects of rheological occlusion characteristic of ischemic damage to the myocardium. In addition, *n*-tyrosol protects the myocardium by improving collateral blood supply.

Thus, *n*-tyrosol exhibits antiarrhythmic activity during myocardial ischemia and reperfusion, which can be explained by its antioxidant, antihypoxic, and hemorheological effects.

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