PHARMACOLOGY AND TOXICOLOGY

Cardioprotective Effects of T3-146, a Cyclic Derivative of γ-Aminobutyric Acid, under Conditions of Reperfusion

P. A. Galenko-Yaroshevskii, S. A. Kryzhanovskii, A. V. Uvarov, A. Yu. Turovaya, P. B. Popov, and A. I. Khankoeva

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 124, No. 11, pp. 533-536, November, 1997
Original article submitted November 22, 1996

Intravenous injection of T3-146, a cyclic derivative of γ-aminobutyric acid (structural analog of piracetam), 5 min prior to reperfusion of the descendent branch of the left coronary artery prevents the development of serious rhythm disturbances and stabilizes hemodynamics and cardiac function. These effects are probably due to the inhibitory effect of this compound on lipid peroxidation in the myocardium.

Key Words: *γ-aminobutyric acid; ischemia; reperfusion; disturbances of cardiac rhythm and hemodynamic; treatment*

Reperfusion of coronary vessels is the most effective approach to correcting myocardial ischemia [11]. However, this procedure can aggravate damage to the myocardium and cause the reperfusion syndrome characterized by high risk of cardiac rhythm disturbances (CRD), including ventricular fibrillation [1,4,12].

Previous studies have demonstrated that drugs stimulating central and peripheral GABAergic stress-limiting systems possess antiarrhythmic and antifibrillatory activity under conditions of acute regional myocardial ischemia and reperfusion [5,7]. In light of this, it seems interesting to study antiarrhythmic and antifibrillatory effects of a new cyclic derivative of γ-aminobutyric acid (laboratory code T3-146) under conditions of reperfusion in cats. This agent is a structural analog of piracetam and possesses cardioprotective properties.

MATERIALS AND METHODS

Experiments were carried out on 96 albino male rats (0.155-0.210 kg) and 60 nonpedigree cats (2.6-3.5 kg). Acute toxicity (mean lethal dose, LD_{50}) of the T3-146 and reference preparations was determined in rats as described previously [6].

Reperfusion CRD were modeled on cats narcotized with Nembutal (40 mg/kg, intraperitoneally) and artificially ventilated [3]. After thoracotomy, the descendent branch of the left coronary artery was occluded near the lower edge of the auricle for 30 min. Removal of the ligature induced reperfusion ventricular arrhythmias which in most cases transformed into ventricular fibrillation. T3-146 and reference preparations were injected intravenously slowly in isotoxic doses (5% LD_{50}) 5 min prior to coronary occlusion. The occurrence of reperfusion ventricular arrhythmias and fibrillation was recorded on an EKIT-04 electrocardiograph.

The effect of T3-146 on the main hemodynamic and cardiac parameters (HCP) was studied on cats narcotized with Nembutal (40 mg/kg, intraperitoneally) and artificially ventilated as described previously [9]. Systemic arterial and left ventricular pressures as well as its first and second derivatives (dP/dt and (dP/dt)/P) characterizing myocardial contractility were recorded. Electrocardiogram in

Department of Pharmacology, Kuban Medical Academy, Krasnodar

0007-4888/97/0011-1091$18.00

standard lead II was recorded throughout the experiment. The time of systolic ejection and diastolic relaxation, stroke and minute volumes, maximum linear blood flow rate and maximum aortal acceleration, double product, and heart work as well as total peripheral resistance (TPR) were determined from the phasic curve of circulation in the ascendant aorta and other parameters. Acute regional ischemia was modeled by occluding the descendent branch of the left coronary artery 1-2 mm below the auricle of the left atrium.

The intensity of lipid peroxidation in rat blood and myocardium under conditions of acute hypoxic hypoxia (nitrogen with 7% O_2, 30 min) was assessed by measuring the content of malonic dialdehyde in the reaction with thiobarbituric acid [8].

The data were processed statistically using standard ANOVA methods [2,6].

RESULTS

Reperfusion ventricular arrhythmias followed by ventricular fibrillation were observed in 90% animals in the control series (Table 1) and only in 10% animals pretreated with T3-146 (50 mg/kg intravenously). Under the given experimental conditions, the effect of the test GABA derivative surpassed that of the reference drugs cordarone and lidocaine injected in isotoxic doses, as well as of its structural analog piracetam.

Taking into account the high antiarrhythmic and antifibrillatory activities of T3-146, we thoroughly studied the effect of this drug on the main HCP under conditions of acute regional ischemia and reperfusion. As seen from Table 2, a 10-min occlusion in the control series resulted in a slight decrease in blood pressure, stroke and minute volumes, myocardial contractility, together with a rise of TPR. By the 35th min of ischemia, abrupt disturbances of the all studied HCP were noted; these shifts persisted after a 40-min occlusion.

Immediately after restoration of blood circulation in the descendent branch of the left coronary artery, serious CRD developed in 4 out of 5 animals, in 2 cats these CRD transformed into ventricular fibrillation (hemodynamic data from these animals were not considered). These CRD were accompanied by further impairment of all studied HCP. In particular, arterial pressure, stroke and minute volumes and myocardial contractility decreased, while TPR increased in comparison with the baseline values (Table 2).

Stabilization of cardiac rhythm occurred on reperfusion minute 15 and was accompanied by stabilization of the main HCP, which remained at this level from the 20th to the 40th minute of reperfusion.

In next experimental series, T3-146 (50 mg/kg intravenously) was slowly injected 5 min before reperfusion (i.e., starting from the 35th min of ischemia). Changes in the main HCP before the start of reperfusion were similar in the control and experimental groups (Tables 2 and 3), whereas their dynamics after reperfusion was different: reperfusion in the control was accompanied by a pronounced decrease (in comparison with the 35th minute of ischemia) in arterial pressure, stroke and minute volumes, and myocardial contractility (Table 2), while in T3-146-treated animals these parameters increased (Table 3), TPR being decreased in both the control and experimental group.

It should be noted that in contrast to the control group, where reperfusion was attended by serious CRD, in T3-146-treated animals we observed only single extrasystoles, and in 2 cats no extrasystoles were recorded.

Thus, injection of T3-146 prior to reperfusion practically completely restored the main HCP and prevented the development of rough CRD.

Bearing in mind the current concept that reperfusion-induced damage to the myocardium is mediated through the cardiotoxic effect of free oxygen radicals [12], we studied the effect of T3-146 (50 mg/kg, intraperitoneally) on the intensity of lipid peroxidation in rat blood and myocardium.

Injection of T3-146 to intact animals had no effect on blood malonic dialdehyde level, but decreased by 21.1% this parameter in the myocardium (Table 4). Acute hypoxia led to a rise of malonic dialdehyde in the blood and myocardium by 78.7 and 10.5%, respectively.

In T3-146-pretreated animals acute hypoxic hypoxia induced only a 22.7% rise of the blood level of malonic dialdehyde, while in the myocardium this

TABLE 1. Antiarrhythmic and Antifibrillatory Activity of T3-146, Cordarone, Lidocaine, and Piracetam in Reperfusion in Cats (n=10)

Drug	Dose, mg/kg	Reperfusion ventricular arrhythmias, number of animals	
		without arrhythmia	without fibrillation
Control		1	1
T3-146	50	9*	9*
Lidocaine	1.5	5	6
Cordarone	10	3	4
Piracetam	400	6	7*

Note. *p<0.05 compared with the control (χ^2 test)

TABLE 2. Effect of Reperfusion after Acute Ischemia on Major HCP in Cats (*M±m*, *n*=5)

Parameter	Background	Ischemia, min			Reperfusion, min			
		10	35	40	1	5	15	30
Blood pressure, mm Hg	116±11	112±14	89±11	88±10*	64±10*	71±12*	75±11*	73±19*
Heart rate, beats/min	176±16	182±20	163±19	163±21	158±19	165±21	160±27	159±23
Stroke volume, ml	2.43±0.4	2.21±0.5	1.71±0.4	1.68±0.5	1.42±0.3*	1.47±0.3*	1.61±0.4*	1.64±0.3*
Minute volume, liter	0.42±0.06	0.4±0.05	0.28±0.05	0.27±0.06*	0.22±0.04*	0.24±0.05*	0.26±0.04*	0.27±0.03*
Heart work, kg/m	0.64±0.07	0.59±0.08	0.33±0.08*	0.31±0.06	0.18±0.06*	0.22±0.06*	0.25±0.06*	0.26±0.05*
Contractility, mm Hg	3192±218	3457±691	2693±664	2565±749	1864±605*	2051±740*	2185±692*	2237±761
Index of energy consumption	20.6±1.4	20.1±2.2	14.7±1.6*	14.4±1.7*	10.1±1.5*	11.4±1.9*	12.6±1.3*	11.7±1.4*
TPR, dyn×sec/cm^{-5}	22073±1931	223777±2354	25403±1852	26048±2678*	23249±2197	23643±1835	23976±1794	22439±2152

Note. *p<0.05 compared with the background.

TABLE 3. Effect of T3-146 (50 mg/kg Intravenously) on Major HCP under Conditions of Reperfusion after Acute Ischemia in Cats (*M±m*, *n*=5)

Parameter	Background	Ischemia, min		Reperfusion, min			
		35	40	1	5	15	30
Blood pressure, mm Hg	102.0±2.37	73.0±2.61	89.0±2.07*	93.0±2.55*	98.0±2.73*	95.0±2.18*	93.0±2.62*
Heart rate, beats/min	181.0±9.06	139.0±13.02	177.0±11.28*	193.0±11.93*	190.0±12.09*	179.0±10.91*	181.0±11.81*
Stroke volume, ml	2.30±0.23	1.57±0.22	2.19±0.19*	2.14±0.2*	2.17±0.21*	2.19±0.18*	2.12±0.21*
Minute volume, liter	0.42±0.03	0.22±0.03	0.39±0.04*	0.41±0.04*	0.41±0.03*	0.39±0.04*	0.38±0.05*
Heart work, kg/m	0.58±0.05	0.23±0.04	0.47±0.05*	0.52±0.06*	0.55±0.04*	0.50±0.05*	0.48±0.06*
Contractility, mm Hg	3192±218	2141±231	3056±242*	3208±256*	3245±248*	3116±294*	3099±285*
Index of energy consumption	18.5±0.9	10.1±1.1	15.8±0.8*	17.9±0.9*	18.6±1.0*	17.0±1.1*	16.8±0.7*
TPR, dyn×sec/cm^{-5}	19409±2007	26519±2698	18238±2169*	18128±1824*	19102±2422*	19467±1653*	19559±2626*

Note. *p<0.05 compared with the control (Table 1).

TABLE 4. Effect of T3-146 (50 mg/kg Intravenously) on the Content of Malonic Dialdehyde in Rat Blood and Myocardium in Acute Hypoxic Hypoxia (*M±m*, *n*=8)

Experimental series	Concentration of malonic dialdehyde	
	blood, μmol/liter	myocardium, nmol/g wet tissue
Intact animals	1.50±0.02	256±8
T3-146	1.62±0.08	202±4
Acute hypoxia	2.68±0.13	283±12
T3-146+acute hypoxia	1.84±0.11*	241±6*

Note. *$p<0.05$ compared with acute hypoxia.

parameter decreased by 5.9% in comparison with intact animals. Thus, in comparison with the effect of acute hypoxia, T3-146 reduced the concentration of malonic dialdehyde in the blood and myocardium by 31.3 and 14.8%, respectively (Table 4).

Our findings suggest that T3-146 prevents the activation of lipid peroxidation in the blood under conditions of acute hypoxia, which presumably underlies high efficiency of this preparation under conditions of coronary reperfusion.

REFERENCES

1. A. M. Babunashvili, Z. G. Natslishvili, S. A. Abugov, *et al.*, *Kardiologiya*, **35**, No. 5, 55-64 (1995).
2. M. L. Belen'kii, *Quantitative Evaluation of Pharmacological Effect* [in Russian], Leningrad (1963).
3. E. I. Geidenshtein, Ya. V. Kostin, N. N. Markelova, *et al.*, *Farmakol. Toksikol.*, **53**, No. 4, 28-30 (1990).
4. P. F. Litvitskii, V. A. Sandrikov, and E. A. Demurov, *Adaptive and Pathogenic Effects of Reperfusion and Reoxygenation of the Myocardium* [in Russian], Moscow (1994).
5. F. Z. Meerson and M. G. Pshennikova, *Stress-Limiting Systems of the Organism and New Principles of Preventive Cardiology* [in Russian], Moscow (1989).
6. V. B. Prozorovskii, *Farmakol. Toksikol.*, **25**, No. 1, 115-119 (1962).
7. V. V. Skribitskii, "Pharmacological activation of stress-limiting system in the therapy of cardiac rhythm disturbances," Author's Synopsis of Doct. Med. Sci. Dissertation [in Russian], Moscow (1993).
8. I. D. Stal'naya and T. G. Garishvili, in: *Current Methods in Biochemistry*, V. N. Orekhovich (Ed.) [in Russian], Moscow (1977), pp. 66-68.
9. A. I. Khankoeva, "Approaches to diminish cardiotoxicity of antiarrhythmic drugs in ischemic myocardium," Author's Synopsis of PhD. Dissertation [in Russian], Rostov-on-Don (1995).
10. J. G. Coghlan, W. D. Flitter, C. D. Ilsley, *et al.*, *Lancet*, **338**, No. 2, 1145-1146 (1992).
11. A. Goldhaber, I. Joshus, N. Weiss, and N. James, *Hypertension*, **20**, No. 1, 118-127 (1992).
12. C. Ibuki, D. J. Hearse, and M. Avkiran, *Cardiovasc. Res.*, **26**, 316-329 (1992).