Effect of the γ-Aminobutyric Acid Derivative TZ-50-2 on Systemic and Cardiac Hemodynamics and Size of Myocardial Necrosis

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The linear derivative of γ-aminobutyric acid TZ-50-2 (4-hydroxy-3-benzylamino-N-benzylbutanamide hemisuccinate) stimulates coronary circulation (particularly in the left ventricular myocardium) in intact cats, decreases vascular resistance, stimulates the blood flow in ischemic endo- and mesocardium, and decreases (similarly as perlinganite, obsidan, and finoptin) the necrotic zone area in experimental myocardial infarction.

Key Words: *γ-aminobutyric acid; cardiohemodynamics; ischemia; myocardial infarction*

GABAergic substances elicit cardioprotective (antianginal and antiarrhythmic) effects under experimental [1] and clinical [10] conditions. Structural modification of physiologically active endogenous compounds is a promising approach to the development of new drugs [11]. Therefore, GABA derivatives with cardioprotective properties have been extensively investigated [3,9].

We examined the effects of a linear derivative of γ-aminobutyric acid (GABA) (laboratory code TZ-50-2, 4-hydroxy-3-benzylamino-N-benzylbutanamide hemisuccinate) on systemic and cardiac hemodynamics and the size of necrotic zone (NZ) in experimental myocardial infarction. The synthesis and some biological properties (local anesthetic and antiarrhythmic activities) of this agent were described elsewhere [12].

MATERIALS AND METHODS

Systemic hemodynamics and local (myocardial) circulation were studied in intact (non-narcotized) cats and in cats with myocardial ischemia (narcotized with sodium ethaminate, 40 mg/kg intraperitoneally), 5 animals per group. Systemic arterial pressure, heart rate (HR), cardiac output, cardiac index, and total peripheral vascular resistance (TPVR) were recorded in all the cats. In group 1, the blood flow and vascular resistance in the right ventricle, interventricular septum, and left ventricular epicardium, mesocardium, and endocardium were recorded. In group 2, the blood flow and vascular resistance were studied in intact and ischemic epi-, meso-, and endocardium.

Systemic arterial pressure and HR were recorded with an SP-01 electrical manometer, amplifiers 566 and 567 (Hugo Sachs), and Mark VII register (Graphtec). Cardiac output and blood flow in the myocardium were measured using four types of 15-μ microspheres labeled with ^{141}Ce, ^{51}Cr, ^{95}Nb, and ^{46}Sc (NEN). The number of microspheres in the spirals before and after the agent injection, in the blood, and in heart specimens (epi-, meso-, and endocardium, interventricular septum, and right ventricular wall) was counted in a Gompu Gamma-1282 γ-scintillator (LKB-Wallac) by detecting each type of microspheres in analysis of the total radiation spectrum. The data were processed using Super-Calc-2 software [6].

The effects of T3-50-2 and reference drugs perlinganite, obsidan, and finoptin on the size of NZ in

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experimental myocardial ischemia were compared in 25 narcotized (sodium ethaminal, 40 mg/kg intraperitoneally) cats. Myocardial ischemia was induced by occlusion of the descending branch of the left coronary artery between its upper and middle thirds. The studied agents were infused intravenously twice, 30 min before and 120 min after ligation of the coronary artery. The size of NZ was measured 24 h after occlusion. The heart was removed from euthanized animals, and the atrium and right ventricle were separated. The left ventricle was dissected in the plane perpendicular to its axis into 5 blocks of the same thickness. The blocks were submerged in medium with tetrazoleum nitroblue, in which intact tissue was stained dark-blue and NZ remained colorless. Then total weight of the block and the necrosis weight were determined, the proportion of NZ calculated, and the degree of NZ decrease in comparison with the control evaluated for each level and for the entire left ventricle [4].

The results were statistically processed as described elsewhere [2,7].

RESULTS

T3-50-2 (5 mg/kg intravenously) significantly increased (by 26.3, 38,9, 29,4, and 35.0%, respectively) blood flow in the right ventricle, interventricular septum, and left ventricular meso- and endocardium and decreased (by 16.8, 23.5, 16.3, 23.4, and 15.7%, respectively) and the vascular resistance of the above-mentioned heart compartments and in the left ventricular epicardium (Table 1). Other parameters did not change. In a dose of 10 mg/kg the agent exerted similar effects on systemic and cardiac hemodynamics, but only the decrease in cardiac index (by 17.9%) and the increase in left ventricular epicardium blood flow (by 27.8%) were statistically significant. Thus, in intact rats TZ-50-2 increased the total coronary blood flow in the right ventricle, interventricular septum, and left ventricle, particularly in its endocardium.

Stimulation of endocardial circulation is particularly important for characterization of the cardioprotective effects of TZ-50-2, because the epi- and endocardial layers are the most sensitive to ischemia due to specific distribution of the blood between these layers [13]. The ability of the studied drug to redistribute coronary blood flow in favor of the ischemic myocardium was evaluated in experiments on narcotized animals with myocardial ischemia.

TZ-50-2 significantly increased the blood flow in ischemic meso- and endocardium (by 77.8 and 123.9%, respectively, *vs.* the ischemia before injection of the drug) and decreased (by 44.1%) vascular resistance in ischemic endocardium (Table 2). The other parameters of systemic and cardiac hemodynamics did not change, except vascular resistance in ischemic myocardium, which exhibited the most pronounced tendency to decrease in comparison with other parameters (by 31.2%).

TABLE 1. Effect of TZ-50-2 on Systemic and Cardiac Hemodynamics in Intact Non-Narcotized Cats

Parameter	Initial value	After drug injection
Systemic arterial pressure, mm Hg	108.7	105.5
Heart rate, str/min	160.5	158.5
Cardiac output, ml/min	295.8	237.1
Cardiac index, ml/min/100 g	13.8	11.8
Total peripheral vascular resistance, mm Hg/ml/min/100 g	8.1	9.4
Right ventricle:		
blood flow, ml/min/g	1.9	2.4
vascular resistance, mm Hg/ml/min/g	69.5	57.8*
Interventricular septum:		
blood flow, ml/min/g	1.8	2.5*
vascular resistance, mm Hg/ml/min/g	91.5	70
Left ventricle:		
blood flow in epicardium, ml/min/g	1.8	2.2
vascular resistance in epicardium, mm Hg/ml/min/g	1.7	2.2*
blood flow in mesocardium, ml/min/g	56.9	48*
vascular resistance in mesocardium, mm Hg/ml/min/g	69.4	58.1*
blood flow in endocardium, ml/min/g	2	2.7*
vascular resistance in endocardium, mm Hg/ml/min/g	79.5	60.9*

Note. Here and in Table 2: *$p<0.05$ *vs.* the initial value.

Thus, TZ-50-2 induced an increase in coronary blood flow and a decrease in vascular resistance in ischemic endo- and mesocardium of narcotized cats with myocardial ischemia.

Some drugs decrease the size of myocardial NZ within a short period after coronary occlusion. This effect is attained with nitrates [8], β-blockers [5], calcium antagonists [14], and other drugs. After we had found out that TZ-50-2 improves blood supply of ischemic myocardium, we investigated the effect of this agent on the size of NZ in experimental myocardial ischemia and compared it with those of perlinganite, obsidan, and finoptin.

TZ-50-2 (5 mg/kg intravenously twice) significantly decreased the NZ: in the control, the left ventricular NZ was 44.3%, while in experiment it was 32%, i.e., 27.8% smaller. Analysis of the antinecrotic effect of TZ-50-2 at different levels of the myocardium showed that limitation of the NZ was the most pronounced at the V and I levels (40 and 30.6% smaller than in the control), and less pronounced at the IV, II, and III levels (by 27.4, 27,2, and 15.7%, Table 3).

After perlinganite (two injections of 1 mg/kg intravenously) the NZ was 34.5%, i.e., 22.2% less than in the control. The protective effect of the drug was more pronounced at the V and II levels of sections (NZ less by 39.4 and 30.9%, respectively, than in the control) and much lower at the III, IV, and I levels (by 16.6, 12.4, and 10.1%, respectively).

Two intravenous injections of obsidan in a dose of 0.25 mg/kg decreased the NZ by 30% (31% in experiment *vs.* 44.3% in the control). The highest protective effect was observed at the I level of myocardial sections (NZ 54.6% less than in the control), while at other levels it was lower: by 39.2, 27.1, 23.5, and 6.8% at the II, V, III, and IV levels, respectively.

After finoptin (0.25 mg/kg twice intravenously) the left ventricle NZ was 33%, which is 25.7% less than in the control. The maximum cardioprotective effect was observed at the I level (NZ 52.1% less than in the control); this effect was the weaker, the further from the base of the heart: II, III, and IV levels with NZ 29.6, 10.4, and 8.4% less and virtually null at the V level (0.6%).

No statistically significant differences between T3-50-2 and the reference drugs were detected, but the effect of each drug was significantly different from the control.

TABLE 2. Effect of TZ-50-2 on Systemic and Cardiac Hemodynamics in Narcotized Cats with Myocardial Ischemia

Parameter	Initial value	After drug injection
Systemic arterial pressure, mm Hg	87.2	84.5
Heart rate, str/min	94.1	98.6
Cardiac output, ml/min	77.6	91
Cardiac index, ml/min/100 g	71.3	96.4
Total peripheral vascular resistance, mm Hg/ml/min/100 g	138.4	105.8
Intact epicardium:		
blood flow, ml/min/g	71.6	90.1
vascular resistance, mm Hg/ml/min/g	151.5	115.8
Intact mesocardium:		
blood flow, ml/min/g	67.4	86.9
vascular resistance, mm Hg/ml/min/g	182.8	114
Intact endocardium:		
blood flow, ml/min/g	66.6	62.1
vascular resistance, mm Hg/ml/min/g	167.9	123.8
Ischemic epicardium:		
blood flow, ml/min/g	48	67.1
vascular resistance, mm Hg/ml/min/g	206.9	153.6
Ischemic mesocardium:		
blood flow, ml/min/g	42.7	75.9*
vascular resistance, mm Hg/ml/min/g	252	173.5
Ischemic endocardium:		
blood flow, ml/min/g	35.6	79.7*
vascular resistance, mm Hg/ml/min/g	266.6	148.9*

TABLE 3. Decrease of Necrotic Zone (% of control) after Two Intravenous Injections of T3-50-2, Perlinganite, Obsidan, and Finoptin in General and at Various Levels of Left Ventricular Myocardium in Cats

Heart levels	T3-50-2	Perlinganite	Obsidan	Finoptin
I	30.6	10.1	54.6	52.1
II	27.2	30.9	39.2	29.6
III	15.7	16.6	23.5	10.4
IV	27.4	12.4	6.8	8.4
V	40	39.4	27.1	0.6
Total value	27.8	22.2	30	25.7

The cardioprotective effects of TZ-50-2 in health and in myocardial ischemia and infarction allow us to regard this compound as a potential antianginal drug.

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