INCREASED SENSITIVITY OF THE CARDIOVASCULAR SYSTEM TO CAPTOPRIL AFTER CORONARY EMBOLIZATION WITH MICROSPHERES

É. A. Gorodetskaya, É. A. Allabergenova, É. B. Moleva, and O. S. Medvedev

UDC 616.127-005.8-092.9-02:616.132.2-005.7-021.6-092-02:615.357:577.175.852.042.2

KEY WORDS: cardiac failure; microspheres; captopril

Embolization of the coronary vessels by microspheres provides a model of the postinfarction state of the myocardium under experimental conditions [8]. The creation of a model of heart failure which adequately reflects the clinical features of this pathology is essential for the study of the pathogenesis of the disease and also for the screening of new drugs. In this investigation we continue to develop our method of embolization of the coronary vessels with microspheres, suggested previously [8] in order to create a model of chronic heart failure in rats.

The aim of this investigation was to study the hemodynamic characteristics of this particular model on conscious rats 21 days after embolization and also to study the response of the cardiovascular system of these animals to the action of captopril, an inhibitor of angiotensin-converting enzyme (for we know that the renin-angiotensin system plays an important role in the development of chronic heart failure) [2, 6, 11-13].

EXPERIMENTAL METHOD

Under pentobarbital anesthesia (40 mg/kg) a polyethylene catheter was introduced into the left ventricle of Wistar rats through the internal branch of the right carotid artery. The method of embolization of the coronary vessels with 15-μ radioactive microspheres, injected into the left ventricle during occlusion of the ascending aorta, which the present writers suggested previously [8], was used (n = 8). Animals (n = 7) undergoing a mock operation, including all the corresponding procedures served as the control but, instead of microspheres, the same volume of physiological saline was injected during occlusion of the aorta. After 21 days animals with catheters implanted in the left ventricle, femoral artery, and jugular vein 24 h before the experiment, were used. The changes in parameters of the general and regional hemodynamics in response to injection of captopril (1 mg/kg, intravenously) was studied in conscious rats, using the method of microspheres labeled with radioactive isotopes [1, 9]. At the end of the experiment the animals were killed with an overdose of pentobarbital, the organs and tissues were removed and weighed, and the number of microspheres trapped in them and also the number of microspheres in a blood sample were determined on a "Compu-Gamma" gamma-counter (LKB-Wallac, Finland) . The cardiac ejection (in ml/min) and blood flow (in ml/min/g tissue) were calculated by standard equations [9], using the "SuperCalc" program package, on a Labtam 3015 computer. The pressure in the left ventricle (LV) and aorta (AP) was recorded by means of CP-01 electromanometers (Century Technology Company, USA). The heart rate (HR) was determined by means of a cardiotachometer, triggered by the pulse wave of AP. The pressure in LV, AP, HR, the rate of rise of pressure in LV (+dP/dt), and the rate of relaxation (—dP/dt) of LV were recorded on a Mark Y automatic writer (Watan Japan). The results were subjected to statistical analysis by Student's paired and unpaired t test. The data are presented in the form M ± m.

Laboratory of Experimental Pharmacology, All-Union Cardiologic Scientific Center, Academy of Medical Sciences of the USSR, Moscow. (Presented by Academician of the Academy of Medical Sciences of the USSR V. N. Smirnov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 112, No. 8, pp. 122-124, August, 1991. Original article submitted November 26, 1990.

0007-4888/91/0008-1063$12.50

TABLE 1. Initial Parameters of Systemic and Regional Hemodynamics in Waking Rats 21 Days after Embolization of the Coronary Vessels or Mock Operation

Parameter	Group	
	control	embolization
Mean arterial pressure, mm Hg	105±7	104±7
Heart rate, beats/min	361±24	347±27
Cardiac index, ml/min/100 g	37,8±1,6	36,7±2,2
Total peripheral resistance, mm Hg/ml/min/100 g	2,84±0,29	2,92±0,30
Stroke volume	0,35±0,04	0,39±0,04
Systolic pressure in left ventricle, mm Hg	137±5	135±5
+dP/dt, 1000 mm Hg/sec	6,51±0,46	6,38±0,47
-dP/dt, 1000 mm Hg/sec	6,18±0,42	5,43±0,33
End-diastolic pressure in left ventricle, mm Hg	8,0±0,9	19,3±1,3*
Blood flow, ml/min/g, in:		
skin	0,16±0,02	0,09±0,01*
muscles	0,19±0,03	0,12±0,03
pancreas	1,66±0,50	0,78±0,13
brain	1,75±0,23	1,14±0,24
small intestine	1,31±0,11	1,14±0,10
liver	2,69±0,45	1,96±0,14
heart	0,12±0,02	0,05±0,02*
kidneys	5,57±0,47	4,43±0,38
diaphragm	5,20±0,42	4,82±0,47

Legend. *$p < 0.05$ compared with control group.

EXPERIMENTAL RESULTS

Values of the original parameters of the systemic and regional hemodynamics of the control rats and rats with embolization of the coronary vessels 21 days after embolization are shown in Table 1. The end-diastolic pressure (EDP) was higher (17 ± 1.4 mm Hg) in the group of rats with embolization of the coronary vessels than in animals undergoing a mock operation (8 ± 0.9 mm Hg), and in six of the eight rats the end-diastolic pressure was 16 mm Hg or more, evidence of heart failure [17]. This result was combined with a significant increase in resistance and reduction of the blood flow in the skin and liver. According to the remaining parameters no significant differences were found between animals of the two groups. The number of microspheres encountered during embolization (for the six rats with raised EDP) was 61,837 ± 11,214 microspheres/g weight of LV or 65,707 ± 12,954 microspheres/g weight of the whole heart. No significant differences were found between the two groups of animals as regards the response to captopril 1. Injection of captopril 1 into the animals undergoing the mock operation caused a fall of BP (by 4.9 ± 1.2%, $p < 0.05$), of the total peripheral resistance (by 17.0 ± 5.3%, $p < 0.05$), and vascular resistance (Fig. 1b) in the pancreas and small intestine, but a rise of HR (by 7.5 ± 2.1%, $p < 0.05$) and of the blood flow in the pancreas and small intestine (Fig. 2). Injection of captopril into rats with heart failure led to a fall 1 of BP (by 8.2 ± 2.2%, $p < 0.01$), total peripheral resistance (by 20.0 ± 2.8%, $p < 0.05$), and EDP (by 34.2 ± 9.8%, $p < 0.05$), and an increase in cardiac ejection (by 15.1 ± 2.4%, $p < 0.05$) and HR (by 9.6 ± 3.0%, $p < 0.05$). This was accompanied by a marked decrease of resistance (Fig. 1) and an increase of the blood flow (Fig. 2) in the skin, kidneys, heart, stomach, small intestine, and diaphragm. This result is in agreement with data obtained in clinical practice [10], indicating that captorpil improves the hemodynamic parameters in patients with heart failure, in whom it reduces BP and the total peripheral resistance and increases the cardiac ejection; captopril has a particularly powerful action on the renal blood flow, increasing it by 60% [3]. In experimental studies captopril increased the renal blood flow by a greater degree in rats with heart failure than in animals undergoing a mock operation [4], whereas in dogs [5] the increase in coronary blood flow in response to captopril was observed only in animals with occlusion of the coronary arteries, and no such effect was seen in the control animals.

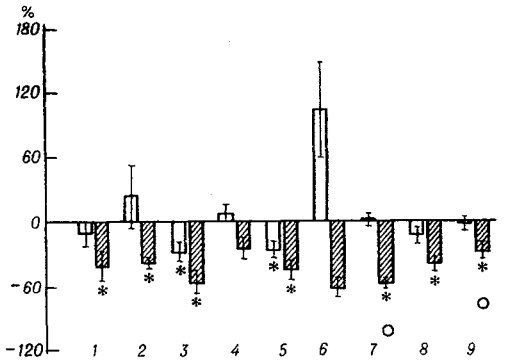

Fig. 1. Changes (in % of initial value) in vascular resistance in skin (1), stomach (2), pancreas (3), brain (4), small intestine (5), liver (6), heart (7), kidneys (8), and diaphragm (9) in response to injection of capropril (1 mg/kg) in conscious control rats (unshaded columns) and rats with embolization of the coronary vessels (shaded columns). Here and in Fig. 2: *p < 0.05 compared with initial level, °p < 0.05 compared with control group.

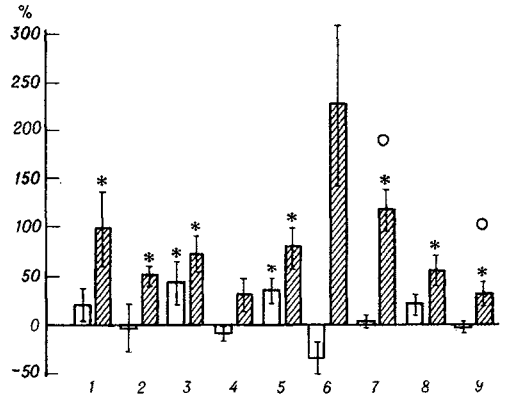

Fig. 2. Changes (in % of initial value) in blood flow in skin (1), stomach (2), pancreas (3), brain (4), small intestine (5), liver (6), heart (7), kidneys (8), and diaphragm (9) in response to injection of captopril (1 mg/kg) in conscious control rats (unshaded columns) and rats with embolization of the coronary vessels (shaded columns).

Thus the sensitivity of the cardiovascular system in the model described above to the action of captopril is increased, and this adequately reflects the state of the renin-angiotensin system in heart failure [2, 6, 11-13]. This means that the model can be used to screen preparations belonging to the angiotensin-converting enzyme group.

LITERATURE CITED

1. O. S. Medvedev, A. N. Murashov, F. E. Meertsuk, and S. F. Dugin, Fiziol. Zh. SSSR, **72**, No. 2, 253 (1986).
2. R. J. Cody, Am. J. Med., **77**, 71 (1984).
3. M. A. Creager et al., Circulation, **64**, 483 (1981).
4. H. Drexler, J. W. Depenbusch, A. G. Truog, et al., J. Pharmacol. Exp. Ther., **241**, 13 (1987).
5. G. Ertl, R. W. Alexander, and R. A. Kloner, Basic Res. Cardiol., **78**, 518 (1983).
6. D. P. Faxon, Am. Heart J., **115**, 1085 (1988).

7. R. Gay, S. Wool, M. Paquin, and G. Steven, Am. J. Physiol., **251**, H483 (1986).
8. E. A. Gorodetskaya, S. F. Dugin, O. S. Medvedev, and E. A. Allabergenova, J. Pharmacol. Meth., **24**, 43 (1990).
9. M. A. Heymann, B. D. Payne, J. I. B. Hoffman, and A. M. Rudolf, Prog. Cardiovasc. Dis., **20**, 55 (1977).
10. S. Kubo, A. Nishioka, H. Nishimura, et al., J. Cardiovasc. Pharmacol., **7**, 753 (1985).
11. M. G. Nicholis, H. Ikram, M. A. Fitzpatrick, and I. G. Crozier, Eur. Heart J., **9**, Suppl., 77 (1988).
12. M. Packer, J. Cardiovasc. Pharmacol., **10**, Suppl. 7, S83 (1987).
13. A. J. G. Riegger, Cardiology, **76**, Suppl. 2, 42 (1989).

ROLE OF CENTRAL AND PERIPHERAL MU- and DELTA-OPIATE RECEPTORS IN MECHANISMS OF THE ANTIARRHYTHMIC ACTION OF ENKEPHALINS

L. N. Maslov and Yu. B. Lishmanov

UDC 616-003.725+615.22

KEY WORDS: enkephalins; arrhythmia; opiate receptors

The writers showed previously that preliminary injection of the synthetic Leu-enkephalin analog D-Ala^2, Leu^5, Arg^6-enkephalin (dalargin) into experimental animals prevents the onset of ventricular fibrillation due to acute myocardial ischemia (AMI) [4]. Almost at the same time identical results were obtained in Professor F. Z. Meerson's laboratory [14]. Both dalargin and its enzymic hydrolysis products can interact with mu-opiate receptors (OR), although their affinity for delta-OR is much greater [1].

It is thus difficult to give an unequivocal answer to the question of the role of either type of OR in the realization of the antiarrhythmic effect of enkephalins, more especially because data in the literature on this question are contradictory [2, 7, 8, 10, 11, 15].

The aim of this investigation was to study the contribution of mu- and delta-OR in the mechanism of the antiarrhythmic action of enkephalins.

EXPERIMENTAL METHOD

Experiments were carried out on 158 male rats weighing 200-250 g. A disturbance of the electrical stability of the myocardium was induced by occlusion of the left descending coronary artery [8]. Dalargin was injected into the femoral vein 10 min before coronary occlusion in a dose of 0.1 mg/kg which, as the writers showed previously, prevents arrhythmias and stress-induced myocardial damage [3, 4]. Morphine was injected intravenously 10 min before AMI in a dose of 1.5 mg/kg, which possesses antiarrhythmic activity [11]. Naloxone also was injected intravenously 5 min before injection of dalargin or 15 min before AMI, in a dose of 0.5 mg/kg to block mu-OR [6, 12], and in a dose of 1 mg/kg to block mu-, delta-, and kappa-OR [6, 12]. Dalargin, in a dose of 1 or 10 μg in 10 μl of 0.9 NaCl, was injected into the 4th cerebral ventricle at the rate of 2 μl/min, through a hollow needle implanted stereotaxically previously (5 days before the experiment), as was done

Laboratory of Radionuclide Methods of Investigation, Research Institute of Cardiology, Tomsk Scientific Center, Academy of Medical Sciences of the USSR, Tomsk. (Presented by Academician of the Academy of Medical Sciences of the USSR R. S. Karpov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 112, No. 8, pp. 124-126, August, 1991. Original article submitted June 20, 1990.

 0007-4888/91/0008-1066$12.50