EFFECT OF PIRACETAM ON BLOOD SUPPLY AND ACTIVITY OF THE INTACT AND ISCHEMIC HEART

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Experimental and clinical observations indicate that piracetam (2-oxo-1-pyrrolidinylacetamide) has a marked antihypoxic action. It increases the resistance of the organism to hypoxia of varied origin [3-5, 7, 8]. Meanwhile the question of the effect of piracetam on the cardiovascular system under normal and pathological conditions has received little study.

The aim of this investigation was to study the effect of piracetam on the blood supply and activity of the intact and ischemized myocardium.

EXPERIMENTAL METHOD

To study the effect of piracetam on the blood supply and activity of the intact myocardium two series of experiments were carried out on cats weighing 2-4 kg, anesthetized with pentobarbital (40 mg/kg, intravenously). In the experiments of series I (six animals) the drug was injected intravenously in a dose of 300 mg/kg, in series II (seven animals) in a dose of 400 mg/kg. The effect of the drug on the blood supply of the heart was judged from changes in the volume velocity of the coronary blood flow, by recording the outflow of blood from the coronary sinus by means of an intervalograph [12]. At the same time, using an oxyhemograph of the 036M type, the oxyhemoglobin concentration was determined in blood from the coronary sinus, so that the oxygen uptake of the intact heart could be calculated. In these same experiments the blood flow in the ascending part of the arch of the aorta was recorded by means of an RKE-1 electromagnetic flowmeter. The following parameters of cardiac activity were calculated: the heart rate, systolic ejection and cardiac output, and the mean acceleration of the blood flow in the aorta, from which the contractile function of the myocardium could be judged. The arterial pressure was measured in the carotid artery by means of an electromanometer.

In a separate series of experiments (on five animals) the effect of piracetam on the blood supply and activity of the heart was studied after total occlusion of the anterior descending branch of the left coronary artery at the boundary between its upper and middle thirds. These experiments were carried out on cats weighing 3.5-4.5 kg, anesthetized with pentobarbital (40 mg/kg intravenously). Piracetam in a dose of 400 mg/kg was injected into the animals 20 min after occlusion of the coronary artery. Parameters of the activity and blood supply of the intact and ischemic hearts were recorded graphically on a Mingograf-81 instrument.

In special series of experiments (six animals in each series) the effect of piracetam, injected intravenously in a dose of 400 mg/kg, on the ATP content in the intact and ischemic heart was studied. In series I the ATP concentration was determined in the left ventricle of the intact heart, in series II in the left ventricle of the intact heart 15 min after injection of piracetam, in III in the left ventricle of the ischemic heart (30 min after occlusion of the anterior descending branch of the left coronary artery), and in IV in the left ventricle of the ischemic heart 15 min after injection of piracetam (occlusion of the coronary artery for 30 min). The experiments were conducted on cats anesthetized with pentobarbital (40 mg/kg, intravenously), under artificial respiration. The ACP concentration was determined by means of kits from Boehringer (West Germany).

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TABLE 1. Effect of Piracetam (400 mg/kg, intravenously) on Blood Supply and Activity of the Intact Heart (changes in %; M ± m, n = 7)

Parameter	Background	Time after injection of drug, min					
		2	5	10	20	30	45
Arterial pressure, mm Hg	95,4±6,4	+17,9±5,1*	+16,9±5,4	+12,6±5,3	+4,7±6,0	+5,7±5,2	+4,2±6,4
Coronary blood flow, ml/min	4,4±0,5	+48,1±12,8**	+33,6±7,8*	+25,8±9,7*	+28,5±6,4**	+25,2±12,0	+19,1±7,7*
Oxygen uptake, ml/min	0,63±0,07	+16,4±13,4	+15,1±6,2	+15,1±6,2	+18,9±5,8**	+27,4±12,2	+24,6±8,6*
Heart rate, beats/min	181,0±9,0	−5,0±1,9*	−6,4±1,3**	−6,6±1,9**	−9,1±4,1	−11,0±4,1*	−12,4±4,6*
Systolic ejection, ml	2,4±0,1	+35,5±4,5***	+34,1±5,6**	+23,4±7,6*	+21,4±7,5*	+18,3±5,5*	+13,4±6,6
Cardiac output, ml/min	432,8±36,5	+29,0±5,6**	+25,7±6,1**	+15,2±7,6	+10,7±9,8	+5,6±7,9	−0,3±8,6
Mean acceleration of blood flow in aorta, cm/sec²	1071,1±76,6	+14,1±5,4*	+15,8±4,0*	+14,7±5,2*	+17,1±5,1*	+16,3±6,4	+15,2±2,1***

Legend. *P < 0.05, **P < 0.01, ***P < 0.001.

TABLE 2. Effect of Piracetam (400 mg/kg, intravenously) on Blood Supply and Activity of the Ischemic Heart (n = 5)

Parameter	Background	20 min after occlusion	Changes in per cent compared with parameters 20 min after occlusion					
			time after injection of drug, min					
			2	5	10	20	30	40
Arterial pressure, mm Hg	112,8±9,7	98,2±6,5 (−10,7+6,3)	+10,3±2,4*	7,8±2,4*	+5,5±1,0*	1,2±3,0	−0,5±7,2	−7,6±7,8
Coronary blood flow, ml/min	7,9±1,7	6,2±1,4 (−22,2±5,5)*	+49,8±15,1*	+43,4±14,8*	+35,0±10,2*	+21,6±12,7	+19,9±14,9	+16,4±19,9
Oxygen uptake, ml/min	0,90±0,17	0,78±0,14 (−12,5±4,9)	−11,3±14,3	+11,5±18,9	+21,3±11,6	+15,3±15,8	+18,1±19,4	+14,5±24,3
Heart rate, beats/min	180,2±11,5	179,2±15,0 (−1,0±2,5)	−5,8±2,4	−3,8±1,8	−2,4±1,4	−1,6±2,1	+2,1±4,3	+4,6±5,9
Systolic ejection, ml	2,2±0,3	1,9±0,3 (−14,6±3,4)*	+35,9±10,9*	+29,7±12,4*	+22,6±7,6*	+12,4±7,8	−2,3±7,4	−17,6±5,3*
Cardiac output, ml/min	390,1±56,3	330,1±49,9 (−15,3±4,1)*	+27,6±8,9*	+24,1±9,9	+19,4±5,9*	10,1±5,6	−0,8±6,2	−14,9±3,6*
Mean acceleration of blood flow in aorta, cm/sec²	1033,9±103,6	899,1±88,8 (−12,5±4,7)	+29,6±46,7**	+27,0±4,0**	+20,1±3,6**	+17,5±3,1**	+7,2±3,2	−0,9±6,5

Legend. Change in parameters in per cent after 20 min of occlusion shown in parentheses. *P < 0.05, **P < 0.01.

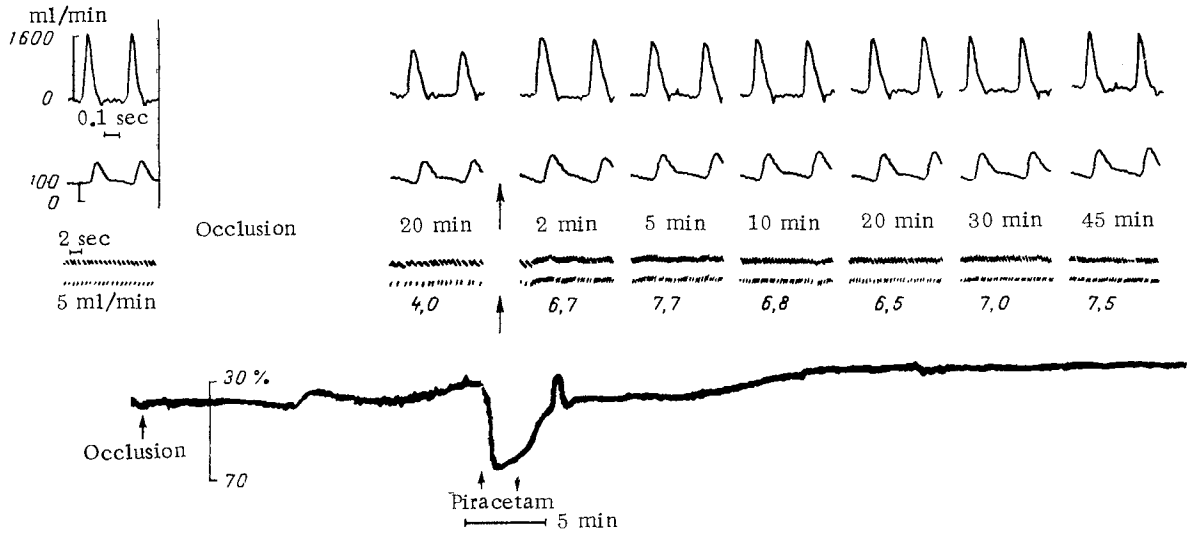

Fig. 1. Effect of piracetam (400 mg/kg, intravenously) on blood supply and activity of the ischemic heart. From top to bottom: velocity of blood flow in ascending part of arch of aorta (in ml/min), blood pressure in carotid artery (in mm Hg), blood outflow from coronary sinus (in ml/min), oxyhemoglobin concentration in coronary venous blood (in %). From left to right: background, 20 min after complete occlusion of anterior descending branch of left coronary artery, 2, 5, 10, 20, 30, and 45 min after injection of piracetam.

EXPERIMENTAL RESULTS

Piracetam in doses of 100 and 200 mg/kg caused virtually no change in the cardiovascular system. In a dose of 300 mg/kg the blood caused slight hypertension (2 min after injection, +13.4 ± 16.7 mm Hg), a very small increase in the systolic ejection and cardiac output, and acceleration of the blood flow in the aorta. These findings agree with observations made by other workers, who showed that piracetam causes slight hypertension and corrects the cardiac output [1, 6].

Piracetam in the above-mentioned dose increased the velocity of the coronary blood flow (2 min after injection, on average by 22.1 ± 8.4%, $P < 0.05$), accompanied by an increase in the oxyhemoglobin concentration in blood of the coronary sinus (on average by 13.8 ± 2.2%, $P < 0.01$). Despite the increased velocity of the coronary blood flow, the oxygen uptake of the intact heart showed no significant change. The effect of the drug lasted 5-15 min.

Piracetam in a dose of 400 mg/kg had a more marked and prolonged effect on the blood supply and activity of the intact heart (Table 1). Under the influence of the drug the oxyhemoglobin concentration in blood in the coronary sinus increased (by 14.7 ± 4.2%, $P < 0.01$) and, consequently, the oxygen uptake of the heart was increased by a much lesser degree than the coronary blood flow. A definite oxygen reserve was thus created in the heart. Piracetam cause slight bradycardia, increase the systolic ejection and cardiac output, and strengthened the contractile function of the myocardium (Table 1). As biochemical investigations showed, piracetam increased the ATP concentration in the intact myocardium by 11.4% (from 5.51 ± 0.11 to 6.14 ± 0.16 μM, $P < 0.01$).

Strengthening of the contractile function of the myocardium due to piracetam, it will be noted, was not connected with stimulation of β-adrenergic structures, for preliminary injection of the β-adrenoblocker propranolol (2 mg/kg, intravenously) did not prevent the potentiating effect of piracetam on contractility of the heart muscle. Bilateral vagotomy likewise did not prevent this effect. Consequently, the positive inotropic action of piracetam is evidently connected with the direct effect of the drug on the myocardium and is not mediated through the autonomic nervous system.

Experiments on the intact heart of experimental animals thus showed that piracetam can strengthen the contractile function of the heart and increase its blood supply, creating a definite oxygen reserve at the same time in the heart. As a result, it might be supposed that the drug would have a beneficial effect on the ischemic myocardium also. Further experiments confirmed this hypothesis. These experiments showed (Fig. 1) that complete occlusion of the anterior descending branch of the left coronary artery leads to a fall in arterial pressure, a decrease in systolic ejection and cardiac output, depression of myocardial contractility, a decrease in the volume velocity of the coronary blood flow, and a decrease in the oxyhemoglobin concentration in coronary venous blood (Table 2). The changes mentioned above were accompanied by a fall in the ATP concentration in the myocardium by 23.4% (from 5.51 ± 0.11 to 4.22 ± 0.17 μmole/g, $P < 0.01$).

Piracetam, injected under these conditions, largely restores the normal parameters of the blood supply and activity of the ischemic heart (Fig. 1, Table 2). It is particularly important to note that under the influence of the drug the oxygen uptake of the ischemic heart increased by a much lesser degree than the coronary blood flow. Piracetam increased the ATP concentration in the ischemic myocardium also (from 4.22 ± 0.17 to 4.81 ± 0.18 μmoles/g, $P < 0.05$). However, the ATP level did not return fully to its control value (5.51 ± 0.11 μmoles/g, $P < 0.05$).

Piracetam thus has a positive action on the blood supply activity, and certain metabolic parameters of the intact and ischemic heart. The data given above must be taken into account when the drug is used under clinical conditions.

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ABILITY OF LIGANDS OF OPIATE RECEPTORS (ENDORPHINS AND EXORPHINS) TO INHIBIT GASTRIC JUICE SECRETION IN DOGS

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It is now reasonably well established that the opioid peptides, ligands of opiate receptors, can modify the functions of the digestive system, including the formation of gastric secretion. However, available evidence on the direction of the secretory effects is contradictory and ambiguous [1, 2, 4, 5]. As a rule investigations of this kind have involved the study of properties of natural compounds of enkephalins, namely leucine- and methionine-enkephalins.

Data on the effect of several opioid peptides of both endogenous and exogenous origin on the acidity of the gastric juice are summarized in this paper. The following synthetic endogenous peptides were studied: γ-endorphin, Des-Tyr-γ-endorphin, and Tyr-D-Ala-Gly-Phe-NH_2-(pNO_2), and activity of the peptide formed by peptic hydrolysis of milk — synthetic casomorphine 1-5 (Tyr-Pro-Phe-Pro-Gly) also was determined [3]. The preparations listed above were obtained in the Laboratory of Peptide Synthesis, All-Union Cardiologic Scientific Center, Academy of Medical Sciences of the USSR, by the classical methods of peptide chemistry.

EXPERIMENTAL METHOD

Experiments were carried out on eight hungry mongrel dogs weighing 16-20 kg, in which gastric fistulas were formed by Basow's method. Gastric acid secretion was stimulated by pentagastrin (PG; from Serva, West Germany), in a dose of 1 μg/kg/h, and in some experiments opiate receptors were blocked by the specific antagonist naloxone (from Narcan, USA) in a dose of 100 μg/kg. The peptides for study were injected after a constant volume of gastric juice had been established after administration of PG. Most of them were used in a stable dose of 30 μg/kg/h, but casomorphine was given in doses increasing by a factor of 10 after each hour of the experiment — 1, 10, and 100 μg/kg/h respectively (10 μg/kg/h is equimolar with 30 μg/kg/h for the other preparations). At the end of perfusion of solutions containing peptides, injection of pure PG was continued for a further hour. The technique of these experiments did not differ in principle from that used previously and it was described in more detail in earlier publications [1, 2]. The results were subjected to statistical analysis by Student's test. Differences were considered significant at a 95% level ($P < 0.05$).

EXPERIMENTAL RESULTS

Data on the action of opioid peptides on gastric secretion in dogs are summarized in Table 1. Injections of most of the opioid peptides studied, whether of endogenous or of exogenous origin, caused considerable inhibition of secretion of gastric juice, as shown by a decrease in the volume of juice secreted and in the rats of HCl production. Comparison of the effectiveness of the antisecretory action of the various preparations showed that casomorphine in a dose of 10 μg/kg/h had the greatest inhibitory potential: the rate of HCl production

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