prolonged administration of the typical neuroleptic haloperidol caused weakening or reversal of the behavioral effects of coerulein. The results of the writers' previous investigations [1, 7], which showed that long-term administration of haloperidol restores the inhibitory effect of coerulein on ^{3}H-spiroperidol binding in experiments *in vivo*, are also evidence of reduced sensitivity of the CCK-8 receptors. Meanwhile prolonged administration of haloperidol significantly reduces the number of high-affinity dopamine$_2$- and serotonin$_2$-receptors [1, 7]. Reduction of the density of these monoaminergic receptors evidently also determines the hyposensitivity of the CCK-8 receptors. Considering the close morphological and functional connection between CCK-8, dopamine, and serotonin, and also the considerable adaptive changes of CCK-8 receptors during long-term administration of the typical neuroleptic, haloperidol, it can be tentatively suggested that CCK-8 plays an important role in the realization of both antipsychotic [3] and side effects of neuropeptics.

LITERATURE CITED

1. E. E. Vasar, A. M. Nurk, M. O. Maimets, and L. H. Allikmets, Byull. Éksp. Biol. Med., No. 1, 72 (1985).
2. R. S. L. Chang, V. I. Lotti, G. E. Martin, et al., Life Sci., 32, 871 (1983).
3. I. N. Ferrier, G. W. Roberts, T. J. Grow, et al., Life Sci., 33, 475 (1983).
4. J. A. Finkelstein, A. W. Stegless, P. A. Martinez, and M. Praissman, Peptides, 5, 11 (1984).
5. P. Frey. Eur. J. Pharmacol., 95, 87 (1983).
6. T. Kadar, A. Pesti, B. Penke, et al., Neuropharmacology, 23, 955 (1984).
7. E. Vasar, M. Maimets, A. Nurk, and L. Allikmets, Psychopharmacol. Bull., 20, 691 (1984).

ACTION OF ANTIHYPOXIC AGENTS ON ISCHEMIC MYOCARDIAL DAMAGE

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UDC 616.127-005.4-085.23-036.8

KEY WORDS: sodium hydroxybutyrate; pyracetam; pyridoxinyl-glyoxylate; creatine phosphokinase; myocardial infarction.

The possibility of limiting the size of a myocardial infarct (MI) by the use of drugs has been discussed widely in recent years. Opposite points of view have been expressed even as regards such traditional "anti-infarct" drugs as the β-adrenoblockers [8, 9, 13].

The aim of this investigation was to study the effect of antihypoxic agents — pyridoxinyl-glyoxylate (glyo-6), sodium hydroxybutyrate, and the α-pyrrolidone derivative pyracetam — on the development of ischemic damage and on the final size of MI resulting from occlusion of the coronary artery.

EXPERIMENTAL METHOD

To assess the effect of the drugs on the development of ischemic damage in the heart following coronary arterial occlusion experiments were carried out on cats weighing 3-4 kg, anesthetized with pentobarbital sodium (40 mg/kg, intravenously), and artificially ventilated. The anterior descending branch of the left coronary artery of the animals was ligated in its middle third. Heparin was injected intravenously in a dose of 1000 U/kg. Blood samples were taken from the coronary sinus before coronary occlusion and 20 and 60 min thereafter. There were four series of experiments. The drugs were injected immediately after coronary arterial occlusion, intravenously: sodium hydroxybutyrate 200 mg/kg, pyracetam 400 mg/kg, and glyo-6 100 mg/kg body weight. In the control series the equivalent volume of physiological saline was injected into the animals. Plasma creatine phosphokinase (CPK) activity was determined by the method in [10]. Linear regression coefficients were determined by Theil's nonparametric test. Significance of differences between angles of slope of the regression lines was determined by Hollander's one-way nonparametric test.

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(Presented by Academician of the Academy of Medical Sciences of the USSR A. V. Val'dman.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 102, No. 11, pp. 585-587, November, 1986. Original article submitted January 13, 1986.

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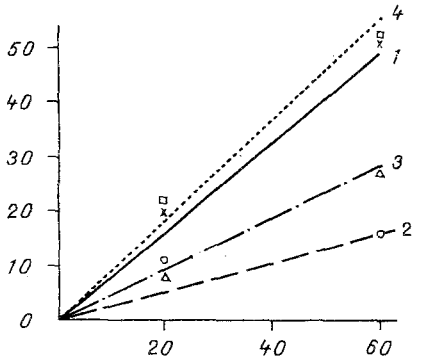

Fig. 1. Effect of sodium hydroxybutyrate (200 mg/kg, pyracetam (400 mg/kg), and glyo-6 (100 mg/kg) on rate of increase of CPK activity in blood from the coronary sinus during coronary arterial occlusion for 60 min. Abscissa, time of occlusion (in min); ordinate, CPK activity (in U/liter). 1) Control ($\Delta CPK = 0.825t$); 2) sodium hydroxybutyrate ($\Delta CPK = 0.273t$); 3) pyracetam ($\Delta CPK = 0.473t$); 4) glyo-6 ($\Delta CPK = 0.915t$). Crosses, circles, tringles, and squares denote mean increase in CPK activity 20 and 60 min after coronary arterial occlusion in control and under the influence of sodium hydroxybutyrate, pyracetam, and glyo-6 respectively.

To study the effect of the drugs on the size of MI, experiments were carried out on non-inbred male albino rats weighing 180-200 g. The total number of animals used in the experiments was 44 (five series with 8-10 rats in each series). Myocardial infarction was produced by the method in [11]. The ECG of the animals was recorded in three standard leads before occlusion of the coronary artery, 5 min after occlusion, and before killing the animals. The rats were killed 72 h after the operation. The heart was removed and frozen sections cut from it. Five sections 25 μ thick were cut every 2 mm, starting from the apex of the left ventricle. The sections were stained with nitro-BT to reveal succinate dehydrogenase activity. To determine the size of MI a mathematical model [4] was used. The size of MI was calculated as the volume of necrotic mass, expressed as a percentage of the total volume of left ventricular myocardium. The drugs were injected intraperitoneally in sessional doses of: sodium hydroxybutyrate 200 mg/kg, pyracetam 400 mg/kg, glyo-6 100 mg/kg body weight. Propranolol, in a sessional dose of 1 mg/kg, was used as the drug for comparison. The scheme of administration of the drugs was as follows: 1st injection 15 min before coronary arterial occlusion, 2nd injection 2 h after occlusion, thereafter two injections daily for the next 2 days. In the control series the animals were given injections of the equivalent volume of physiological saline. The results were subjected to statistical analysis and the significance of differences determined by Student's t test.

EXPERIMENTAL RESULTS

It is well known that the degree of increase of CPK activity in the blood is an important parameter of the severity of ischemic damage [6, 12]. The time course of the increase in CPK activity during acute moycardial ischemia reflects the rate of transition from reversible to irreversible ischemic damage. It has been shown that, during coronary arterial occlusion, drugs with anti-ischemic action reduce CPK activity in blood flowing from the ischemic focus [5, 7].

According to the results of experiments on cats with coronary arterial occlusion for 60 min, the antihypoxic agents had different effects on the rate of rise of CPK activity in blood on the coronary sinus: The GABA derivatives sodium hydroxybutyrate and pyracetam considerably reduced it, whereas glyco-6 caused no change. In the control series of experiments, for instance, 60 min after coronary arterial occlusion the increase in CPK activity in blood from the coronary sinus of the cats was 50.8 ± 5.2 U/liter, whereas in experiments with injection of sodium hydrobybutyrate and pyracetam, the increase in CPK activity was only 16.5 ± 6.5 U/liter ($P < 0.05$) and 27.5 ± 8.2 U/liter ($P < 0.05$) respectively. Glyo-6 had no effect on CPK activity in blood of the coronary sinus compared with the control (the increase amounted to 51.8 ± 11.4 U/liter). The linear regression coefficient in the control series of experiments was 0.825. In experiments in which sodium hydroxybutyrate and pyracetam were given the coefficient was reduced to 0.273 and 0.473 respectively ($P = 0.06$). Glyo-6 caused virtually no change in the linear regression coefficient ($\beta = 0.915$; $P > 0.1$) (Fig. 1).

Consequently, unlike glyo-6, sodium hydroxybutyrate and pyracetam, in acute regional myocardial ischemia, delay the development of ischemic damage. This conclusion is in agreement with the results of previous investigations showing that sodium hydroxybutyrate and pyracetam improved the functional state of an acute ischemic focus in the myocardium [3]. An important role in this action of the drugs may be played by their ability to improve the coronary collateral circulation [2] and to reduce the permeability of cell membranes [1].

It was interesting to discover whether the ultimate size of MI was limited by the drugs tested. The answer to this question was obtained in experiments conducted on rats with MI of 3 days' duration. Electrocardiographic investigations showed that within a few minutes after occlusion of the coronary vessel marked changes were observed in the ECG in standard leads (elevation of the ST segment and enlargement of the T wave). Three days after coronary occlusion the QS complex or a deep Q wave was usually present on the ECG, evidence of the development of MI.

A macrohistochemical study of the hearts of rats with MI showed that the drugs with antihypoxic properties chosen for study, when injected in accordance with a particular schedule, did not change the ultimate size of the ischemic focus in the heart. Meanwhile propranolol, which was chosen as the comparison drug, considerably reduced the size of the necrotic focus. For instance, when physiological saline was injected, the size of MI was 37.5 ± 2.7% ($n = 10$), when propranolol was injected it was 23.8 ± 2.6% ($P < 0.01$, $n = 8$), sodium hydroxybutyrate 38.4 ± 3.6% ($n = 8$), pyracetam 41.2 ± 3.0% ($n = 9$), and when glyo-6 was injected it was 38.5 ± 2.8% ($n = 9$). Our data on the ability of propranolol to reduce the size of an experimental MI are in agreement with observations of other workers [8].

Thus none of the drugs with antihypoxic properties studied reduces the size of an experimental MI. Meanwhile, in the case of sodium hydroxybutyrate and pyracetam it will be clear that the anti-ischemic action of certain drugs under conditions of prolonged coronary arterial occlusion, may be expressed only as slowing of the development of the ischemic focus in the heart, and not as limitation of the size of the necrotic lesion.

LITERATURE CITED

1. N. S. Bashirova, A. I. Usmankhodzhaev, and A. K. Paleologu, Vopr. Med. Khimii, No. 3, 61 (1985).
2. I. B. Tsorin and G. G. Chichkanov, Pharmacological Correction of Oxygen-Dependent Pathological States [in Russian], Moscow (1984), pp. 161-62.
3. G. G. Chichkanov and I. B. Tsorin, Farmakol. Toksikol., No. 2, 49 (1985).
4. P. J. Boor and E. S. Reynolds, Am. J. Clin. Path., 68, 387 (1977).
5. H. Boudoulas, P. E. Karayannacos, R. P. Lewis, et al., J. Surg. Res., 24, 469 (1978).
6. W. D. Bussman, D. Passek, W. Seidel, and M. Kaltenbach, Circulation, 63, 615 (1981).
7. K. M. Fox, A. P. Selwyn, and E. Welman, Clin. Cardiol., 3, 47 (1980).
8. R. A. Kloner and E. Braunwald, Cardiovasc. Res., 14, 371 (1980).
9. T. Peter, M. K. Heng, B. N. Singh, et al., Circulation, 57, 534 (1978).
10. S. B. Rosalki, J. Lab. Clin. Med., 69, 696 (1967).
11. A. I. Selye, E. Bajusz, S. Grasso, and B. Mendell, Angiology, 11, 398 (1960).
12. W. E. Shell, J. E. Lavelle, J. W. Covell, and B. D. Sobel, J. Clin. Invest., 42, 114 (1973).
13. D. M. Yellon, J. M. Downey, and D. J. Hearse, G. Ital. Cardiol., 14, 892 (1984).