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# PHARMACOLOGIC CORRECTION OF DISTURBANCES OF CARDIAC CONTRACTILITY IN STRESS

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UDC 616.12-008.3-02:613.863

KEY WORDS: stress; cardiac contractility; glycogen; drugs.

Previous investigations have shown that emotional stress (ES) causes marked excitation of the adrenergic and pituitary-adrenal systems [3], followed by activation of lipid peroxidation (LPO) and disturbance of oxidation and phosphorylation in the mitochondria of the heart [5], by structural changes in the myocardium [11], and also by depression of cardiac contractility [4]. It has also been shown that excessive excitation of the adrenergic and pituitary-adrenal systems [6, 7, 12] and disturbances of the metabolism and structure of the heart [10] can be prevented by the use of drugs acting selectively on different components of the pathogenesis of stress injury to the heart.

In this investigation the effect of certain metabolites of natural antistressor systems of the body and membrane protectors on cardiac contractility and also on the glycogen content in the myocardium was studied in animals during stress, for this problem has not been studied adequately.

## EXPERIMENTAL METHOD

Experiments were carried out on 144 male albino rats weighing 190-230 g. ES was produced in the form of an anxiety neurosis by the method described previously [6, 7]. The animals were divided into six groups: 1) control, 2) animals subjected to ES; groups 3, 4, 5, and 6 of animals received sodium hydroxybutyrate (GHBA), prolactin, propranolol, and ionol respectively. GHBA was injected in a dose of 100 mg/kg intraperitoneally 30 min before ES and 3 h after the beginning of exposure to stress, prolactin was injected in a dose of 2.5 units/100 g subcutaneously 60 min before ES, propranolol in a dose of 5 mg/kg subcutaneously 30 min before ES, and ionol in a dose of 120 mg/kg intraperitoneally once a day for 3 days before ES.

The contractile function of the heart was studied under conditions of relative rest and during isometric contraction (compression of the aorta for 30 sec) with respect to the following parameters: the developed pressure ($P_d$), velocity of contraction ($V_c$) and relaxation ($V_r$), and the intensity of functioning of structures (IFS), calculated as the product of heart rate and developed pressure, divided by the weight of the left ventricle. The investiations were conducted under pentobarbital anesthesia (8 mg/100 g) with an open chest and under artificial respiration. The pressure in the left ventricle was measured by means of a VI6-6TN electromanometer and recorded photographically on the N-105 oscilloscope [1]. The glycogen content in the heart muscle of the rats was determined by the method in [15]. Contractility of the heart was studied and the glycogen concentration measured 45 h after the end of exposure to stress, at the time of maximal changes in metabolism, structure, and function of the heart [5].

## EXPERIMENTAL RESULTS

ES evoked marked depression of cardiac contractility (Tables 1 and 2). Whereas in a state of relative rest the parameters characterizing cardiac contractility were depressed by 15-20%, after compression of the

Central Research Laboratory and Department of Pharmacology, Irkutsk Medical Institute. (Presented by Academician of the Academy of Medical Sciences of the USSR V. V. Zakusov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 100, No. 8, pp. 206-208, August, 1985. Original article submitted October 4, 1984.

 

TABLE 1. Effect of GHBA, Prolactin, Propranolol, and Ionol on Cardiac Contractility after Exposure to ES (M±m)

| Parameter | Experimental conditions (n = 12) | Relative test | Compression of aorta | |
|---|---|---|---|---|
| | | | 5 sec | 25 sec |
| $P_d$, mm Hg | Control | 109±4,5 | 211,5±9,7 | 197,6±10,8 |
| | ES | 87,3±5,1** | 133,3±12,9*** | 117,6±15,4*** |
| | GHBA + ES | 101,0±4,6 | 209±11,2 | 191±8,8 |
| | Prolactin + ES | 112,5±5,1 | 201,3±4,5 | 190,1±8,9 |
| | Propanolol + ES | 110,9±3,4 | 205±5,1 | 187,7±9,9 |
| | Ionol + ES | 99,8±6.1 | 195,9±10,9 | 179,9±12,3 |
| IFS, mm Hg/min/mg | Control | 101,4±3,3 | 185,8±11 | 155,4±15,7 |
| | ES | 74,5±7,7* | 104,2±8,6*** | 84,0±10,0*** |
| | GHBA + ES | 100,9±8,8 | 180,1±12,1 | 160,9±16,2 |
| | Prolactin +ES | 99,7±9,7 | 172,4±11,3 | 148,1±15,9 |
| | Propanolol+ES | 92,4±9,1 | 167,9±9,9 | 149,9±13,3 |
| | Ionol +ES | 97,9±10,1 | 161,9±12,9 | 139,9±16,1 |
| $V_c$, mm Hg/sec | Control | 4406±247 | 7716±188 | 6422±470 |
| | ES | 3650±239* | 4817±344* | 3650±458** |
| | GHBA + ES | 4040±300 | 7019±197 | 6195±425 |
| | Prolactin + ES | 4320±250 | 7912±177 | 6097±451 |
| | Propanolol + ES | 4100±225 | 6800±191 | 6045±491 |
| | Ionol + ES | 3995±299 | 6742±201 | 5922±488 |
| $V_r$, mm Hg/sec | Control | 2206±146 | 2953±213 | 2763±237 |
| | ES | 1717±185* | 1667±161*** | 1500±122*** |
| | GHBA + ES | 2350±166 | 2900±220 | 2609±240 |
| | Prolactin + ES | 2199±138 | 2830±210 | 2582±240 |
| | Propanolol+ES | 2064±199 | 2790±199 | 2650±214 |
| | Ionol + ES | 2097±187 | 2699±209 | 2507±199 |

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

TABLE 2. Effect of GHBA, Prolactin, Propranolol, and Ionol on Glycogen Concentration in Myocardium of Animals with ES (M±m)

| Experimental conditions (n = 12) | Glycogen concentration, mg/g |
|---|---|
| Control | 5,52±0,26 |
| ES | 2,06±0,05* |
| GHBA + ES | 5,25±0,32 |
| Prolactin + ES | 4,97±0,27 |
| Propanolol + ES | 4,94±0,3 |
| Ionol + ES | 4,49±0,25 |

Legend. *P < 0.001.

aorta for 5 sec they were reduced by more than 30%. Even greater changes were found in the animals of this group after the heart had worked for 25 sec under isometric conditions. In animals subjected to ES the values of $P_d$, $V_c$, $V_r$, and IFS were lower than in the control by 40.5, 43.1, 45.7, and 45.9% respectively.

This reduction in the values of parameters of cardiac contractility took place against a background of a sharp decrease in the glycogen concentration in the myocardium, by 2.7 times below the control level.

In view that glycolysis, although supplying the cell with only a very small part of its usable ATP, constitutes a unique and essential component of the mechanism supplying energy for the work of the contractile apparatus of the cardiomyocytes can now be taken as firmly established [9], especially as regards provision for working of the Ca pump during relaxation of the heart muscle [17]. Depression of cardiac contractility, including a decrease in the velocity of relaxation, discovered during ES is thus evidently largely associated with a fall in the myocardial glycogen level – the main substrate for glycolysis in the myocardial cell.

When the possible mechanisms of the stress-induced disturbances of cardiac contractility are assessed, consideration must also be paid to previous evidence that stress induces disturbances of oxidative phosphorylation in mitochondria of the heart muscle [5], focal structural changes in the myocardium of contractural and necrobiotic nature [11], and also the accumulation of calcium in the sarcoplasm of the myocardial cell [14].

Depression of cardiac contractility in ES arises as the result of a complex series of disturbances of the metabolism and structure of heart muscle, in which an important role is played by inhibition of the energy supply for processes of contraction and relaxation of the myocardium, due largely to a decrease in production of glycolytic ATP on account of a fall in the glycogen level and in the rate of its resynthesis [13].

Data given in Tables 1 and 2 on the effect of GHBA, prolactin, propranolol, and ionol on cardiac contractility and on the glycogen content in the myocardium during stress, show that all the substances tested prevent depression of cardiac contractility and the fall in the myocardial glycogen concentration.

Analysis of the effectiveness of action of the various preparations shows that sodium hydroxybutyrate, a central inhibitor capable of depressing stress-induced activation of the adrenergic and pituitary systems [7], prolactin, which can increase the nonspecific resistance of the body [16], and limit excitation of the adrenergic and pituitary-adrenal systems during exposure to stress [6], the β-blocker propranolol, which prevents the action of high concentrations of catecholamines [2], and the antioxidant ionol, which blocks excessive activation of LPO in the heart [8] and reduces the development of the stress reaction, all act in roughly the same way. It was shown previously that these substances prevent stress-induced disturbances of oxidative phosphorylation in the mitochondria of the heart [10] and structural damage to myocardiocytes [6, 7, 12].

Consequently, irrespective of their point of application on the various links of the pathogenetic chain of stress-induced injury to the heart, drugs can prevent disturbances of the metabolism, structure, and function of the heart arising during emotional stress.

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