to stress, but they can also be regarded on their own account as criteria for evaluating this reaction at the level of nerve-tissue relations.

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DISTURBED EXTENSIBILITY AND DEPRESSION OF CONTRACTILITY OF THE MYOCARDIUM IN STRESS TREATED WITH URIDINE, A COFACTOR IN GLYCOGEN RESYNTHESIS

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UDC 616.127-009.12-02:613.863]-085.31:547.963.3]

KEY WORDS: stress; myocardium; glycogen; uridine; extensibility.

It has recently been shown that the myocardium of rats exposed to stress differs from that of control animals by a marked decrease in its extensibility.

This phenomenon is accompanied by depression of the tension capable of being developed by the myocardium and, as a first approximation, it was explained by a disturbance of relaxation, as a result of which an excess of actomyosin bridges remained in the myofibrils of the "stressor" myocardium in diastole [1, 3, 5]. Analysis of this phenomenon must pay heed to the fact that under the influence of stress disturbances of glycolysis regularly develop in the myocardium, where they are expressed as a fall in the concentration and inhibition of resynthesis of glycogen [4]. Since glycolysis plays an important role in the functioning of the membrane Ca^{++} pump, which is responsible for relaxation [2, 6], it seemed probable that it was disturbances of ATP regeneration in the glycolysis system that could be an important link in the chain leading to disturbances of extensibility and depression of contractility during stress. In that case correction of the disturbances arising in the glycolysis system by the creation of an excessive concentration of substrate or administration of cofactors of glycogen resynthesis could abolish the stressor disturbances of extensibility and the depression of contractility of the myocardium. To test this hypothesis, the effect of high concentrations of glucose and the glycogen resynthesis cofactor uridine on extensibility and contractility of isolated atria from animals exposed to stress was studied.

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(Presented by Academician of the Academy of Medical Sciences of the USSR P. D. Gorizontov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 96, No. 11, pp. 11-13, November, 1983. Original article submitted February 1, 1983.

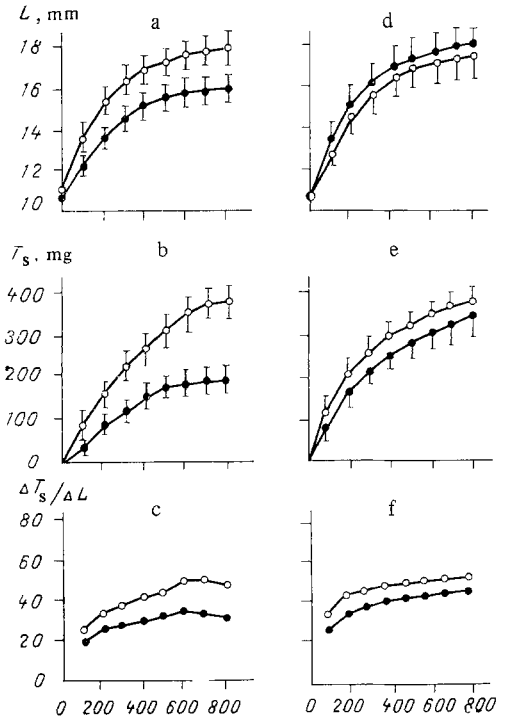

Fig. 1

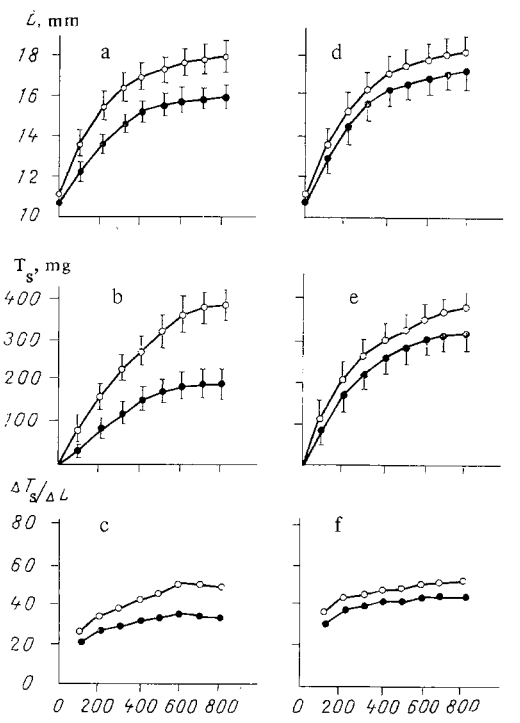

Fig. 2

Fig. 1. Effect of glucose concentration in the external solution on extensibility (a, d), developed systolic tension (b, e), and efficiency of Starling mechanism (c, f) in the atria of rats exposed to stress. a, b, c) With normal glucose concentration (5.5 mM); d, e, f) with raised glucose concentration (22 mM). Abscissa, resting tension of atrium, T_r (in mg); ordinate: a, d) length of atrium (in mm); b, e) developed systolic tension (in mg); c, f) ratio $\Delta T_s/\Delta L$ (in mg/mm). Empty circles — control, filled circles — stress.

Fig. 2. Disturbance of extensibility of myocardium (a), of developed systolic tension (b), and of efficiency of Starling mechanism (c) of atria in rats exposed to stress, and abolition of this phenomenon by addition of uridine to external solution in concentration of 2×10^{-4} M (d, e, f). Legend as to Fig. 1.

EXPERIMENTAL METHOD

Experiments were carried out on male Wistar rats weighing 180-220 g. Emotional-painful stress (EPS) was produced in the form of an anxiety neurosis by Desiderato's method [7]. After the end of EPS the animals were decapitated, the right atrium was removed and placed in a thermostatically controlled bath (34°C) with oxygenated Krebs–Henseleit solution (95% O_2, 5% CO_2, pH 7.4), the base of the atrium was fixed rigidly, and the apex of the auricle was attached to the F-50 myograph of a Physiograph DMP-4B ink-writing apparatus (from Narco Biosystems, USA). In each experiment parallel recordings were made of the function of one control and one "stressor" atrium. Altogether 36 of these paired experiments were carried out and divided into three series. In series I the atrium contracted in ordinary Krebs–Henseleit solution, in series II the glucose concentration in the medium was raised from 5.5 to 22 mM, i.e., fourfold, and finally, in series III uridine (from Reanal, Hungary) was added to the medium in a concentration of 2×10^{-4} M. The weight and the initial length of the right atrium of rats exposed to stress did not differ significantly from those of the control rats. After being placed in the incubation medium the atrium contracted spontaneously for 40-50 min, after which it was gradually stretched by means of a weight to the length L_{max} at which it developed maximal systolic tension. Changes in length were recorded by means of a micrometer for every 100 mg increase in the load. The atrium contracted under isometric conditions. The following physiological parameters were determined: 1) extensibility of the myocardium, estimated from the increase in length of the atrium (ΔL) during stretching by the applied load — resting tension (T_r); 2) the developed systolic tension (T_s), characterizing the force

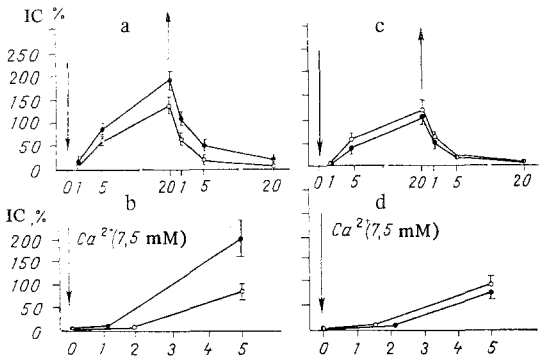

Fig. 3. Increase in hypoxic (a) and hypercalcium (b) contracture of atrial myocardium of rats exposed to stress and abolition of this phenomenon by addition of uridine to external solution in concentration of 2×10^{-4} M (c, d). From top to bottom: beginning of action of hypoxia (a, c) and excess of Ca^{++} (b, d): arrow pointing upward indicates beginning of reoxygenation (a, c). Abscissa: a, c) time of action of hypoxia and reoxygenation (in min), b, d) time of action of excess Ca^{++} (in min); ordinate, IC (in %). Empty circles — control, filled — stress.

of myocardial contraction and increasing in accordance with Starling's law with stretching of the atrium; 3) the efficiency of the Starling mechanism, i.e., the ratio of the increase in T_s (ΔT_s) to the increase in length of the atrium (ΔL), i.e., $\Delta T_s/\Delta L$. This parameter, in the writers' view, is important for it directly answers the question of the increase in the force of myocardial contraction per unit increase of length by which the myocardium reacts during stretching; 4) dependence of developed tension on length of atrium, i.e., the Starling curve, plotted by expressing length as a percentage of L_{max} and T_s in milligrams. The resistance of the myocardium to hypoxia and to excess Ca^{++} was estimated by the change in the index of contracture (IC) developed by these factors, equal to the ratio of the increase in resting tension (ΔT_r) arising during contracture to the value of T_s before the beginning of action of the factor inducing contracture (T_{init}):

$$IC = \frac{\Delta T_r \times 100}{T_{init}} \%$$

EXPERIMENTAL RESULTS

It will be clear from Figs. 1 and 2 that after exposure to stress the extensibility of the myocardium was definitely disturbed: the atrial muscle fibers became more rigid, and when stretched by a load of between 100 and 800 mg the increase in their length was 33-25% less than in the control (Fig. 1a). This means *a priori* that during stress, because of incomplete stretching, the increase in length of the sarcomeres in diastole ought to be impaired, i.e., the Starling curve should flatten out on a plateau. With an equal load on the heart, i.e., an equal force stretching the myocardium in diastole, this itself ought to lead to a marked decrease in the developed tension. The curves in Fig. 1b show that if the force applied to stretch the atrium was equal, the developed tension was significantly reduced in animals exposed to stress. At maximal resting tension, i.e., definitely on the plateau of the Starling curve, it was reduced by almost half. Further analysis shows that such a considerable post-stress decrease in developed tension was due not only to a disturbance of myocardial extensibility, but also to certain other causes. In fact, it will be clear from Fig. 1c that the value of the developed tension per unit increase in length of the muscle, i.e., the efficiency of the Starling mechanism, was sharply reduced in the heart muscle of animals exposed to stress. In other words, even if the myocardium of stressed animals can stretch, it responds by a smaller increase in developed tension than in the control.

The curves in Fig. 1, d-f reflect the main result of this series of experiments and show that with a fourfold increase in the glucose concentration all disturbances of extensibility and contractility caused by stress disappear: the difference between the atria of the control

and stressed animals was not significant. Figure 2 shows that uridine has an exactly similar action, abolishing the stress-induced disturbances of extensibility and contractility just as effectively as an increase in glucose concentration. The effect of uridine on the magnitude of hypoxic and hypercalcium atrial contracture of the control and stressed animals is illustrated in Fig. 3. Under the influence of hypoxia (Fig. 3a) and an increase in the Ca^{++} concentration (Fig. 3b) the resting tension was considerably increased and contracture developed, and was significantly greater in the stressed atrium than in the control; in the presence of uridine the contracture was much weaker — the resistance of relaxation of the myocardium to hypoxia and to excess of Ca^{++} increased significantly under the influence of this cofactor of glycogen resynthesis. A phenomenon paradoxical at first was observed: the protective effect of uridine was greater on the atrium of animals exposed to stress than in the control. Hypoxic contracture was actually reduced by uridine in the atrium after stress by about half, whereas hypercalcium contracture was reduced by almost two thirds. The effect in the control was much less. As a result, both types of contracture appeared to be more marked for the control animals than for the stressed animals in the presence of uridine. This potentiation of the effect of uridine by previous exposure to stress may perhaps be explained on the grounds that the stress-induced glycogen deficiency increases the sensitivity of the glycogen–synthetase system to excess of cofactor. An increase in penetration of the nucleoside through the stress-damaged cardiomyocyte membranes may also play an important role. What is important in the context of this description is that the cofactor of glycogen resynthesis can, in principle, abolish not only poststress disturbances of extensibility and the depression of contractility of the myocardium, but can restore resistance of the heart to hypoxia and to excess of Ca^{++}, in whose transport glycolysis plays an important role, or may actually increase them above the control level.

These facts are evidence that disturbances arising under the influence of stress in the glycolysis system play an important role in the development of depression of the contractile function of the myocardium and of its resistance to hypoxia and to excess of Ca^{++}. Uridine, the cofactor of glycolysis, abolishes these disturbances.

It has now been proved that stress, which always accompanied myocardial infarction, causes substantial disturbances of extensibility and depression of contractility of nonischemic regions of the heart in a manner quite similar to that described above. The results thus open up prospects for the use of uridine to correct disturbances of contractility of nonischemic regions of the heart in myocardial infarction.

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