hypertension in rats and leads to an increase in the Na^+ excretion of these animals compared with its corresponding value in rats with an intact sympathetic innervation of the kidney and receiving DOCA and NaCl [13].

LITERATURE CITED

1. M. M. Borisov, A. Mukhammedov, I. M. Rodionov, et al., Ontogenez, No. 3, 311 (1977).
2. V. G. Pinelis, A. V. Kozlov, T. P. Vakulina, et al., Byull. Éksp. Biol. Med., No. 10, 31 (1982).
3. V. S. Poleshchuk and L. I. Nebol'sina, in: Proceedings of the 9th World Congress of Cardiologists [in Russian], Vol. 2, Moscow (1982), p. 271.
4. M. V. Chernov, I. M. Rodionov, and I. A. Sokolova, Kardiologiya, No. 9, 101 (1980).
5. J. Axelrod, Clin. Sci., 51, Suppl. No. 3, 415 (1976).
6. E. Ayitey-Smith and D. R. Varma, Br. J. Pharmacol., 40, 175 (1970).
7. L. J. Beilin, D. N. Wade, A. J. Honour, et al., Clin. Sci., 39, 793 (1970).
8. K. N. Berecek, M. Stocker, and F. Gross, Circ. Res., 46, 619 (1980).
9. J. de Champlain and M. R. Van Amerigen, Circ. Res., 31, 617 (1972).
10. B. Folkow, M. Hallback, Y. Lundgren, et al., Acta Physiol. Scand., 80, 93 (1970).
11. A. C. Guyton, in: Arterial Pressure and Hypertension, Philadelphia (1980), pp. 1-513.
12. A. W. Jones, Hypertension, 3, 631 (1981).
13. R. E. Katholi, A. J. Neftilan, and S. Oparil, Hypertension, 2, 266 (1980).
14. A. P. Provoost and W. De Jong, Clin. Exp. Hypertension, 1, 177 (1978).
15. W. Rascher, A. Schömig, R. Dietz, et al., Eur. J. Pharmacol., 75, 255 (1981).

PREVENTION OF DISTURBANCES OF CARDIAC CONTRACTILITY DURING LONG-TERM STRESS BY PRELIMINARY ADAPTATION TO SHORT-TERM STRESS

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As a result of prolonged exposure to stress, damage to heart muscle may arise under the influence of an excess of catecholamines [3, 11], its contractile function may be disturbed, and its resistance to hypoxia and to excess of calcium may be lowered [4, 6]. When the ways of preventing stress injuries of this kind are studied it must be remembered that during repeated exposure to stress of limited duration and, in particular, during repeated immobilization of animals, the response to stress gradually diminishes: Excitation of the adrenergic and pituitary–adrenal systems becomes weaker [10].

The object of the present investigation was to study the possibility of using adaptation of animals to repeated short-term stress in order to prevent disturbances of cardiac contractility during long-term immobilization stress.

EXPERIMENTAL METHOD

Experiments were carried out on male Wistar rats weighing 160-240 g. The animals were divided into four groups: 1) control, 2) long-term immobilization stress, 3) adaptation to repeated short-term immobilization stress, 4) adaptation to short-term immobilization stress

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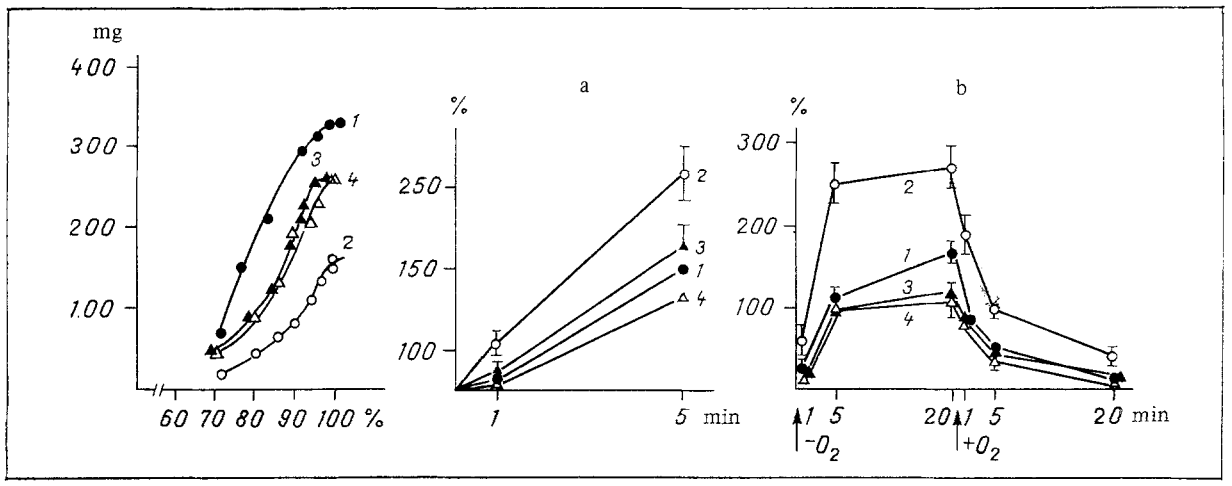

Fig. 1 Fig. 2

Fig. 1. Effect of preliminary adaptation to short-term stress on development of depression of the Starling curve in animals exposed to long-term stress. Abscissa, length of atrium (in percent of l_{max}, taken as 100); ordinate, developed tension (in mg). Here and in Fig. 2: 1) control, 2) immobilization stress, 3) adaptation to short-term stress, 4) adaptation + immobilization stress.

Fig. 2. Effect of preliminary adaptation to short-term stress on development of hypercalcium (a) and hypoxic (b) contracture of heart muscle in animals exposed to long-term stress. Abscissa, time of experiment (in min); ordinate, index of contracture (in percent).

+ long-term immobilization stress. Each group contained from 8 to 11 animals. Long-term immobilization stress was evoked by fixation of the animals lying on their back for 6 h; all the limbs under the head were secured. Adaptation to short-term stress was carried out by similar fixation of the animals, but on the first day the rats were tied for only 15 min, on the second day for 30 min, on the third day for 45 min, and on the next ten days for 1 h.

With this procedure, long-term immobilization stress regularly gave rise to the development of ulcers of the gastric mucosa; the mean length of the ulcers per stomach was 7.7 mm. Repeated short-term immobilization never caused the development of gastric ulcers, but led to a decrease in the animals' body weight by 20%. Long-term immobilization stress after preliminary adaptation to short-term stress gave rise to less marked ulcers of the gastric mucosa: The mean length of the ulcers was 5.2 mm. The immobilization procedures used caused no changes in weight of the different parts of the heart, notably the right atrium, which was used as the physiological test object. The weight of the atria in all series was 22-23 mg.

The contractility of the right atrial myocardium was assessed by the method described previously [1]. Extensibility of the atrium was judged from the increase in length (Δl) during gradual stretching by loads of 100 mg up to maximal length. Myocardial contractility was judged from the maximal developed tension (T_d) during isometric contraction, and also from the length versus developed tension curve (Starling curve).

To assess the reaction of the atrium to excess of calcium, the calcium concentration in the working solution was increased threefold for 5 min, and to assess the reaction of the atrium to hypoxia, oxygenated working solution was replaced by nonoxygenated for 20 min. The reaction to both factors was assessed as the index of contracture (IC), developing under the influence of excess of calcium or hypoxia. IC is given by the ratio of tension during contracture to the developed tension before the beginning of action of the factor inducing contracture.

The adrenoreactivity of the atrium also was studied. This was determined by the increase in developed tension in response to increasing concentrations of noradrenalin (NA) in the working solution: 3×10^{-8}, 1×10^{-7}, 1×10^{-6}, and 3×10^{-6} g/ml. Adrenoreactivity was estimated quantitatively as the reciprocal of the NA concentration inducing a reaction equal to half the maximal strength [3].

TABLE 1. Effect of Preliminary Adaptation to Repeated Stress on Disturbances of Contractile Function Evoked by Long-Term Stress

Experimental conditions	Load, mg	Changes in length (Δl), mm	Developed tension (T_d), mg
Control (n=9)	200	4,1±0,20	151,4±12,0
	400	5,7±0,25	251,9±22,50
	600	6,6±0,20	317,1±32,40
	800	7,0±0,20	335,0±35,0
Stress (n=8)	200	2,79±0,26***	40,0±6,83***
	400	4,29±0,38*	85,0±15,0***
	600	5,05±0,23*	135,0±18,21***
	800	5,17±0,23*	123,3±8,8***
Adaptation (n=11)	200	3,33±0,21*	82,8±9,41**
	400	4,83±0,28*	174,5±12,91**
	600	5,67±0,33*	223,0±41,48
	800	6,30±0,33	256,0±47,39
Adaptation + stress (n=11)	200	3,64±0,12	80,0±6,17
	400	5,08±0,21	177,1±16,57
	600	5,94±0,25	277,1±19,61
	800	6,37±0,24	257,5±21,75

Legend. n) Number of animals in group. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

EXPERIMENTAL RESULTS

The results given in Table 1 show that long-term immobilization stress, like the emotional-painful stress in previous investigations [1, 9], caused a marked decrease in extensibility of the myocardium with the development of poststress rigidity, and at the same time it led to depression of the developed tension and efficiency of realization of the Starling mechanism. These parameters of contractile function were lowered by 50-60%. The Starling curve was correspondingly depressed (Fig. 1). As Table 1 and Fig. 1 show, adaptation to short-term stress itself gave rise to a small decrease in parameters of atrial contractile function and to moderate depression of the Starling curve. Meanwhile long-term stress does not lead to a decrease in extensibility, the principal parameters of contractile function, or significant depression of the Starling curve in adapted animals.

The dynamics of atrial contracture developing in response to an excess of calcium and to hypoxia is illustrated in Fig. 2. Long-term immobilization stress, like the emotional-painful stress in investigations published previously [1], substantially reduced the resistance of the myocardium to excess of calcium and hypoxia. As a result the index of contracture in these tests was considerably higher in animals exposed to immobilization stress than in the control. Adaptation to short-term stress had no significant effect on the degree of contracture, but at the same time it completely prevented the potentiating effect of stress on the development of calcium and hypoxic contracture. Moreover, in adapted animals exposed to stress the contracture was weaker than in the control.

Determination of the adrenoreactivity of the atria of the adapted rats showed that after adaptation, adrenoreactivity (0.54 ± 0.04) was 1.6 times less ($P < 0.02$) than that of the control atria (0.87 ± 0.11).

On the whole the results are evidence that preliminary adaptation to short-term stress reduces the adrenoreactivity of the myocardium and prevents the combination of disturbances of contractile function of the heart muscle typical of stress, namely poststress rigidity, depression of the developed tension, and a decrease in resistance of the myocardium to excess of calcium and to hypoxia.

When the probable mechanism of this phenomenon is contemplated two factors must be borne in mind. The first is that during exposure to stress, activation of the inhibitory mechanisms of the brain has been demonstrated: the GABA-ergic inhibitory system [6], the enkephalin system [2], etc. During repeated exposure to stress and, correspondingly, repeated activation of these systems, their functional power may increase. This, in turn, may lead to reduction of the stress reaction, and it may thus prevent adrenergic injuries to the heart muscle during long-term exposure to stress.

The second hypothesis is that the action of an excess of catecholamines on the heart during stress is accompanied regularly by activation of the cellular regulatory mechanisms which limit the adrenergic effect, namely the prostaglandin system [10, 13, 14], the system responsible for adenosine production [8, 9], and the antioxidant systems [4]. A gradual increase in the activity of these systems during repeated exposure to short-term stress could be the cause of the reduction of adrenoreactivity discovered in the present experiments, and which evidently plays a role in the limitation of the damaging effect of catecholamines during long-term stress.

A comparative experimental analysis of the role of central and cellular mechanisms leading to an increase in resistance of the body during adaptation to stress would appear to be very promising.

LITERATURE CITED

1. E. Ya. Vorontsova, M. G. Pshennikova, and F. Z. Meerson, Kardiologiya, No. 11, 68 (1982).
2. G. A. Kulkybaev and D. N. Kareeva, Zdravookrh. Kazakhstana, No. 6, 37 (1980).
3. B. N. Manukhin, Physiology of Adrenoreceptors [in Russian], Moscow (1968).
4. F. Z. Meerson, Adaptation, Stress, and Prophylaxis [in Russian], Moscow (1981).
5. F. Z. Meerson, Usp. Fiziol. Nauk, No. 2, 7 (1983).
6. F. Z. Meerson, R. I. Lifshits, and V. I. Pavlova, Vopr. Med. Khim., No. 1, 35 (1981).
7. M. G. Pshennikova, E. Ya. Vorontsova, and F. Z. Meerson, Byull. Éksp. Biol. Med., No. 12, 15 (1982).
8. R. M. Berne, Circ. Res., 47, 807 (1980).
9. F. G. Dobson, Fed. Proc., 39, 1173 (1980).
10. W. Hseuh, P. C. Isakson, and P. Needleman, Prostaglandins, 13, 1073 (1977).
11. K. L. Keim and E. B. Sigg, Pharmacol. Biochem. Behav., 4, 289 (1976).
12. H. Selye, The Pluricausal Cardiopathies, Springfield (1961).
13. A. Wennmann, Acta Biol. Med. Ger., 35, 1127 (1976).
14. A. Wennmann, Prostaglandins, 15, 113 (1978).