LITERATURE CITED

1. E. D. Gol'dberg, A. M. Dygai, I. V. Bogdashin, et al., Patol. Fiziol. Éksp. Ter., No. 4, 29 (1988).
2. E. D. Gol'dberg, A. M. Dygai, A. Yu. Zaritskii, et al., Byull. Éksp. Biol. Med., No. 12, 710 (1989).
3. E. D. Gol'dberg, A. M. Dygai, V. P. Shakhov, et al., Patol. Fiziol. Éksp. Ter., No. 5, 32 (1988).
4. P. D. Gorizontov, O. I. Belousova, and M. I. Fedotova, Stress and the Blood System [in Russian], Moscow (1983).
5. A. M. Dygai and V. P. Shakhov, Role of Intercellular Interactions in the Regulation of Hematopoiesis [in Russian], Tomsk University Press, Tomsk (1989).
6. E. V. Kirienkova, "Role of corticosteroids and T lymphocytes in the regulation of medullary hematopoiesis during the stress reaction," Author's Abstract of Dissertation for the Degree of Candidate of Medical Sciences, Tomsk (1987).
7. I. V. Miroshnichenko, N. I. Sharova, A. A. Yarilin, and V. I. Talaev, Immunologiya, No. 3, 35 (1989).
8. V. I. Seledtsov, A. P. Suslov, and B. D. Brondz, Biol. Memb., **4**, No. 12, 1313 (1987).
9. A. I. Cheredeev and L. V. Koval'chuk, Progress in Science and Technology. Series: Immunology [in Russian], Vol. 19, Moscow (1989).
10. I. L. Cnertkov and O. A. Gurevich, The Hematopoietic Stem Cell and Its Microenvironment [in Russian], Moscow (1984).
11. P. Crocker and S. Gordon, J. Exp. Med., **162**, 993 (1985).
12. S. Mizel, Workshops on Macrophage Functions, New York (1979), pp. 407-416.
13. J. Schrader and C. Nossel, Immunol. Rev., **53**, 61 (1980).
14. S. Vogel, S. Douches, E. Kaufman, and R. Neta, J. Immunol., **138**, 2143 (1987).

COMPARISON OF THE EFFECT OF ADAPTATION TO STRESS AND TO HIGH ALTITUDE HYPOXIA ON RESISTANCE OF THE HEART TO REPERFUSION INJURY AFTER TOTAL ISCHEMIA

F. Z. Meerson, I. Yu. Malyshev, and V. I. Vovk

UDC 616.12-005.4-092.9-02:613.863]-092:612.17.014.49.08

KEY WORDS: adaptation; stress; high altitude hypoxia; reperfusion; ischemia; rat myocardium

During repeated exposure to stress or hypoxic situations, adaptation develops, not only increasing the body's resistance to severe stress or acute hypoxia, but also giving rise to a broad spectrum of protective cross-effects, i.e., it protects the body against direct ischemic [4], chemical [14], and cold [11] injuries. So far as the heart is concerned it has been shown that animals adapted to short-term stress or to periodic exposure to high-altitude hypoxia acquire additional resistance to ischemic and reperfusion arrhythmias, reproduced in the whole organism [2, 3]. A common feature of the cardioprotective effects of the two forms of adaptation is that activation of stress-limiting systems plays a role in them: GABA-ergic [4], opioidergic [9], antioxidative [2], prostaglandin [4], etc. The difference between these effects is very clearly exhibited at the heart level, where adaptation to hypoxia has a primary antiischemic effect, i.e., due to adaptive growth of

Research Institute of General Pathology and Pathological Physiology, Academy of Medical Sciences of the USSR, Moscow. (Presented by Academician of the Academy of Medical Sciences of the USSR G. N. Kryzhanovskii.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 112, No. 7, pp. 18-20, July, 1991. Original article submitted September 12, 1990.

 0007-4888/91/0007-0916$12.50

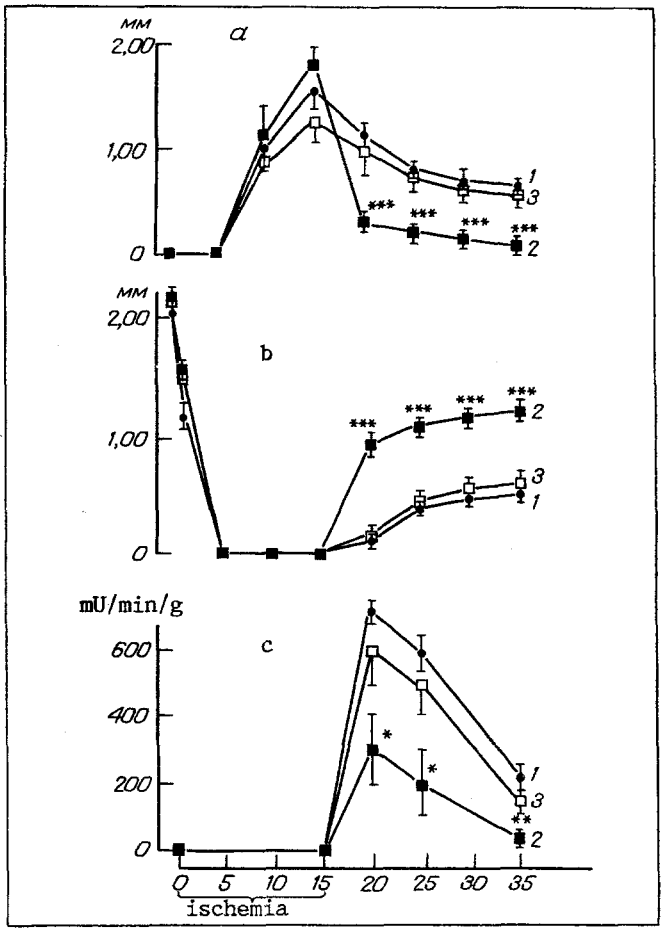

Fig. 1. Effect of adaptation to stress and to high-altitude hypoxia on contracture (a), amplitude of contraction (b), and release of creatine kinase (c) into perfusion fluid of isolated rat heart during total ischemia and subsequent reperfusion. Abscissa, time, in min, after beginning of experiment; 1) control. 2) adaptation to stress, 3) adaptation to hypoxia (seven experiments in each series). Significant differences from control: $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

the coronary blood flow and an increase in the efficiency of the oxygen transport and substrate oxidation systems [13], the zone of primary ischemia is reduced almost by half immediately after ligation of the coronary artery, and the zone of necrosis also is correspondingly reduced [7].

Adaptation to stress, on the other hand, has no antiischemic effect, but whereas the zone of primary ischemia is unchanged, the volume of necrosis, measured 2 days after ligation of the coronary artery, is reduced by more than 40%. In other words, the cardioprotective action of adaptation to hypoxia is mainly vasodilator and antiischemic in nature, whereas adaptation to stress is mainly cytoprotective [7].

The aim of this investigation was to continue comparing the protective effects of adaptation to stress and hypoxia. Preliminary adaptation to both factors, moreover, was used to protect the isolated heart of the adapted animals against total ischemia and subsequent reperfusion, i.e., from the reperfusion paradox, in which growth of coronary collaterals cannot possibly play a role in protection of the heart.

EXPERIMENTAL METHOD

Experiments were carried out on male Wistar rats weighing 250-300 g. Adaptation to stress was carried out in the same way as in previous studies [8, 12], namely by fixing the rats in the supine position on alternate days for 1 h, with a

total of eight immobilizations. Adaptation to hypoxia was induced by daily "ascents" in a pressure chamber, with a gradual increase of "altitude" to 4000 m. The course consisted of 40 exposures to hypoxia lasting 5 h. After the end of adaptation, the control and adapted animals were heparinized (2000 U/kg, intraperitoneally) and anesthetized with pentobarbital (50 mg/kg, intraperitoneally). The heart was then quickly removed and connected to a Langendorff perfusion system. The conditions of perfusion were fully described previously [12]. Mechanical activity of the heart and the electrocardiogram were recorded by means of a TD-112S isotonic transducer and specialized modules of the RM-6000 polygraph ("Nihon Kohden," Japan). The reperfusion paradox was reproduced [10] by restoring the coronary blood flow after 15 min of total ischemia, when the flow was completely absent. Damage to the heart was evaluated on the basis of disturbances of its rhythm, contractile function, and release of creatine kinase (CK) into the perfusion fluid. CK activity was determined spectrophotometrically, using kits from the firm "Labsystems" (Finland). The results were subjected to statistical analysis by Student's test.

EXPERIMENTAL RESULTS

The curves in Fig. 1 show the response of isolated hearts in the control, after adaptation to stress, and to hypoxia, to reperfusion after total ischemia. Ischemia led to marked contracture, which was about the same in the three series compared. The amplitude of contractions before ischemia did not differ in hearts of the control and adapted animals, but 5 min after creation of ischemia it was 0 both in the control and in the two types of adaptation. During reperfusion, the hearts of animals adapted to stress showed sharply increased resistance to injury, whereas those of animals adapted to hypoxia did not differ from the control. The protective effect of adaptation to stress was definitely manifested after 5 min of reperfusion, when the amplitude of contractions of the hearts of the adapted animals was 8.8 times greater than in the control. After reperfusion for 20 min the amplitude of contractions in the control was 0.49 mm and, consequently, this parameter was restored by 22%. During adaptation to stress, the amplitude of contractions at this time was 2.4 times greater than in the control, but the degree of its recovery was 51%. It will also be clear from Fig. 1 that this accelerated postischemic restoration of the amplitude of contractions during adaptation to stress was caused by the more rapid disappearance of contracture. It will also be clear from Fig. 1 that adaptation to hypoxia did not limit contracture or depression of the amplitude of contraction during reperfusion.

The anticontractural effect of adaptation to stress during reperfusion was accompanied by an antiarrhythmic action. For instance, the total duration of tachycardia and ventricular fibrillation, calculated per single heart, was 246 ± 16 sec in the control and 119 ± 12 sec during adaptation to stress ($p < 0.001$). No antiarrhythmic effect was present during adaptation to hypoxia.

Adaptation to stress led to direct protection of the heart against reperfusion damage, with respect to such an important criterion as release of CK into the perfusion fluid. In the control, CK activity in the perfusion fluid after 5 min of reperfusion reached 719 mU/min/mg weight of the heart, compared with 302 mU/min/mg during adaptation to stress. Adaptation to hypoxia did not lead to a decrease in the outflow of CK into the perfusion fluid, i.e., in the modern view, to injury to the sarcolemma [10]. Thus adaptation to stress, unlike adaptation to hypoxia, has a marked membrane protective action and protects the heart unequivocally against the reperfusion paradox — the most powerful damaging factor in cardiology.

When the powerful cardioprotective effect of adaptation to stress is evaluated, it must be recalled that such adaptation leads to an increase in resistance of the isolated heart not only to the reperfusion paradox, but also to toxic concentrations of catecholamines [5] or Ca^{2+} [12], and also increases the resistance of the main organelles of the myocardium, namely elements of the sarcoplasmic reticulum [12], mitochondria [7], and nuclei [8], to proteolysis. This combination of changes is described as the phenomenon of adaptive stabilization of structures (PASS) [6] and it is the most probable basis for the cardioprotective effect of adaptation to stress. The protective effect of adaptation to hypoxia is evidently unconnected with the development of any significant degree of PASS, but as was shown above, is due mainly to growth of the coronary flow and to an increase in the efficiency of the oxygen transport and oxidation substrate system. It will be evident that the protective effect of these mechanisms plays a positive role in local ischemia [1], but it cannot be realized in total ischemia of the heart. The protective effect of adaptation to hypoxia was correspondingly absent in the experiments described above.

The profound differences in the mechanism of the cardioprotective effect of the two forms of adaptation examined above suggests that their combined use could prove to be a very effective factor in protection of the heart.

LITERATURE CITED

1. V. I. Vovk, Abstracts of Proceedings of the 4th All-Union Congress of Pathophysiologists [in Russian], Vol. 1, Moscow (1989), p. 480.
2. F. Z. Meerson, M. G. Pshennikova, T. G. Sazontova, and L. M. Belkina, Vestn. Akad. Med. Nauk SSSR, No. 6, 47 (1987).
3. F. Z. Meerson, E. E. Ustinova, E. Kh. Orlova, et al., Fiziol. Zh. (Kiev), **34**, No. 4, 71 (1988).
4. F. Z. Meerson and M. G. Pshennikova, Adaptation to Stress Situations and Physical Exertion [in Russian], Moscow (1988).
5. I. Yu. Malyshev, Byull. Éksp. Biol. Med., No. 4, 411 (1989).
6. F. Z. Meerson, Kardiologiya, No. 3, 6 (1990).
7. F. Z. Meerson, Protection of the Heart Against Stress and Ischemia [in Russian], Moscow (1991).
8. F. Z. Meerson and I. Yu. Malyshev, Byull. Éksp. Biol. Med., No. 5 (1991).
9. M. G. Pshennikova, Patol. Fiziol., No. 3, 85 (1987).
10. D. J. Hearse, J. E. Baker, and S. M. Humphrey, J. Molec. Cell. Cardiol., **12**, No. 7, 733 (1980).
11. A. Kuroshima, C. Habara, and A. Vehara, Pflüg. Arch., **402**, 402 (1984).
12. F. Z. Meerson, I. Yu. Malyshev, and T. G. Sazontova, Basic Res. Cardiol., **85**, No. 1, 96 (1990).
13. D. V. Tappan, B. B. Reynafarje, V. H. Potter, et al., Am. J. Physiol., **190**, 93 (1957).
14. J. Wallace and M. Cohen, Am. J. Physiol., **247**, 6127 (1984).

ANTIARRHYTHMIC EFFECT OF ANTIBODIES TO DIGOXIN IN EXPERIMENTAL MYOCARDIAL INFARCTION (THE ARRHYTHMOGENIC ACTION OF ENDOGENOUS DIGOXINLIKE FACTOR)

A. Ya. Bagrov, M. M. Veveris, I. E. Ganelina, K. A. Nikiforova, V. L. Osipov, N. I. Rukoyatkina, and P. Stolba

UDC 616.12-005.4-036.11-06

KEY WORDS: endogenous digoxinlike factor; myocardial ischemia; arrhythmias

The blood and several tissues of man and animals contain a substance (or substances) possessing immunoreactivity and biological properties similar to those of digitalis glycosides, and which has been called endogenous digoxinlike factor (EDLF) [6, 10]. The chemical structure of EDLF has not yet been discovered but it has been shown that, since it possesses natriuretic activity and inhibits active sodium transport through the plasma membrane in different kinds of tissues, this substance participates in the regulation of water and mineral metabolism and is involved in the pathogenesis of arterial hypertension [14]. One proof of the latter hypothesis has been obtained in experiments during which administration of antidigoxin serum (ADS), which binds EDLF, caused the blood pressure (BP) to fall in rats with certain forms of experimental hypertension [15]. Digitalis glycosides are known to give rise to serious disturbances of the cardiac rhythm such as

I. N. Dzhanelidze Leningrad Emergency Aid Research Institute. I. M. Sechenov Institute of Evolutionary Physiology and Biochemistry, Academy of Sciences of the USSR. I. P. Pavlov Institute of Physiology, Academy of Sciences of the USSR, Leningrad. Institute of Organic Synthesis, Academy of Sciences of the Latvian SSR, Riga. Institute of Endocrinology, Prague, Czechoslovakia. (Presented by Academician of the Academy of Medical Sciences of the USSR A. I. Vorob'ev.)

Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 112, No. 7, pp. 20-22, July, 1991. Original article submitted February 16, 1989.