Effect of Adaptation to Physical Exercise on α-Adrenoceptor Reactions of Isolated Resistance Artery during Acute Experimental Myocardial Infarction

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The contractile reactions of the caudal artery mediated by α-adrenoceptors do not significantly differ during experimental myocardial infarction in nonadapted rats and rats adapted to graded physical exercise (swimming). In nonadapted rats, experimental myocardial infarction produces a drastic inhibition of the contractile responses in comparison with nonadapted intact rats, which is related to desensitization of α-adrenoceptors. In adapted rats the contractile reactions markedly increased during myocardial infarction due to high sensitivity and density of α-adrenoceptors. Therefore, adaptation mobilizes the reserve capacities to normalize blood pressure during experimental myocardial infarction.

Key Words: *α-adrenoceptors, experimental myocardial infarction; resistance artery; adaptation to physical exercise*

Adaptation to physical exercise has been a long-standing and actual problem in physiology. Advantages of a trained organism and, in particular, enhanced resistance to damaging and adverse factors are well known. Adaptation to physical exercise can be preventive and therapeutic means, for example in myocardial infarction. There is evidence that the drop in blood pressure (BP) during myocardial infarction is determined by both decreased cardiac output and altered reactivity of resistance vessels [9]. Preadaptation to physical exercise greatly restricts acute hypotension provoked by myocardial infarction [7]. However, the mechanisms involved in this protective effect of adaptation at the vascular receptor level are not clear.

In the present study we compare functional state of α-adrenoceptor apparatus of a resistance artery during experimental myocardial infarction (EMI) in rats adapted and not adapted to graded physical exercise.

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MATERIALS AND METHODS

Experiments were performed on male Wistar rats weighing 250-300 g. Adaptation consisted of 30 sessions of forced swimming at water temperature of 32°C. The duration of the first session was 15 min, and duration of each following session increased by 5 min up to the final duration of 60 min.

EMI was produced according to Selye by ligating the left coronary artery [11]. The rats were decapitated 3 h postinfarction.

BP on the tail artery was measured in alert rats by noninvasive method using a DMP-4F Physiograph (Narco Bio-Systems).

Arterial segment (8 mm) was cut from the proximal part of the caudal artery, cannulated at both ends, and placed into a perfusion chamber. The vessel bathed in physiological saline (37°C) was perfused with Krebs—Henseleit solution supplied by a peristaltic pump (LKB) at a rate of 2 ml/min. Vascular reaction was assessed by changes in the perfusion pressure measured with a pressure transducer (Statham).

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Electrical stimulation of nerve terminals in the vascular wall was performed with a electrode couple. One electrode was a metal cannula inserted into the vessel, while another electrode was delivered outside the vessel. Stimulation was performed with rectangular pulses of alternating polarity (0.1 msec duration, 50 V amplitude, 2, 4, 6, 8, and 10 Hz repetition rate). The following vasoactive chemicals (Sigma) were added to the perfusion solution: nonselective adrenoceptor agonist norepinephrine (3×10^{-7}, 5×10^{-7}, and 10^{-6} g/ml), α_1-adrenoceptor agonist phenylephrine (8×10^{-7}, 10^{-6}, and 5×10^{-6} g/ml), and α_2-adrenoceptor agonist clonidine (5×10^{-6}, 10^{-5}, 5×10^{-5} g/ml).

Functional state of adrenoceptors was evaluated by ED_{50} and B_{max} calculated using LIGAND software. The results were statistically analyzed using Student's *t* test.

RESULTS

Contractile reactions to a non-selective adrenoceptor agonist norepinephrine in the caudal arteries isolated from nonadapted rats and from the rats adapted to physical exercise were similar (Fig. 1, *a*). EMI drastically inhibited the contractile response in nonadapted rats in comparison with that in the intact nonadapted rats and greatly enhanced it in the rats adapted to physical exercise.

Similar changes were observed in experiments with electrical stimulation and application of α_1-adrenoceptor agonist phenylephrine and α_2-adrenoceptor agonist clonidine (Figure 1, *b-d*). Table 1 shows that ED_{50} increased after EMI, but decreased pronouncedly in rats adapted to physical exercise and in adapted rats subjected to EMI. Distribution density of α-adrenoceptor (indirectly indicated by B_{max}) significantly increased in adapted rats. EMI does not affect distribution density of α-adrenoceptors in both intact and adapted rats.

Therefore, EMI considerably decreases the α-adrenoceptive contractile responses of resistance vessels in rats. This decrease is probably related to desensitization of α-adrenoceptors. In rats adapted to physical exercise, EMI drastically enhances responsiveness of the resistance artery due to an increase in sensitivity and density of α-adrenoceptors.

Our findings generally agree with the data of other authors, who observed reduced sensitivity of α-adrenoceptors in blood vessels after myocardial infarction [12].

Although the effect of receptor desensitization is known for a long time, the mechanisms underlying this effect are not clear. Since stress component greatly contributes to vascular tone perturbations during myocardial infarction [1], one of these mechanisms could be triggered by a drastic increase in blood catecholamine concentration. This increase can activate free-radical oxidation and disturb lipid microenvironment of the receptors thus altering signal transduction from receptors to intracellular messengers [5]. Adaptation to physical exercise restricts this stress reaction and can prevent these disturbances [3]. In addition, adaptation greatly enhances capacity of the endogenous antioxidant systems and correspondingly restricts free-radical damage to membranes [6].

Another possible mechanism of decreased vascular responsiveness to constrictor stimuli after acute myocardial infarction is hyperproduction of NO, potent vasodilator both in the whole organism and in the vascular wall [13]. NO produces a strong inhibitory effect on adrenergic transduction by inhibiting the release of neurotransmitters [4,10]. Preliminary stimulation of the NO-synthesizing systems, which is characteristic of adaptation to physical exercise [2], efficiently downregulates the pathological hyperproduction of NO and protects the vessels from its damaging effect [7].

Irrespective to what mechanism plays the main role in the protective effect of adaptation to physical exercise, the efficiency of such adaptation shown here on isolated vessels is also corroborated by the data on BP shifts in alert rats (Table 2). In fact, the postinfarction decrease of BP in adapted rats was significantly less pronounced than in nonadapted rats.

The decreased sensitivity of vascular adrenoceptors in acute phase of myocardial infarction plays a major role in the well-known clinical phenomenon of vascular nonresponsiveness to constrictor stimuli,

TABLE 1. Effect of Phenylephrine on Dissociation Constant (K_d) and Maximum Contractile Reaction (B_{max}) of Isolated Caudal Artery (*M±m*)

Experimental series	K_d, M	B_{max}, mm Hg
Control	$8.4\pm0.9\times10^{-6}$	113.8±15.0
Myocardial infarction	$13.8\pm1.3\times10^{-6}$*	101.4±20.3
Adaptation to physical exercise	$2.15\pm0.2\times10^{-6}$*+	155.4±18.1*
Myocardial infarction after adaptation to physical exercise	$3.3\pm0.6\times10^{-6}$*+	156.8±21.0*

Note. Here and in Table 2: $p<0.05$ *compared to the control and **compared to myocardial infarction.

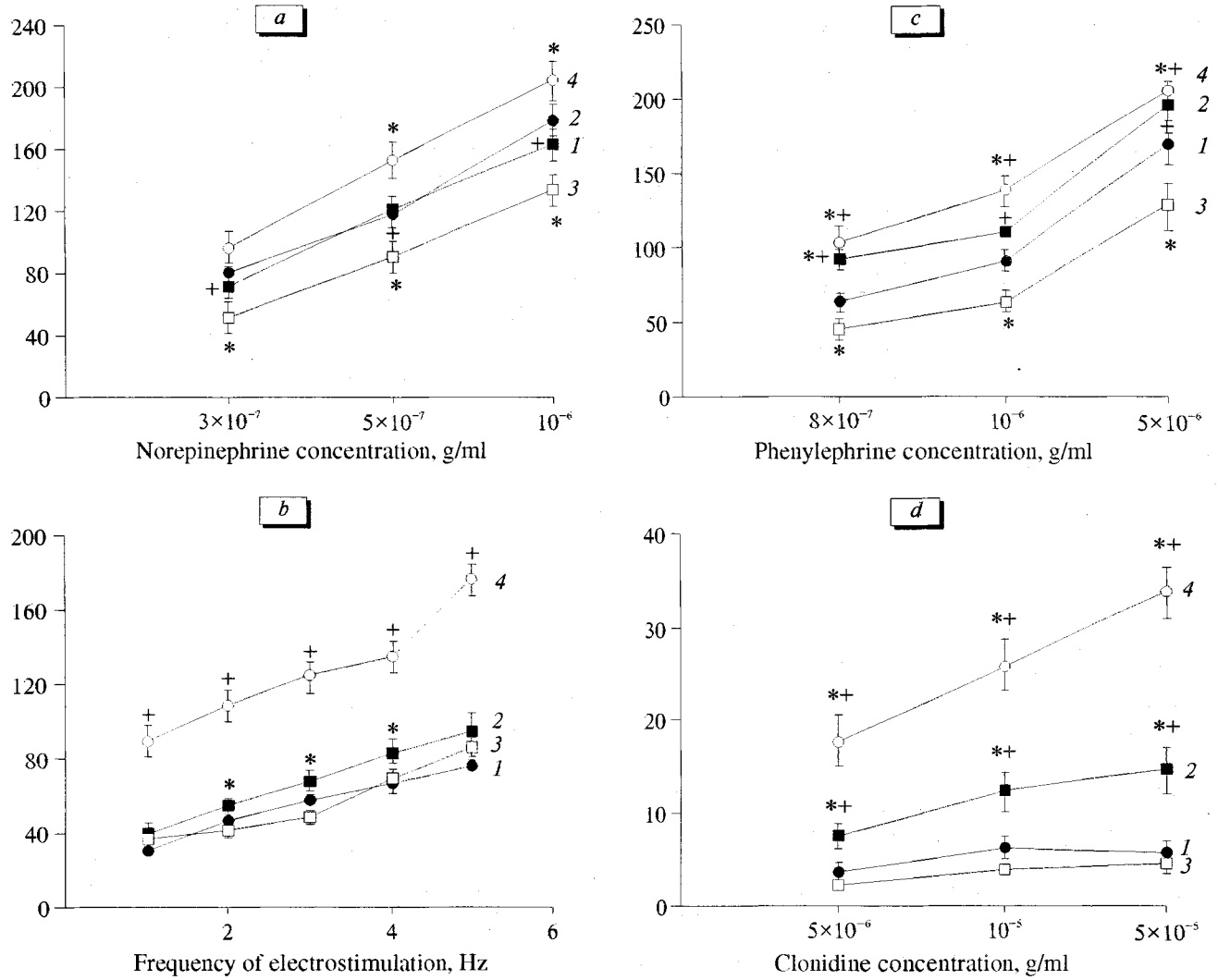

Fig. 1. Effects of norepinephrine (*a*), electrical stimulation (*b*), phenylephrine (*c*), and clonidine (*d*) on contraction of isolated caudal artery. Ordinate: perfusion pressure, mm Hg. *1*) intact control, *2*) adaptation to physical exercise, *3*) experimental myocardial infarction (EMI), *4*) adaptation to physical exercise+EMI. $p<0.05$: *compared to intact control, **compared to EMI.

which can result in a fatal outcome due to cardiogenic shock [9]. In this work we showed that in adapted rats resistance vessels preserve their capacity to respond to adrenergic stimuli, and are characterized by enhanced sensitivity and high density of adrenoceptors. Therefore, there is a possibility to eliminate acute postinfarction hypotension by injection of exogenous catecholamines and/or by mobilization of the endogenous sympathoadrenal system. Indeed, adaptation to physical exercise mobilized compensatory reaction, although it did not prevent the drop of BP after EMI (Table 2). There is evidence that other modes of adaptations such as adaptation to short-term stress characterized by similar protective effects also promote normalization of BP after myocardial infarction due to mobilization of intrinsic compensatory resources [8].

TABLE 2. Effect of Adaptation to Physical Exercise on Blood Pressure (BP) during Experimental Myocardial Infarction in Rats (*M*±*m*)

Experimental series	BP, mm Hg
Control	110±2
Myocardial infarction	74±4*
Adaptation to physical exercise	108±4
Myocardial infarction after adaptation to physical exercise	87±3+

Therefore, preadaptation to physical exercise enhances constrictor reactions of resistance vessels in response to stimulation of α-adrenoceptors, thus mobilizing the reserve potencies to normalize BP after acute EMI.

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