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# Reduced Vasoconstriction and Enhanced Vasodilation of the Isolated Resistive Artery during Adaptation to Periodic Hypoxia

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**Key Words:** *adaptation to hypoxia; tone of resistive vessels*

The myogenic tone of resistive blood vessels is known to drop during adaptation to periodic hypoxia [6], inhibiting hereditary hypertension in SHR rats [4], the pathogenesis of this condition being similar to that in humans. This adaptation lowers arterial pressure in the initial stages of essential hypertension [5]. However, many aspects of the antihypertensive effect of adaptation to periodic hypoxia have not yet been clarified. For example, the effect of this adaptation on the α- and β-adrenergic responses of resistive arteries is unclear, although their increased tone is known to be an important factor in the development of hypertension.

The aim of the present work was to study the effect of adaptation to periodic hypoxia on the reactions mediated by the α- and β-adrenergic receptors of the isolated rat caudal artery, as well as on the level of the endothelium-dependent relaxation induced by acetylcholine.

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## MATERIALS AND METHODS

Experiments were carried out on Wistar male rats weighing 350-400 g. Adaptation to periodic hypoxia was carried out in a pressure chamber for 30 days, four hours daily, at an "altitude" of 5000 m. The course of adaptation was started at 1000 m and the "altitude" was gradually increasedover five days.

An arterial segment approximately 8 mm long was taken from the proximal end of the caudal artery of decapitated rats. Cannulas were inserted in both ends of the segment, which was then placed in an incubation chamber. Perfusion with Krebs-Henseleit solution (37°C) was performed at a constant flow rate (2 ml/min) [1]. The reactions of the perfused vessel were assessed by the changes in the perfusion pressure recorded with a KSP-4 potentiometer with the aid of a Statham pressure sensor (USA).

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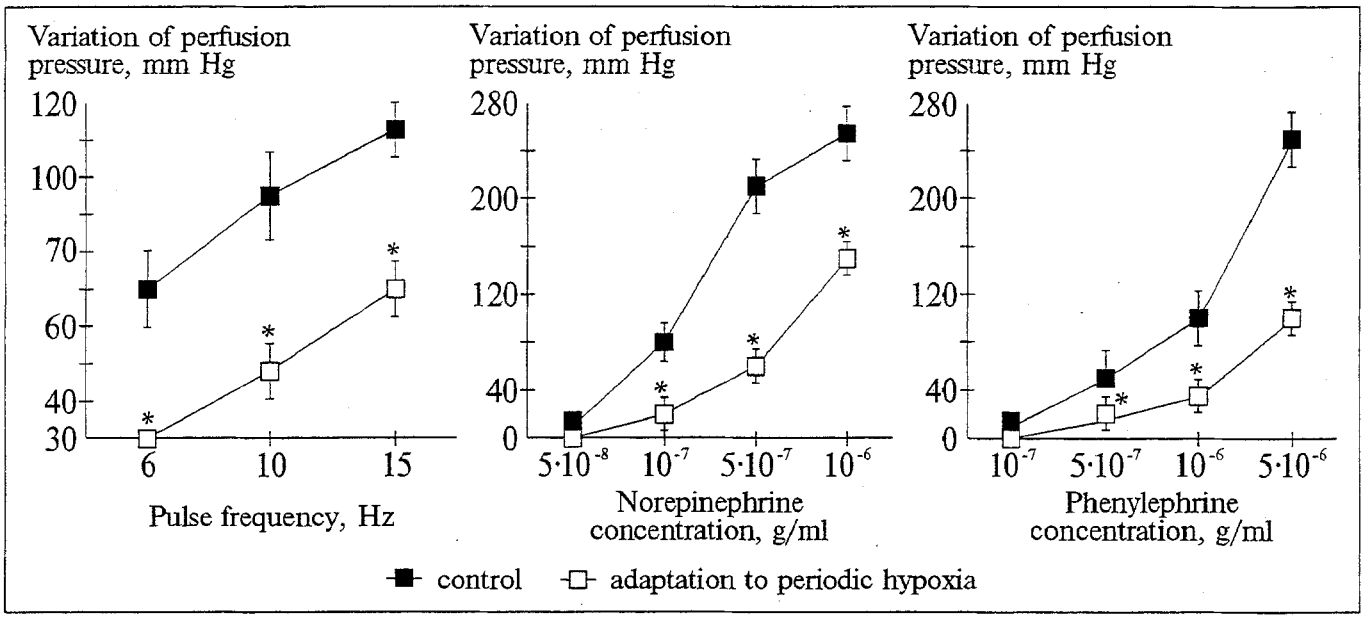


**Fig. 1.** Effect of adaptation to periodic hypoxia on vasoconstrictive reaction of isolated rat caudal artery under the influence of: *a*) transmural electrostimulation of nerve endings; *b*) norepinephrine; *c*) phenylefrine. Asterisk: $p<0.05$ as against the control.

Transmural electrostimulation of the nerve endings was performed using two electrodes, a metal cannula inserted into the vessel serving as one of them and the second electrode being attached externally. Electrostimulation was performed with alternating rectangular pulses of the following parameters: pulse duration 0.1 msec, voltage 50 V, and frequency 6, 10, and 15 Hz.

The adrenergic responses of the vessel studied were analyzed using norepinephrine (Serva, Germany) in doses of $5\times10^{-8}$, $10^{-7}$, $5\times10^{-7}$, and $10^{-6}$ g/ml, phenylefrine (Serva, Germany) in doses of $10^{-7}$, $5\times10^{-7}$, $10^{-6}$, and $5\times10^{-6}$ g/ml, isoproterenol (Sigma, USA) in a dose of $10^{-7}$ g/ml, and acetylcholine (Sigma, USA) in a dose of $5\times10^{-7}$ g/ml.

The study of acetylcholine- and isoproterenol-induced vasodilation was carried out against the background of a norepinephrine-induced contractile response. The norepinephrine concentration was chosen so as to maintain the vasoconstrictive reactivity of the arterial segment at a level of 100 mm Hg.

The results were subjected to statistical analysis using the Student *t* test.

## RESULTS

The results presented in Fig. 1, *a* show that adaptation to periodic hypoxia led to a twofold decrease of the contractile responses of the isolated caudal artery to transmural electrostimulation of the nerve endings in the wall of the vessel. A decrease of neurogenic contractile responses in the isolated artery can be caused by the processes associated with increased norepinephrine release from the nerve plexuses in the presynaptic region as well as by the processes associated with desensitization of the postsynaptic receptors. We thought it of interest, therefore, to analyze the responses of the isolated vessel at a constant norepinephrine level in the perfusion fluid (physiological saline).

The data in the Fig. 1, *b* suggest that adaptation to periodic hypoxia induces on average a 2.3-fold decrease in the vasoconstrictive responses of the isolated caudal artery under the influence of exogenous norepinephrine. This effect may be associated with a

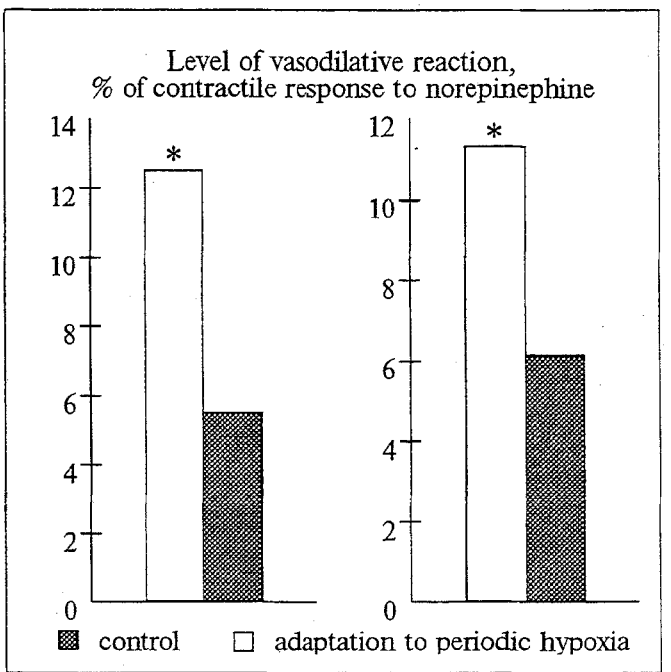


**Fig. 2.** Effect of adaptation to periodic hypoxia on vasodilative reactions of isolated rat caudal artery under the influence of: *a*) isoproterenol; *b*) acetylcholine.

change in the sensitivity of the adrenoreceptors distributed in the wall of the vessel, as well as with a change in the density of their distribution.

Since norepinephrine is a nonspecific agonist of the adrenergic receptors, the state of the α- and β-adrenergic receptors after adaptation to periodic hypoxia was investigated separately of using selective α- and β-agonists.

The development of the vasoconstrictive response of the isolated rat caudal artery to electrostimulation is known to be mediated by the $\alpha_1$-adrenoreceptors [8,9]. The "dose-effect" curves in Fig. 1, *c* show that the level of vasoconstrictive responses of the isolated artery dropped 2.6 times, on the average, under the influence of phenylefrine, that is, $\alpha_1$-adrenoreceptor desensitization occurred.

A decrease of vasoconstrictive responses under the influence of norepinephrine can not only result from $\alpha_1$-adrenoreceptor desensitization, but also be promoted by enhancement of the vasodilative reactions mediated by the $\beta_2$-adrenergic receptors. This suggestion is confirmed by the data presented in Fig. 2, *a*, which show that after adaptation to periodic hypoxia the norepinephrine-potentiated arterial tone reliably drops under the influence of isoproterenol as compared with the control.

Similar results were obtained in studies of endothelium-dependent relaxation. The level of endothelium-dependent relaxation was assessed by the vasodilative reaction to acetylcholine of an isolated artery contracting under the influence of norepinephrine ($5\times10^{-7}$ g/ml). As is shown in Fig. 2, *b*, adaptation promotes an increase of the vasodilative reaction to acetylcholine. Since the vasodilative effect of acetylcholine is mediated by an endothelium-derived relaxing factor (EDRF), these data suggest that adaptation to hypoxia increases the ability of the endothelium of the resistive arteries to release EDRF (nitric oxide or a direct inducer of vasodilation) as a response to acetylcholine [8,10,11].

Hence, adaptation to periodic hypoxia causes $\alpha_1$-adrenoreceptor desensitization and $\beta_2$-adrenoreceptor activation in the rat caudal artery, this manifesting itself as a reduced level of constrictive reactions as well as an elevated level of dilative and, particularly, of endothelium-dependent reactions.

It is well known that the general resistance of the peripheral vessels is lowered in rats adapted to periodic hypoxia [3]. The significance of this phenomenon seems to be determined by the tissue demand for an increased blood flow during oxygen deficiency. Obviously, the decrease of the peripheral vascular resistance is caused by functional changes of the vascular adrenoreceptors together with such factors as a reduction of the myogenic and structural component in the vascular bed [3,5] and an increased number of functioning microvessels [2]. This hypothesis is confirmed by our findings demonstrating $\alpha_1$-adrenoreceptor desensitization and $\beta_2$-adrenoreceptor activation and is in agreement with the data on reduced perfusion pressure in the posterior part of the rat body during sympathetic nerve stimulation after adaptation to hypoxia [3,7].

The functional changes of the α- and β-adrenergic receptors and the increased endothelium-dependent relaxation under the effect of hypoxia may play a role in the mechanism of the above-mentioned antihypertensive effect of adaptation to hypoxia.

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