Peculiarities of Adrenergic Regulation of Smooth Muscles in Rabbit Pulmonary Arteries

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Muscle tension recording was used to study adrenergic contractile reactions of pulmonary artery smooth muscles in rabbits. Stimulation of α-adrenoceptors induced contraction of pulmonary artery smooth muscle cells. Endothelium partially inhibited the contractile effect of α-adrenoceptor agonists. Activation of smooth muscle β-adrenoceptors in pulmonary arteries produced a dual dose-dependent effect (relaxation at agonist concentrations of 10 nM-1 μM and contraction at concentrations above 10 μM). The contractile effect of β-adrenoceptor activation in smooth muscle cells is a specific feature of pulmonary arteries probably related to peculiarities of cAMP-signaling in these cells.

Key Words: *pulmonary arteries; smooth muscles; adrenoceptors; endothelium; cAMP*

Considerable attention is now focused on mechanisms controlling vascular tone in pulmonary circulation [5]. Smooth muscle cells (SMC) of pulmonary artery branches are involved in the maintenance of adequate ventilation and perfusion. Abnormality of the ventilation-perfusion relationships is a leading symptom of bronchial asthma and other respiratory diseases [6,7]. There are some indications on essential differences in physiological reactions of systemic and pulmonary vessels [3,4,6-8]. Our aim was to study the peculiarities of adrenergic regulation of smooth muscle contractile activity in rabbit pulmonary arteries and the role of endothelium in these processes.

MATERIALS AND METHODS

The study was carried out on smooth muscle segments of lobar and segmental branches of pulmonary arteries isolated from non-narcotized rabbits sacrificed by cervical dislocation. After dissection of the heart and lungs, the pulmonary artery and its branches were isolated, and 2-3-mm vascular segments were prepared. Some segments were mechanically denuded.

The segments were perfused (37°C) with bubbled Krebs solution containing (in mM): 120.4 NaCl, 5.9 KCl, 1.2 NaH_2PO_4, 1.2 $MgCl_2$, 2.5 $CaCl_2$, 15.5 $NaHCO_3$, and 11.5 glucose (pH 7.30-7.35). This saline was used to prepare conditioning (40 mM KCl) and testing solutions (epinephrine hydrochloride, norepinephrine hydrotartrate, phenylephrine, isoproterenol, and propranolol). All test agents were used in concentrations of 1 nM-100 μM.

Mechanical tension (MT) developed by the segments was recorded in near-isometric mode on a 6MX1B mechanotron. The data were analyzed statistically.

The effect of test agents on MT of smooth muscle segments was accessed as percentage of the precontraction amplitude.

RESULTS

Epinephrine (0.001-100 μM) induced a dose-dependent contraction of all denuded segments of lobar branches of the pulmonary artery (Fig. 1, *a*).

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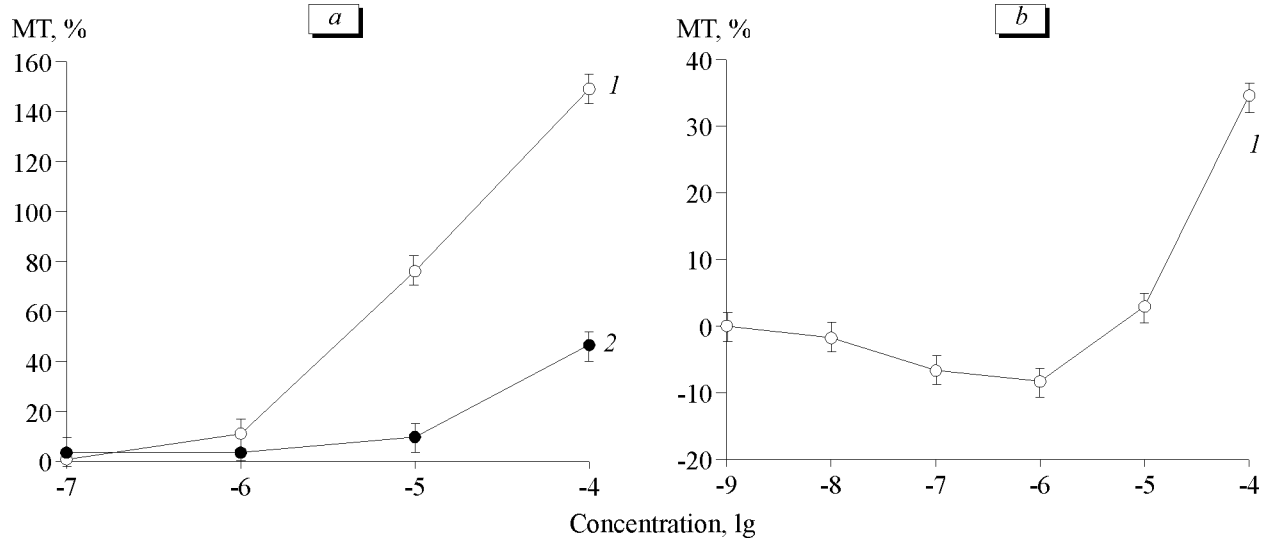

Fig. 1. Dose-dependent effects of epinephrine (*a*) and isoproterenol (*b*) on mechanical tension (MT) developed by smooth muscle segments of rabbit pulmonary artery. *1*) denuded segments; *2*) intact segments.

For evaluation of the role of endothelium in the realization of adrenergic contractile response we examined the effect of epinephrine on basal tone of pulmonary artery segments with intact endothelium. Epinephrine (0.1-100 μM) induced vascular contraction, but the amplitude of these responses was lower that in series with denuded segments (Fig. 1, *a*). This can be explained by production of endothelium-derived relaxation factor by endothelial cells of pulmonary vessels (similarly to that in systemic circulation). The nature of this factor is probably related to NO metabolism.

Similar results were obtained in the experiments with norepinephrine and α-adrenoceptor agonist phenylephrin in the presence of β-receptor blocker propranolol (10 μM). The doses inducing the half-maximum response to the effect of norepinephrine were 1.2 μM and 0.6 μM in denuded and intact segments, correspondingly. Phenylephrine induced contraction of both denuded and intact segments. In both cases, endothelium inhibited contractile responses.

These findings suggest that α-adrenergic regulation in pulmonary SMC does not principally differ from that in systemic vessels [5,7].

Principally different results were obtained in experiments with β-adrenoceptor agonist isoproterenol. In concentrations of 0.1-1 μM this agent induced relaxation of all segments, but in concentrations of 10-100 μM it induced contraction of all segments (Fig. 1, *b*). The amplitude of contractions attained 150.2±4.8% (n=12, p<0.05). We found no published data on β-adrenergic contractile effects in vascular SMC.

Activation of β-adrenoceptors in vascular smooth muscles in systemic circulation activates adenylate cyclase and stimulates production of cAMP. CAMP activates cAMP-dependent protein kinase, which potentiates relaxation of SMC due to phosphorylation of kinase of myosin light chain [1,2,8].

This probably implies peculiar performance and regulation of cAMP-dependent signal system in SMC of pulmonary arteries. To test this hypothesis, we used phosphodiesterase blockers vinpocetine (0.1-100 μM) and theophylline (0.1-100 μM). Phospho-

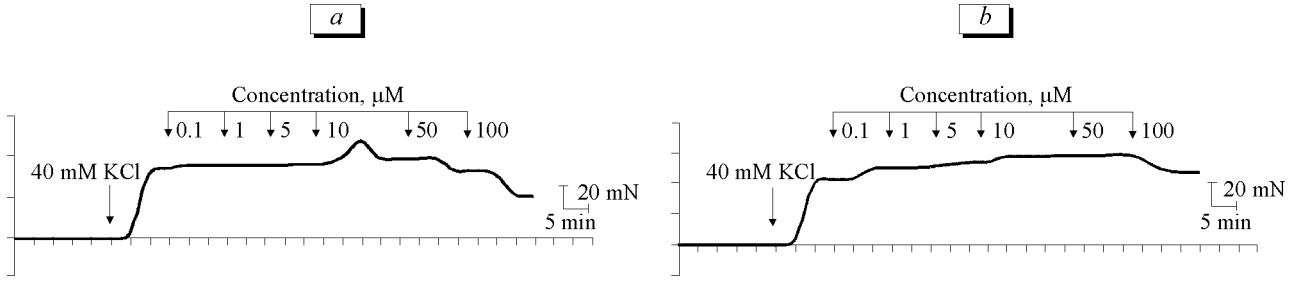

Fig. 2. Effect of vinpocetine (*a*) and theophylline (*b*) on mechanical tension (MT) developed by segments of rabbit pulmonary artery (experimental records).

diesterase cleaves cyclic nucleotides, while phosphodiesterase blockers potentiate the effects of cAMP-dependent signal system.

In 50% cases, vinpocetine (10 μM) increased MT to 132.5±3.7% of the precontraction amplitude (n=10, p<0.05). The contractile response lasted for 5 min and was followed by spontaneous relaxation (Fig. 2). Theophylline also induced contraction of 50% segments, but no spontaneous relaxation was observed in these cases (Fig. 2).

Our findings suggest that activation of cAMP-dependent signaling system can produce a constrictor response in smooth muscles of pulmonary artery. The important role in this response (similarly to that in cardiomyocytes) can be played by cAMP-dependent phosphorylation of Ca^{2+} channel protein calciductin, which increased membrane calcium conductance [1,2]. It can be assumed that this effect prevails under certain conditions in vascular smooth muscles of pulmonary circulation.

The revealed peculiarities of adrenergic control of pulmonary circulation vessels can be of crucial importance. The β-adrenoceptors agonists used as bronchial spasmolytic preparations can simultaneously provoke constriction of pulmonary arteries thus increasing arterial pressure in pulmonary circulation and aggravating the course of the disease.

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