ELECTROPHYSIOLOGICAL INVESTIGATION OF EXCITATION-CONTRACTION COUPLING DURING α-ADRENORECEPTOR ACTIVATION IN VASCULAR SMOOTH MUSCLES

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Chemosensitive Ca channels, controlled by α-adrenoreceptors, are known to take part in the excitatory action of noradrenalin (NA) on smooth muscle cells (SMC) of the pulmonary artery [1] and portal vein [3].

Vascular α-adrenoreceptors are divided into two types — α_1 and α_2, which have different pharmacological characteristics and are distributed unequally in different blood vessels [7, 9, 13, 14]. Na activates both types of α-adrenoreceptors and induces contraction of vascular smooth muscles [12, 14]. However, the mechanisms by which activation of these receptors leads to contraction of muscle cells differ, and have been inadequately studied [5-7, 9].

To explain these differences it was decided to investigate the effect of prazosin on electrical and contractile responses of muscle cells in the portal vein and pulmonary artery, induced by NA.

Prazosin is used in clinical practice for the treatment of essential hypertension and chronic heart failure [2]. Its hypotensive action is associated with specific blocking of α_1-adrenoreceptors of veins and arteries [4, 12].

EXPERIMENTAL METHOD

Experiments were carried out on longitudinal muscle strips of the portal vein and circular strips of the pulmonary artery of a rabbit, by a modified single sucrose gap technique.

The composition of the Krebs' solution was as follows (in mmoles/liter): NaCl — 120.4, KCl — 5.9, $NaHCO_3$ — 15.5, NaH_2PO_4 — 1.2, $MgCl_2$ — 1.2, $CaCl_2$ — 2.5, glucose 11.5. The temperature of the solution was maintained at 36°C, pH 7.4.

Electrical and contractile activity of the muscle strip was recorded simultaneously on the graph paper tape of a KSP-4 automatic potentiometer.

EXPERIMENTAL RESULTS

SMC of the rabbit portal veins possess spontaneous electrical and contractile activity. Action potentials (AP) generated by SMC of the portal vein are calcium in nature. Ca^{++} ions entering the cell during AP generation trigger their contractile mechanisms [11]. During stimulation of muscle cells by direct currents of opposite polarity, anelectrotonic and catelectronic potentials are generated. The frequency of spontaneous AP on the catelectrotonic potential was considerably increased, and this was accompanied by an increase in the frequency of phasic contractions of the strip (Fig. 1a).

Addition of NA in a concentration of 10^{-6} mole/liter led to membrane depolarization to 7 mV and to an increase in the frequency of spontaneous AP and of phasic contractions, which underwent summation to form indented or continuous tetanus, depending on the initial frequency of spontaneous AP and phasic contractions of the muscle strips (Fig. 1a). Against the amplitude of NA-induced depolarization the amplitude of the electrotonic potentials was reduced almost by half.

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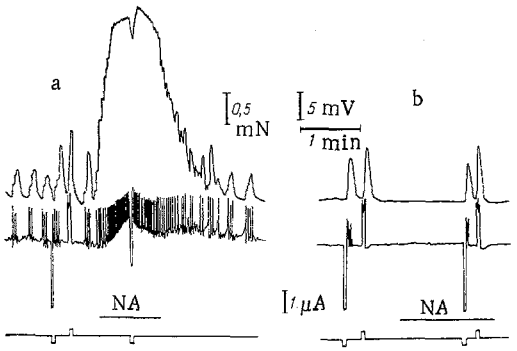

Fig. 1. Effects of NA (10^{-6} moles/liter) on electrical and contractile activity of SMC of portal vein: a) in normal Krebs' solution; b) after administration of prazosin ($5 \cdot 10^{-7}$ moles/liter). Here and in Fig. 2, from top to bottom: contractile activity, electrical activity, pulses of electric current; downward deflection denotes hyperpolarizing, upward — depolarizing current.

Prazosin (10^{-7} mole/liter) had no significant effect on spontaneous or electrically-induced activity of the muscle cells of the portal vein. With an increase in its concentration to 10^{-6} mole/liter spontaneous activity of the muscle cells was totally inhibited. Meanwhile, electrical and contractile activity of the muscle cells, induced by a depolarizing current, and also the anode-breaking response were preserved (Fig. 1b). By the 2nd-3rd minute of action of prazosin (10^{-7}-10^{-6} mole/liter) addition of NA (10^{-6} mole/liter) caused no changes in membrane potential (MP) or contractile activity of the muscle cells of the portal vein (Fig. 1b).

SMC of the pulmonary artery do not possess spontaneous electrical or contractile activity. Hyperpolarizing and depolarizing pulses of electric current lead to generation of anelectrotonic and catelectrotonic potentials. A local potential, accompanied by contraction of the muscle strip, appeared on the catelectrotonic potentials (Fig. 2a).

Addition of NA (10^{-6} mole/liter) led to membrane depolarization by 5-7 mV and to tonic contraction of the muscle strip. In the presence of NA excitability of the muscle cells increased, and this was shown by the appearance of fast oscillations on the catelectrotonic depolarization and an increase in the contractile response (Fig. 2a). Noradrenalin-induced depolarization in SMC of the pulmonary artery, just as in the portal vein, was accompanied by a decrease in membrane resistance, probably connected with increased membrane permeability for Na^+ and (or) Cl^- ions [1].

Prazosin (10^{-7}-10^{-6} mole/liter) did not affect the initial level of resting potential or contraction of the membrane of SMC in the pulmonary artery. However, by the 2nd minute of action of prazosin the reaction of SMC to NA (10^{-6} mole/liter) had already changed significantly, as shown by the absence of membrane depolarization and also of oscillations of MP on the catelectrotonic potential. The membrane resistance was unchanged under these conditions. However, the contractile response of the muscle strip from the pulmonary artery was partly preserved, to the extent of 35% of its initial value (Fig. 2b).

On washing the muscle strips with Krebs' solution spontaneous activity of the muscle cells of the portal vein and the response of the blood vessels tested to NA were completely restored.

The excitatory action of NA on SMC of the portal vein was complex in character. The contractile response of the muscle cells was the result both of the frequency of spontaneous AP, increased due to depolarization, and activation of the chemosensitive inflow of Ca^{++} ions, controlled by α-adrenoreceptors [3, 11]. Against the background of the action of prazosin inhibition of the noradrenalin response was observed. This could be evidence that both membrane depolarization by NA and the chemosensitive inflow of Ca^{++} ions are controlled, in this case, predominantly by α_1-adrenoreceptors.

The contractile response of SMC of the pulmonary artery under the influence of NA, unlike that of the portal vein, was not completely inhibited by prazosin. This shows that the excitatory action of NA in the rabbit pulmonary artery is mediated not only through α_1-adrenore-

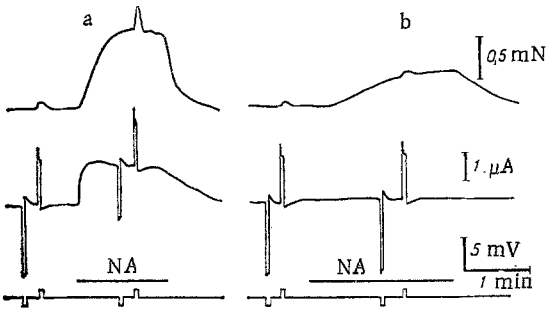

Fig. 2. Effect of NA (10^{-6} mole/liter) on electrical and contractile activity of SMC of pulmonary artery: a) in normal Krebs' solution; b) after action of prazosin (10^{-6} mole/liter) for 20 min.

ceptors but also, evidently, through α_2-adrenoreceptors. Just as in the portal vein, prazosin abolished NA-induced membrane depolarization of the pulmonary artery and a considerable fraction (about 65%) of tonic contraction. It has been shown on muscle strips of the dog saphenous vein [9], rat caudal artery [6], and rabbit mesenteric artery [10] and auricular artery [15], that prazosin inhibits NA-induced depolarization. On the basis of their results these workers concluded that α_1-adrenoreceptors mediate depolarization which, in turn, opens voltage-dependent Ca channels and leads to contraction of blood vessels through electromechanical coupling. However, our own previous investigations [1] showed that the main role in activation of noradrenalin contraction of SMC of the pulmonary artery is played by Ca^{++} ions, entering the cell through voltage-independent chemosensitive Ca channels, controlled by noradrenalin receptors. Meanwhile, comparatively few Ca^{++} ions enter the cell through voltage-dependent uninactivated Ca channels. Noradrenalin depolarization is responsible only for a small fraction (about 20%) of the contractile response of the muscle strip from the pulmonary artery. Consequently, about 45% of the total NA-induced contraction of SMC of the pulmonary artery is effected through chemosensitive Ca channels controlled by α_1-adrenoreceptors. NA-induced contraction in the presence of prazosin can be attributed to activation of chemosensitive Ca channels controlled by α_2-adrenoreceptors.

The hypotensive action of prazosin is linked both with cessation of the inflow of Ca^{++} ions through Ca channels controlled by α_1-adrenoreceptors, and with a decrease in the inflow of Ca^{++} ions through voltage-dependent Ca channels, due to removal of depolarization induced by α_1-adrenoreceptors.

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