The increase in the relative blood volume of the lungs during electrical stimulation of the nerves may reach on average 13% of the initial value, and this may account for the significant increase in the blood flow through the lungs without any appreciable rise of pressure in the pulmonary arterial bed [11], for the blood flow, other conditions being the same, depends on the fourth power of the width of the lumen of the blood vessel. An important role in this situation is probably played also by the central part of the lobe.

Further increase in blood volume is evidently limited by the lowering of distensibility of the pulmonary vessels, and it could hardly be possible without an appreciable rise of blood pressure in the pulmonary circulation.

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IONIC MECHANISM OF THE EXCITATORY ACTION OF NORADRENALIN ON SMOOTH-MUSCLE CELLS OF THE RABBIT PULMONARY ARTERY

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The excitatory effect of noradrenalin (NA) on smooth-muscle cells of the pulmonary artery is manifested as their contraction, to an amount which depends on the NA concentration. If the NA concentration is 10^{-8}-10^{-7} M, this contraction is not accompanied by any significant changes in membrane potential (MP). Under the influence of higher doses of NA the contractile response is increased and depolarization of the smooth-muscle cell membrane is observed [4, 5]. Some workers also have reported an increase in the electrical excitability of muscle cells of the pulmonary artery under the influence of NA, by a mechanism not yet explained [3, 4, 7]. Investigations of the turnover of radioactive Na^+, K^+, and Cl^- ions have shown that membrane permeability for them is increased under these conditions [5]. However, if membrane conductance is judged from the value of the electrotonic potentials, under different experimental conditions both an increase [5] and a decrease [3, 4, 8] in conductance have been found under the influence of large doses of NA.

The aim of this investigation was to continue the study of the mechanism of the excitatory action of NA on smooth-muscle cells of the pulmonary artery. Attention was directed mainly to the study of the mechanism of noradrenalin depolarization and of the increase in electrical excitability of the membrane.

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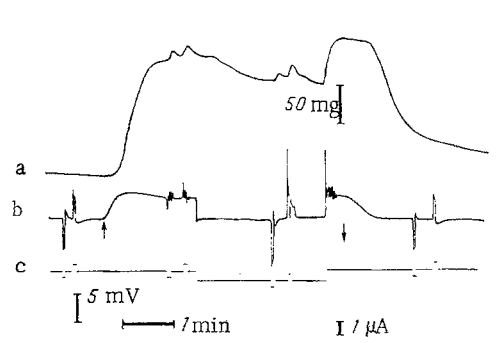

Fig. 1

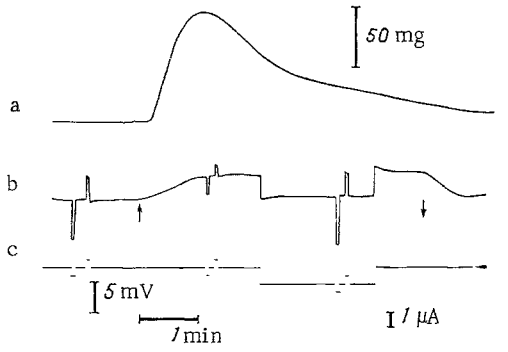

Fig. 2

Fig. 1. Action of NA on contractile (a) and electrical (b) activity of muscle cells of pulmonary artery. Electrotonic potentials evoked by pulses of electric current (c) whose amplitude was unchanged throughout the experiment. Arrows indicate times of addition and removal of NA (5×10^{-6} M).

Fig. 2. Action of NA on contractile and electrical activity of muscle cells of pulmonary artery bathed in calcium-free solution. Legend as to Fig. 1.

EXPERIMENTAL METHOD

Electrical and contractile activity of the circular muscle fibers of the rabbit pulmonary artery were recorded simultaneously by means of a modified single sucrose gap technique [1]. Voltage clamping experiments were carried out with a double sucrose gap. Capacitance currents and the linear part of the leakage currents were automatically deducted during recording. The solutions and experimental conditions used were the same as in previous investigations [2]. Calcium-free solution contained 1 mM EGTA and 12 mM of Mg^{++} ions to stabilize the membrane.

EXPERIMENTAL RESULTS

Application of impulses of inward and outward currents to a muscular strip of the pulmonary artery bathed in normal Krebs' solution was accompanied by an- and catelectrotonic potentials. As a rule, if the hyperpolarizing current was blocked, an anode-opening response appeared in the form of weak (1-2 mV) depolarization, resembling local excitation (Fig. 1). A local potential of the same amplitude, but shorter duration, appeared against the background of catelectrotonic depolarization.

On addition of NA to the Krebs' solution in a concentration of 5×10^{-6} M depolarization of the muscle cell membrane by 5-7 mV took place and was accompanied by contraction of the muscle strip. Against the background of noradrenalin depolarization the amplitude of the electrotonic potentials was reduced by more than half. The excitability of the membrane was increased under these circumstances, as shown by the onset of rapid oscillations of MP during catelectrotonic depolarization, and also on blocking of the hyperpolarizing current. These oscillations were accompanied by phasic contractions of the muscle strip (Fig. 1).

Anelectrotonic repolarization of the NA-depolarized membrane to its initial level was accompanied by partial relaxation of the muscle strip and by a marked decrease in membrane conductance (Fig. 1). The amplitude of the anelectrotonic potentials was increased under these circumstances on average by 50% compared with its value in normal Krebs' solution. Catelectrotonic depolarization of the repolarized membrane led to generation of an action potential (AP) with an amplitude of 10-15 mV, accompanied by phasic contraction. Blocking the repolarizing current also was accompanied by AP generation, followed by rapid oscillations of MP. These changes in MP were accompanied by considerable contraction of the muscle strip. The action of NA was reversible. On rinsing the muscle strip with normal Krebs' solution the resting potential and conductance of the muscle cell membrane and mechanical tension of the strip were restored to their initial values.

If the muscle strip bathed in calcium-free solution was treated with NA (in the same concentration) a contractile response also developed (Fig. 2), but in this case the contraction was transient in character and was not observed in response to the repeated action of NA. In addition, the rate of rise and, in particular, the amplitude of the noradrenalin contraction were reduced in calcium-free solution. Anelectrotonic membrane repolarization in calcium-free solution did not affect the character of contraction induced by NA.

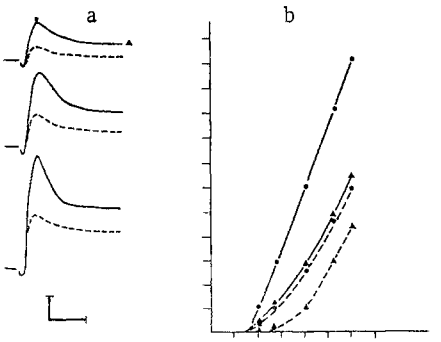

Fig. 3. Transmembrane currents (a) and current-voltage characteristics (b) for fast (circles) and steady-state (triangles) outward currents, recorded by voltage clamp method in normal solution (continuous lines) and in presence of 5×10^{-6} NA (broken lines).

Experiments with anelectrotonic repolarization of the NA-depolarized membrane in normal and calcium-free solutions showed that the principal role in activation of the noradrenalin contraction is played by Ca^{++} ions, entering the cell through potential-independent chemosensitive Ca-channels, controlled by noradrenalin receptors. At the same time, comparatively few Ca^{++} ions enter the cell through potential-dependent, inactivated Ca-channels, for anelectrotonic repolarization is accompanied by only very weak relaxation of the muscle strip. So far as contraction arising in calcium-free solution is concerned, it is evidently activated by Ca^{++} ions which are liberated during the action of NA on intracellular binding sites.

In the present investigations noradrenalin depolarization was accompanied by a decrease in membrane resistance, which was probably connected with an increase in membrane permeability for Na^+ and (or) Cl^- ions. However, this increase in permeability proved to be potential-dependent and not dependent on the presence of Ca^{++} in the external solution (see Fig. 2). The fact that during anelectrotonic depolarization the membrane resistance in the presence of NA was higher than initially (in normal Krebs' solution), makes it less likely that Na- and Cl-channels participate in the initiation of noradrenalin depolarization. That is why the most probable primary cause of its appearance is a decrease in permeability for K^+ ions. In the course of development of depolarization, potential-dependent channels for Na^+ and (or) Cl^- ions, activated by noradrenalin receptors, are opened, and this leads to further depolarization of the membrane. As soon as the MP level reaches the threshold of activation of potential-dependent uninactivated K-channels, whose conductance in the muscle cells of the pulmonary artery is fairly high [2], these channels are opened and depolarization ceases. As a result of this, membrane conductance is higher than initially both for Na^+ and Cl^- ions and for K^+ ions.

The potential-dependence of the noradrenalin effect revealed by these experiments is evidently the cause of the contradictory data on changes in membrane conductance during the action of NA obtained under different experimental conditions [3-5, 8]. Since changes in conductance were estimated from changes in the amplitude of anelectrotonic potentials, the result was dependent on the choice of magnitude of the testing pulses of hyperpolarizing current. If the amplitude of the electrotonic potentials was low, an increase in membrane conductance was found. If, however, the amplitude of the anelectrotonic potentials under the influence of NA exceeded the level of noradrenalin depolarization, the potential-dependent channels closed and an increase in membrane resistance, connected with a decrease in conductance for K^+ ions, was found.

It can be concluded from the data in Figs. 1 and 2 that the gradually increasing AP generated by muscle cells of the pulmonary artery in the presence of NA are calcium in nature, for they disappear in calcium-free solution. However, the cause of the increased membrane excitability under the influence of NA is not yet clear. Accordingly it was decided to study the effect of NA on transmembrane ionic currents under voltage clamp conditions. The writers showed previously that electrical inexcitability of these muscle cells is connected with early activation of fast K-channels carrying the outward current [2]; this current, moreover, is so

strong that the inward component of the transmembrane current could be recorded only in the presence of TEA ions, which partially block K-channels. In the present experiments, after subtracting the capacitance component of the current arising during a shift of transmembrane potential, a component of the inward current preceding activation of the fast K channels was found in normal solution also. However, the inward current observed reaches its peak value before the capacitance current has ended and, consequently, before the assigned transmembrane potential is established. It cannot therefore be analyzed by the voltage clamp method, for when the action of NA on transmembrane currents was investigated, only changes in the fast and steady-state outward currents were analyzed.

In a concentration of 5×10^{-6} M, NA was found to cause appreciable reduction of conductance of the K-channels carrying both the fast inactivated and the steady-state outward current (Fig. 3a). The threshold for the fast outward current was practically unchanged under these circumstances, and only the slope of the current—voltage characteristic curve was reduced. For the steady-state component of the outward current the current—voltage characteristic curve was shifted to the right along the voltage axis by approximately 3 mV without any change in its slope (Fig. 3b). This shift is evidently reflected in the value of noradrenalin depolarization, which depends on the threshold of activation of slow K channels. Meanwhile, an increase in excitability of the muscle cells may be connected with a decrease in conductance of channels for the fast outward current, for in this case the fast outward current will prevent regeneration of the AP by a lesser degree. However, as a result of noradrenalin depolarization most of the Ca-channels carrying the fast inward current are in an inactivated state and do not take part in the excitation process. That is why electrical stimulation leads only to small oscillations of MP. During membrane repolarization inactivation of the Ca-channels is abolished and the cells become capable of generating an AP.

The excitatory action of NA on smooth-muscle cells of the pulmonary artery is thus effected through activation of chemosensitive Ca-channels which are the main pathway of entry into the cell of Ca^{++} ions which activate contraction, through a decrease in conductance of the potential-independent K-channels, leading to initial membrane depolarization, through activation of chemosensitive potential-dependent Na- and (or) Cl-channels, which increase membrane depolarization, and also through a decrease in conductance of potential-dependent fast and slow K-channels, bringing about an increase in excitability of the muscle cells and determining the magnitude of noradrenalin depolarization.

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