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CELL BIOPHYSICS

The Role of Inwardly Rectifying Potassium Channels in the Relaxation of Rat Hind-Limb Arteries

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Abstract—An increase in the extracellular K^+ concentration, which causes relaxation of arteries due to the activation of inwardly rectifying potassium channels, can occur in some organs under intensive metabolism, as well as endothelium-dependent hyperpolarization. The aim of this work was a comparison of the contribution of these channels in the regulation of the tone of arteries that supply skeletal muscles and the skin. The reactions of skin-region arteries (a subcutaneous artery and its branch) and gastrocnemius muscle arteries were recorded in the isometric mode. During the contraction caused by α_1-adrenoceptor agonist, the relaxation reactions upon an increase in extracellular K^+ concentration and on acetylcholine in the presence of inhibitors of NO-synthase and cyclooxygenase were recorded (to detect the effects of endothelium-dependent hyperpolarization). The muscle arteries at both effects showed a pronounced relaxation, which was strongly suppressed by Ba^{2+} ions (blockers of inwardly rectifying potassium channels); both reactions did not exceed 20% in the skin arteries. Thus, the regulatory effect of inwardly rectifying potassium channels in the muscle arteries is much higher than in the skin arteries which is consistent with the idea about the functioning of these arteries in the organism.

Keywords: smooth muscle, potassium ions, endothelium-dependent hyperpolarization, methoxamine, gastrocnemius-muscle arteries, subcutaneous artery

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INTRODUCTION

The blood supply of organs depends on the tone of the arteries that supply them. There are many and diverse mechanisms for the regulation of the tone of arteries; the contribution of each of them can depend on the specific bloodstream region. The potassium channels of smooth-muscle cells (SMCs) play an important role in regulation of the vascular tone. Potassium channels are key regulators of the level of SMC membrane potential: opening of K^+-channels at physiological values of the membrane potential results in SMC hyperpolarization and their relaxation [1].

An increase in the conductivity with a rise of extracellular K^+ concentration ($[K^+]_{out}$) [4] is a peculiarity of inwardly rectifying potassium channels (K_{IR}-channels), namely, the $K_{IR}2.1$ and $K_{IR}2.2$ subtypes that are expressed in SMCs [2, 3]. K_{IR}-channels carry the inward K^+-current, whose value linearly depends on the membrane potential level, if the membrane potential is more negative than the equilibrium potassium potential. A small outward current is recorded if the membrane potential is more positive than the equilibrium potassium potential. With an increase in depolarization, the outward K^+-current rapidly decreases and then disappears; this is caused by the influence of positively charged Mg^{2+} and polyamines that block the K_{IR}-channel pore from the cytoplasmic side [5, 6]. K_{IR}-channel activation with an increase in $[K^+]_{out}$ can be caused by the following mechanisms: first, an increase in $[K^+]_{out}$ results in a shift of the current-voltage characteristic in the positive direction (which can cause an increase in outward K^+-current through K_{IR}-channels in the area of membrane potential values close to the SMC rest potential [1, 7]. Second, an increase in $[K^+]_{out}$, K^+ ions from the outside side of the membrane can electrostatically reject positively charged Mg^{2+} and polyamines [8]. As well, data exist that show that K^+ can directly interact with K_{IR}-channels, probably changing the conformation of these

Abbreviations: SMCs, smooth-muscle cells; K_{IR}-channels, inwardly rectifying potassium channels; $[K^+]_{out}$, extracellular K^+ concentration; EDH, endothelium-dependent hyperpolarization.

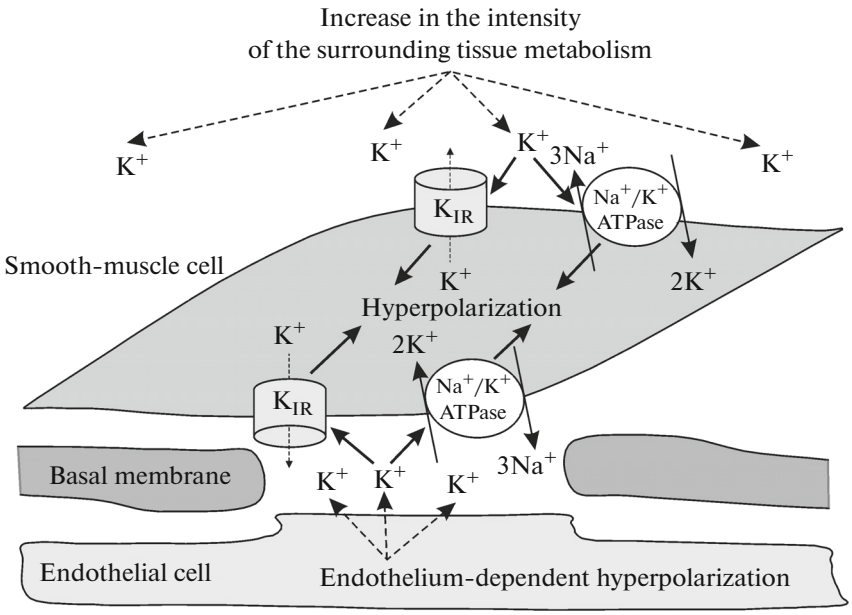

Fig. 1. Mechanisms of the hyperpolarization of smooth-muscle artery cells with an increase in $[K^+]_{out}$. The surrounding tissue or endothelium can be a source of K^+. In the first case, the increase in $[K^+]_{out}$ is global; in the second case, it occurs locally between endothelial and smooth-muscle cells and is one of the mechanisms of endothelium-dependent hyperpolarization. The hyperpolarizing effect of K^+ can be associated with the activation of inwardly rectifying potassium channels (K_{IR}-channels) and/or Na^+/K^+-ATPase.

channels [9]. The fact that an increase in K^+ current through K_{IR}-channels with an increase in $[K^+]_{out}$ can occur, even in the case of the absence of intracellular blocking molecules, supports this point of view [10].

The contribution of K_{IR}-channels to the regulation of the tone of arteries can depend on the specific region of the bloodstream. An increase in the metabolic intensity in some organs (such as the brain, skeletal muscles, and heart) is associated with a significant increase in $[K^+]_{out}$ resulting in K_{IR}-channel activation and vessel SMC relaxation [11–13]. SMC hyperpolarization with an increase in $[K^+]_{out}$ can be also associated with activation of Na^+/K^+-ATPase [12]. However, K^+-dependent regulation of the tone of arteries in other organs has been poorly studied; it primarily regards the skin arteries.

An increase in $[K^+]_{out}$ can occur not only globally (with an increase in the intensity of the tissue metabolism), but also locally (during endothelium activation) (Fig. 1). Normally, the secretory activity of the endothelium is directed at the production of vasodilatation factors [14]. The main factors of endothelium-dependent relaxation include NO, prostacyclin, and endothelium-dependent hyperpolarization (EDH) [15]. As opposed to excitable cells, for which an increase in activity is associated with depolarization, activation of the endothelium leads to its hyperpolarization, for which K^+ exit through Ca^{2+}-dependent channels of intermediate and small conductivity is a major mechanism [15]. A local increase in $[K^+]_{out}$ in the locations of the approximation of endothelial and smooth-muscle cells activates K_{IR}-channels and Na^+/K^+-ATPase of SMC (which leads to SMC hyperpolarization and vessel relaxation). In addition, a hyperpolarizing signal can be transmitted to SMCs through myoendothelial gap junctions or by other mechanisms [15]. It should be noted that the EDH contribution in endothelium-dependent relaxation and EDH mechanisms can significantly vary depending on the vascular region and size of vessels [16–18].

The aim of the present work was to establish the contribution the K_{IR}-channels make in the regulation of the tone of arterial vessels in two functionally different regions of the rat hind limb (skin and skeletal muscles). For this, we studied the reactions of skin and skeletal-muscle arteries upon an increase in $[K^+]_{out}$, as well as the EDH component of endothelium-dependent relaxation of these arteries. The K_{IR}-channel contribution to these reactions was estimated according to the effect of their blocker Ba^{2+}.

MATERIALS AND METHODS

Male rats of the Wistar line at the age 3–5 months (with a body weight of 270–440 g) obtained from the Institute for Biomedical Problems (Russian Academy of Sciences) were used in the experiments. All manipulations with animals were made according to the Rules of Research with the use of Experimental Ani-

mals (1977). The rats were kept under standard vivarium conditions with free access to food and water.

The Object of Study and Procedure

Two skin region arteries (a subcutaneous artery and a branch of this artery in the distal direction) and gastrocnemius-muscle arteries (that feed its lateral and medial heads) were selected as objects for the study. Rats were decapitated using a guillotine and the studied arteries were isolated. Arterial ring segments (2 mm in length) were fixed in a myograph (410A, 420M or 620M, DMT, Denmark) for the recording of contractions in the isometric mode. The signals from tensometric sensors were digitized at a frequency of 10 Hz using an analog-to-digital converter (E14-140, L-CARD, Russia) and recorded using the PowerGraph 3.3 program (DISoft, Russia).

A solution of the following composition (mM) was used: NaCl, 120; $NaHCO_3$, 26; KCl, 4.5; $CaCl_2$, 1.6; $MgSO_4$, 1; NaH_2PO_4, 1.2; D-glucose, 5.5; EDTA, 0.025; HEPES, 5. The solution was permanently aerated with carbogen (95% O_2 + 5% CO_2) for oxygenation and the maintenance of a pH value of 7.4. The extension of the preparation that is optimal for the manifestation of contractile activity was determined after heating to 37°C; the internal vessel diameter that corresponds to a pressure of 100 millimeters of mercury was also calculated during this procedure [19]. The preparations were then activated by the sequential addition of noradrenaline (10^{-5} M) and methoxamine (agonist of α1-adrenoreceptors, 10^{-5} M); the duration of each contraction was 5 min and the interval was 15 min. The endothelium function was estimated according to the reaction to acetylcholine (10^{-5} M) against the background of a pre-contraction caused by noradrenaline (10^{-6} M).

Experimental Protocol

The "concentration–effect" dependence on methoxamine in the concentration range from 10^{-8} to 10^{-4} M was recorded at the beginning of the experiment. The maximum force of the preparation contraction (100%) and methoxamine concentration at which the contraction force was 70% of the maximum (the level of the preparation pre-contraction during the estimation of the effect of relaxing stimuli), were determined according to this dependence. The relaxation reactions were recorded: (1) for an increase in $[K^+]_{out}$ by the addition of the stock KCl solution (2.5 M) in the volume required for an increase in $[K^+]_{out}$ (in the range from 5.75 to 19.5 mM, the effect of each concentration was 2 min) and (2) for acetylcholine (from 10^{-9} to 10^{-5} M, the effect of each concentration was approximately 1 min). To detect the EDH component, reactions to acetylcholine were studied in the presence of NO-synthase (L-NNA, 100 μM) and cyclooxygenase (indomethacin, 10 μM) inhibitors.

The reactions on an increase in $[K^+]_{out}$ and acetylcholine were studied twice in each experiment. In the first "concentration–effect" dependence, the initial reactions of preparations on an increase in $[K^+]_{out}$ or acetylcholine were estimated. The preparations were then distributed for groups that initially did not differ in reactions on the studied effects (data not shown). In the second "concentration–effect" dependence, the effects of K_{IR}-channel blockade (Ba^{2+}, 30 μM) separately and in combination with Na^+/K^+-ATPase inhibition (ouabain, 1 mM) were studied. In addition, a second "concentration–effect" dependence in one of the groups was conducted in the absence of blockers ("control conditions").

Processing of Results

The reactions to different methoxamine concentrations were evaluated according to the increase of the recorded force for the sensitivity of the preparation to methoxamine according to $-\log EC_{50}$, where EC_{50} is the concentration of agonist at which the contraction response is 50% of the maximum.

The average value of the contraction force at 2 min after each increase of the concentration was calculated during the processing of the "concentration–effect" dependences for KCl. The minimum value of the contraction force (that is, the largest relaxation) during the effect of each concentration of the substance was determined during the processing of the "concentration–effect" dependences for acetylcholine. The obtained values were expressed in the percentage of the pre-contraction value (the force of the contraction caused by methoxamine before the addition of the first vasorelaxant).

All data are presented as the mean ± mean error. The statistical analysis of the results was done in the GraphPad Prism 6.0 program (GraphPad, Software Inc., United States). The two-factor analysis of variance was used for repeated measures with the Tukey adjustment for multiple comparisons. Differences were considered to be statistically significant at $p < 0.05$.

RESULTS

Characteristics of Arteries

The internal diameter of the subcutaneous artery was 603 ± 11 μm; for the subcutaneous artery branch it was 275 ± 11 μm, while for the gastrocnemius-muscle arteries it was 306 ± 6 μm. The maximum contraction force of the subcutaneous artery was 34 ± 1 mN; for the subcutaneous artery branch it was 17 ± 1 mN and for the gastrocnemius-muscle arteries it was 20 ± 1 mN. Based on these data, it is possible to consider

that the subcutaneous artery branch and gastrocnemius-muscle arteries are comparable in internal diameter and maximum contraction force. The sensitivity of the subcutaneous artery, its branch, and gastrocnemius-muscle arteries to methoxamine did not differ; the $-\log EC_{50}$ values were 6.03 ± 0.02, 6.02 ± 0.03, and 5.99 ± 0.02, respectively.

Arterial Reactions to an Increase in $[K^+]_{out}$

In the subcutaneous artery, an increase in $[K^+]_{out}$ in the range from 5.75 to 19.5 mM caused moderate relaxation, which was the most pronounced at $[K^+]_{out}$ of 7.5 mM (to 20% of the level of the initial contraction) (Figs. 1a and 1b). In the subcutaneous artery branch, relaxation with an increase in $[K^+]_{out}$ was almost absent (Figs. 1c and 1d). As opposed to the skin arteries, an increase in $[K^+]_{out}$ caused a significant relaxation of the gastrocnemius-muscle arteries (in the range from 8.25 to 19.5 mM more than by 80%) (Figs. 1e and 1f).

The K_{IR}-channel-blockade did not change the subcutaneous artery reaction to an increase in $[K^+]_{out}$. The joint K_{IR}-channel and Na^+/K^+-ATPase blockade resulted in the suppression of the dilatation reaction of a subcutaneous artery during the effect of low $[K^+]_{out}$ (Fig. 1b). The effects of K_{IR}-channel and Na^+/K^+-ATPase blockade were absent in the subcutaneous artery branch, where relaxation with an increase in $[K^+]_{out}$ was not pronounced (Fig. 1d).

In the gastrocnemius-muscle arteries, the K_{IR}-channel blockade resulted in a decrease in relaxation in the $[K^+]_{out}$ range from 5.75 to 12 mM and to its almost complete suppression at higher $[K^+]_{out}$ values (Fig. 1f). The joint K_{IR}-channel and Na^+/K^+-ATPase blockade almost completely removed the relaxation during the effect of low $[K^+]_{out}$ concentrations; however, a decrease in the contraction force was observed during the effects of moderate and high $[K^+]_{out}$ (Fig. 1f). The profile of such a force decrease indicates that it is not associated with the effect of $[K^+]_{out}$, but occurs spontaneously. To test this hypothesis, we made an additional series of experiments, in which did we not perform an increase in $[K^+]_{out}$, but still observed a spontaneous force decrease with time in the presence of Ba^{2+} and ouabain (Fig. 1f, dotted line).

Reaction of Arteries on Acetylcholine

All of the studied arteries demonstrated a pronounced relaxation for acetylcholine, which was 80–90% from the initial pre-contraction level (Figs. 2a–2c, curves *1*). However, the contribution of EDH (determined as the component of the relaxation reaction after NO-synthase and cyclooxygenase blockade) differed greatly: it was poorly pronounced in the subcutaneous artery and its branch, while it was a significant part of the reaction to acetylcholine in the gastrocnemius-muscle arteries (Fig. 2).

The K_{IR}-channel blockade did not change the EDH component of the endothelium-dependent relaxation of the subcutaneous artery (Fig. 2a); however, it completely removed the EDH component in the subcutaneous artery branch (Fig. 2b). In the gastrocnemius-muscle arteries, the EDH component of the endothelium-dependent relaxation significantly decreased after K_{IR}-channel blockade (Fig. 2c). Such an effect of the K_{IR}-channel blocker was the most pronounced in the range of acetylcholine concentrations from $3 \cdot 10^{-7}$ to 10^{-5} M. The EDH component of endothelium-dependent relaxation was completely inhibited in all of the studied arteries during the joint K_{IR}-channel and Na^+/K^+-ATPase blockade.

DISCUSSION

According to these data, the gastrocnemius-muscle arteries demonstrated pronounced relaxation to an increase in $[K^+]_{out}$ and a large EDH component of the reaction to acetylcholine; both reactions significantly decreased after the K_{IR}-channel blockade. In the skin arteries, the reaction to an increase in $[K^+]_{out}$ and the effect of EDH were poorly pronounced. These reactions occur without the involvement of K_{IR}-channels in the subcutaneous artery; however, the K_{IR}-channel blockade removed a small EDH component of the reaction in the subcutaneous artery branch.

Mechanisms of Gastrocnemius-Muscle Artery Relaxation with an Increase in $[K^+]_{out}$

A significant K_{IR}-channel contribution to relaxation caused by an increase in $[K^+]_{out}$ was previously demonstrated for arteries of other skeletal muscles. As an example, K^+-induced relaxation of m. cremaster arteries in rats was shown to be completely caused by K_{IR}-channel activation [11]. In our work, the K_{IR}-channel blocker only decreased the relaxation of the gastrocnemius-muscle arteries upon an increase in $[K^+]_{out}$, but did not suppress it completely; the residual reaction component was caused by the effect of Na^+/K^+-ATPase. Similarly, the EDH component of the reaction to acetylcholine decreased with the K_{IR}-channel blockade and was removed with a joint K_{IR}-channel and Na^+/K^+-ATPase blockade.

It is interesting that the effect of the K_{IR}-channel blocker was more pronounced in both cases against the background of high $[K^+]_{out}$ values or acetylcholine. In contrast, the effect of Na^+/K^+-ATPase was manifested in the area of low $[K^+]_{out}$. A similar dependence of the effect of blockers on $[K^+]_{out}$ was previously

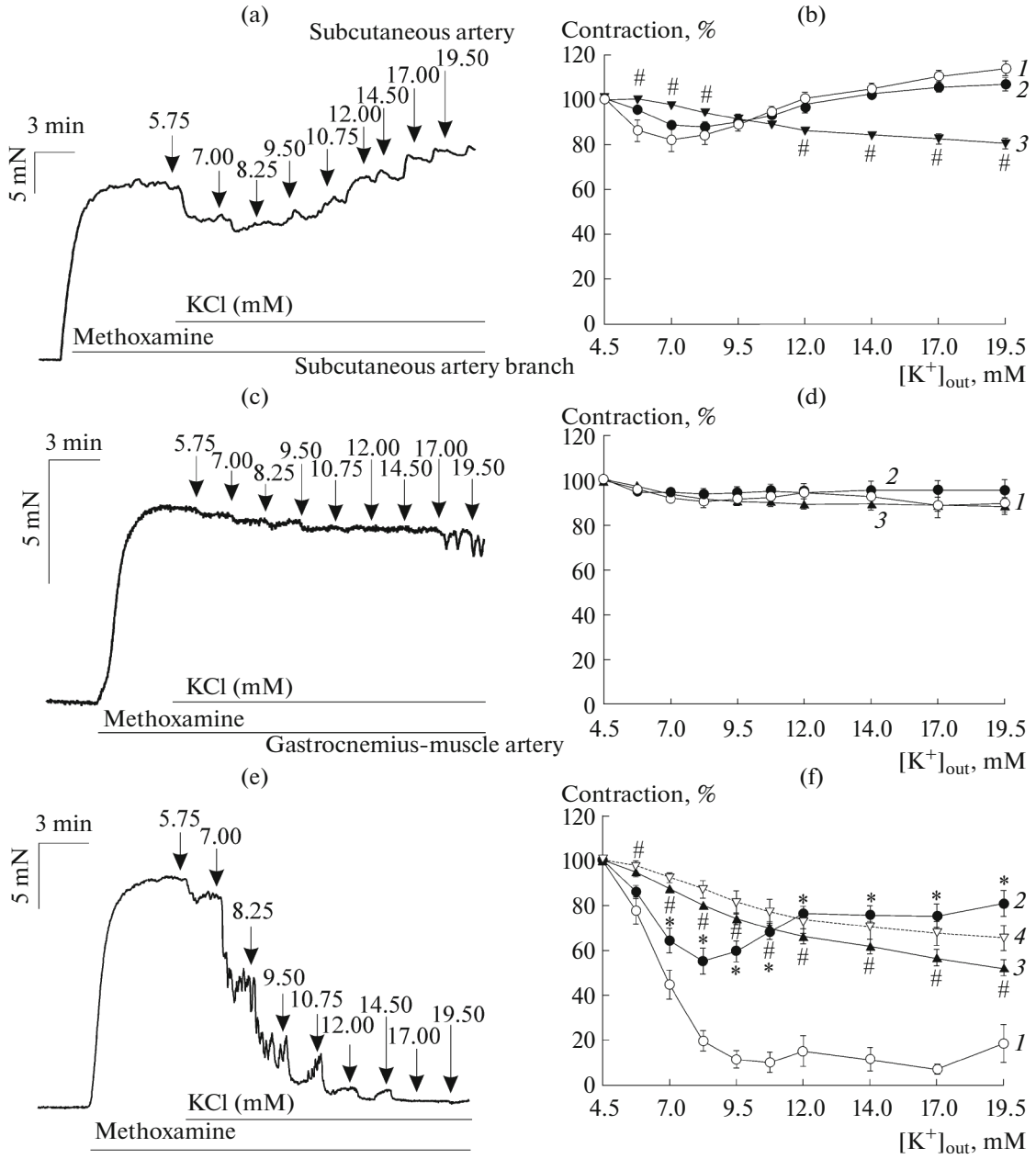

Fig. 2. Reactions of arteries to an increase in $[K^+]_{out}$. Subcutaneous artery: (a) original experiment; (b) "concentration–effect" dependences under control conditions (curve *1*, $n = 9$), in the presence of Ba^{2+} (curve *2*, $n = 6$) or Ba^{2+} with ouabain (curve *3*, $n = 4$). Subcutaneous artery branch: (c), original experiment; (d) "concentration–effect" dependence under control conditions (curve *1*, $n = 7$), in the presence of Ba^{2+} (curve *2*, $n = 6$) or Ba^{2+} with ouabain (curve *3*, $n = 7$). Calf-muscle arteries: (e), original experiment; (f) "concentration–effect" dependence under control conditions (curve *1*, $n = 10$), in the presence of Ba^{2+} (curve *2*, $n = 9$) or Ba^{2+} with ouabain (curve *3*, $n = 6$), as well as a spontaneous decrease in the contraction force in the presence of Ba^{2+} and ouabain without an increase in $[K^+]_{out}$ (curve *4*, $n = 4$). *, #, $p < 0.05$ as compared with the curve *1*.

demonstrated in the experiments on rat-brain arteries [11]. It is considered that the effect of Na^+/K^+-ATPase in the area of high $[K^+]_{out}$ values is limited by its saturation with K^+, as well as a decrease in intracellular Na^+ concentration, which can arise with an increase in the activity of this pump [7]. In this regard, the involvement of K_{IR}-channels for the maintenance of relaxation in the area of relatively high $[K^+]_{out}$ values is required. If we assume that $[K^+]_{out}$ between the endothelium and SMCs depends on the degree of endothelial activation, the reason that the effect of Na^+/K^+-ATPase is manifested in the area of low acetylcholine concentrations, while the effect of K_{IR}-channels occurs in the area of higher concentrations, becomes clear.

In the presence of Ba^{2+} and ouabain the gastrocnemius-muscle arteries lost the ability to maintain stable tone; ouabain, but not the K_{IR}-channel blockade, had this effect. We had to use a high ouabain concentration (1 mM) for a complete Na^+/K^+-ATPase blockade, since the α1 isoform of this enzyme in rodents is not sensitive to ouabain. It was demonstrated that violation of ionic SMC homeostasis can occur with a continuous incubation of arteries with a high ouabain concentration [20]. It is also known that such an effect can result in a decrease in the Ca^{2+} sensitivity of the SMC contractive apparatus; in this case, the contraction force decreases [21]. However, the effect of ouabain was not accompanied by a spontaneous decrease in the tone of the arteries in the presence of L-NNA and indomethacin. Based on this, it is possible to assume that the relaxing ouabain effect is partially associated with its effect on the endothelium and/or affects the signaling pathways activated in SMCs by NO-synthase and/or cyclooxygenase products.

It is known that K_{IR}-channels can occur in both endothelial and smooth-muscle cells [9]. We assume that "smooth-muscle" K_{IR}-channels were mainly involved in the relaxation of arteries with an increase in $[K^+]_{out}$. According to other authors, the removal of the endothelium does not change the contribution of K_{IR}-channels to the relaxation of heart and brain arteries caused by an increase in $[K^+]_{out}$ [22]. At the same time, K_{IR}-channels located in the endothelium can be involved in EDH dependent relaxation of arteries [23]. K^+ that leaves the endothelium through Ca^{2+}-activated potassium channels of small and intermediate conductivity [15, 24] can activate endothelial K_{IR}-channels in an autocrine manner (which will increase the hyperpolarization of endothelial cells and facilitate the entrance of Ca^{2+} into them). In turn, Ca^{2+} will additionally activate Ca^{2+}-activated potassium channels of small and intermediate conductivity located in the endothelium (completing the positive feedback in the EDH mechanism).

Skin Arteries are Poorly Sensitive to an Increase in $[K^+]_{out}$

The role of K_{IR} in the regulation of the tone of the skin arteries has been poorly studied. We studied the reactions of two skin-region arteries that differed in their diameter and location in the bloodstream; the subcutaneous artery branch was similar to the gastrocnemius-muscle arteries in diameter and contraction force.

It is known that arteries of different branching orders in other organs can significantly differ in their reactions to an increase in $[K^+]_{out}$ and the EDH contribution in endothelium-dependent relaxation [18, 25]. However, we demonstrated that no such dependence is observed in the skin: the subcutaneous artery and its branch relaxed slightly, both with an increase in $[K^+]_{out}$ and during the effect of EDH; both reactions

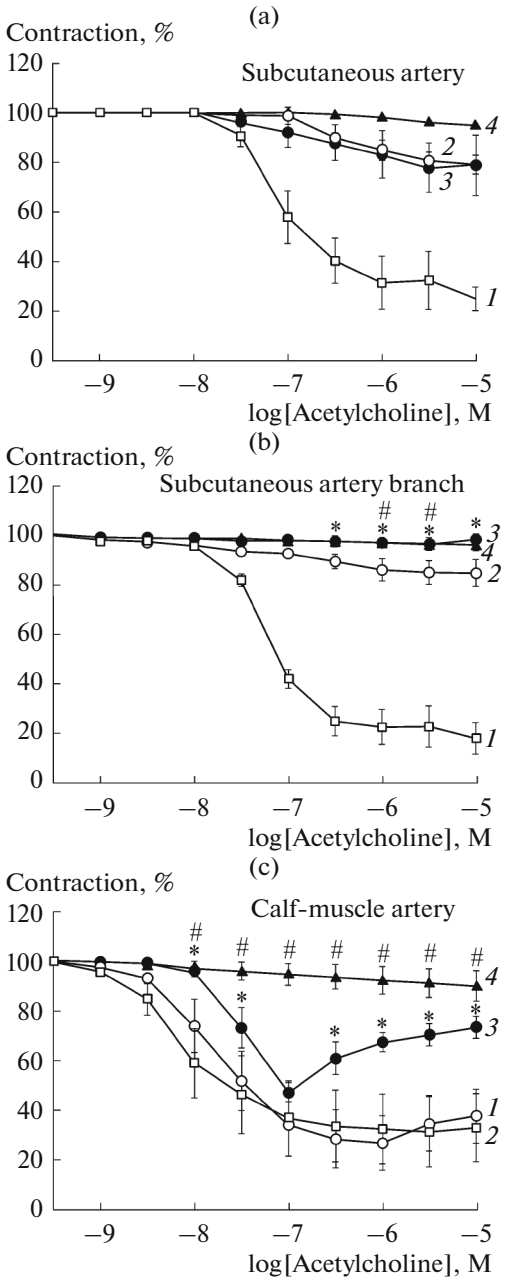

Fig. 3. Endothelium-dependent relaxation of arteries on acetylcholine. Subcutaneous artery (a): curve *1*, control ($n = 6$); curve *2*, L-NNA + indomethacin ($n = 6$); curve *3*, Ba^{2+} + L-NNA + indomethacin ($n = 3$); curve *4*, Ba^{2+} + ouabain + L-NNA + indomethacin ($n = 1$). Subcutaneous artery branch (b): curve *1*, control ($n = 5$); curve *2*, L-NNA + indomethacin ($n = 5$); curve *3*, Ba^{2+} + L-NNA + indomethacin ($n = 6$); curve *4*, Ba^{2+} + ouabain + L-NNA + indomethacin ($n = 7$). Calf-muscle arteries (c): curve *1*, control ($n = 6$); curve *2*, L-NNA + indomethacin ($n = 6$); curve *3*, Ba^{2+} + L-NNA + indomethacin ($n = 6$); curve *4*, Ba^{2+} + ouabain + L-NNA + indomethacin ($n = 5$). *, #, $p < 0.05$ as compared with the curve *2*.

were much milder than in the gastrocnemius-muscle arteries. The subcutaneous artery relaxation with an increase in $[K^+]_{out}$ did not change in the presence of Ba^{2+} but was blocked by ouabain (that is, it was caused by the effect of Na^+/K^+-ATPase). It is remarkable that relaxation and, respectively, the effect of ouabain were manifested in the area of low $[K^+]_{out}$. EDH relaxation of the subcutaneous artery also disappeared in the presence of ouabain. In addition to the subcutaneous artery, such a "total" dependence of relaxation reactions on the activity of Na^+/K^+-ATPase is typical for some other peripheral arteries, for example, small mesentery arteries [2].

The subcutaneous artery branch did not relax with an increase in $[K^+]_{out}$ (independently of the presence of Ba^{2+}), but demonstrated a low level of relaxation (which was removed by the K_{IR}-channel blockade) under the effect of EDH. Such different recruitment of K_{IR}-channels via two effects can be explained by the location of these channels in the vessel wall. K_{IR}-channels located between the endothelium and SMCs can be activated during a local increase in $[K^+]_{out}$ but can be inaccessible to "external" K^+ due to the screening by endothelial and smooth-muscle cells. Thus, the contribution of K_{IR}-channels is small in the skin arteries, but can be increased with a decrease in the artery diameter (for example, in the kidney) [25].

CONCLUSIONS

We demonstrated that K_{IR}-channels play an important role in the reactions of skeletal-muscle arteries both during a global increase in $[K^+]_{out}$ and during the activation of the endothelium. These reactions are pronounced much more weakly in the skin arteries than in skeletal-muscle arteries. This means that K_{IR}-channels are more important for the regulation of the tone of skeletal-muscle arteries than skin region arteries.

Such a conclusion is consistent with ideas about the role of K^+ as a local regulator of vessel tone. K^+-dependent relaxation and the role of K_{IR}-channels as its key mediators should be more pronounced in organs in which the intensity of metabolic processes and the speed of the bloodstream can be changed over a wide range; the skeletal muscle is such an organ [26]. As opposed to muscles, the bloodstream in the skin is mainly regulated by nerve effects, while the contribution of local regulatory mechanisms is small. Correspondingly, the contribution of K_{IR}-channels to the regulation of the tone of skin arteries is small.

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