EFFECT OF RESTRICTION OF OXYGENATION OF VASCULAR SMOOTH MUSCLES ON CONTRACTILE EFFECTS OF DIRECT ELECTRICAL AND MECHANICAL STIMULATION

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Modern views on the mechanisms of regulation of vascular tone are based on abundant experimental data showing the sensitivity of vascular smooth muscles to neurogenic stimuli, to stretching, and to products of cell metabolism [6, 8, 10]. The writers recently showed that when oxygenation of the perfusion fluid is restricted, responses of rhythmically active vascular smooth muscles to electrical stimulation [1, 3] and to graded stretching [4] are weakened. There is evidence [2, 3, 7, 12] that the cause of this phenomenon is the lowered excitability of smooth muscle cells of the vessel wall when their oxygenation is restricted. However, the possibility cannot be ruled out that changes in reactivity of vascular smooth muscles may be due to the effect of oxygen deficiency on the mechanisms of neuromuscular synaptic transmission. The object of the present investigation was to study the effect of oxygen deficiency on contractile responses evoked by direct electrical and mechanical stimulation of vascular smooth muscles.

EXPERIMENTAL METHOD

Experiments were carried out on preparations of the rat portal vein after sympathetic transmission had been blocked (by perfusion with Krebs' solution with the addition of guanethidine in a concentration of 2 mg/liter for 30 min before the beginning of the experiment and throughout its course) and on segments of the extra-abdominal part of the human umbilical vein after sympathetic denervation [5, 14]. The vessels for testing were placed in a thermostatically controlled chamber enabling continuous perfusion of the preparations with Krebs' solution at 37°C, and were subjected to initial passive stretching with a force of $3 \cdot 10^{-3}$-$7 \cdot 10^{-3}$ N. Contractile activity of the smooth msucles was recorded by means of a 6MKhZS mechanotron transducer. Electrical stimulation was by square pulses (20 V, 20 msec, 16 Hz). A special mechanical system provided rapid stretching of the preparation with an assigned force, subsequent removal of the force, and recording of isometric contractile activity. The partial pressure of oxygen (pO_2) in the perfusion fluid varied between 181, 40, and 25 gPa. The value of pO_2 directly near the surface of the preparation was monitored polarographically; pH of the buffer solution was measured by the pH-340 instrument.

EXPERIMENTAL RESULTS

Perfusion of the portal vein preparations with Krebs' solution containing guanethidine to block sympathetic transmission led after a delay of about 30 min to abolition of the effect of electrical stimulation of the sympathetic fibers, together with a marked rise in the level of tonic contraction of the smooth muscles and a considerable increase in amplitude of their phasic contractions. This was perhaps due to the direct effect of guanethidine on the membrane of the smooth-muscle cells, causing its depolarization and increased excitability.

Under the same conditions the writers previously [1] compared contractile responses of smooth muscles of the portal vein to direct electrical stimulation during perfusion with normally oxygenated and hypoxic Krebs' solutions. Restriction of the oxygenation level (pO_2 about 40-25 gPa) reduced the effect of direct stimulation of smooth muscles of the vascular wall on average to 36.0 $\pm$ 8.6%.

After blocking of sympathetic transmission rapid stretching of the portal vein preparation with a force of $3 \cdot 10^{-3}$ and $6 \cdot 10^{-3}$ N during perfusion with normally oxygenated Krebs' solution (pO_2 181 gPa) caused a distinct myogenic reaction, the intensity of which depended on the magnitude of the stretching force. The amplitude of phasic contractions of the smooth muscles was increased on average from $5.32 \cdot 10^{-3} \pm 0.44 \cdot 10^{-3}$ to $7.19 \cdot 10^{-3} \pm 0.58 \cdot 10^{-3}$ N and from $5.17 \cdot 10^{-3} \pm 0.40 \cdot 10^{-3}$ to $8.28 \cdot 10^{-3} \pm 0.55 \cdot 10^{-3}$ N, respectively, i.e., by 35 and 60% compared with the initial level (Fig. 1). (Fig. 1).

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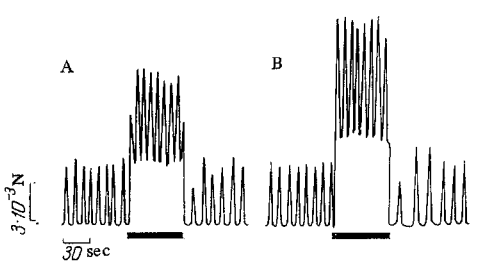

Fig. 1

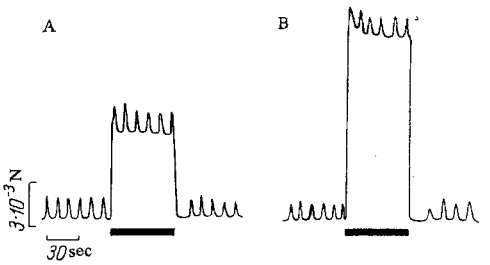

Fig. 2

Fig. 1. Contractile responses of smooth muscles of rat portal vein to stretching with different force during perfusion with oxygenated Krebs' solution (pO_2 = 181 gPa). A) Source of stretching $3 \cdot 10^{-3}$ N and B) $6 \cdot 10^{-3}$ N.

Fig. 2. Contractile responses of smooth muscles of rat portal vein to stretching with different force during perfusion with hypoxic Krebs' solution (pO_2 = 40 gPa). A) Force of stretching $3 \cdot 10^{-3}$ N and B) $6 \cdot 10^{-3}$ N.

Under these conditions a fall in the oxygenation level of the perfusion fluid (pO_2 not more than 40 gPa) not only reduced the visible manifestations of rhythmic myogenic activity [1-4], but also caused a significant weakening of the contractile responses of smooth muscles of the portal vein to rapid stretching: A force of $3 \cdot 10^{-3}$ and $6 \cdot 10^{-3}$ N led to an increase in amplitude of the phasic contractions from $1.58 \cdot 10^{-3} \pm 0.14 \cdot 10^{-3}$ to $1.82 \cdot 10^{-3} \pm 0.10 \cdot 10^{-3}$ N and from $1.58 \pm 10^{-3} \pm 0.14 \cdot 10^{-3}$ to $1.99 \cdot 10^{-3} \pm 0.13 \cdot 10^{-3}$ N, respectively, or by 15 and 26% on average, i.e., only half the increase observed during normal oxygenation (Fig. 2). There was no change in the pH of the buffer solution.

Normalization of the oxygenation level of the perfusion fluid led to recovery of the original degree of tonic contraction of the smooth muscles, of the amplitude of phasic contraction ($5.24 \cdot 10^{-3} \pm 0.35 \cdot 10^{-3}$), and also the intensity of their responses to stretching (to $6.94 \cdot 10^{-3} \pm 0.64 \cdot 10^{-3}$ N during stretching with a force of $3 \cdot 10^{-3}$ N and to $8.41 \cdot 10^{-3} \pm 0.71 \cdot 10^{-3}$ N during stretching with a force of $6 \cdot 10^{-3}$ N). The response of the vascular smooth muscles to oxygen deficiency in the perfusion fluid was thus completely reversible.

Smooth muscles of the isolated vessels of the umbilical cord as a rule have the property of automatic contraction. The amplitude of phasic contractions of the smooth muscles of the umbilical vein was usually higher than that of the arteries and their response to stretching was more clearly defined [11, 13], so that it is preferable to use these preparations. In cases when rhythmic contractile activity of the smooth muscles of the umbilical vein was not observed initially, a phenomenon of "stringent conditions of excitation" [9] often took place: In response to an electrical or mechanical stimulus, the vascular preparation during testing switched from the resting state to a self-oscillating cycle. This state of automatic rhythmic activity after a single triggering stimulus was maintained for several hours.

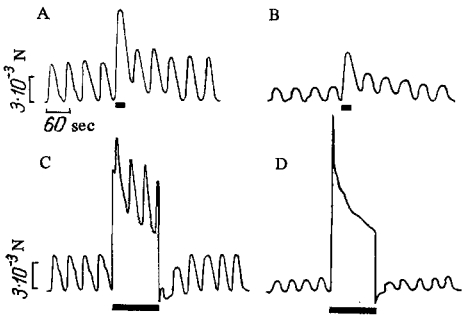

Fig. 3. Contractile responses of smooth muscles of umbilical vein to electrical stimulation (A, B) and stretching (C, D) during perfusion Krebs' solution. A, C) pO_2 = 181 gPa; B, D) pO_2 = 26 gPa.

Under normal oxygenation conditions (pO_2 = 181 gPa) rhythmic activity of the smooth muscles of the umbilical vein was recorded in the form of phasic contractions (amplitude $3 \cdot 10^{-3}$ and $5 \cdot 10^{-3}$ N, mean frequency two contractions per minute). A fall in the oxygenation level (pO_2 = 26 gPa) led to a reduction in amplitude of the phasic contractions by 50-67%. The effect of direct electrical stimulation of the smooth muscles under these conditions also was less marked: On average it did not exceed 48% of that observed under normal oxygenation conditions (Fig. 3A, B). The response of the smooth muscles of the umbilical vein to oxygen deficiency also was completely reversible.

If the normal level of oxygenation of the perfusion fluid was maintained, rapid stretching of the umbilical vein preparation with a force of $10 \cdot 10^{-3}$ N led to a marked increase in tonic contraction and an increase in the amplitude of phasic contractions on average by 60% compared with initial values. With a fall in the oxygenation level (pO_2 = 26 gPa) the active myogenic response to stretching was virtually absent (Fig. 3C, D).

It can be considered from the results of these experiments that the substantial reduction in the observed increase in smooth muscle contraction in response to electrical stimulation and in the active myogenic response to rapid stretching is connected with lowering of the reactivity of the vascular smooth muscles when their oxygenation is restricted. The ability of the vascular wall to correct the effects of neurogenic and myogenic influences, based on this phenomenon, may in turn be one of the mechanisms whereby oxygen deficiency participates in the regulation of regional vascular tone.

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