LACTIC ACID AS A FACTOR IN CHANGES OF VASCULAR REACTIVITY

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Results showing that contractile responses of isolated vascular segments to electrical stimulation are replaced by relaxation if the preparations are contained in a solution with lactic acid are described. Ability to contract is not completely lost under these circumstances but it is manifested only during very strong stimulation. The changes in the character of response to electrical stimulation are connected both with changes in the pH of the solution and with the specific action of the lactic acid.

KEY WORDS: *Lactic acid; vascular reactivity*

The question of the role of lactic acid as a possible physiological factor in vasodilatation has been discussed by several writers. The lactic acid concentration rises during working hyperemia [9] and also during atrophy of muscles; vasodilatation is also observed in these cases. The character of the vascular responses of skeletal muscles is connected with the properties and metabolism of the surrounding tissue [4, 13]. An increase in the lactic acid concentration in the blood during vasodilatation induced by stimulation of the sympathetic chain in the presence of ergotoxin and resperine has been interpreted by some workers as the result of the metabolic influence of the sympathetic system on the muscle fiber [1, 3]. Since the direct effect of lactic acid on vascular tone is weak, this suggests that lactic acid can acquire the role of a regulatory factor as a vasodilator by modifying the reactive properties of the vessels [2].

In this investigation the effect of lactic acid on contractile responses of isolated vascular segments to electrical stimulation was studied. These responses are regarded as the results of the direct action of the electric current on the membrane of the smooth-muscle cells [7, 8].

EXPERIMENTAL METHOD

Isometric responses of rings of the distal part of the aorta and femoral arteries of cats and rabbits (external diameter from 0.6 to 3 mm, width 1-2 mm) to electrical stimulation (varying in frequency, strength, and duration) were recorded by means of a mechanotron of the 6MKhIS type. The preparations were kept in aerated salt solution to which lactic acid was added up to concentrations of 0.1 and 5.5 mg/ml (or 1-55 mM); the pH of the solution changed accordingly from 7.4 to 5.5.

EXPERIMENTAL RESULTS AND DISCUSSION

The effect of lactic acid on the tone of the isolated vascular segments depended on its concentration in the solution. With relatively low concentrations (0.1-1 mg/ml) the tone of the preparations remained unchanged or fell, whereas in high concentrations the tone of the smooth-muscle structures of the vessels increased. Differences in the vasomotor action of different concentrations of lactic acid have also been observed in the intact animal [2].

The changes in the vascular responses to electrical stimulation also depended on the dose of lactic acid and they consisted of weakening of the contraction or its replacement

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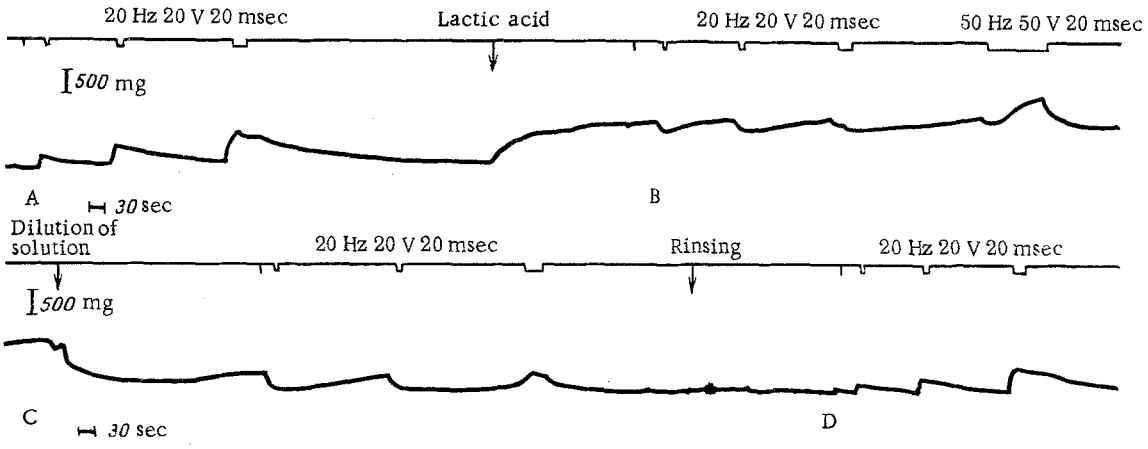

Fig. 1. Effect of lactic acid on response of isolated vascular segments to electrical stimulation. A) Initial responses; B, C, D) responses after addition of lactic acid and its partial and complete removal from the solution, respectively. From top to bottom: marker of stimulation, change in tonic contraction of smooth-muscle elements of vessels (mechanogram of vascular segment).

by relaxation. The latter was particularly characteristic of relatively moderate doses of lactic acid. However, the ability of the vessels to respond by contraction was not lost, but very strong stimulation was required to manifest it. Results obtained during stimulation of a ring from the cat femoral artery are shown in Fig. 1. A change in the duration of the stimulating volley from 1 to 30 sec (with a constant frequency of 20 Hz and strength of 20 V, duration of each pulse 20 msec) was accompanied by an increase in the strength of the contrations. After the addition of a relatively large dose of lactic acid (3.6 mg/ml), leading to an appreciable rise in the original tonic contraction of the vascular segment (by 900 mg), the character of the responses of the preparation to electrical stimulation with the same quantitative characteristics changed radically. In response to stimulation for 1, 5, and 10 sec, instead of the contraction observed previously, relaxation developed. This relaxation also took place if the duration of the stimulating volley was increased to 30 sec, but in this case, the initial relaxation was immediately followed by a very weak contractile response. To evoke a marked constrictor response very strong stimulation was required (50 Hz, 50 V, duration 2 min). In this case also, however, the contraction developed immediately after initial relaxation. On partial dilution of the solution in the chamber (a decrease in the lactic acid concentration) the tonic contraction of the preparation was reduced and, against this background, short stimulation continued to evoke relaxation of the vascular ring, whereas stimulation for 30 sec led to its contraction. In this case not only was the well-known dilator action of small doses of lactic acid manifested, but a change to the opposite type of response to stimuli which previously had caused contraction was observed. Complete replacement of the solution led to recovery of the original contractile response to all types of stimulation used. These results point to the reversibility of changes in vascular responses induced by lactic acid.

Under the influence of lactic acid, not only was the response of contraction replaced by relaxation, but the threshold of the contractile responses was also shifted toward higher frequencies, strengths, and duration of stimulation. After partial rinsing of the preparation or complete replacement of the solution the thresholds of the contractile responses conversely were reduced.

Although in principle the level of tone is of great importance for vascular reactivity, the role of the initial tonic contraction of the vascular segments modified by lactic acid in the determination of the character of responses to electrical stimulation was evidently not decisive. In fact, dilator responses to stimulation which arose against the background of tonic contraction raised by lactic acid still persisted even after restoration of normal tone following partial removal of the lactic acid from the solution surrounding the preparation. Conversely, radical changes in vascular responses (replacement of dilatation by constriction) also took place even when the initial tone was unchanged as the result of total removal of the lactic acid.

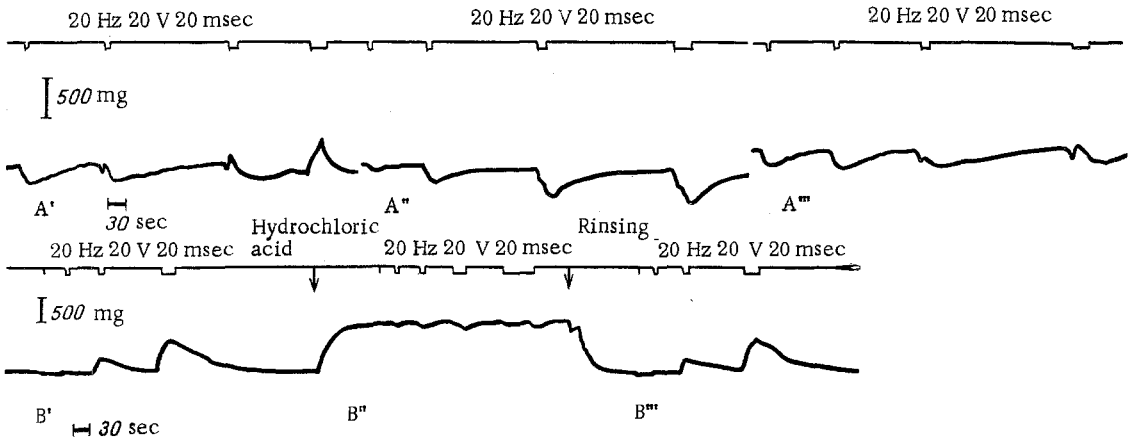

Fig. 2. Effect of pH of solution on response of isolated vascular segments to electrical stimulation. A', A", A'") responses before and after addition of lactic acid and subsequent addition of alkali restoring normal pH of solution. B', B", B'") responses before and after addition of hydrochloric acid and its subsequent removal from solution respectively. From top to bottom: marker of stimulation, change in tonic contraction of smooth-muscle elements of vessels (mechanogram of vascular segment).

Lactic acid also changed the character of vascular responses to electrical stimulation if its addition had no significant effect on the tone of the preparations (Fig. 2). A vascular ring from the distal part of the rabbit aorta responded initially by relaxation (constant parameters 20 Hz, 20 V, 20 msec). A multiphasic response of relaxation followed by contraction and, again, by relaxation occurred to stimulation for 10 to 20 sec. Contraction was observed to stimulation of the ring for 40 sec. After the addition of lactic acid to the solution relaxation of the preparation arose both to stimulation for 5 sec and to longer periods of stimulation. After addition of lactic acid the relaxation responses were preserved and the thresholds of stimulation for the development of contractile responses were increased, i.e., the range of the stimulating action within which relaxation of the vessels arose was widened.

Some workers connect changes in vascular reactivity under the influence of lactic acid with the change in pH of the solution, since similar changes arose during the passage of 100% CO_2 through the solution [14]. In the present experiments the addition of hydrochloric acid to the solution evoked similar changes in the character of the vascular responses to electrical stimulation; replacement of contraction by relaxation (Fig. 2). Subsequent rinsing of the preparation to remove the acid lowered its tone and restored the contractile responses. It has also been shown that contractile responses of strips of veins [15] and also of the pulmonary artery of dogs and rabbits [12] to electrical stimulation are weakened in an acid medium. However, the changes evoked by lactic acid in the responses were partly preserved even after restoration of the original pH value. After normalization of the pH of the solution by the addition of alkali, the initial values and character of the responses to electrical stimulation were not fully restored (Fig. 2). Consequently, when it acts on the reactivity of the smooth-muscle elements of vessels, lactic acid may behave both as a specific factor and as an agent modifying pH. These observations are in agreement with those of other workers [11] who found that the contractile responses of strips of aorta and pulmonary and mesenteric arteries of rabbits to adrenalin, when reduced by the action of lactic acid, were not restored if the pH was maintained at 7.0. The addition of sodium lactate instead of lactic acid did not reduce the vascular responses to adrenalin.

The vasomotor effect of lactic acid is explained by the action of H^+ on the membrane mechanism of excitation [5]. Laborit and Weber [11] consider that the hypotonic action of lactic acid is explained by its replacement of bicarbonate cations and by an increase in the concentration of carbonic acid. These workers consider that during the formation of salts of carbonic acid the source of Na^+ and K^+ ions is ATPase, which stabilizes the Ca^{2+} inside the endoplasmic reticulum. By acting directly on the excitability of the membrane of the smooth-muscle cells and on the mechanism of coupling of excitation and contraction [7, 8], electrical stimulation evidently finds the reactive structures of the vessels in a functional

state modified by lactic acid, and this determines the character of the response. The action of lactic acid on the ionic permeability of the cell membrane can also be a basis for the change in vascular reactivity [6].

By its specific action and its effect on the pH of the solution, lactic acid thus changes the responses of the smooth-muscle elements of blood vessels to electrical stimulation. This confirms the view that lactic acid, as a natural metabolic factor, influences the vessels and the blood stream not only directly, but also by modifying their reactive properties toward stimulating factors. Under the influence of lactic acid there is a tendency for the smooth-muscle cells of the vessels to respond by relaxation to stimuli which previously evoked contraction. A change in the reactivity of the vessels could perhaps be the mechanism of their regulation by lactic acid.

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