QUANTITATIVE CHARACTERISTICS OF PRESSOR REFLEXES TO APPLICATION OF LACTIC ACID TO THE EPICARDIAL AND PERICARDIAL REFLEXOGENIC ZONES

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Experiments on vagotomizedcats showed that the action of lactic acid solutions on the epicardial and pericardial reflexogenic zones evokes interoceptive and nociceptive pressor reflexes. The threshold concentration for interoceptive reflexes is 2 mM and for nociceptive reflexes from 3 to 15 mM.

The relationship between interoceptive and nociceptive pressor reflexes in response to the action of potassium ions and acetylcholine on the epicardium and pericardium of vagotomized animals has been studied previously [4, 8]. In the investigation described below these relationships were studied when another stimulus (lactic acid) was used. This metabolite is formed in an increased quantity in some pathological conditions [14] and also during intensified cardiac activity [6].

The main purpose of the investigation was to determine the lactic acid concentrations capable of inducing interoceptive and nociceptive reflexes when applied to the epicardium and pericardium connected to the brain and spinal cord only by nerve fibers of spinal origin.

EXPERIMENTAL METHOD

Experiments were carried out on 10 cats anesthetized with urethane (1-1.5 g/kg). After preliminary vagotomy and application of artificial respiration the anterior parts of the 5th and 6th left ribs were removed. The pericardium was opened and sutured to the edges of the wound in the chest wall. The heart was irrigated with lactic acid solutions whose concentrations ranged from 1.5 to 62.5 mM, and whose pH values ranged correspondingly from 3.35 to 2.5. After each stimulation the pericardial cavity was rinsed out with 80-100 ml warm Ringer's solution. The interval between successive stimulations was about 15 min. The character and magnitude of the response were assessed from changes in the pressure in the femoral artery.

EXPERIMENTAL RESULTS AND DISCUSSION

Application of lactic acid in concentrations of 1.95-62.5 mM to the epicardium and pericardium of vagotomized cats evoked pressor responses which were abolished by local application of procaine (Fig. 1A). It thus follows that the elevation of the arterial pressure was reflex in origin. In one experiment, application of lactic acid solutions in concentrations of 4.8 mM and above, and in another experiment in concentrations of 31.2 mM and above, led to the development of depressor reflexes. However, these were not neurogenic, because they persisted (Fig. 1B) after extirpation of the stellate ganglia and intravenous injection of atropine (1 mg/kg).

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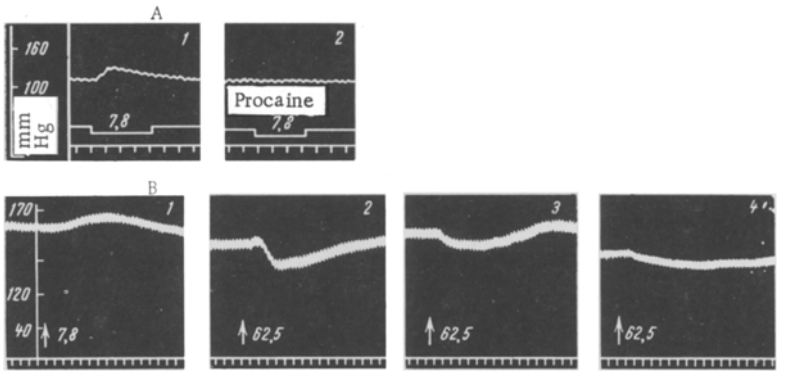

Fig. 1. Pressor (A) and depressor (B) responses to application of lactic acid to the epicardium and pericardium. In A: 1) response to application of lactic acid; 2) absence of response after preliminary irrigation of epicardium and pericardium with procaine; in B: 1) pressor reflex to action of a relatively low concentration of lactic acid; 2) depressor reflex after application of high concentration of lactic acid; 3) preservation of depressor effect after injection of atropine; 4) depressor effect after removal of stellate ganglia. From top to bottom: blood pressure, marker of stimulation, time marker 5 sec, zero line of time marker. Numbers denote lactic acid concentration (in mM).

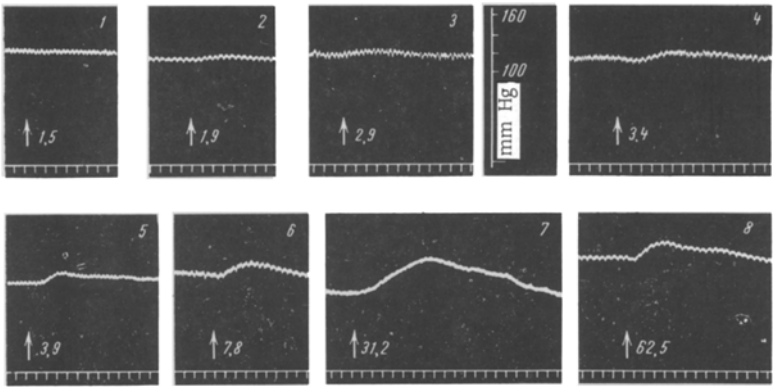

Fig. 2. Relationship between amplitude of vasomotor reflexes and lactic acid concentration. From top to bottom: blood pressure, time marker 5 sec, zero line of time marker. Numbers by arrows show lactic acid concentration (in mM).

Depressor responses of this type (Fig. 1B) are most likely to be due to resorption of lactic acid [16] and to its vasodilator action [11, 13]. In Kulaev's experiments [2] on cats with intact bulbar and spinal fibers, application of 0.1-3% acetic acid solution to the pericardium evoked pressor reflexes in almost every case.

Judging from the changes in arterial pressure, threshold reflexes in 7 experiments occurred when the lactic acid concentration was 1.95 mM, and in 3 experiments 2.92 mM.

After an increase in the lactic acid concentration up to 31.2 mM the amplitude of the pressor reflexes increased. However, a further increase (up to 62.5 mM) in the acid concentration gave a smaller increase in arterial pressure. The concentration–effect curve now consisted of three parts (Fig. 3B). The first part of the curve corresponded to relatively low concentrations of the acid and was gently sloping in character. In the region between 8 and 30 mM, the amplitude of the reflexes increased considerably,

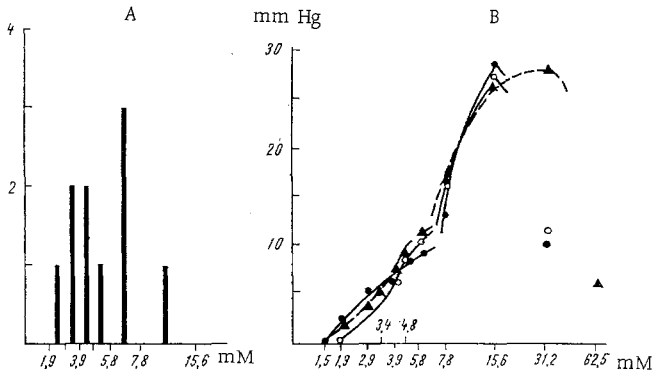

Fig. 3. Histogram of scatter of thresholds of nociceptive responses (A) and concentration–effect graphs (B). In A: abscissa, lactic acid concentration (in mM) required to evoke nociceptive reflexes; ordinate, number of experiments. In B: abscissa, lactic acid concentration (in mM), ordinate, degree of elevation of blood pressure (in mm Hg).

thus producing a second branch of the concentration–effect curve. Injection of very high concentrations of lactic acid into the pericardial cavity evoked slight vasomotor reflexes, and the third branch of the curve was formed.

All the experiments gave a similar type of curve. However, the region where the second branch began varied over a wide range, from 3 to 15 mM (Fig. 3A). The scatter of the results in the region of the flexion of the curve prevented averaging of the results of all 10 experiments. This was possible only for 3 experiments (Fig. 3B). The same type of curve was obtained in response to stimulation of the spinal afferent system of the epicardium and pericardium by potassium ions and acetylcholine [4, 8], and also in response to the action of these substances on other reflexogenic zones [1, 9].

The first part of the concentration–effect curve relates to interoceptive reflexes, while the region of transition to the second branch corresponds to the threshold of nociceptive stimulation [7].

It was, in fact, accompanied not only by changes in the blood pressure but also by other characteristic responses to pain. Blood taken from the caudal vena cava of a vagotomized animal immediately after stimulation of the heart has been shown to exhibit a positive inotropic effect on the frog's heart perfused by Straub's method, starting in a concentration corresponding to the appearance of the second branch of the curve. In addition, when the stimulating substance was applied in a concentration very close to the point of inflection, potentiation of the electrical activity of the flexor muscles of the left forelimb was observed [5].

The threshold concentrations necessary for appearance of nociceptive reflexes obtained in these experiments (3-15 mM or, in pH units, 3.25-2.85), agree with those obtained by other workers [10]. In their experiments, the application of lactic acid to the base of a cantharidin blister gave rise to a sensation of pain in man starting from pH 3.0-4.0. In view of the facts described above, the first part of the concentration–effect curve can be regarded as interoceptive, and the second part as nociceptive.

Are these threshold concentrations of lactic acid close to the variations in its concentration encountered under natural conditions?

Many investigators [12, 14, 15] have obtained evidence that in a state of relative rest the blood lactic acid concentration is 10-20 mg%. However, during muscular work, myocardial hyperfunction, and also in an inflammatory exudate, the lactic acid concentration rises sharply to 100-250 mg% [6, 12, 14].

The spinal afferent system of the epicardium and pericardium has been found to be highly sensitive to the action of lactic acid: interoceptive reflexes appeared in response to an increase in concentration of between 2 and 3 mM (or 18 and 27 mg%), while nociceptive reflexes appeared at concentrations of 3-15 mM (or 27-135 mg%). Accordingly the fluctuations in lactic acid concentration taking place under natural conditions can, in principle, evoke an interoceptive and nociceptive reflex.

It must be emphasized that the pressor character of the reflexes to lactic acid stimulation of the spinal afferent system of the epicardium and pericardium is analogous to that of reflexes to stimulation of the same zones with potassium ions and acetylcholine. Meanwhile, during lactic acid stimulation the pressor reflexes, having reached their maximum, decrease rapidly with a further increase in the lactic acid concentration (Fig. 3B). A possible explanation of this fact is that many acids, in high concentrations, have an inhibitory action on the peripheral portion of the spinal afferent system [3].

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