CHANGES IN THRESHOLD OF EPICARDIAL AND PERICARDIAL STIMULATION ASSOCIATED WITH INFLAMMATION AND VIBRATION OF THE CHEST WALL

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Autonomic (principally vasomotor) and somatic components of the "nociceptive" response produced in animals by the action of potassium ions on the epicardium and pericardium were investigated in experiments on vagotomized dogs. The minimum algogenic dose of potassium for the intact heart membranes was found to be about 30 mmoles/liter, falling in the presence of inflammation to 10-15 mmoles/liter. Vibration of the juxtacardiac zone of the chest wall inhibits the development of the nociceptive response to potassium ions in concentrations of up to 125 mmoles/liter.

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The sensory function of the intact epicardium and pericardium has been studied in considerable detail [4, 6, 8, 12]. However, the sensitivity of inflamed membranes of the heart has not, apparently, been investigated.

Potassium ions liberated from excited cells can act as a natural adequate stimulus of tissue receptors [7, 11]. An excess of potassium is known to accompany any injury. At the same time, potassium ions can act as algogenic stimuli [3, 11, 14].

Under normal conditions, the threshold nociceptive effect in cats anesthetized with urethane arises when the potassium concentration is 31.2 mmoles/liter [8]. Bearing in mind that its concentration in an inflammatory exudate is 7-12 mmoles/liter [17], it is reasonable to conclude that under natural conditions potassium in this concentration cannot give rise to pain.

For the reasons given above it was decided to compare threshold concentrations of potassium for development of the "nociceptive response" from the intact and inflamed epicardium and pericardium.

A second reason for this investigation was investigations showing that causalgia can be effectively treated by therapeutic procedures such as immersion of the limb in a bath with gently moving water, followed by massage [18]. Trent [22] has reported a case of the release of pain when the patient struck a hard surface with his fingers.

Attempts were made to prevent the development of the nociceptive response by a similar procedure. The effect of factors reducing and increasing the threshold of this response was studied.

EXPERIMENTAL METHOD

Experiments were carried out on dogs anesthetized with urethane (1 g/kg). Under artificial respiration, a window was formed in the chest wall, to which the opened pericardium was carefully sutured. A warm solution of KCl, in a dose of 3 ml, was injected into the pericardial sac. The concentration of KCl was increased with successive stimuli (7.8, 10.4, 15.6, 20.8, 31.2, 62.5, and 125 mmoles/liter). The stimulus was rinsed away with 200 ml Ringer's solution (38°). The interval between stimuli was about

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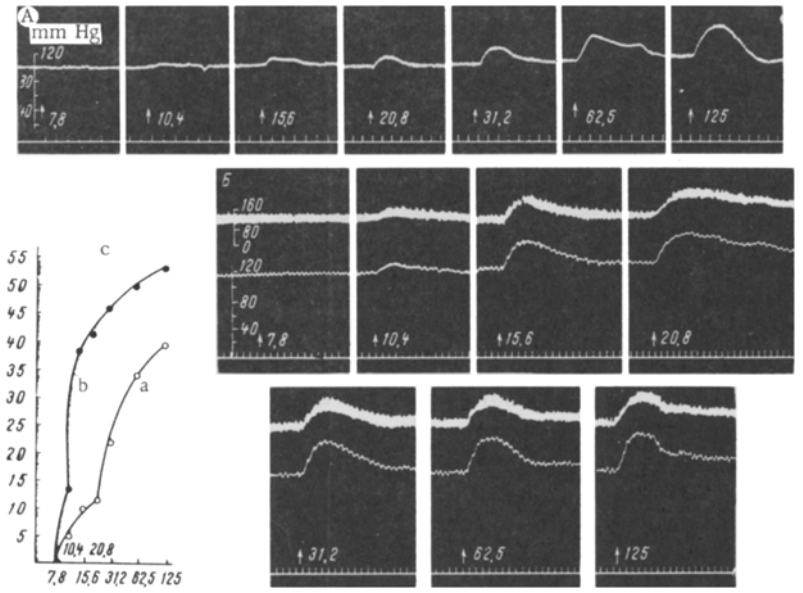

Fig. 1. Relationship between amplitudes of vasomotor reflexes and potassium ion concentrations applied to intact (A) and inflamed (B) heart membranes. From top to bottom: blood pressure, time marker (5 sec), also acting as zero line of blood pressure; arrows show beginning of stimulation, numbers give KCl concentration (mmoles/liter); a) pressure recorded by mercury manometer; b) by mercury and spring manometers; c) effect of experiments. Abscissa, KCl concentration (in mmoles/liter); ordinate, amplitude of reflex increase in blood pressure (in mm Hg). A) Reflexes with epicardium and pericardium intact, B) inflamed.

15 min. During stimulation, observations were made on the pupillary reaction, the motor response, and the blood pressure in the femoral artery. The blood pressure was recorded by a mercury (mean pressure) and spring (maximum and minimum) manometer.

Taking into account the results of physiological and clinical observations indicating the special role of spinal fibers in the transmission of nociceptive stimuli from the heart [5, 15], and also the avoidance of effects connected with the vagus nerve system, in all the experiments the vagus and aortic nerves and, in some experiments, the phrenic nerves also, were divided before the beginning of stimulation.

Three series of experiments were carried out on 24 animals. In 9 experiments of series I the nociceptive response was determined for the intact epicardium and pericardium. In 8 experiments of series II the threshold was determined in the presence of pericarditis caused by injection of 0.2 ml turpentine or the same volume of 2% tincture of iodine into the pericardial cavity. The threshold of the nociceptive response was established 3-4 days after operation. In experiments of series III on 7 animals, besides nociceptive stimulation of the intact pericardium, vibration (3 mm, 50 Hz) was applied to the juxtacardiac zone of the chest wall.

EXPERIMENTAL RESULTS

Stimulation of the epicardium and pericardium with potassium ions in these experiments gave rise to pressor effects (Fig. 1A), disappearing after irrigation of that zone with 2% procaine solution. The increase in arterial pressure usually began with a KCl concentration of 10.4 mmoles/liter, and increased progressively with each new stimulation. However, the pressor reflexes were varied in character. In 7 of 9 experiments, starting with a concentration of 31.2 mmoles/liter, the steepness of the reflex rise in blood pressure increased appreciably, while the amplitude of the reflexes became disproportionately large (Fig. 1c). In addition, after administration of KCl in a concentration of 31.2 mmoles/liter, in 6 experiments movements of the left fore-limb, twitching of the left ear, and dilatation of the pupils were observed. Consequently, a complex of autonomic and motor reflexes, belonging to the category of a nociceptive response [23], developed.

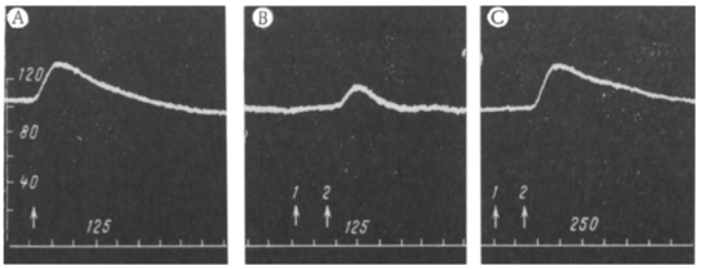

Fig. 2. Inhibition of nociceptive reflexes from heart membranes during application of vibration to juxtacardial region of the chest wall. From top to bottom: blood pressure (mercury manometer), time marker (5 sec), also acted as zero line of blood pressure; arrow indicates application of KCl solution, numbers show KCl concentration (in mmoles/liter); on kymograms B and C, arrow 1 denotes beginning of vibration, arrow 2 application of KCl solution.

Weighty evidence that reflexes to stimulation of the heart membranes by KCl in a concentration of 31.2 mmoles/liter are of the nociceptive category is given by the results of experiments in which potassium was applied to the human skin. If applied in concentrations close to this, a sensation of pain is produced [17]. Objections against the comparison of thresholds obtained with and without anesthesia are invalid. Recent investigations have shown that urethane, in certain doses, can block ascending activation of arousal, but that under these conditions activating nociceptive influences can still reach the cortex without awakening the animal [1].

In the experiments of series II, potassium ions were applied to the epicardium and pericardium 3-4 days after preliminary injection of turpentine or iodine solution into the pericardial cavity. The morphological picture of the epicardium and pericardium in this period revealed marked inflammation. The pericardium was dull, matt, and thickened; its vessels were injected and dilated. The pericardial cavity contained up to 20 ml of turbid fluid. Deposits of fibrin, consisting of grey films, easily removed with a knife, were present on the epicardium and inner surface of the pericardium near the orifices of the venae cavae, atria, auricles, and apex of the heart. Extensive areas of proliferating cells, mainly polymorphs, desquamation of endothelium, and penetration of the vessel walls and surrounding tissues with fibrin were determined microscopically.

After application of KCl to the inflamed pericardium and epicardium, a considerable decrease of threshold was observed (Fig. 1b). In 5 of the 8 experiments the group of reflex responses characterizing the nociceptive response developed with a concentration not of 15.6 mmoles/liter, but of 3-10.4 mmoles/liter. What is the explanation of this decrease in the threshold algogenic doses when the membranes are inflamed?

It has recently been discovered that activation of proteases and kinins [16], which can lower the minimum algogenic dose of potassium, takes place during inflammation. For example, after the action of bradykinin, the threshold for KCl was lowered from 31.2 to 7.8 mmoles/liter, i.e., by four times [10].

In the experiments of series III, together with application of nociceptive stimulation from the epicardium and pericardium, a vibrator attached to the chest wall was switched on. As a result, the minimum algogenic dose of KCl was regularly increased by 3-4 times.

Application of KCl solution to the heart membranes in a concentration of 125 mmoles/liter evoked a strong pressor reflex with a steeply rising curve (Fig. 2a). The vasomotor response was accompanied by movement of the left limb or of the whole shoulder girdle, opening of the mouth, and dilatation of the pupils. The development of all these components of the nociceptive response was prevented by vibration of the chest wall near the heart. In particular, the character of the pressor response was changed: the amplitude of the reflex was reduced almost by half, and the rise in arterial pressure was less steep (Fig. 2b).

Vibration of the chest wall in 6 of the 7 experiments did not inhibit development of the nociceptive response complex following injection of KCl into the pericardial cavity in a concentration of 250 mmoles/liter

(Fig. 2c). After switching off the vibrator, the pressor reflex and other components of the nociceptive response developed completely. Identical results were obtained by other workers exerting pressure on the skin (15-20 mm Hg) or touching it [2].

The results of the present experiments agree well with the new theory of pain – the theory of valve control [20]. Its authors consider that a definite ratio between activities of thick and thin nerve fibers is one of the chief factors in pain development: pain is formed when activity of thin slow-conducting fibers of group C exceeds that of thick, fast-conducting A-fibers. In fact, nociceptive impulses due to the action of potassium on the epicardium and pericardium are transmitted chiefly through the inferior cardiac nerves, consisting almost exclusively of thin fibers [13]. Meanwhile, impulses produced by vibration of the chest wall were directed into the spinal cord. Vibration, pressure, touch, and other such factors are known to intensify the flow of impulses particularly strongly in the thick A-fibers [21]. In this group of experiments, impulses along the systems of thick and thin fibers were thus directed simultaneously into the spinal cord. Under these circumstances the nociceptive response was inhibited.

LITERATURE CITED

1. P. K. Anokhin, Biology and Neurophysiology of the Conditioned Reflex [in Russian], Moscow (1968).
2. A. I. Bakuradze, Proceedings of the Beritashvili Institute of Physiology [in Russian], No. 5, Tbilisi (1943), p. 107.
3. L. A. Baraz and V. M. Khayutin, Fiziol. Zh. SSSR, No. 10, 1289 (1961).
4. N. V. Danilov, in: Nervous Regulation of the Circulation and Respiration. Abstract of Proceedings [in Russian], Moscow (1951), p. 19.
5. A. Irasek, The Surgery of Pain [in Russian], Prague (1959).
6. B. S. Kulaev, The Reflexogenic Zone of the Heart. Potential Possibilities and Role. Doctoral Dissertation [in Russian], Moscow (1967).
7. V. A. Lebedeva, Mechanisms of Chemoreception [in Russian], Moscow – Leningrad (1965).
8. Yu. E. Malyarenko and V. M. Khayutin, in: Physiology and Pathology of the Circulation [in Russian], Moscow (1967), p. 17.
9. V. I. Skok, Fiziol. Zh. SSSR, No. 5, 610 (1969).
10. R. S. Sonina and V. M. Khayutin, Fiziol. Zh. SSSR, No. 3, 291 (1967).
11. V. M. Khayutin, Vasomotor Reflexes [in Russian], Moscow (1964).
12. V. N. Chernigovskii, in: Neurohumoral Regulation in Activity of Organs and Tissues [in Russian], Leningrad (1941), p. 41.
13. A. M. Brown, J. Physiol. (London), 190, 35 (1967).
14. C. A. Keele and D. Armstrong, Substances Producing Pain, London (1964).
15. R. Leriche, Bases de la Chirurgie Physiologique, Paris (1955).
16. G. P. Lewis, Physiol. Rev., 40, 647 (1960).
17. O. Lindahl, Acta Physiol. Scand., 51, Suppl. 179 (1961).
18. W. K. Livingston, Ann. N. Y. Acad. Sci., 50, 247 (1948).
19. P. Mario, Riv. Path. Sper., 1, 149 (1926).
20. R. Melzack and P. D. Wall, Science, 150, 971 (1965).
21. I. M. Tasaki, Nervous Transmission, Springfield (1953).
22. S. E. Trent, J. Nerv. Ment. Dis., 123, 356 (1956).
23. R. S. Woodworth and C. S. Sherrington, J. Physiol. (London), 31, 234 (1904).