EFFECT OF ACETYLCHOLINE ON SENSITIVITY OF THE CARDIAC MEMBRANES TO PAIN

Yu. E. Malyarenko and L. V. Chanturiya

UDC 612.172.6-06:612.181.5

Experiments on vagotomized cats and on cats anesthetized with urethane showed that "painless" concentrations of potassium ions became algogenic under the influence of acetylcholine. It is postulated that pain arising in the heart may be the result of accumulation of acetylcholine as the result of reduced cholinesterase activity or excessive activity of cholinergic fibers.

As a result of negative emotions some people develop pain in the heart, an organ with a powerful cholinergic innervation. It has recently been shown that negative emotions are accompanied by activation not only of the sympathetic, but also of the parasympathetic nervous system [7, 13]. Acetylcholine increases the excitability of spinal afferent fibers [8, 12] responsible for the conduction of nociceptive impulses [3-5, 10].

With these facts in mind, the hypothesis was put forward that the increase in sensitivity of the spinal fibers of the heart up to the level of hyperalgesia may be the result of accumulation of acetylcholine through reduced cholinesterase activity, especially in conjunction with activation of cholinergic fibers. The object of the investigation described below was to test this hypothesis.

EXPERIMENTAL METHOD

In cats anesthetized with urethane (1-1.5 g/kg) and vagotomized cats under artificial respiration the anterior part of the 5th and 6th left ribs was removed. The pericardium was opened and sutured to the edges of the thoracic wound.

In the experiments of series I (8 animals) KCl solution in a concentration of 7.8 to 62.5 mmoles/liter, heated to 37°C, was injected into the pericardial cavity and the threshold of the nociceptive response determined. After each stimulation the pericardial cavity was washed out with 60-70 ml warm Ringer's solution. The interval between stimulations was 10 min. The next stage of the experiment was to determine the minimal algogenic potassium ion concentration after injection of acetylcholine into the pericardial cavity in a concentration of 0.001 μg/ml, which can be regarded as physiologically permissible [9]. Immediately before application of the potassium ions, the acetylcholine was washed out with Ringer's solution.

In the 5 experiments of series II the amplitude of the cardiovascular reflexes evoked by 2 M NaCl solution before and after irrigation of the cardiac membranes with acetylcholine was compared and the relationship between the amplitude of the response and repeated stimulation with the same potassium ion concentration (31.2 mmoles/liter) was determined.

EXPERIMENTAL RESULTS AND DISCUSSION

It was hoped to show by the experiments of series I that excitability of the spinal afferent system of the epicardium and pericardium is increased by the action of acetylcholine in the same way as has been

Department of Normal Physiology, Rostov Medical Institute. (Presented by Academician V. V. Parin [deceased].) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 73, No. 2, pp. 11-15, February, 1972. Original article submitted April 7, 1971.

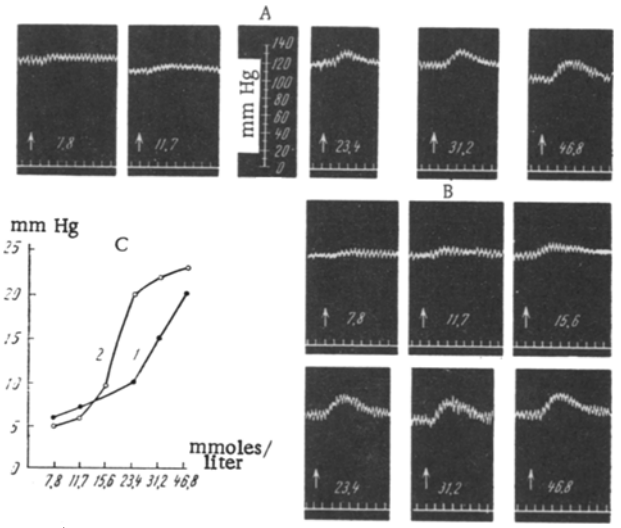

Fig. 1. Quantitative characteristics of cardiovascular reflexes in response to stimulation of cardiac membranes with potassium ions before (A) and after application of acetylcholine to the membranes (B). Blood pressure recorded by mercury manometer. Figures show potassium ion concentration (in mmoles/liter). Arrow indicates moment of stimulation. Time marker (3 sec) also serves as zero line for blood pressure. In graph (C): 1) increase in blood pressure in response to potassium ions before application of acetylcholine; 2) after injection of acetylcholine into pericardial cavity.

shown for the reflexogenic zone of the small intestine [8], the skin of the forearm [14], and the dorsal roots of the spinal cord [12].

As Fig. 1A shows, application of potassium ions to the reflexogenic zone of the epicardium and pericardium induced changes in arterial pressure in concentrations starting with 7.8 mmoles/liter. The writers have previously shown that these changes in pressure are reflex in origin [5]. On application of potassium ions in a concentration of 31.2 mmoles/liter, the vasomotor reflex increases more steeply and becomes disproportionately large, as is clearly seen in the concentration vs reflex graph in Fig. 1C. The zone of the characteristic incisura on the graph is interpreted as the minimal algogenic concentration. After this zone more marked cardiovascular reflexes appear [11], the catecholamine concentration in the blood is increased, and increased electrical activity is visible in the electromyogram of the left forelimb [4]. Nociceptive effects in one experiment of this series were observed after concentrations of 23.4 mmoles/liter, in 4 experiments after 31.2 mmoles/liter, and in 2 experiments after 46.8 mmoles/liter, while in yet another experiment manifestations of a nociceptive response were found after 62.5 mmoles/liter.

After preliminary irrigation of the cardiac membranes with acetylcholine, the amplitude of the reflexes in response to algogenic potassium concentrations increased substantially (Fig. 1B, C). For instance, with potassium ion concentrations of 31.2 mmoles/liter the amplitude of the reflex before application of acetylcholine averaged 19.3 ± 2.2 mm Hg, while after application it averaged 24.9 ± 2.35 mm Hg, i.e., there was an increase of 24%. The threshold of the nociceptive reflex also fell: in one experiment to 11.7 mmoles/liter, in one to 15.6 mmoles/liter, in four to 23.4 mmoles/liter, and in two to 31.2 mmoles/liter.

Acetylcholine can thus convert hitherto nonalgogenic stimuli into algogenic. However, two objections can be raised to this conclusion. First, according to Vvedenskii [1], each successive stimulus can evoke a more marked response because the previous stimulus increases the excitability of the reflexogenic field.

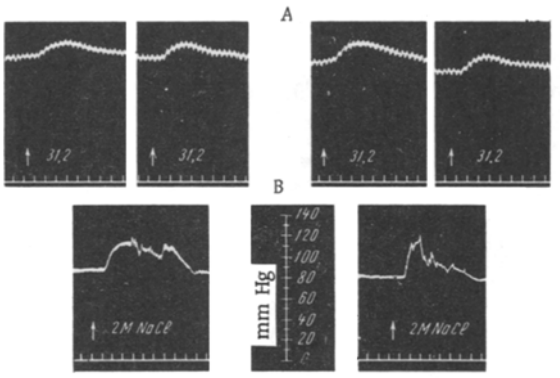

Fig. 2

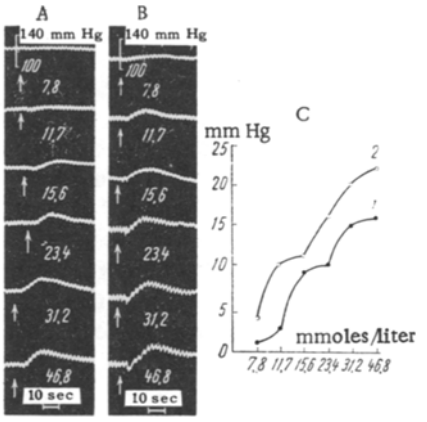

Fig. 3

Fig. 2. Vasomotor reflexes in response to repeated injections of potassium ions into the pericardial cavity (A) and increased sensitivity of the pericardial reflexogenic zone to sodium ions against the background of an excess of acetylcholine (B). Legend as in Fig. 1.

Fig. 3. Increase in sensitivity of spinal afferent system of epicardium and pericardium to potassium ions before (A) and after suppression of cholinesterase activity combined with activation of the cholinergic structures of the heart (B). C) Graphs plotted from kymographic data. Legend as in Fig. 1.

Second, under the influence of acetylcholine, bound potassium is converted into the active form [2], thereby increasing the strength of stimulation of the solution applied.

These problems were solved by the experiments of series II. They showed that repeated stimulation by the same concentration of potassium ions usually evoked an increase in response up to the 3rd or 4th stimulation. The amplitudes of the reflexes shown in Fig. 2A are in the following order: 12, 13, 17, and 14 mm Hg. The increase in amplitude of each successive reflex, judging from the mean values, was 1.5 ± 0.37 mm Hg. This means that the preceding stimulus could not have caused any substantial increase in the response amplitude.

Comparison of the amplitudes of the reflexes in response to injection of 2 M NaCl solution into the pericardial cavity before and after sensitization with acetylcholine shows a marked increase in the excitability of the cardiac afferents (Fig. 2B). Whereas before administration of acetylcholine the mean amplitude of the reflex was 20.6 ± 2.1 mm Hg, after application of acetylcholine it rose to 25.1 ± 2.9 mm Hg, an increase of 21%. In the experiment demonstrated, the amplitude of the reflex increased by 72% after acetylcholine sensitization (38 mm Hg compared with 22 mm Hg in the initial state). Consequently, acetylcholine considerably potentiates the action not only of potassium, but also of sodium ions.

It may be assumed that a disturbance of cholinesterase synthesis or a decrease in its activity, such as takes place for example after ligation of the coronary artery [6], leads to an excess of acetylcholine and to sensitization of nerve fibers. A combination of increased activity of the cholinergic system and decreased cholinesterase activity may contribute to a still greater accumulation of acetylcholine and to the corresponding appearance or continuation of nociceptive sensation.

A situation similar to that described above was created in experiments which are still only in the preliminary stage. Physostigmine was injected into the pericardial cavity and the cardiac branch of the vagus nerve was stimulated. Since urethane anesthesia abolishes the action of physostigmine, in these experiments chloralose anesthesia was used.

In these experiments the threshold of the nociceptive reflex was reduced from 23.4-46.8 to 11.7-23.4 mmoles/liter KCl, while the amplitude of the vasomotor reflexes was increased in the zone both of the interoceptive and of the nociceptive reflexes (Fig. 3).

A possible explanation of the onset of pain in the heart could therefore be that an excess of acetylcholine can increase the nociceptive sensitivity of spinal afferents.

LITERATURE CITED

1. N. E. Vvedenskii, Transactions of the Physiological Laboratory of St. Petersburg University [in Russian], No. 3, St. Petersburg (1908), p. 134.
2. P.A. Kometiani, Sh. V. Dolidze, and E. É. Klein, Biokhimiya, No. 9, 218 (1944).
3. Yu. E. Malyarenko, Byull. Éksperim. Biol. i Med., No. 2, 3 (1970).
4. Yu. E. Malyarenko, Byull. Éksperim. Biol. i Med., No. 4, 3 (1971).
5. Yu. E. Malyarenko and V. M. Khayutin, in: Mechanisms of Neuro-Humoral Regulation of Autonomic Functions [in Russian], Leningrad (1970), p. 43.
6. M. E. Raiskina, N. A. Onishchenko, B. M. Shargorodskii, et al., Methods of Intravital Investigation of Cardiac Metabolism [in Russian], Moscow (1970).
7. P. V. Simonov, Theory of Reflection and the Psychophysiology of Emotions [in Russian], Moscow (1970).
8. R. S. Sonina, in: Abstracts of Proceedings of the 10th Conference of Junior Research Workers of the Institute of Normal and Pathological Physiology [in Russian], Moscow (1964), p. 32.
9. T. M. Turpaev, The Mediator Function of Acetylcholine and the Nature of the Cholinergic Receptor [in Russian], Moscow (1962).
10. E. B. Khaisman and L. G. Fedorova, Acta Anat. (Basel), 76, 505 (1970).
11. V. M. Khayutin, Vasomotor Reflexes [in Russian], Moscow (1964).
12. P. E. Chernilovskaya, Investigation of Vasomotor Reflexes Evoked by the Action of Some Chemical Stimuli on the Tissues of the Limb and Dorsal Root Fibers, Candidate's Dissertation, Moscow (1970).
13. E. Gellhorn and G. Loofbourrow, Emotions and Emotional Disorders [Russian translation], Moscow (1966).
14. C. A. Keele and D. Armstrong, Substances Producing Pain, London (1964).