IONO-HUMORAL INTERRELATIONS DURING THE APPEARANCE AND DEVELOPMENT OF VAGAL INHIBITION OF THE HEART

COMMUNICATION III. CHANGES IN THE EFFECT OF THE VAGUS NERVE WITH ATROPINIZATION OF THE HEART

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In spite of the fact that data exist in the literature on the change in the effect of stimulating the vagus nerve on atropinized visceral organs, until now the idea of the exclusion of the effect of the vagus nerve by means of atropine has been widespread in physiology.

In Communication I we set forth experimental data on the effect of atropine on a mechanogram and electrogram of the heart. It was established that atropine increases and stabilizes the resting potential of the heart muscle, and does not alter the form and duration of the monophase action potentials. The data of the report showed a change in the effect of acetylcholine on an atropinized heart; under these conditions acetylcholine proved to be incapable of changing in the usual way the rate of the restored processes taking place in the heart following depolarization of cellular structures. These data permitted us to suggest that atropine, stabilizing the resting potential of the heart muscle, must first of all disturb the normal process of an increase in polarizibility of cellular structures during stimulation of the vagus nerve. Proceeding from the experimental data and the theoretical conclusions of M. G. Udelnov [2, 3], we assumed that under these conditions the greatest changes will be observed in the chronotropic index of vagal inhibition of the heart.

The present communication is devoted to an examination of the forms of the manifestation of the effect of the vagus nerve on an atropinized heart.

EXPERIMENTAL METHODS

The experiments were conducted during all seasons of the year on frog hearts isolated according to A. F. Samoilov's method. The use of the A. F. Samoilov preparation (the heart on a Straub cannula and in a circular perfusion system, connected with the frog's head by the vagosympathetic trunks) permitted stimulation of the nucleus of the vagus nerve in the medulla oblongata and the cephalic sympathetic ganglion. This method made it possible to obtain pure vagus and sympathetic effects during parallel perfusion of the isolated heart. Stimulation was accomplished by means of movable needle electrodes joined with a Dubois-Reymond coil; the voltage in the primary circuit was 4 v. Cardiac mechanograms and electrograms maintained simultaneous recording (see Communication I).

Following the recording of 3-5 normal vagal effects on a heart perfused with Ringer solution, atropine was introduced into the cannula, and at varied time intervals repeated stimuli were applied to the medulla oblongata.

EXPERIMENTAL RESULTS

In all of the experiments, following atropinization of the heart the effect of vagal inhibition was replaced by a marked sympatheticomimetic effect. The change in vagal effect after the injection of atropine into the heart in a concentration of 10^{-5} can be seen in Figure 1 (I and II). The sympatheticomimetic effect is manifested in an increase in the strength of contractions and in the speed of the rhythmic activity of the heart. This effect is highly stable; in the experiment cited, 14 subsequent stimulations gave identical results (Figure 1, II). After 40 minutes the atropine solution was replaced with Ringer's solution and stimulation of the medulla oblongata was once again accompanied by an inhibitory effect (Figure 1, III).

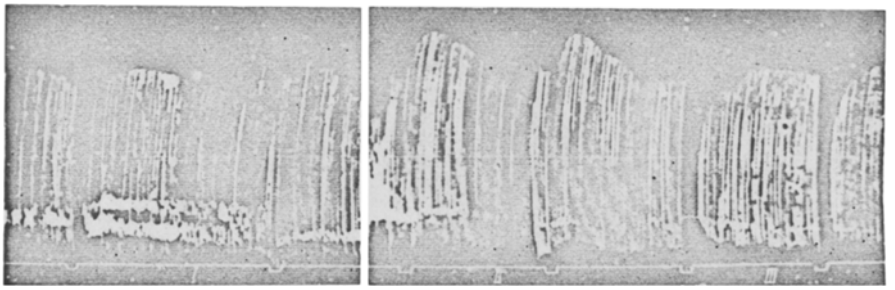

Fig. 1. The change in vagal effect under the influence of atropine (10^{-5}). Vagal effect in conjunction with stimulation of the medulla oblongata before and immediately after the action of atropine (I), 1 hour after the action of atropine and following washing out with Ringer's solution (II). Distance between inductor coils —12 cm. Duration of stimulation —10 seconds.

During the course of the experiments we were faced with the question of the nature of the sympathetico-mimetic effect. In Figure 2, a, Segment I shows the typical inhibitory effect of stimulation of the medulla oblongata; a small increase in the amplitude and strength of the contractions of the heart is apparent in the aftereffect. In spite of differential stimulation of the fibers of the vagus nerve, one could assume that after the introduction of atropine precisely this sympathetic aftereffect is stengthened. Segments II and III show the development of a stable sympatheticomimetic effect during stimulation of the medulla oblongata after the introduction of atropine (in the given experiment 12 identical results were obtained). Figure 2, b shows the change in the effect of stimulation of the cephalic sympathetic ganglion after atropinization of the heart: the introduction of atropine reduces the sympathetic effect (this phenomenon was observed in all of the experiments). Figure 2,c completely eliminates the possibility that the participation of sympathetic fibers in the development of sympatheticomimetic effects is a result of stimulation of the vagus nerve. This kymogram was obtained on a permanently desympathetized frog heart; even in this case stimulation of the medulla oblongata after the introduction of atropine was accompanied by a marked sympatheticomimetic effect.

In studying the relationships of the inotropic and chronotropic properties of vagal inhibition during atropinization of the heart, we established that stimulation of the medulla oblongata immediately after injection of atropine in concentrations of 10^{-6} — 10^{-5} is accompanied by the development of a positive chronotropic effect; the negative inotropic effect disappears after a certain period of atropine influence. Thus atropine affects first of all the chronotropic index of vagal inhibition. This regularity was particularly well-marked in the experiments with continuous perfusion of the heart.

This continuous perfusion is effected by a Straub cannula with a side outlet; introduced into the cannula is a small funnel with a fine, almost capillary outlet which passes freely into the horn of the cannula. The small funnel is filled with Ringer's solution, which is continuously renewed by means of drops falling from a large funnel fastened above the cannula; the excess fluid exits from the side outlet of the cannula. If an active substance (atropine, for example) is introduced into the small funnel, it will at once begin to be washed out by new drops of Ringer's solution. In this manner one can observe the change in vagal effect as atropine is washed out of the heart.

The experiments showed that with continuous perfusion the negative inotropic effect is restored first of all (in the presence of a positive chronotropic effect), and then a negative chronotropic effect is produced by stimulation of the medulla oblongata.

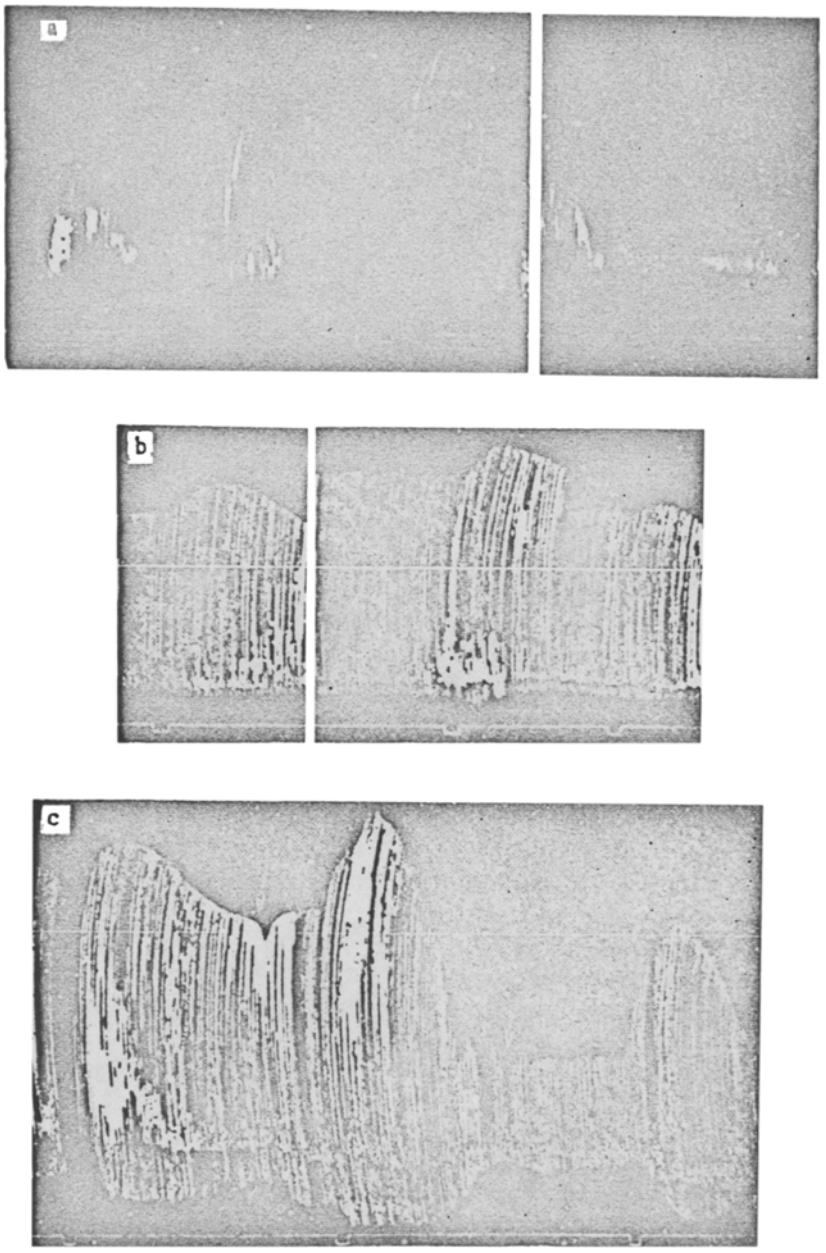

Fig. 2. Change in vagal effect in conjunction with stimulation of the medulla oblongata (a) and the sympathetic ganglion (b) on a normal and a permanently desympathetized heart (c) before and after (↓) the action of atropine (10^{-5}). Distance between the inductor coils in the experiments on the normal heart (a, b) –19 cm; in the desympathetized heart (c) –12 cm. Duration of stimulation –10 seconds.

In this connection it was necessary to establish the sequence of changes in the reaction of the hearts to acetylcholine and stimulation of the vagus nerve during atropinization of the heart and washing it with Ringer's solution. The experiments showed that after atropinization the capacity of cardiac muscle to respond to stimulation of the medulla oblongata is initially altered by a reduction in heart rate; then the negative inotropic effect

disappears. Finally the reaction of the heart to acetylcholine is changed.

The literature contains indications of the great sensitivity of the chronotropic effect to atropine [5, 6].

Thus one can conclude that in the process of atropinization of the heart exclusion of the vagal effect does not occur, but only the form of its manifestation is altered.

Stimulation of the vagus nerve under these conditions is accompanied by positive chronotropic and inotropic effects, which increase in the process of gradual atropinization, attain a maximal value and are stabilized. It has been established that sympathetic fibers do not take part in this reaction; the inaccuracy of the assumption of the possibility of the stimulation of chromaffin tissue is shown in the work of A. V. Kibyakov and L. V. Tukhvatullina [1].

In our supplementary experiments the atropinized heart secreted a greater than normal amount of vagal substance. These data are in agreement with the results of Brucke [4]. Consequently the sympatheticomimetic effect does not result from the secretion and influence of small amounts of acetylcholine.

This effect cannot be caused by the activiation of accelerating fibers in the vagus nerve trunk, since in the work of M. G. Udelnov [2, 3], the absence of specific accelerating fibers in the trunk of the vagus nerve of the frog and of warm-blooded animals has been demonstrated.

In view of the particular sensitivity of the chronotropic effect of vagus inhibition to the action of atropine, we examined the shifts in polarization which occur in an atropinized heart in conjunction with stimulation of the vagus nerve.

In our theoretical assumptions we proceeded from the data of M. G. Udelnov [2, 3], who established a causal relationship between reduced heart rate and increased resting potential in conjunction with stimulation of parasympathetic nerves.

The vagal effect was produced either by placing a small crystal of rock salt on the nuclei of the medulla oblongata or by their electrical stimulation. Figure 3 shows the development of the vagal effect before and after atropinization. As is evident from Figure 3, a, placing a small salt crystal on the medulla oblongata before

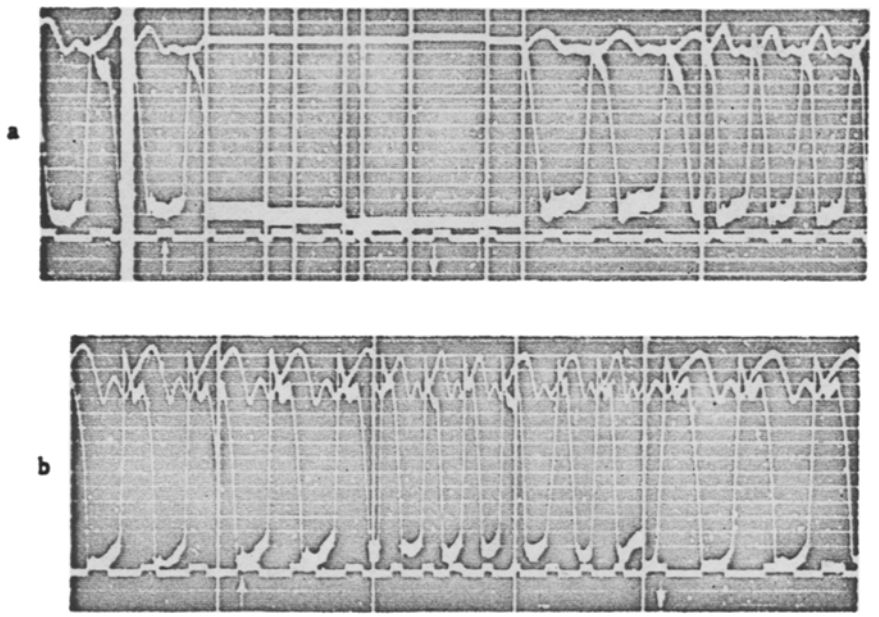

Fig. 3. Mechanograms (upper curves) and electrograms (lower curves) of the heart, recorded in conjunction with stimulation of the medulla oblongata with a small crystal of NaCl.

atropinization is accompanied by the development of cessation of the heart and an increase in the resting potential of the cardiac muscle. Following atropinization (Fig. 3, b) during stimulation of the nuclei of the vagus nerve a slight increase in heart rate is observed in the presence of a parallel reduction in resting potential and a lowering of the amplitude of the monophase action potential. A similar phenomenon was recorded in all 65 cases.

Thus the electrophysiological experiments also attest to a change in vagal effect, but not its exclusion, under the influence of atropine.

The results obtained in comparison with the data in the literature permit one to assume that atropine prevents the possibility of positivization of cardiac muscle in the presence of stimulation of the vagus nerve. Atropine by itself is capable of augmenting the resting potential, but, collaterally, it emerges also as a stabilizer of the level of polarity of the cardiac muscle. Accepting the point of view of M. G. Udelnov, one can maintain that the number of impulses arriving by way of the vagus nerve is insufficient in the atropinized state for the creation of positivization, and thus for inhibition of the heart. Under these conditions the usually "inhibitory" impulsation produces an effect of negativization, characteristic of the action of a sympathetic nerve; there occurs a parallel increase in heart rate and in the amplitude of heart contractions. In this case the minor amount of impulses arriving by way of a sympathetic nerve is incapable of producing any effect.

We suggest that the data presented confirm the viewpoint of M. G. Udelnov relative to the leading role of shifts in polarization during the emergence and development of vagal inhibition of theheart. They also show that atropine influences first of all the initial resting potential of cardiac muscle, eliminating the possibility of changing it during development of vagal inhibition of the heart. The absence of positivization under these conditions causes the replacement of the inhibitory effect from irritation of the vagus nerve by one of stimulation.

SUMMARY

In normal atropinized and chronically desympathetized frog hearts the effect of vagus nerve stimulation is altered but not excluded.

Stimulation of the nuclei of the vagus nerve in the medulla oblongata causes a constant sympatheticomimetric effect. The same is to be seen in chronically desympathetized frogs. During atropinization and washing the negative chronotropic effect caused by vagus stimulation was replaced by a positive one. The last to be altered was the reaction of the heart to acetylcholine.

The atropinized heart secretes more vagus substances than the normal one.

Stimulation of the vagus nuclei after atropinization causes a slight diminution of the resting potential of the heart muscles, diminishing at the same time the amplitude of monophase action potentials.

LITERATURE CITED

[1] A. V. Kibyakov and L. V. Tukhvatullina, Byull. Eksptl. Biol. i Med., Vol. 26, No. 5, pp. 347-349 (1948).

[2] M. G. Udelnov, The Materials of Clinical and Experimental Electrocardiograph,* pp. 129-138, Moscow (1953).

[3] Ibid., The Material of Clinical and Experimental Electrocardiography,* pp. 139-146, Moscow (1953).

[4] G. L. Brown and W. A. Maycock, J. Physiol., 1937, Vol. 101, pp. 369-374.

[5] R. Hazard and E. Corteggiani, and J. Cheymol, Compt. rend. soc. biol., 1946, Vol. 140, pp. 83-84.

[6] H. Fredericq and Z. Bacq, Compt. rend. soc. biol., 1934, Vol. 116, pp. 647-650.

* In Russian.