FLUCTUATIONS IN HEART RATE CAUSED BY PROLONGED SYMPATHETIC STIMULATION

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A great deal of attention has been paid to the problem of the two opposite effects mediated by the nerves supplying the heart. A number of facts have been accumulated concerning the action of the vagus on the work of the heart. Some authors attribute the biphasic influence of this nerve to the liberation of acetylcholine [4, 5, 8, etc.], while others explain it in terms of the opposed effects of acetylcholine and adrenalin [1, 7, 9, and others]. There are some results which indicate that the prolonged action of acetylcholine brings about the liberation of its antagonist adrenalin, through the occurrence of internal compensatory changes; the reverse relationships were obtained for the action of adrenalin [10 and others].

In this context, the Sechenov-Mechnikov phenomenon is of special importance; the effect is that prolonged stimulation of the vagus for up to 40 minutes induces in the frog heart periods of depression alternating with recovery. Experiments in our laboratory [2, 3] have established that, during the depressive phases, acetylcholine is excreted, and during recovery, adrenalin is formed.

In the present article we report results of experiments performed to explain the nature of the effect of prolonged sympathetic nerve stimulation on the heart, and to determine the neurohumoral changes which take place in cardiac muscle in these circumstances.

METHOD

Experiments were carried out on Rana temporaria hearts isolated by Straub's method. Stimulation was applied at the level of the second and third sympathetic ganglia; sawtoothed pulses were applied at a frequency of 20 cps, and at a voltage which was adjusted separately for each experiment. Parallel experiments were set up to determine the influence of certain drugs applied during prolonged sympathetic stimulation. (Details of the concentration of the substances used will be given when the experiments are described.)

RESULTS

It was found that, during prolonged sympathetic stimulation, the Sechenov-Mechnikov phenomenon occurs, that is to say, there are phasic changes in the activity of cardiac muscle, as shown by phases of increased and decreased output. Figure 1 shows the results of one typical experiment. In all phases of increased activity following prolonged stimulation, the heart rate was higher than normal. Cessation of the stimulation always caused a return to normal heart work.

Having obtained a biphasic sympathetic effect, we decided to determine, by applying certain drugs, the neurohumoral changes accompanying prolonged sympathetic stimulation, and to find what part was played by these changes in the occurrence of the different phases of activity of cardiac muscle. For this purpose we studied the action of ergotamine, atropine, and ascorbic acid on the periodicity.

Action of ergotamine. From our own and from published results, it might be expected that the origin of a period of increased heart activity is due to the periodic appearance in the heart of adrenalinlike substances. To test this hypothesis, an injection of $1 \cdot 10^{-4}$ ergotamine was made into a heart which was exhibiting the periodicity effect. Such an injection will eliminate the normal action of adrenalin. Figure 1 shows the results of a typical experiment. The kymogram shows clearly the influence of the drug on the phasic changes of cardiac activity produced by prolonged sympathetic stimulation. Five to six minutes after injecting the substance, the heart usually stopped for a long period, and began again only when stimulation ceased.

The elimination by ergotamine of the active phase indicates evidently that adrenalinlike substances are concerned in inducing this phase. According to some Hungarian workers [9 and others], ergotamine does not eliminate the secondary effect of adrenalin, which is due to the liberation of acetylcholine. From this result, it might be concluded that the prolonged arrest of the heart by ergotamine, given together with sympathetic stimulation, might be due to the accumulation of acetylcholine. However, according to Kh. S. Koshtoyants, it is possible that oxidation products of adrenalin and, in particular, adrenoxin, may be concerned in the development of the

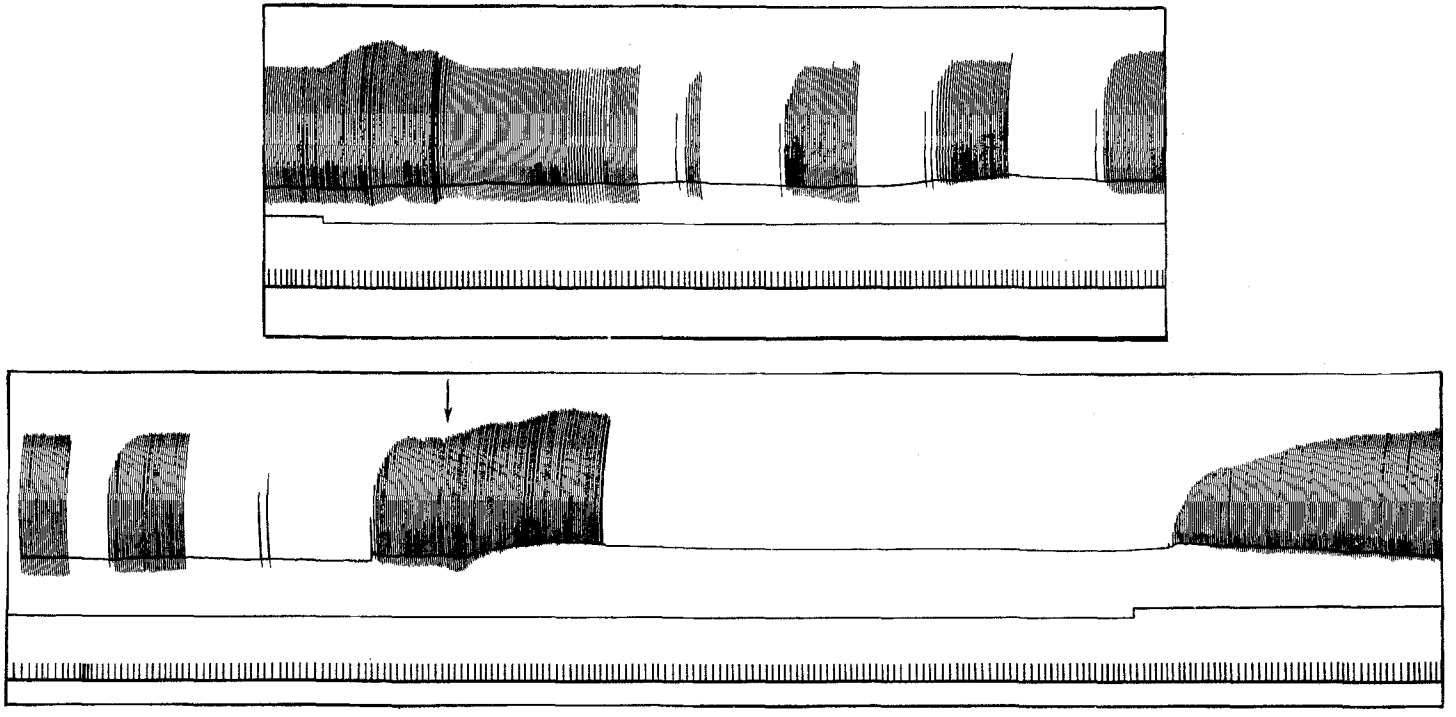

Fig. 1. Effect of ergotamine on the periodic activity of the heart during prolonged sympathetic stimulation. Phases of increased and decreased cardiac activity can be seen. Curves, from above downward: Contraction of cardiac muscle; stimulus marker; 5-sec time-marker; the arrow indicates moment of injection of ergotamine (concentration $1 \cdot 10^{-4}$). Strength of stimulus 11 v.

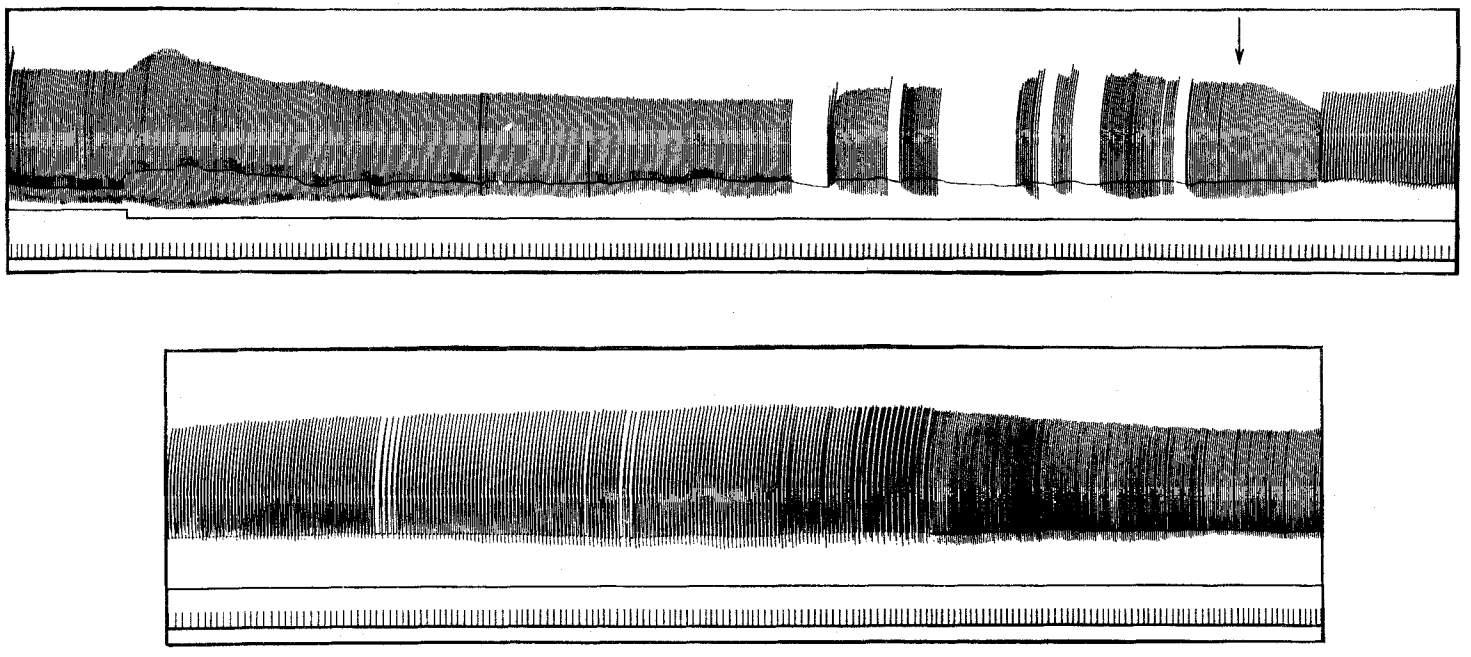

Fig. 2. Effect of atropine on the periodic activity of the heart during prolonged sympathetic stimulation. Curves, from above downward: Contraction of cardiac muscle; stimulus marker; 5-sec time-marker; the arrow indicates the injection of atropine (concentration $1 \cdot 10^{-4}$). Stimulus strength 10 v.

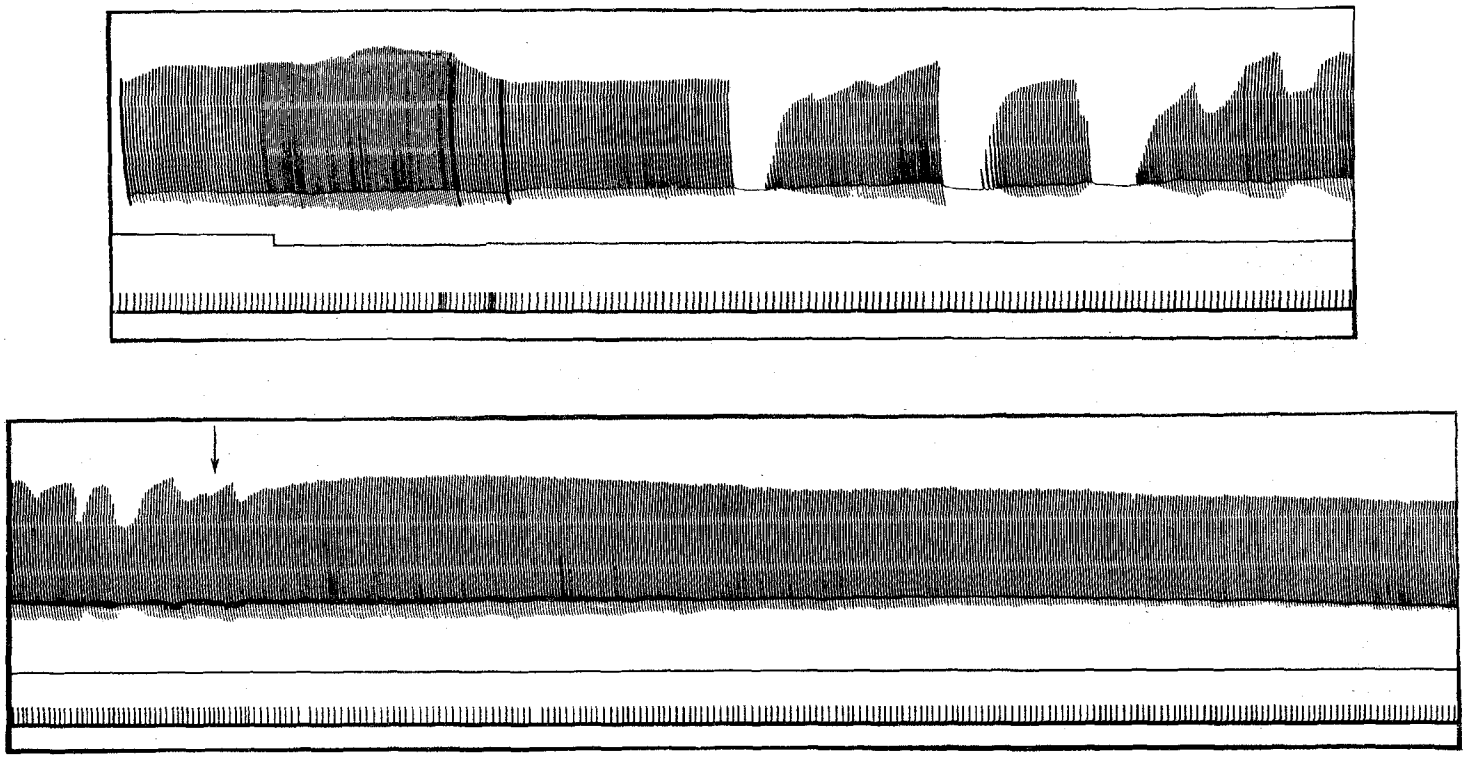

Fig. 3. Effect of ascorbic acid on the periodic activity of the heart during prolonged sympathetic stimulation. Curves, from above downward: Contraction of cardiac muscle; stimulus marker; 5-sec time-marker; the arrow indicates the injection of ascorbic acid (concentration $1 \cdot 10^{-3}$). Stimulus strength 8v.

depressed phase. Here we may note that ergotamine enhances the depressive action of adrenoxin [6].

Both hypotheses have been examined experimentally. To test the possibility that acetylcholine was concerned in the production of the depressive phases, we carried out a number of experiments with atropine.

Action of atropine. We used $1 \cdot 10^{-5}$ atropine in order to alter the action of acetylcholine. In Fig. 2 are shown the results of a typical experiment. From the kymogram it can be seen that atropine, injected after periodic activity has been established by prolonged sympathetic stimulation, eliminates the depressed phase, but that nevertheless the return toward normal is not complete. The curve shows a marked reduction in rate to half the normal value. These results show that there must be some additional influence responsible for the depressed phase.

To test the hypothesis that oxidation products of adrenalin are responsible for the depressed phase, we carried out a number of experiments designed to study the action of ascorbic acid on the heart during prolonged sympathetic stimulation.

Action of ascorbic acid. Our reasoning was based on the fact that ascorbic acid will stabilize any sympathetic effect on the heart by preventing the oxidation of adrenalin. Having established periodic phases of decreased and increased heart output, we introduced $1 \cdot 10^{-3}$ ascorbic acid through a cannula. In Fig. 3, it can be seen that, after the substances have been introduced, the periodicity ceases, because the depressed phase has been eliminated; there is also a characteristic increase in amplitude. Under these circumstances, continuation of the stimulus brings about no changes either in the amplitude or the rate of the contractions.

From this set of experiments, we obtained a clear idea as to the part played by adrenalin oxidation products in initiating the depressed phase, and found that ascorbic acid, which stabilizes the oxidation of adrenalin, completely eliminates it. This result is in agreement with the statement of Kh. S. Koshtoyants that during prolonged sympathetic nerve stimulation, it is not the adrenalin-like substances themselves, but their oxidation products, which bring about the liberation of acetylcholine.

Our experiments have demonstrated that during prolonged sympathetic stimulation, there is an alternation of phases of stimulation and suppression of the heartbeat (Sechenov phenomenon). The phenomenon is apparently due to periodic biochemical changes which occur as a result of the prolonged action of adrenalinlike substances and their oxidation products.

SUMMARY

Experiments on isolated Rana temporaria hearts were carried out in order to determine the effect of prolonged sympathetic nerve stimulation on cardiac action, and to study the neurohumoral shifts in cardiac muscle produced. The sympathetic chain was stimulated for 30 minutes at the second and third ganglia. In several experiments, it was found that periodic changes in cardiac muscle activity occurred, as shown by periods of increased and decreased cardiac action. The intensified phase was associated with the appearance of adrenalinlike substances in the heart, while the depressed phase was connected first, with the appearance of acetylcholine, and secondly, with that of adrenalin oxidation products. Thus, the phasic changes induced by prolonged sympathetic nerve stimulation are evidently due to periodic biochemical changes caused by the prolonged action of adrenalinlike substances and their oxidation products.

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*See English translation.