SOME NON-VAGAL CARDIAC DEPRESSOR MECHANISMS

I. P. Garanina and T. B. Tolpegina

From the Chair of Pathological Physiology (Director: Assistant Professor M. A. Erzin), Kazan Medical Institute (Director: Assistant Professor R. A. Viaselev)

(Received May 20, 1957. Presented by Prof. V. V. Parin, Active Member AMN SSSR)

There is some evidence in the literature of the importance of the initial reactivity of the heart for the achievement of the ultimate effects originated by stimulation of cardiac nerves. Thus, N. E. Vvedenskii has shown that "a nerve which is usually stimulatory may change into a depressor nerve" [2]. V. B. Boldyrev [1], in his experiments on an isolated frog's heart, observed that prolonged stimulation of the sympathetic nerve led to depression of cardiac activity, and even to its total cessation. N. L. Iastrebtsova and M. G. Udel'nov [7] have shown that stimulation of the sympathetic nerves in the presence of foci of cardiac necrosis exacerbate the condition of functional depression. We have, however, been unable to find any analogous references to such effects in mammals, or to their possible relation to toxic or infectious conditions of the organism.

The nervous regulation of the heart of animals with modified reactivity has for a number of years been the subject of study in the Chair of Pathological Physiology of the Kazan Medical Institute [3, 6].

The present paper deals with changes in the sympathetic regulation of the action of the heart of animals suffering from typhoid infection and intoxication.

EXPERIMENTAL METHODS

We used dogs and guinea pigs as experimental animals. We made myographic recordings of the cardiac contractions of dogs under pentothal narcosis, with artificial respiration. For the study of the functional state of the sympathetic centers regulating cardiac activity, we divided both the cervical vagus nerves, and stimulated the distal portion of one of them for 15-25 seconds, using an induction current, potential in the primary coil 4 v, distance between the coils 120-30 mm. Stimulation was applied before and after injection into the vertebral artery of 0.2-2 ml of typhoid toxin. Guinea pigs were infected by subcutaneous inoculation with a live culture (strain 62) of typhoid bacteria (3 inoculations at daily intervals: the 1st of 500 million organisms, and the 2nd and 3rd each of 1 billion organisms), and were taken for experiment 3-5 weeks after the first inoculation. The experiments were performed on isolated heart preparations, perfused with Tyrode's solution containing eserine (1 : 100,000), at 37-38°. The heart contractions were registered myographically, before and after inclusion into the perfusion fluid of complete typhoid antigen at dosage levels not causing any change in the cardiac activity of uninfected animals (2-4 mg). The perfusates from the isolated hearts, collected during reaction with the antigen, were further examined for their content of physiologically active substances (sympathin, acetylcholine), assayed from their effect on an eserinized uninfected guinea pig heart, on a denervated cat nictitating membrane, and on a frog's heart.

EXPERIMENTAL RESULTS

We took 18 dogs for our first series of experiments. Stimulation of the vagus before injection of toxin caused acceleration and strengthening of the heart beat in 13 dogs; similar effects were found by other workers using similar methods [4]. There was no change in 4 dogs, and cardiac activity was depressed in one dog, which had just produced a litter. After injection of toxin into a vertebral artery we frequently observed retardation and weaken-

ing of cardiac activity, which may be related to a depressed functional state of cardiac sympathetic centers, due to the action of the toxin. Stimulation of the proximal part of the severed vagi after injection of toxin, using stimuli of the same strength as before, caused a wekening of the sympathetic effect. We observed a diphasic effect in 10 of our experiments, consisting in a transition from a sympathetic to a parasympathetic effect, as evidenced by a fall in the amplitude and rate of the contractions (Fig. 1).

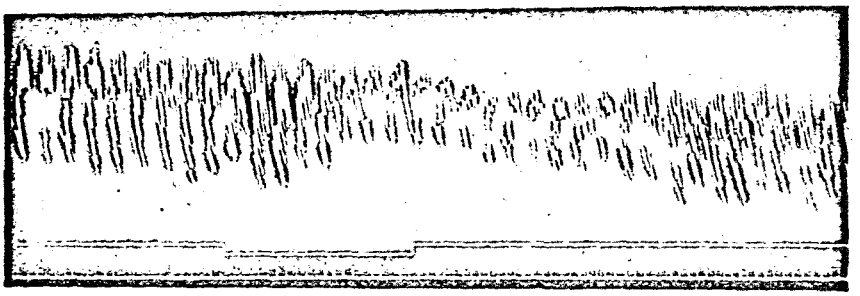

Fig. 1. Cardiogram of a dog's heart during stimulation of the proximal segment of the severed left vagus nerve, against a background of intoxication. Explanation of tracings (from above down): recording of heart contractions, signal showing stimulation, time marker.

Depression of cardiac activity was observed in particular in those experiments in which the rhythm and amplitude of cardiac contractions had been unaffected by stimulation of the proximal segment of the severed vagus before injection of toxin.

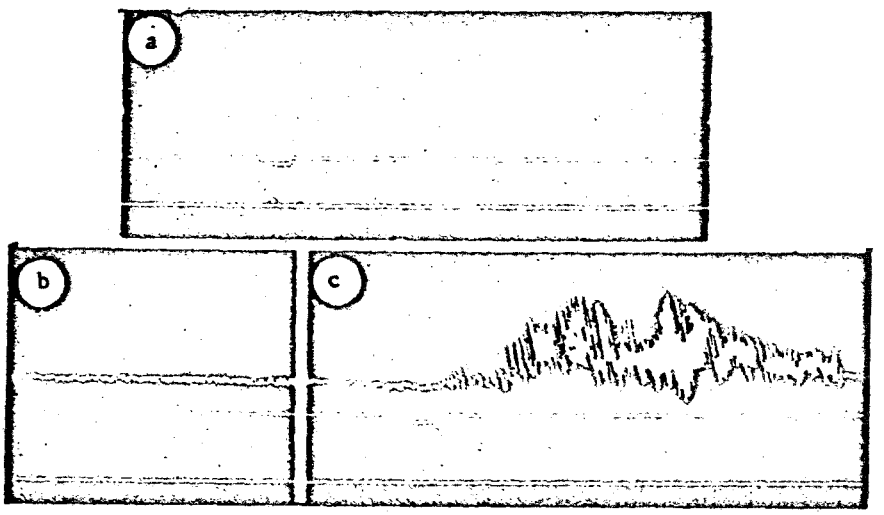

Fig. 2.
a) Changes in heart contractions of an infected guinea pig caused by introduction of 2 mg of complete typhoid antigen; b) effect of perfusate collected from the heart of an infected guinea pig, before administration of antigen, on the heart of an uninfected guinea pig; c) effect of perfusate collected from the heart of an infected guinea pig, after administration of antigen, on the heart of an uninfected guinea pig. Explanation of tracings (from above down): recording of heart contractions, signal of injection of antigen, time marker.

In the second series of experiments, performed on 25 guinea pigs, we found that typhoid antigen, administered at the above-indicated times after infection, usually produced a marked sympathetic reaction of the isolated heart, manifested as increase in rate and amplitude of the contractions. Examination of the perfusates showed the presence of sympathin. We hence concluded that the positive chrono- and ino-tropic effect was a result of stimulation of the adrenergic structures of the heart by the antigen. A different form of reaction to antigen was, however,

observed in 5 guinea pigs, under identical experimental conditions; depression of cardiac activity was manifested, in the form of retardation of the heart rhythm, with diminution in amplitude, sometimes supervening after a preceding exaltation (diphasic effect). As in the preceding experiments, we examined the perfusates for their content of physiologically active substances, in order to elucidate the nature of this effect. The perfusates gave rise to a positive ino- and chrono-tropic effect on the heart of an uninfected guinea pig, showing that they contained sympathin (Fig. 2).

We thus observed depression of cardiac activity in dogs treated with typhoid toxin, under conditions such that transmission of inhibitory impulses from the heart through the ordinary pathways — the vagus nerves — was totally excluded. We hence assumed that the inhibitory effect on the heart must have been effected through the sympathetic system.

Under somewhat different experimental conditions, although also related to the action of typhoid antigens on the organism, guinea pigs also gave a vagus effect when the sympathetic nerve supply of the heart was stimulated. This was shown by the presence of sympathin in the perfusates.

V. B. Boldyrev's experiments [1], similarly to ours, gave evidence of sympathetic transmission during depression of cardiac activity caused by stimulation of the sympathetic nerve of a frog's heart.

This unusual form of sympathetic reaction, manifested as depression of cardiac activity, may be related to the change in reactivity of the organism due to typhoid infection or intoxication.

In dogs, such an effect should be interpreted as being due to the action of toxin on centers of sympathetic innervation of the heart, and only to a smaller degree to its direct action on the heart, since the toxin was injected into the vertebral artery, and in small doses; the toxin caused depression of activity of sympathetic nerve centers. Subsequent stimulation of the proximal portion of the severed vagus nerves still further lowered the functional activity of the sympathetic centers, and this was manifested in the form of a pessimal reaction, which was in some cases preceded by a brief period of stimulation. This interpretation is in consonance with O. A. Mikhaleva's physiological studies [5], from which it appeared that depression of cardiac activity may result not only from vagus stimulation, but also from lowering of tonus of sympathetic centers.

The pessimal effect found in experiments on isolated guinea pig hearts may be ascribed to modification in reactivity of the myoneural apparatus of the heart towards sympathin, which is released as a result of the action of typhoid antigen. The incidence of this type of reaction in only a relatively small group of animals is probably due to their low initial level of physiological lability of the sympathetic nervous system. This is shown by the prevalence of depression of cardiac activity after administration of toxin to those animals which previously either did not react to stimulation, or gave only a weak reaction.

We conclude from our results that disturbances of the functional state of cardiac sympathetic nerve centers may be the cause of some of the forms of bradycardia encountered in typhoid patients, and that changes in reactivity of the sympathetic structures of the heart itself may also be implicated.

SUMMARY

The characteristic features of the cardiac sympathetic effect were studied in guinea pigs and dogs during experimentally induced typhoid fever intoxication and infection. It was established that depression of the cardiac activity in these conditions may take place by means of sympathetic innervation. The change of the functional condition of the sympathetic centers, as well as the change in the reactivity of the neuromuscular apparatus of the heart to typhoid fever antigens, plays a definite role in development of the phenomenon referred to above.

LITERATURE CITED

[1] V. B. Boldyrev, Arkh. Biol. Nauk SSSR 44, No. 2, 61-90 (1936).

[2] N. E. Vvedenskii, Selected Works,* Part 2, 675, Leningrad, 1951.

[3] I. P. Garanina, Arkh. Patol. No. 1, 92-97 (1956).

[4] O. D. Kurmaev, Mechanism of Action of Extracardial Nerves on the Mammalian Heart,* Doctoral Dissertation, Kazan, 1950.

* In Russian.

[5] O. A. Mikhaleva, Contributions to Evolutional Physiology,* 1, 239-245, Moscow, 1956.

[6] T. B. Tolpegina, Arkh. Patol., No. 1, 28-34 (1951).

[7] N. L. Iastrebtsova and M. G. Udel'nov, Problems of Pathology and Physiology of the Heart,* pp. 190-193, Moscow, 1955.

* In Russian.