

PHYSIOLOGY

INTEROCEPTIVE REGULATION OF BLOOD COAGULATION

COMMUNICATION III

REFLEX INFLUENCE OF ANTIGENIC STIMULI ON BLOOD COAGULATION

D. M. Zubairov

Department of Pathological Physiology (Head — Docent M. A. Erzin),
Kazan State Medical Institute

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We have shown in previous communications reflex changes in blood coagulation can be obtained by action of chemoreceptors and baroreceptors in the carotid sinus and the arch of the aorta.

Acceleration of blood coagulation has been obtained by A. L. Komendantova [7] on presenting a resolving dose of antigen simultaneously to intestinal and spleen receptors. Slowing of blood coagulation was observed by A. N. Gordienko [3] and T. A. Nazarova [8] when peptone and resolving dose of antigen were allowed to act on the carotid sinus zone. However, experiments with foreign serum acting on the carotid sinus zone [8] were carried out without analgesia, and fear and pain are known to be accompanied by considerable changes in blood coagulation; moreover, the stimulus was introduced into the carotid sinus sac by puncturing the wall of the carotid sinus — a procedure leading to powerful stimulation of baroreceptors. E. N. Budigaev [2] found that anesthesia of the carotid sinuses had no effect on slowing of blood coagulation in peptone shock.

Since altered, allergic reactivity of the organism is thought to be implicated [6, 12 and others] in the pathogenesis of diminished blood coagulability and of some types of hemorrhagic diathesis, especially those associated with excess of antithrombin, we decided to investigate anew the reflex influence of antigens on blood coagulation in the organism with unchanged and with altered immunobiological reactivity, and also to trace the dynamics of changes in blood coagulation, which had not been done by earlier investigators.

EXPERIMENTAL METHOD

A total of 54 experiments was performed, of these 10 on normal and 44 on sensitized dogs. Dogs sensitized with horse serum given subcutaneously in amounts 0.2 ml/kg body weight on 2 successive days were subjected to experiments 15-25 days after administration of antigen. The methods of analgesia, perfusion of the carotid sinus and collection of blood specimens have been described previously [4]. Coagulation time was determined by the Fonio method and in Bazaron's apparatus. The carotid sinus receptors were acted upon by whole horse serum (1 ml) and solutions of nicotine and acetylcholine in concentrations from 10^{-4} to 10^{-7} in volumes of from 0.25 to 1 ml.

In experiments with intravenous administration of resolving dose of antigen to sensitized animals simultaneous recordings were made of blood pressure, respiration and blood coagulation rate. All cases presented a picture of anaphylactic shock. The absence of desensitization indicated complete isolation of the carotid sinus from the general circulation.

EXPERIMENTAL RESULTS

In the first series of experiments blood coagulation time was studied during introduction of horse serum into the perfusion fluid of the carotid sinus in unsensitized dogs. No reflex changes in blood coagulation were obtained in most of the experiments in this series, but toward the end of the experiments coagulation time usually diminished (Fig. 1). This is evidently connected with the effect of anesthesia, liberation of thromboplastin from damaged tissues and some degree of anemia of the carotid sinus receptors.

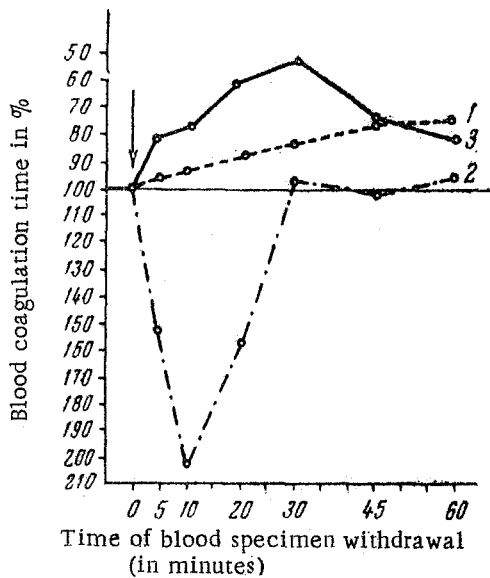


Fig. 1. Rate of blood coagulation during action of horse serum on the carotid sinus of unsensitized dogs (1), sensitized dogs (2), during stimulation of carotid sinus chemoreceptors in sensitized dogs with nicotine and acetylcholine solutions (3), ↓ beginning of stimulation.

anaphylactic shock. In one case transient slowing of blood coagulation was followed by definite acceleration of the latter, as in experiments with stimulation of carotid body receptors by chemical agents.

On the whole the reflex changes in blood coagulation observed were considerably smaller than slowing of blood coagulation seen in general anaphylactic shock in the same animals.

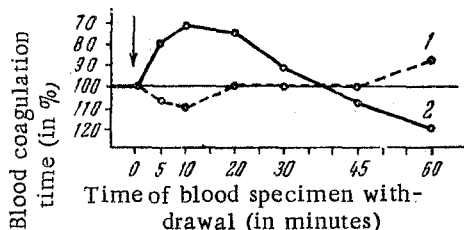


Fig. 2. Rate of blood coagulation in vagotomized dogs under the influence of a resolving dose of horse serum on the denervated carotid sinus (1) and on carotid sinus with intact sinus nerve (2).

0.005 to 0.4 ml, intravenously) as were known to exceed the amount which could penetrate from the perfusing fluid. It was found that small doses of specific serum produced no substantial changes in blood coagulation in sensitized dogs. Deviations of coagulation time in these cases were even smaller than in control experiments in which the carotid sinus was perfused without being stimulated.

In one of 7 experiments introduction of horse serum led to slight increase in the amplitude of respiratory movements and some decrease in blood coagulation time, but the latter was much less marked in degree and duration than the effect produced by stimulation of chemoreceptors by nicotine or acetylcholine. Intactness of the neural connections of the carotid sinus was checked after all the experiments by reflex change in respiration in response to administration of acetylcholine solution.

In the second series of experiments a study was made of the change in blood coagulation time after introduction of a resolving dose of antigen into the fluid perfusing the carotid sinus of sensitized dogs. In most of these experiments coagulation time showed an initial increase. It doubled, on the average, in the course of 10 minutes. After this it began to diminish, approaching the initial value. The period of slowed coagulation fluctuated in individual experiments within the range of 10 to 60 minutes.

In 6 out of 10 experiments the initial delay of blood coagulation was followed by its acceleration, the coagulation time becoming even shorter than the initial, a phenomenon not usually observed in general

Assessment of mean results reveals only reflex slowing of blood coagulation (Fig. 1), while the acceleration phase is blurred by individual variations.

Since vascular isolation of the carotid sinus does not give complete guarantee of absence of antigen resorption into the general circulation, control experiments were carried out with determination of the antigen in the blood after its introduction into the carotid sinus perfusate. When precipitation serum with a titer of 1:80,000 was used it was found that with the method employed not even 0.005 ml horse serum penetrated into the general circulation. However, in the absence of greater assurance, we injected sensitized dogs in 4 experiments with such amounts of horse serum (from

In order to study the specificity of the slowing of blood coagulation obtained in response to stimulation of carotid sinus zone receptors by foreign serum a third series of experiments was staged in which 10 sensitized dogs were subjected to perfusion of the carotid sinus with fluid containing stimulating substance of nonantigenic nature: acetylcholine and nicotine. The mean curve (Fig. 1) illustrating these 10 experiments shows that when the chemoreceptors are stimulated by acetylcholine or nicotine the coagulation time is nearly halved. As in nonsensitized dogs, the blood coagulation rate reaches the greatest value on the 20th-30th minute after beginning of stimulation; increased coagulability persists for about 1 hour.

On the basis of references [13, 5, 9 and others] to the significance of parasympathetic innervation in slowing blood coagulation a fourth and fifth series of experiments were carried out on sensitized dogs with transected cervical vagi. The time which elapsed from the moment of vagal transection to the beginning of blood coagulation time determination was about 2 hours.

The fourth series of experiments (10) was a control one. In this series blood coagulation time was studied in vagotomized dogs after introduction of a resolving dose of antigen into the fluid perfusing the denervated carotid sinus and during perfusion of the carotid sinus without stimulating agents. No consistent changes in blood coagulation time were discovered in these experiments (Fig. 2).

In the fifth series the action of resolving dose of antigen on intact carotid sinus receptors of vagotomized dogs produced no appreciable change in blood coagulation time in 2 experiments out of 10 and definite acceleration in the remaining 8 which was, however, considerably less in degree and duration than that observed on stimulation of carotid sinus receptors by chemical stimuli. The curve representing the mean results of 8 experiments is shown in Fig. 2.

Our data and some of the literature data [1, 11, etc.] suggest that reflex slowing of blood coagulation in sensitized dogs observed when a resolving dose of antigen is allowed to act on carotid sinus receptors is mediated by excitation of the vagal center through stimulation of depressor baroreceptors of the carotid sinus. Increase of tone in smooth muscle of sensitized animals under the influence of specific serum is a well-established fact [14, 10, etc.]. Contraction of the carotid sinus walls is as real a stimulus as a rise in hydrostatic pressure [11].

This explains the reason why our data coincide with E. Perlik's [12] observations that increase in pressure in the carotid sinus leads to a definite increase in the concentration of heparin-antithrombin with simultaneous decrease in the concentration of prothrombin, factor V and factor VII.

SUMMARY

In the majority of cases injection of horse serum into the perfusate of the carotid sinus of normal dogs causes no reflex change of coagulation time. However, if the same stimulus is administered to previously sensitized dogs a reflex increase of coagulation time takes place. This prolongation is most pronounced in 10 minutes. In a number of cases, this delay in blood coagulation is replaced by its acceleration. Preliminary vagotomy removes reflex delay of blood coagulation.

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