MECHANISM OF CORONARY THROMBOSIS PRODUCED BY NEUROGENIC ACTION ON ANIMALS WITH EXPERIMENTAL ATHEROSCLEROSIS

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The authors' previous observations [10] showed that as a result of acute neurogenic action (by injecting air into the lateral ventricles) on rabbits with experimental atherosclerosis, in some cases thrombosis of comparatively large branches of the coronary arteries developed. Cholesterol feeding alone or injection of air into the ventricles alone did not cause the formation of a thrombus in the coronary vessel. The work of B. A. Kudryashov and his collaborators [1-3] has clearly demonstrated the importance of neurohumoral mechanisms in the regulation of the function of the physiological anticlotting system of the body.

The object of this investigation was to study the changes taking place in the clotting and anticlotting mechanisms as a result of acute neurogenic action on healthy rabbits and on rabbits with experimental atherosclerosis.

EXPERIMENTAL METHOD

Experiments were conducted on 14 sexually mature rabbits weighing 2450-3600 g. The seven rabbits of group 1 were fed with cholesterol and then subjected to acute neurogenic action in the form of injection of air into the lateral ventricle. The seven rabbits (controls) of group 2 also received an injection of air into the lateral ventricle, but without preliminary cholesterol feeding.

Blood samples were taken from all the animals before and after the injection of air into the lateral ventricle, roughly 10-15 min after the appearance of changes in the electrocardiogram (EGG) demonstrating myocardial ischemia, for investigation of the indices of the clotting and anticlotting systems of the rabbits.

As indices of the clotting power of the blood, the fibrinogen content of the blood [11] and the plasma heparin tolerance [12] were determined. The reactions of the anticlotting system were assessed from the change in the content of free heparin in the blood [13] and in the fibrinolytic activity, investigated by Bidwell's method. The use of the Hartert thromboelastograph (Hellige) provided objective information of the changes in the principal phases of coagulation of the blood and of the state of the anticlotting and lytic properties of the blood.

The blood samples for analysis were taken from the left ventricle of all the rabbits by puncture through the chest wall. The experiments were carried out entirely on unanesthetized animals. Taking the blood for determining the initial indices was always done in identical conditions, with the animal fixed to a frame and the needle inserted through the rabbit's skull to the level of the lateral ventricles.

EXPERIMENTAL RESULTS AND DISCUSSION

Compared with the control animals, the rabbits with atherosclerosis in a state of nervous excitation were found to have a lowered plasma heparin tolerance (M = 25.57 min), a lowered fibrinogen concentration in the blood (M = 184.3 mg%), an increased content of free heparin in the blood (M = 6.6 units/ml), and higher indices of fibrinolytic activity (M = 46.4%). The corresponding values for the control animals were 14.28 min, 366.42 mg%, 5.09 units/ml, and 27.83%. Statistical analysis showed that the differences observed were highly significant ($P < 0.01$) for all indices.

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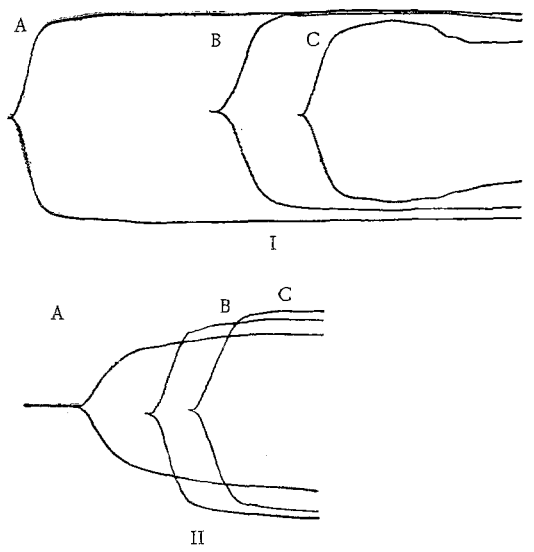

Thromboelastograms of control rabbits (I) and of rabbits with experimental atherosclerosis (II). A – thromboelastogram before injection of air into the lateral ventricle; B – thromboelastogram recorded 15 min after the appearance of ischemic changes in the EGG following injection of air into the lateral ventricle; C – thromboelastogram recorded 30 min after the appearance of ischemic changes in the EGG following injection of air into the lateral ventricle.

Demonstrative results were also obtained by thromboelastography. The thromboelastograms of the rabbits with atherosclerosis were characterized by an increase in the reaction time (R), an increase in the duration of clot formation (K), and a lower maximal elasticity of the thrombus (E). The mean values of these indices were 9.25, 7.06 min, and 139.12, and in the control group 2.55, 2.77 min, and 347.7 respectively. The thromboelastograms of rabbits of the two groups are shown in the figure as examples.

The nervous excitation or stress associated with the preparatory procedures thus caused an increase in the anticlotting properties of the blood of the rabbits with atherosclerosis, just as in healthy animals. Possibly in these conditions the body develops an appropriate protective reaction to the stimulus, preventing the formation of a thrombus. These findings are in agreement with those observed by E. I. Chazov and V. G. Ananchenko [6] in association with stress in man caused by prolonged hypokinesia.

Further observations showed that the character of the reaction depended on the degree of neurogenic action. Whereas in response to relatively weak action the animal developed a protective reaction marked by an increase in the anticlotting properties of the blood, in response to stronger action, such as the injection of air into the lateral ventricle, the opposite type of reaction was observed.

In the rabbits with atherosclerosis, by comparison with the initial figures the plasma heparin tolerance was sharply increased (M = 14.4 min), the concentration of fibrinogen in the blood was almost doubled (M = 358.57 mg%), the content of free heparin in the blood was lowered (M = 4.4 units/ml), and the fibrinolytic activity was reduced by more than half (M = 20%). The changes in these indices were statistically significant ($P < 0.01$). In the same conditions distinct changes were observed in the thromboelastograms, in which the reaction time was considerably shortened (from 9.25 to 2.31 min), the time taken for formation of the clot was reduced (from 7.06 to 3.31 min), and the maximal elasticity of the thrombus was increased (from 139.1 to 332.8).

Whereas the changes were considerable in the animals with atherosclerosis, in the control group they were less evident.

The plasma heparin tolerance was 18.16 min, the fibrinogen concentration 352.6 mg%, the free heparin concentration 5.76 units/ml, and the fibrinolytic activity 35.4%.

The results described thus show that in response to injection of air into the lateral ventricle of animals with atherosclerosis, the clotting properties of the blood were intensified and its anticlotting and lytic factors were depressed. No such changes were found in the control animals.

The content of free heparin in the blood in both the healthy rabbits and the animals with atherosclerosis was much higher than that reported in the literature. This confirms the suggestion that, if the function of the anticlotting system is reasonably intact, nervous excitation leads to an increase in the anticoagulant properties of the blood.

The authors' experiments have shown [8, 9] that besides causing disturbances of cardiovascular activity and of the EGG, injection of air into the lateral ventricle also leads to a sharp rise in the adrenalin content in the myocardium and to a parallel decrease in its content in the adrenals. From these investigations, and also from experiments with pharmacological agents, it was concluded that the pathological effects caused by injection of air into the lateral ventricle are due largely to overactivation of the sympathico-adrenal system, developing in response to generalized stimulation of the subcortical brain structures and reflected, in turn, in the state of the thrombus-forming properties of the blood.

The pattern of the clotting and anticlotting mechanisms in experimental atherosclerosis after neurogenic stimulation is similar to that observed by other authors in experimental and clinical investigations [4, 5, 7].

The following hypotheses may be put forward on the basis of the analysis of the changes in the clotting and anticlotting systems arising in response to neurogenic action in rabbits with experimental atherosclerosis and in control animals. In animals with experimental atherosclerosis, which are already potentially capable of developing thrombosis, even strong but adequate stimuli of the nervous system can activate the anticlotting mechanisms protecting the body against thrombosis. However, the compensatory powers of animals with atherosclerosis are inadequate to counteract the effect of an intensive and inadequate neurogenic stimulus, causing not only circulatory disturbances in the heart but also depression of the anticlotting system. In some cases this process ends in coronary thrombosis. This interpretation of the results of these experiments to some extent explains why in normal conditions no tendency toward thrombosis is found in rabbits with experimental atherosclerosis.

The compensatory powers of the anticlotting system are thus depressed in rabbits with atherosclerosis when the threat of intravascular clotting arises, in contrast to the plasticity of this system in healthy animals.

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