REACTIVITY OF ARTERIES IN THE EARLY STAGE OF DEVELOPMENT OF EXPERIMENTAL CHOLESTEROL ATHEROSCLEROSIS IN DOGS

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With the appearance and development of a pathological process, including experimental atherosclerosis, defensive reactions arise in the body, and the central nervous system plays a part in their formation and regulation. These reactions are masked by the developing pathological process both during their formation and at a time when they are definitively established. Meanwhile, during the study of atherosclerosis in experimental animals it is mainly the late stages of the condition that are investigated, when marked morphological changes are present in the vessels. In consequence of this, the earliest stages of the process, i.e., when the defensive reactions are evidently being formed, have escaped investigation. Yet at the same time it would be of the utmost interest to know which links in the complex chain of reactions of the organism during the development of the patholocial process are in fact adaptive and defensive.

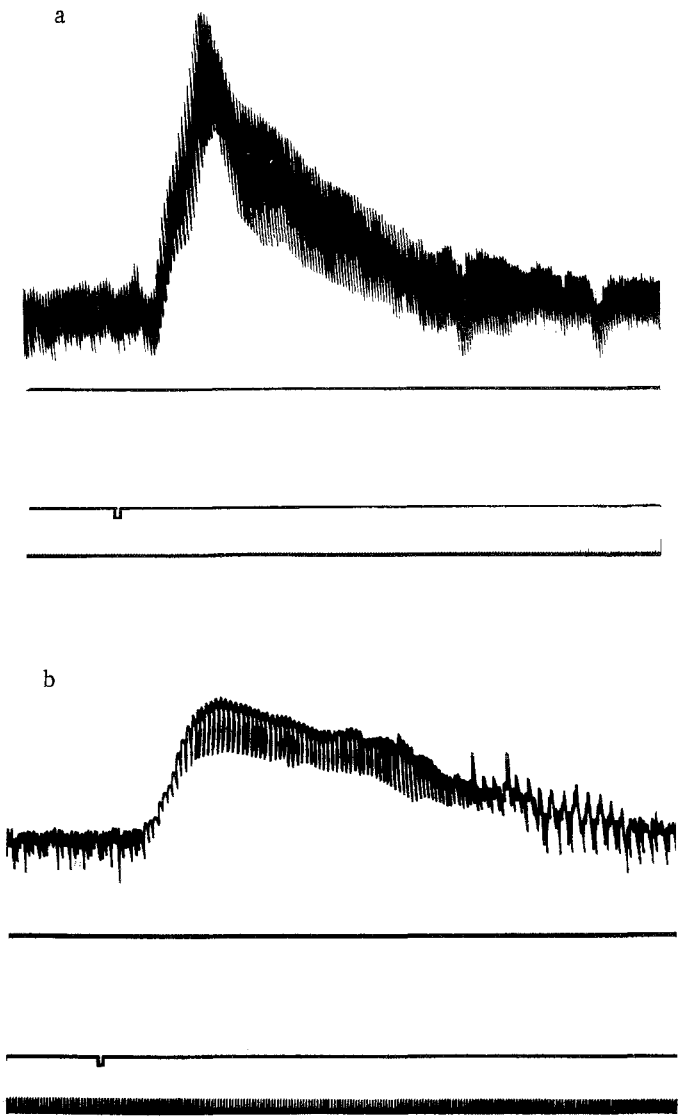
In previous investigations certain conclusions have been drawn regarding the purpose and character of the influences of the nervous system on the arterial wall in experimental atherosclerosis [7]. The object of the present investigation was to study the reactivity of the vasoconstrictor center, and also the contractile power of the arterial walls in the intact organism and in the isolated heart during the early stage of development of experimental cholesterol atherosclerosis in dogs and in association with the administration of adrenalin, which plays an active part in the regulation of vascular tone.

EXPERIMENTAL METHOD

Experiments were conducted on 14 male dogs aged 2-4 years, weihging from 16 to 27 kg, divided into two groups. The main group consisted of 10 dogs, receiving a 20% solution of cholesterol in sunflower oil daily for 45-60 days in a dose of 1 g cholesterol/kg body weight and 1.5 g 6-methylthiouracil daily in powder form. These substances were given to the animals mixed with minced meat. A control group consisted of 4 dogs, of which two (Nos. 3 and 11) received 6-methylthiouracil alone and two (Nos. 9 and 13) cholesterol alone in the same doses and for the same periods of time. The cholesterol concentration in the venous blood (by Able's method) and the lipoprotein concentration, followed by electrophoresis on paper, were estimated regularly in all the animals, not less often than once every 3 weeks.

EXPERIMENTAL RESULTS

The weight of the animals of the experimental group increased during the experiment by 2-3 kg, and that of the control animals by 1-2 kg. The blood cholesterol concentration of the animals of the experimental group rose 5-10 fold, of dog No. 5-17-fold, and of dog No. 6 – 20-fold, while at the same time the α-lipoprotein concentration fell and the β-lipoprotein concentration rose. The blood cholesterol concentration of the dogs receiving cholesterol alone rose by 50-100%, and that of the dogs receiving 6-methylthiouracil alone – by 100-200%. At the end of the experiment the dogs were sacrificed by exsanguination under morphine anesthesia and after injection of 5000 units



Arterial pressure of dogs before production of atherosclerosis (a), in an early stage of atherosclerosis (b). Marker on line of stimulation – moment of intravenous injection of adrenalin; time marker (1 sec).

of heparin. Postmortem examination of 2 dogs of the experimental group, receiving both cholesterol and 6-methylthiouracil, showed lipoidosis of the branches of the thyroid artery, visible to the naked eye (dogs Nos. 5 and 6). Marked lipoid infiltration of the juxtamedullary zone of the kidneys was found in the dogs of the experimental group, and also in the dogs of the control group.

In the heart very slight changes were seen in the coronary vessels, in the form of a focal lipoidosis of the intima and, to some extent, of the media. Neither macro- nor microscopic changes were found in the cardiovascular system of the dogs of the control group.

In some experiments the changes in arterial pressure were investigated after intravenous injection of adrenalin. For this purpose the arterial pressure in the femoral artery was measured by means of a mercury manometer in each of the 14 animals. The animals were anesthetized with morphine, and the site of the skin incision was anesthetized with ethyl chloride. Adrenalin was injected several times in each experiment, in fairly high doses (0.2-0.3 ml of 1:1.000 solution) in relation to the body weight. After the animals had been fed on cholesterol and 6-methylcholesterol for 45-60 days, the arterial pressure remained at its previous level, but in response to the injection of adrenalin, instead of the increase in the maximal arterial pressure by 200-250% observed in the experiments performed before cholesterol feeding began, it increased by not more than 100-150%. The minimal pressure now rose by a smaller

amount, and the pulse pressure fell sharply, mainly on account of the smaller rise in the maximal pressure. The latent period (the time from the moment of injection of adrenalin to the beginning of the rise of pressure) increased appreciably. The increase in pressure became less steep, and the whole curve, after the initial, less marked rise, became almost a horizontal plateau, with a very sloping descent, maintained over a long period of time (see figure). In some of the atherosclerotic dogs the minimal arterial pressure after cessation of the action of adrenalin fell temporarily below the initial value. In the initial experiments an increase in the dose of adrenalin by 50-100% caused such a sharp rise in arterial pressure that the mercury shot out of the manometer. The injection of larger doses of adrenalin in the final experiments caused a less marked rise of arterial pressure, although it retained all the typical features described above.

These facts indicate a lowering of the reactivity of the vasoconstrictor center and, possibly, a slight increase in the reactivity of the vasodilator center. After injections of adrenalin into the control dogs, the reaction of the arterial pressure in the concluding experiments remained the same, both quantitatively and qualitatively, as in the initial experiments.

There is considerable evidence that the arteries of isolated, denervated hearts, taken from the cadavers of persons dying from atherosclerosis or from animals with experimental atherosclerosis, react by more marked changes in their lumen to perfusion with vasoconstrictor and vasodilator substances than the vessels of healthy hearts [1-8].

Corresponding acute experiments were carried out on animals in an early stage of experimental atherosclerosis before the appearance of definitive plaques. The Kravkov–Pisemskii technique was used in the investigation, which allows the ability of the arterial wall to contract during perfusion of the vessel with adrenalin solution to be determined quantitatively from the changes in the lumen of the vessel. Experiments were performed on arteries of isolated, denervated hearts taken from 10 dogs with experimental atherosclerosis, from 2 dogs receiving 6-methylthiouracil, from 2 dogs receiving cholesterol, and from 4 intact dogs. To judge the changes in the lumen of the vessels and, consequently, the contractile activity of the arteries, the magnitude of their lumen when perfused with Ringer–Locke solution was taken as the initial value (100%). The temperature of the perfusion fluid was maintained between 37 and 39°; the fluid was saturated with oxygen. The change to perfusion with adrenalin solution was made after the size of the lumen of the vessels during perfusion with Ringer–Locke solution had remained stable for not less than 5 min. When perfused with adrenalin solution of high concentration (1 : 5,000,000-1 : 1,000,000), the coronary arteries of the arrested heart reacted by contraction.

In our experiments perfusion with 1 : 5,000,000 adrenalin solution caused the lumen of the arteries from the hearts of dogs with experimental atherosclerosis to contract by 50%, of dogs receiving cholesterol alone – by 27%, of dogs receiving 6-methylthiouracil alone – by 16%, and of intact dogs – by 20%. The contraction of the atherosclerotic vessels was more abrupt. When perfused with Ringer–Locke solution cooled to 28°, the lumen of the coronary arteries of the dogs with atherosclerosis contracted considerably (by up to 60%). Sometimes the reaction was paradoxical, manifested by a marked dilatation of the lumen (to 130%). The facts obtained demonstrate the increased and qualitatively abnormal reactivity of the isolated, denervated, atherosclerotic vessels. The changes in the lumen of the blood vessels of the control and intact dogs in response to perfusion with cold Ringer–Locke solution were much less in degree. In nearly all cases perfusion with adrenalin solution and with cooled Ringer–Locke solution caused fibrillation of the hearts of the atherosclerotic dogs. In similar conditions, fibrillation developed in the hearts of 2 intact dogs and in a heart taken from a dog receiving cholesterol alone.

Analysis of these results suggests the presence of inverse relationships between the change in the reactivity of the arteries of the intact dogs with experimental atherosclerosis, on the one hand, and the change in the reactivity of the walls of the isolated denervated arteries of the hearts of the same animals, on the other hand.

In the arteries of the isolated hearts of dogs with atherosclerosis, in response to injection of adrenalin a more abrupt and more marked constriction of their lumen took place; they also reacted more strongly than the coronary arteries of the intact and control dogs, and they sometimes reacted paradoxically to the cold stimulus. At the same time, in the intact organism, as the development of experimental atherosclerosis proceeded, the lumen of the arteries underwent a much smaller degree of constriction in response to injection of adrenalin than before the onset of the lesion. Consequently, in atherosclerosis, the vasomotor activity of the arteries in the intact organism showed a considerable degree of limitation. These facts cannot be regarded as the result of a lesion of the vessel walls, if only because nothing more than an initial, ill-defined lipoidosis was found histologically in the cardiovascular system of the experimental animals. Such insignificant changes in the vessel wall could hardly modify so systematically and purposively the reactivity of the cardiovascular system of their own accord in the early stage of development of the

disease. At this stage of the atherosclerotic process it is evident that the primary change affects the reactivity of the vasomotor center, and that the reactivity of the vessel walls becomes modified as a secondary effect.

The responsible role of the central nervous system in limiting the contractile activity of the vessel walls of the intact organism in atherosclerosis is also shown by the higher than normal contractility of the atherosclerotic vessels, demonstrable after their isolation from the influence of the central nervous system.

Since in the presence of very slight initial atherosclerotic changes in the vessels, the contractile activity of their wall was much more restricted than normally, it may be assumed that this phenomenon is a protective measure of the organism, brought about by the central nervous system in response to the incipient disease.

SUMMARY

In experimental atherosclerosis in dogs vascular reactivity becomes changed at the early stage of the process, prior to the development of specific morphological changes.

A suggestion was made that reactivity changes serve as a protective measure for the organism, formed by the nervous system in response to the disease.

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