EXPERIMENTAL MODEL OF ATHEROSCLEROSIS INDUCED BY INJECTING ACHTYLCHOLINE INTO THE MESENCEPHALIC RETICULAR FORMATION

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KEY WORDS: atherosclerosis; acetylcholine; reticular formation.

The complexity and great diversity of the etiologic factors and pathogenetic mechanisms lying at the basis of the development of atherosclerosis are reflected in the large number of experimental models of this disease; each model, moreover, reflects a particular stage of development of our ideas on the formation of the atherosclerotic process. Together with the widely known alimentary methods of modeling this disease [10, 4] there also exist methods based on action against the endocrine system [6, 8] or carbohydrate metabolism [5]. Often investigators have used a combination of different methods to obtain better results of modeling of the atherosclerotic process. For instance, an atherogenic diet has been combined with suppression of thyroid gland function by methylthiouracil [3]. Peroral administration of cholesterol combined with local injection of paraffin into the region of the middle hippothalamus [2], and led to atherosclerotic lesions of the aorta in 80% of the experimental animals in the course of 2 months. The role of the neural factor in the pathogenesis of atherosclerosis has been demonstrated on neurogenic models of the disease [8, 9]. Meanwhile the neurochemical nature of the central mechanisms involved in the development of atherosclerosis has not been adequately studied.

In this paper an experimental model of atherosclerosis in rabbits, involving repeated injections of acetylcholine (ACh) into the mesencephalic reticular formation, is suggested.

EXPERIMENTAL METHOD

Experiments were carried out on 22 adult chinchilla rabbits weighing 2.5-3.0 kg. Under local procaine anesthesia cannulas were implanted in the reticular nucleus of the tegmentum mesencephali (AP +6, D = 2.5, V = 12), using coordinates from the brain atlas [10]. The cannulas were fixed to the rabbits' skull by Noracryl polyacrylamide glue. The animals were used in the experiments 14 days after the operation. ACh was injected into the above-mentioned brain structure by means of the microinjector of a chemical electrode, in the form of a 1% solution (the ACh solution was made up immediately before use in physiological saline), in a volume of 10 μl (dose 100 μg) on alternate days for 30 days. Rabbits with implanted cannulas receiving physiological saline injections in a volume of 10 μl by the same schedule, served as the control. The rabbits were given the usual vegetable diet. At the end of the experiment the animals were killed by air embolism under ether anesthesis, and the locations of the cannulas and the degree of involvement of the aorta in the atherosclerotic process were verified histologically.

EXPERIMENTAL RESULTS

Morphological investigation of the aorta of the experimental animals showed oval formations of firm consistency on the intima, projecting above the surface (Fig. 1b), and in some cases they were confluent and gave the intima a nodular appearance and narrowed the lumen of the aorta. Microscopically lipid deposits were visible in the Intima, foci of accumulation of lipids also

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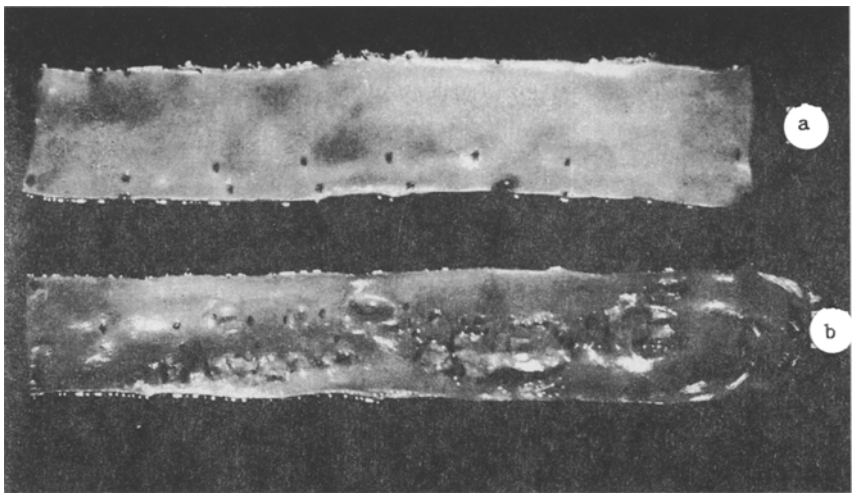

Fig. 1. Naked eye preparations of aorta of control (a) and experimental (b) rabbits. Magnification 2×.

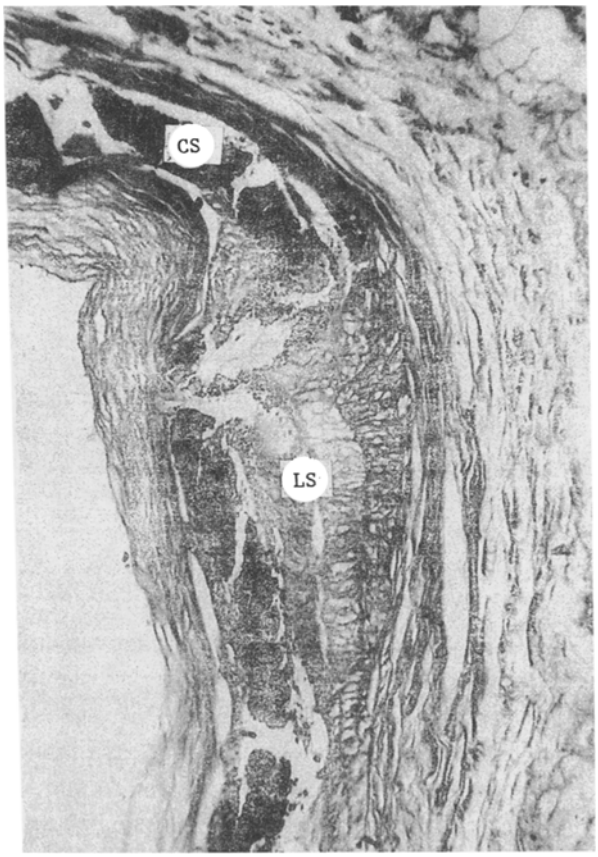

Fig. 2. Plaque in wall of rabbit aorta on 30th day of experiment. Deposits of calcium salts (CS) clearly visible; liposclerosis (LS) predominates in other parts. Hematoxylin and eosin, 100×.

were seen in the plaques, and around them fibrous tissue was formed, and surrounded by large deposits of calcium salts (Fig. 2). These features corresponded to lipoidosis, liposclerosis, atheromatosis, and atherocalcinosis [7]. The macroscopic and microscopic features of atherosclerosis of the aorta described above were observed in all the experimental animals on the 30th day after the beginning of ACh administration.

On morphological investigation of the aorta of rabbits receiving local injections of physiological saline, no evidence of pathology of the aorta tissue could be found any of the ten control animals (Fig. 1a).

The method described above thus enables a model of atherosclerosis to be obtained in rabbits with a high degree of reproducibility and in a relatively short time. On the other hand, the results described above indicate an essential role of the cholinergic structures of the mesencephalic reticular formation in the mechanisms of formation of this pathological condition, and the model can be used to study the neurochemical mechanisms lying at the basis of development of atherosclerosis, and also experimentally to develop new methods of treatment of this disease.

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EFFECT OF EXTREMAL FACTORS ON THE MECHANISMS OF HEMOLYSIS

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Under extremal influences (hypoxia, low atmospheric pressure, blood loss, injection of foreign agents) a stereotyped response of the blood system was observed: hemolysis (erythrodieresis), followed by activation of erythropoiesis, stimulation of nonspecific resistance, and regeneration of the tissues [2, 4, 6-8, 11-14]. The mechanisms of the so-called extremal erythrodieresis have not been explained. A definite role in the origin of increased erythrocyte destruction under the influence of stress has been attached to an increase in the titer of antierythrocytic antibodies, tissue hemolysins, and an intracellular defect of the erythrocytes. A probable role of the kidneys in this process has been mentioned in some publications [10].

The aim of this investigation was to study an autoimmune humoral and cellular component of erythrodieresis (ED), dependent on the kidney and induced by injection of phenylhydrazine and of a uranyl–glycerol mixture, and by acute blood loss.

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