MORPHOLOGICAL AND HISTOCHEMICAL CHANGES IN HYPOTHALAMIC NEUROSECRETORY NUCLEI, NEUROHYPOPHYSIS, AND CARDIOVASCULAR SYSTEM IN EXPERIMENTAL ATHEROSCLEROSIS

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Experiments on rats showed that in the initial stages of lipoidosis and liposclerosis, increased accumulation of neurosecretory substance and changes in structural properties take place mainly in cells of the supraoptic nuclei of the hypothalamus. In the late stages, when marked atherosclerosis of the vessels is present, increased accumulation of neurosecretion is also found in cells of the paraventricular nuclei and in the neurohypophysis.

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Experimental and clinical investigations have demonstrated a connection between lesions of the hypothalamus, both infectious and traumatic, and morphological and physiological changes in various systems of the body [6, 18, 23], including disturbances of lipid metabolism, frequently accompanied by atherosclerotic changes in the vessels. This has been observed both clinically [4, 10, 11, 15, 21] and experimentally [27, 30].

However, few investigations have so far been carried out to study structural changes in the hypothalamus, especially of its nuclei producing neurosecretion, accompanying disturbance of lipid and, in particular, cholesterol metabolism. Data on this problem in the literature are few in number and contradictory in nature [5, 12, 14, 24]. However, the morphological and physiological study of the hypothalamus is unquestionably important and even essential because it is in this structure that the regulation of the principal autonomic functions of the body is concentrated [1, 3, 9, 11, 22, 25, 28, 31], and in the modern view disturbance of these functions is directly related to the pathogenesis of atherosclerosis [2, 13, 19].

The object of the present investigation was to compare morphological and histochemical changes in the neurosecretory nuclei of the hypothalamus, in the neurohypophysis, and cardiovascular system during development of experimental atherosclerosis.

EXPERIMENTAL METHOD

Experimental atherosclerosis was produced in rabbits by feeding with crystalline cholesterol mixed with chopped root vegetables in a dose of 1 g/kg [26]. The serum cholesterol concentration was determined by the Éngel'gardt–Smirnova method.

The investigations were carried out 30-200 days after the beginning of the experiment. The supraoptic and paraventricular nuclei of the hypothalamus and the neurohypophysis were studied in serial sections from these regions stained by Bargmann and Maiorova, and also by Nissl's method. In each case the relative percentage of neurosecretory cells in each separate phase of the secretory cycle was calculated [7, 8, 16, 20]. Blood vessels (large trunks and visceral vessels) were investigated for lipids and elastic tissue (Sudan III, Van Gieson, resorcin–fuchsin). Mucopolysaccharides of the ground substance were detected by the combined method of Bertelsen and Jensen [29].

Analogous areas of the brain, heart, and blood vessels of intact rabbits were investigated by the same methods as the control. Altogether 45 animals were used in the experiment.

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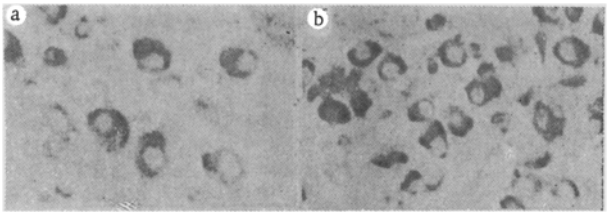

Fig. 1. Healthy rabbit. Paraventricular (a) and supraoptic (b) nucleo of hypothalamus (400 ×).

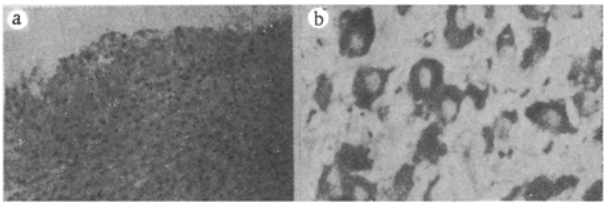

Fig. 2. Rabbit 70 days after beginning of cholesterol administration. Aorta: definitive atherosclerotic plaque (a; 140 ×). Supraoptic nucleus of hypothalamus: modified cells with increased content of neurosecretion (b; 400 ×).

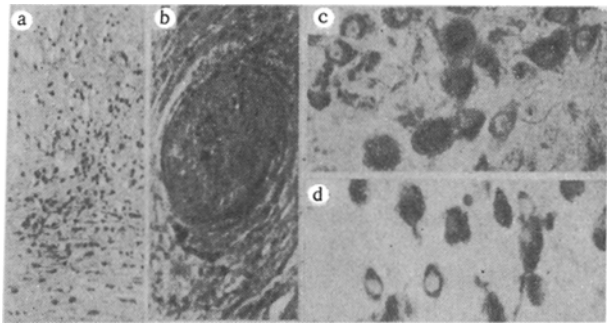

Fig. 3. Rabbit 200 days after beginning of cholesterol adminstration. Section through thoracic aorta with total atheromatosis (a; 140 ×); atherosclerotic plaques in coronary artery (b; 140 ×); supraoptic nucleus of hypothalamus: cells with small vacuoles at the periphery and an increased content of neurosecretion (c; 400 ×); paraventricular nucleus of hypothalamus; modified cells with increased content of neurosecretion (b; 400 ×).

EXPERIMENTAL RESULTS

The relative percentage of cells in the various phases of the secretory cycle in the supraoptic nuclei of the hypothalamus in normal rabbits was as follows: beginning of synthesis of neurosecretion 55%, phase of accumulation 41%, phase of liberation 4%. Compared with the paraventricular nuclei, the supraoptic cells were more compactly arranged (Fig. 1). The neurohypophysis consisted of a collection of axon endings of neurosecretory cells, some of which formed Herring's bodies.

Administration of exogenous cholesterol to the animals was accompanied by increased cholesteremia and atherosclerotic changes in the cardiovascular system. These changes were expressed to different degrees, determined by individual sensitivity of the rabbits to exogenous cholesterol [17].

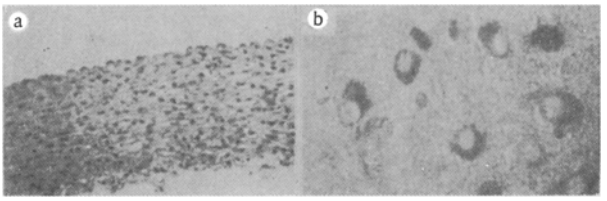

Fig. 4. Rabbit 200 days after beginning of cholesterol administration. Aorta (a; 140 ×) and paraventricular nucleus of hypothalamus (b; 400 ×); no change.

This relationship was observed most clearly in the early stages of the experiment (45th-70th day). In some animals only moderate cholesteremia was present (120-170 mg%), with the initial changes of lipoidosis. In these cases neither in the supraoptic nor the paraventricular nuclei, nor in the neurohypophysis, were any significant abnormalities observed.

In other animals at the same periods of the experiment, a more marked hypercholesteremia was present (400-1800 mg%), and definitive atherosclerotic plaques were found in the aorta, with large lipid droplets in the interstices of the plaques and accumulations of lipophages (Fig. 2a). Acid mucopolysaccharides were predominant in the enlarged masses of ground substance. The number of large cells in the phase of accumulation of neurosecretion was increased in the supraoptic nuclei to 80%. Neurosecretion filled not only the cell body, but also its processes, intertwining with each other to form a network (Fig. 2b). Total reduction of the tigroid had occurred in the cells packed with neurosecretion. Neither morphological nor histochemical changes were found in the paraventricular nuclei or neurohypophysis.

In the late stages of the experiment (200th day), when severe hypercholesteremia (1500-2000 mg%) was present, the atheromatosis was widespread in character, causing total involvement of the aorta and the great vessels (Fig. 3a) and also of the visceral vessels. The definitive plaques in the myocardium almost completely obliterated the lumen of the medium-sized and small arteries (Fig. 3b). The ground substance filling the interstices of the plaque and the widened intermembranous spaces of the media, now contained neutral as well as acid mucopolysaccharides. Most cells in the supraoptic nuclei were enlarged and altered in shape. The number of cells with optically empty vacuoles, forming a punched-out border around their body, was increased. The tigroid was reduced. Compared with previous periods, pycnomorphic cells were somewhat more numerous, and the number of cells in the phase of accumulation of neurosecretion was reduced to 56% (Fig. 3c). Neurosecretory substance accumulated in the cells of the paraventricular nuclei, filling both the body and processes (Fig. 3d). In the posterior lobe of the pituitary, neurosecretory substance filled all its tissue forming large Herring's bodies.

Somewhat different results were obtained in a few (resistant) rabbits, in which the serum cholesterol level showed no substantial rise throughout the experiment, reaching only 120 mg% by the 200th day. Macroscopic and microscopic examination revealed no structural changes in the blood vessels or in the supraoptic and paraventricular nuclei of the hypothalamus and the neurohypophysis (Fig. 4).

The experimental results showed that the severity of structural and functional changes in the neurosecretory nuclei of the hypothalamus is closely connected with the character of the atherosclerotic changes in blood vessels.

In the presence of total atherosclerosis of the vascular system, increased accumulation of neurosecretion took place not only in the supraoptic nuclei, but also in the paraventricular nuclei of the hypothalamus and in the neurohypophysis, evidence of disturbances of the neurosecretory function of the entire hypothalamohypophyseal neurosecretory system.

If neurosecretion produced by cells of the anterior division of the hypothalamus is regarded as one component in the complex mechanism of neurohumoral regulation of autonomic function, it can be postulated that hyperproduction of biologically active substances during hypercholesteremia may act unfavorably on the course of metabolism, including lipid metabolism, and also on regulation of the nutrition of the blood vessel walls, thus aggravating the atherosclerotic process as a whole.

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