# EFFECT OF FUNCTIONAL OVERSTRAIN OF THE CNS ON ENDOGENOUS CHOLESTEROL METABOLISM AND ON STRUCTURAL CHANGES IN BLOOD VESSELS AND THE HYPOTHALAMO-HYPOPHYSEAL NEUROSECRETORY SYSTEM

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In rabbits in which functional overstrain of the CNS was produced for two years changes developed in cholesterol metabolism (an increase in the total cholesterol level and a relative decrease in its esterified fraction), accompanied by fatty degeneration of the liver and, in some cases, by lipoidosis of the aorta and the intramural arteries of the myocardium. Under these conditions morphological changes (an increase in the volume of the nuclei of neurons of the supraoptic region) indicating changes in the secretory function of the hypothalamo-hypophyseal neurosecretory system developed.

This investigation is a continuation of work devoted to the study of the role of prolonged functional overstrain of the CNS in the pathogenesis of atherosclerosis [1-5, 7-11].

During overactivity of the CNS, disturbances of cholesterol metabolism were compared with morphological changes in the hypothalamo-hypophyseal neurosecretory system, blood vessels, and viscera.

## EXPERIMENTAL METHOD

Overstrain of the CNS was produced in five male rabbits by two or three repetitions of 100-day cycles of random alternation of periods of "work" and "rest" [2, 4]. The experiment lasted two years. Three rabbits acted as the control. Every 15-20 days the concentration of total, esterified, and free cholesterol in the blood and the mean daily excretion of bile acids with the feces were determined [1]. The initial values of the parameters of cholesterol metabolism were determined before the first 100-day cycle.

To characterize the conditioned-reflex activity of the rabbit the positive conditioned-reflex responses were counted and expressed as a percentage of the total number of stimuli. Conditioned-reflex changes in respiration (holding the breath, rapid breathing, change in amplitude, etc.) were analyzed separately. These changes were assessed as a weak conditioned-reflex response. After the end of the experiments the aorta and intramural blood vessels of four experimental and two control rabbits were subjected to histological investigation.

The neurosecretory system was studied in serial brain sections by Gomori's method in Maiorova's modification [6] and by Nissl's method. The volume of the nuclei of the neurons also was determined [13].

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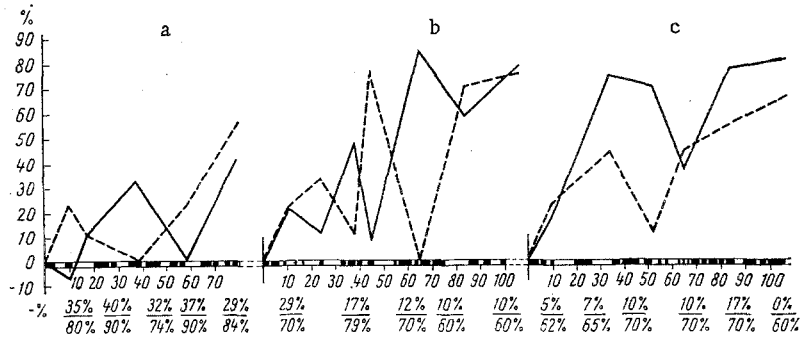


Fig. 1. Blood cholesterol concentration and mean daily excretion of bile acids (in % of initial level) during 100-day cycles of random alternation of periods of "work" (1) and "rest" (2): a) first 100-day cycle; b) second 100-day cycle; c) third 100-day cycle. Continuous line represents blood cholesterol, broken line shows excretion of bile acids. Fraction under curves shows number of positive conditioned-reflex responses (in % of total number of stimuli in that particular period of the experiment); numerator – breath holding, denominator – total number of positive responses (breath holding + change in respiration).

## EXPERIMENTAL RESULTS

The parameters of cholesterol metabolism and bile acid excretion in the control rabbits during the experiment were within normal physiological limits. The total cholesterol concentration in the blood was 37 ± 7.6 mg%, cholesterol esters 25.0 ± 6.5 mg%, and free cholesterol 13.0 ± 3.9 mg%. The mean daily excretion of bile acids was 34.0 ± 5.7 mg. The original values in the experimental rabbits were indistinguishable from those given above.

In the experimental rabbits the conditioned-reflex response was manifested as changes in the frequency and amplitude of the respiratory movements and, less frequently, by respiratory arrest. The conditioned reflex was formed quickly (on the third-fourth day of the experiment) and was stable. The percentage of positive responses varied from 50 to 90. During repeated cycles of sustained conditioned-reflex activity the number of positive conditioned-reflex responses decreased. The experimental rabbits did not develop a noticeable neurosis.

The blood cholesterol level rose in all the animals during functional overstrain of the CNS (up to 170-180% of its initial value). There was a marked tendency toward a relative decrease of the esterified cholesterol fraction, possibly the result of the diminution of liver function caused by the developing fatty degeneration [4]. During the repeated cycles the cholesterol level rose progressively.

The curves reflecting changes in the cholesterol level in all the animals showed a well-marked fluctuating character. With an increase in strain on the CNS the curve of the blood cholesterol concentration rose, but it still remained wave-like in character (Fig. 1). In all the experimental rabbits a statistically significant increase in the excretion of bile acids was observed, but these excretion curves likewise fluctuated throughout the cycle. The degree of fluctuation decreased slightly toward the end of the 100-day cycle of sustained conditioned-reflex activity (Fig. 1).

Toward the end of the experiment small discrete areas of lipoid infiltration of the slightly thickened intima and adjacent inner layer of the media were detected on the inner surface of the aorta of one of the experimental rabbits (Fig. 2A). In the other experimental rabbits no changes were present in the wall of the aorta. In one rabbit (Fig. 2B) focal lipoid infiltration of the wall of a medium-caliber coronary artery was found in the myocardium of the left ventricle. In another case a diffuse-focal fatty infiltration of the muscle fibers of the myocardium was observed (Fig. 2C). All the experimental animals showed fatty degeneration of the liver (Fig. 2D). In one of them, in addition, lipoidosis of the wall of the hepatic artery was present.

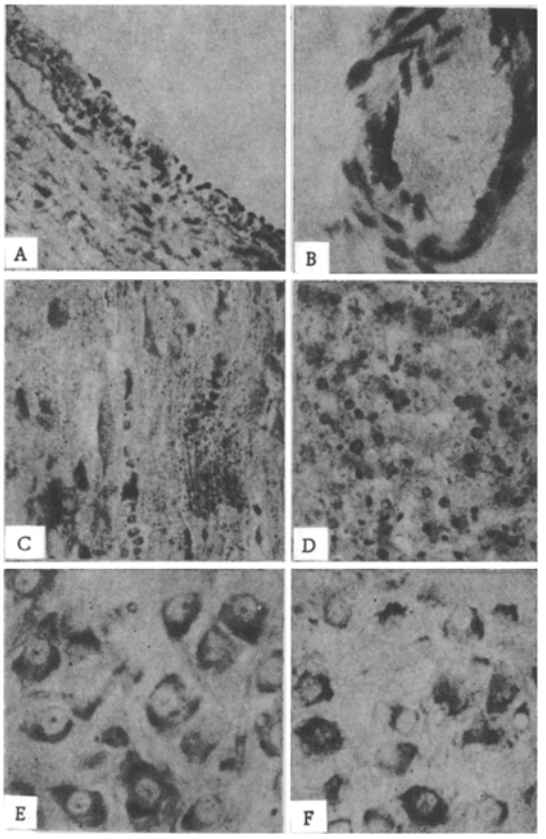


Fig. 2. Structural changes in organs during prolonged overstrain of the CNS: A) lipoidosis of the aorta. Rabbit No. 9. (Here and in B, C, D – stained by Goldman's method; 200×); B) focal lipoid infiltration of wall of coronary artery. Rabbit No. 14; C) fatty degeneration of muscle fibers of myocardium. Rabbit No. 12; D) fatty degeneration of the liver. Rabbit No. 12; E) supraoptic nucleus of hypothalamus of rabbit No. 14 after functional overstrain of the CNS. (Here and in F – stained by Gomori–Maiorova method; 400×); F) the same in a control rabbit.

Considering that the development of lipoidosis of the blood vessels in rabbits is associated as a rule with the administration of exogenous cholesterol [12, 14] the changes now discovered in the blood vessels and myocardium in animals on an ordinary diet may have been due to disturbance of endogenous cholesterol metabolism as a result of overstrain of the CNS.

On histological examination of the hypothalamus a very small quantity of neurosecretory substances was found. The neurons of the supraoptic and paraventricular nuclei were large in size and contained swollen nuclei (Fig. 2E). On karyometry a statistically significant ($P < 0.001$) increase in volume of the nuclei of the neurons of the supraoptic region was found in the experimental rabbits.

In one of the rabbits in which the excretion of bile acids was high, the increase in the blood cholesterol level was very slight, the signs of lipoidosis in the blood vessels were weak, and the changes in the neurosecretory system of the hypothalamus were least marked by comparison with the other experimental animals.

The results of this investigation show that during prolonged functional overstrain of the CNS changes are observed in cholesterol metabolism which in every case are accompanied by fatty degeneration of the liver, and in individual cases by lipoidosis of the aorta and the intramural artery of the myocardium.

Functional strain on the CNS evidently leads to changes in the secretory function of the hypothalamo-hypophyseal neurosecretory system.

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