

INVESTIGATION OF THE ROLE OF PROLONGED EMOTIONAL STRESS IN THE GENESIS OF HYPERCHOLESTEREMIA AND HYPERTENSION*

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In experiments on freely moving rabbits, exposed to prolonged (for 2 h) interrupted stimulation of negative emotiogenic zones of the hypothalamus through implanted electrodes daily for 4 months, the development of a lasting endogenous hypercholesteremia and of a mild but lasting hypertension was observed. Changes in the cholesterol concentration were greater if stimulation continued in conjunction with daily feeding of the rabbits with small doses of methylthiouracil.

KEY WORDS: emotional stress; hypercholesteremia; hypertension.

The role of the hypothalamus in disturbances of cholesterol metabolism has still received little study even though Lang [5] postulated some time ago on the basis of clinical observations that the development of hypercholesteremia may be connected with functional disturbances in precisely that region. The results of the few experimental studies of this problem are extremely contradictory. However, only a few of these investigations involved chronic hypothalamic stimulation [2, 4, 7, 10], and these also gave different results. Furthermore, there are virtually no investigations in which an attempt was made to draw a parallel between changes in the blood cholesterol level, the arterial blood pressure, and emotional-behavioral responses accompanying them. This is a very important matter, for the hypothalamus plays an active part in the formation of emotional states and the decisive role in the effect of nervous and humoral influences on them [3].

A previous investigation [9] showed that relatively brief (30 sec) stimulation of the hypothalamic emotiogenic zone, giving rise to a negative emotional-behavioral response, leads to a prolonged (up to 1 h) increase in the blood cholesterol concentration and to elevation of the arterial pressure during stimulation.

These facts suggested that prolonged, chronic stimulation of negative emotiogenic zones of the hypothalamus or prolonged emotional stress could lead to the development of lasting endogenous hypercholesteremia and also, possibly, hypertension. This paper describes a study to test this hypothesis.

EXPERIMENTAL METHOD

Unipolar electrodes were implanted into the medial region of the hypothalamus, in accordance with the coordinates of a stereotaxic atlas [11], in experiments on male rabbits (8) weighing 3 kg. The criterion of correct implantation was a negative emotional-behavioral response; in addition, the location of the electrodes was verified histologically. Six rabbits acted as the control. For electrical stimulation a special autonomous original microstimulator was used, its size and weight being such that the experiments could be carried out on freely behaving rabbits. The microstimulator was placed in the pocket of a special "waistcoat" tailored for the rabbits and connected by two flexible leads to the implanted electrodes through a terminal fixed to the

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rabbit's head. Two weeks after implantation of the electrodes the animals were stimulated by square pulses with a duration of 3 msec and a frequency of 50 Hz, with variable amplitude. The stimulus amplitude at which a negative emotional response of anxiety and fear (about 4-5 V) was chosen for each rabbit. The stimulation was interrupted and was given daily for 2 h. Blood was taken every 10 days from the auricular vein. Cholesterol was determined by Abel's method. The blood pressure was measured in the carotid artery, exteriorized into a skin flap.

EXPERIMENTAL RESULTS

The results showed that daily chronic stimulation of the negative emotiogenic zone of the hypothalamus led within 1 month to an increase in the blood cholesterol concentration from the normal level of 29.9 ± 2.9 mg % to 42 ± 3.09 mg % ($P < 0.01$), i.e., on average by 44% compared with the initial level. Almost the same changes in cholesterol level (43.3 ± 4.3 mg %) also were observed in the second month of stimulation ($P < 0.01$). The cholesterol level in the control rabbits varied within normal limits (from 28.3 ± 1.4 to 27 ± 2.29 mg %).

Modification of the hormonal profile by depressing the function of the thyroid gland, closely connected through the liver with cholesterol metabolism [6a], by small doses of methylthiouracil (0.05 g/kg daily), led after only a month of chronic stimulation to a much greater increase in the blood cholesterol concentration (up to 61.8 ± 8.2 mg % compared with initially ($P < 0.01$) i.e., an average increase of 110%. This action was manifested earlier than the effect of methylthiouracil on the cholesterol level in the control rabbits.

Toward the end of the first month of stimulation the blood pressure of most rabbits rose on average from 113 ± 1.46 to 121 ± 2.2 mm Hg ($P < 0.05$), i.e., by 7%. In the second month of stimulation the blood pressure of some rabbits continued to rise. For the group as a whole, however, the blood pressure was not significantly changed by comparison with the first month of stimulation. During the third and fourth months of stimulation the blood pressure reached 124 ± 1.9 mm Hg ($P < 0.01$), i.e., it rose on average by 10% compared with the initial level. Methylthiouracil had no demonstrable effect on the blood pressure, for in the rabbits which developed lasting hypertension a tendency for the blood pressure to rise was observed from the beginning of stimulation and it developed gradually.

In most rabbits elevation of the blood pressure as a result of chronic stimulation coincided with an increase in the blood cholesterol, although the two effects differed in their latent period and in the degree of deviation. However, in two rabbits with an apparently identical emotional-behavioral response, either an increase of blood pressure only or an increase in the blood cholesterol concentration only was observed.

The general conclusion can be drawn from these findings that prolonged chronic stimulation of negative emotiogenic zones of the hypothalamus or prolonged emotional stress can lead to the development of mild but persistent hypercholesteremia and hypertension. These lasting changes obtained under chronic experimental conditions are perhaps the sequel to prolonged circulation of excitation over the limbic structures of the brain, as Sudakov [8] confirmed by the results of his acute experiments. They could also be the result of activation of the hormonal component. Judging from the fact that the weight of the adrenals in rabbits subjected to hypothalamic stimulation was 3.5 times greater than in intact animals or animals receiving methylthiouracil alone, an important role can be ascribed to the adrenals in the compensatory mechanisms arising in response to prolonged emotional stress caused by hypothalamic stimulation. Disturbance of hormonal homeostasis by methylthiouracil brought to light this state of stress of the neuro-endocrine system and was the "conditional factor" [12] for the more marked effect of prolonged emotional stress on the blood cholesterol level than on the arterial blood pressure.

In the writers' view, these findings confirm Myasnikov's hypothesis [6] that common pathological processes at the subcortical level lie at the basis of development of hypercholesteremia and hypertension, and also Anokhin's views [1] on the role of prolonged negative emotional states in disturbances of the mechanisms of self-regulation of autonomic functions capable of creating the conditions for initiating the development of cardiovascular diseases.

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