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CHANGES IN COLLAGEN METABOLISM DURING CHRONIC ELECTRICAL STIMULATION OF THE MESENCEPHALIC RETICULAR FORMATION

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The formation of behavioral, emotional, and somato-autonomic reactions in stress takes place with the participation of the brain reticular formation [7]. Stimulation of the mesencephalic reticular formation most frequently causes the blood pressure to rise, due to increases in the heart rate, myocardial contractility, and vascular tone [4]. Electrical stimulation of this region leads to changes in activity of the hypothalamo-hypophyseo-adrenocortical system [8], which may be accompanied by metabolic changes.

The aim of this investigation was to study the character of collagen metabolism in the aortic wall and myocardium during long-term and frequent electrical stimulation of the mesencephalic reticular formation.

EXPERIMENTAL METHOD

Chronic experiments were carried out on 26 adult rabbits weighing 2.5-3 kg. Under local procaine anesthesia bipolar nichrome electrodes were inserted into the experimental and control animals into the reticular nucleus of the tegmentum mesencephali, at coordinates taken from a stereotaxic brain atlas (AP +6, V −15, S −2.5). The animals were used in the experiments 10-11 days after the operation. Square pulses (3-4 V, 70 Hz, 0.5 msec, duration 1 h) were used for electrical stimulation on alternate days for 30 and 90 days. At the

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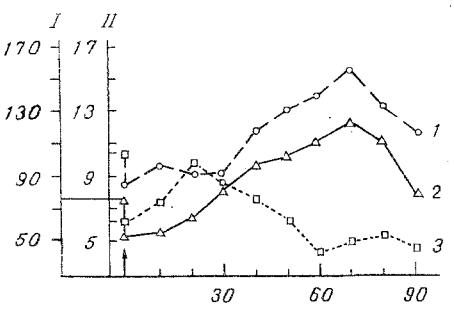

Fig. 1

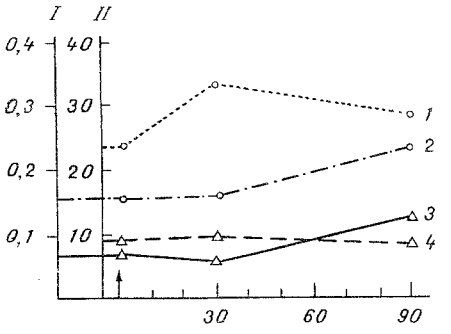

Fig. 2

Fig. 1. Changes in blood levels of 11-HCS (2), and of free (1) and bound (3) hydroxyproline during electrical stimulation of reticular formation. Abscissa, duration of stimulation (in days); ordinate: I) 11-HCS concentration (in μg/liter); II) free and bound hydroxyproline concentrations (in μmoles/liter). Arrow indicates beginning of stimulation.

Fig. 2. Changes in concentrations of total (1) and free (2) hydroxyproline in aortic wall and of free (3) and total (4) hydroxyproline in wall of left ventricle during electrical stimulation of reticular formation. Ordinate: concentrations of I) free, and II) total hydroxyproline (in g hydroxyproline/kg weight of dry, defatted tissue). Remainder of legend as in Fig. 1.

end of the experiments the animals were killed by air embolism under ether anesthesia and the location of the electrodes were verified histologically. Blood for biochemical tests was taken from the marginal vein of the rabbit's ear every 10 days in the course of the experiment, 30 min after electrical stimulation. Plasma levels of 11-hydroxycorticosteroids (11-HCS) [9] and of free and bound hydroxyproline [11] were determined. Concentrations of free and total hydroxyproline were studied in the wall of the thoracic aorta and in the wall of the left ventricle [10].

EXPERIMENTAL RESULTS

During long-term electrical stimulation of the reticular formation an increase in the plasma free hydroxyproline concentration was observed starting from the 40th day of the experiment. Whereas its concentration in the control animals was 10.67 ± 0.40 μmoles/liter, on the 70th and 90th days it was 43.7 and 16.4% higher, respectively, than initially. The plasma peptide-bound hydroxyproline level in the control animals was 6.96 ± 0.28 μmoles/liter. In the course of the experiments this parameter was increaed on the 20th and 30th days, when it was 50.1 and 24.7% higher, respectively, than initially, but later it returned to normal and by the end of the expeirment it was reduced by 22.13%. The free hydroxyproline concentration in the wall of the aorta and left ventricle was 0.158 ± 0.006 and 0.078 ± 0.003 g/kg weight of dry, defatted tissue, respectively; on the 30th day of the experment it was the same as in the control, and by the 90th day of the experiment it was 49.3 and 29.5% higher, respectively, than initially. Meanwhile the total hydroxyproline concentration, which was 23.08 ± 2.19 and 8.62 ± 0.55 g/kg weight of dry, defatted tissue in the aorta and myocardium of the control animals, respectively, was increased on the 30th day of the chronic experiment by 41.9% in the aorta, but unchanged in the myocardium, and on the 90th day of electrical stimulation its level in the aorta was 25.1% higher than initially, whereas in the wall of the left ventricle it was reduced by 20.8%. The plasma 11-HCS concentration in the control animals was 75.66 ± 6.55 μg/liter. During the first days of electrical stimulation this parameter fell by 29.3%, but later it returned to the initial level, and by the 40th day it was increased, being 83.5% higher than the control value, but by the end of the experiment it had again fallen to its initial level (Figs. 1 and 2).

Long-term electrical stimulation of the reticular formation led to changes in the central neurohumoral regulatory mechanisms of metabolism and of autonomic reactions. During

stimulation of structures of the limbico-reticular complex activation of the sympathico-adrenal and hypothalamo-hypophyseo-adrenocortical systems takes place. This is accompanied by a pressor response [2, 4], which leads to structural changes in the connective tissue of the arterial wall and to collagen accumulation in it [2, 3]. There is much evidence that adrenocortical hormones can influence connective tissue metabolism [5, 12, 14]. The action of glucocorticoids on connective tissue can be defined as a whole as catabolic [14]. However, it is manifested in the presence of high concentrations of these hormones, and if their concentration is low, not above the physiological level, these hormones may have the opposite kind of action: they may reduce hydroxyproline excretion and reduce collagen breakdown, thus promoting maturation of collagen and its transition into insoluble fractions [6, 15]. Free hydroxyproline is not utilized in collagen biosynthesis, and is formed when this protein is broken down [5]. Meanwhile peptide-bound hydroxyproline in the blood stream is a degradation product of soluble collagen [1, 13].

Under the present experimental conditions during the first 30 days of electrical stimulation collagen accumulation in the aorta was intensified, in agreement with data in the literature. However, the increase in the blood concentration of peptide-bound hydroxyproline suggests intensification of catabolism of soluble collagen fractions. This process is largely compensated by synthesis of the basic connective-tissue protein, as is shown by elevation of the total hydroxyproline level. Predominance of anabolism in the aorta is evidently a useful compensatory reaction of the aortic wall to hypertension, caused by stimulation of the reticular formation. Predominance of synthesis is still maintained on the 90th day, despite the high 11-HCS level and intensification of collagen catabolism, as is shown by the raised free hydroxyproline level both in the aortic wall and in the blood plasma.

A rather different response was observed on the part of the connective tissue in the wall of the left ventricle. On the 30th day of electrical stimulation no marked changes of collagen metabolism took place, as was confirmed by the stable levels of free and total hydroxyproline. On the 90th day of the experiments the high free hydroxyproline level and lowering of the total hydroxyproline concentraiton indicate an uncompensated increase in the intensity of connective tissue catabolism in the wall of the left ventricle.

Under these experimental conditions an increase in the free hydroxyproline concentration and, consequently, in the intensity of reactions of connective tissue catabolism, coincided with an increase in the blood 11-HCS concentration, which is in agreement with data in the literature on the direction of action of these hormones on collagen metabolism.

Long-term electrical stimulation of the mesencephalic reticular formation thus leads to activation of adrenocortical function and also to changes in collagen metabolism, with its accumulation in the aorta and with a decrease in the content of this biopolymer in the wall of the left ventricle.

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