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DIMINISHED CHEMOSENSITIVITY OF SENSOMOTOR CORTICAL NEURONS DURING ADAPTATION TO STRESS AND ITS ROLE IN THE PREVENTION OF FIBRILLATION IN ACUTE MYOCARDIAL ISCHEMIA

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Under the influence of acute ischemia, arrhythmias and fibrillation of the heart, often terminating in death, arise regularly in conscious animals of various species [4-6]. A definite role in the mechanism of these arrhythmias is played by overexcitation of the frontal cortex, induced by acute ischemia; it irradiates to certain hypothalamic centers and, from them, to the adrenergic centers of the brain stem, and so exerts a powerful adrenergic influence on the heart [6]. It has also been found that intracerebral injection of inderal (propanolol), which blocks this mechanism [6], or adaptation to stress, limiting the stress reaction [2], regularly limits fibrillation of the heart and death of conscious animals from acute ischemia. Observations in recent years have shown that this kind of protective effect is due to activation of stress-limiting systems, i.e., opioidergic, GABA-ergic, and serotoninergic systems, during adaptation; the mediators of these systems may limit excitation of the brain centers, and thus play a definite role in the pathogenesis of arrhythmias [1-3]. It may accordingly be postulated that adaptation with the aid of activation of stress-limiting inhibitory systems or in other ways may depress excitability of neurons of the sensomotor and, in particular, the frontal cortex, and thus limit excitation of the whole system of centers involved in the onset of fibrillation of the heart [2].

The aim of this investigation was to compare the effect of adaptation to short-term immobilization stress on the chemosensitivity of sensomotor cortical neurons and on the resistance of the rat heart to arrhythmias arising in conscious animals during acute ischemia.

EXPERIMENTAL METHODS

Experiments were carried out on male Wistar rats weighing 180-200 g. The animals were adapted by daily fixation in the supine position; the first day for 15 min, the second for 30 min, and thereafter 10 times for 1 h each time. Next, in acute experiments on animals immobilized with α-tubocurarine, a miniature micromanipulator was secured to the skull, and by means of it a triple-barreled structured electrode was inserted to the level of layers IV-V of the sensomotor cortex. The electrodes were filled with 3 M NaCl solution (recording electrode), a 2 M solution of acetylcholine (ACh; pH 4.0), and a 0.2 M solution of noradrenaline (NA) bitartrate. Neurotransmitters were applied to the neurons by electrophoresis (30-40

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TABLE 1. Effect of Adaptation to Immobilization Stress on Sensitivity of Sensomotor Cortical Neurons to ACh and NA

Mediator applied	Character of response	Group of animals: control (n = 111)	Group of animals: adaptation (n = 48)	Change, %
ACh	Activation	42±5	25±6	—39
	No response	24±4	56±7*	+133
	Inhibition	34±4	15±5	—56
NA	Activation	41±5	23±6*	—44
	No response	22±4	60±7*	+172
	Inhibition	37±5	17±5	—54

Note. Here and in Table 2, relative numbers of activated, areactive, and inhibited neurons given (in %); n) number of neurons; *p < 0.05 compared with control.

TABLE 2. Characteristics of Response of Sensomotor Cortical Neurons of Control and Adapted Rats to Microiontophoretic Application of ACh and NA

Mediator applied	Character of response	Group of animals: control (n = 26) background	control (n = 26) application	control (n = 26) change	adaptation (n = 48) background	adaptation (n = 48) application	adaptation (n = 48) change
ACh	Activation	2,5±0,6	4,9±0,9	+96	2,0±0,3	3,4±0,5	+70
	No response	3,6±0,7	3,5±0,7	—3	3,9±0,3	3,9±0,3	0
	Inhibition	3,1±1,1	1,6±0,8	—49	3,1±0,7	2,1±0,2	2—82
NA	Activation	2,2±0,5	4,5±0,8	+104	2,9±0,3	3,9±0,3	+34
	No response	2,4±0,5	2,7±0,6	+12	3,2±0,2	3,1±0,2	—3
	Inhibition	2,6±1,0	0,6±0,2	—77	3,2±0,4	2,1±0,5	—34

nA) for 30 sec (holding current not more than 4-5 nA). Unit activity was recorded before (for 1.5 min), during (30 sec), and after microiontophoresis of the drugs (2 min). Intervals of the spike discharge 60 sec in duration, before and after microiontophoretic application of the drugs, were used for analysis. The criterion of the response of a neuron to iontophoresis of the neurotransmitters was a change in firing rate of the neurons by not less than 20%. Altogether 111 neurons in the control animals and 48 neurons in animals adapted to stress were recorded. In the second stage of the experiments, during reproduction of arrhythmias in conscious rats, the method in [4], which is in two stages, was used. In the first stage, under ether anesthesia a ligature was applied beneath the descending branch of the left coronary artery, and in the second stage (1 week later), without anesthesia an incision 5 mm long was made in the skin and the ligature was drawn tight, thus causing coronary occlusion and acute myocardial ischemia. This last manipulation was carried out under electrocardiographic control. The quality of the arrhythmias was judged from the ECG, and their frequency and duration were estimated quantitatively in stress-adapted and control animals. The data were subjected to statistical analysis by Student's test.

EXPERIMENTAL RESULTS

With respect to the relative number of neurons activated, areactive, and inhibited by application of ACh and NA, the adapted animals differed sharply from the control group (Table 1). The relative number of areactive neurons in the adapted animals was 2-2.7 times greater than in the control, and the relative number of neurons responding to microiontophoretic application of the neurotransmitters in the adapted animals, on the other hand, was reduced by 39-56% (the relative number of inhibited neurons in this case fell by a greater degree).

A more detailed and informative assessment of the effect of adaptation on chemosensitivity of the neurons is dependent on the calculation of other parameters: changes in spontaneous activity, the intensity of the average response to application of the neurotransmitters. These data are given in Table 2.

TABLE 3. Effect of Adaptation to Immobilization Stress on Cardiac Arrhythmias during Acute Ischemia

Parameter	Control (n = 20)	Adaptation (n = 20)
Number of animals with different types of arrhythmias:		
with extrasystoles	20	8
with ventricular tachycardia	17	4
with ventricular fibrillation	17	4
Total duration of arrhythmias, sec	1015	217
Number of dying animals	12	3

The average value of the neuronal response to ACh and NA in the adapted animals was found to be much less than in the controls. Depression of the response to NA was particularly marked in the adapted animals. In the case of activation, for instance, the intensity of the neuronal responses of the control animals to NA was doubled, whereas in the adapted animals it was increased by only 34%; in the case of inhibition, the intensity of the neuronal responses of the control animals was reduced by 77% and that of the experimental animals by 34%. Responses to ACh also were considerably weakened, although by a lesser degree than those to NA, and these changes were on the borderline of significance (Table 2).

When this new fact is assessed, at least two possible explanations must be considered. First, activation of central stress-limiting systems in the brain demonstrated previously — the accumulation of opioid peptides, serotonin, and GABA in the corresponding centers — may depress reactivity and, in particular, the adrenoreactivity of cortical neurons, thereby preventing triggering of the neurodynamic process which, in the modern view, is realized in response to the action of an endogenous or exogenous stressor, and leads to disturbances of the cardiac rhythm. Second, as a result of the intensive afferent flow and of increased secretion of neurotransmitters into the presynaptic spaces of the neurons during repeated exposures to stress, the process of desensitization of the neurons, known to take place during adaptation [7], may be realized at the synaptic membrane level. This is one possible cause of the change in chemosensitivity of neurons to various neurotransmitters.

Irrespective of the mechanism of the fact thus revealed, it must be recalled that despite the very considerable decrease in the number of cortical neurons responding to the principal mediators of nervous excitation demonstrated by these experiments, all the principal behavioral responses and, in particular, formation of food and defensive conditioned reflexes, followed the normal course in stress-adapted animals. The situation is therefore that these reactions are realized by fewer neurons but on account of their more efficient performance of their controlling function, i.e., one of the main features of long-term adaptation can be observed, namely its economy.

The results of an experiment to assess the effect of preliminary adaptation to stress on the intensity of arrhythmias and fibrillation of the heart in conscious animals during acute ischemia, are given in Table 3. Acute ischemia in conscious animals with a closed chest led in 17 of 20 cases to fibrillation of the heart, and 12 of the animals died from cardiac arrest. During adaptation, fibrillation developed in only four animals, of which three died. In other words, adaptation to stress reduced the frequency of fibrillation and the mortality from acute ischemia by several times.

The results of the investigation as a whole are evidence that adaptation to short periods of stress significantly reduces the chemosensitivity and, in particular, the adrenergic reactivity of neurons in layer IV of the sensomotor cortex and, at the same time, reduces the frequency of fibrillation and the mortality of the animals from acute cardiac ischemia by several times. This fact is in harmony with the view that adaptation to stress situations exerts an antiarrhythmic cardioprotective effect largely through depression of excessive excitation of the brain centers involved in the response of emotional-painful stress to acute cardiac ischemia.

This general situation has recently served as the basis for the use of activators or metabolites of central stress-limiting systems, namely sodium valproate, which indices GABA

accumulation, serotonin analogs, and so on, as antiarrhythmic agents [2]. Thus the principle of stimulation of stress-limiting systems of the body has definite prospects for practical use in cardiology.

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ACOUSTIC RESISTANCE OF ADIPOSE TISSUE AS A PARAMETER OF ITS FUNCTION

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The view that adipose tissue is a metabolically inert variety of connective tissue has been revised in recent years. Fat cells have been shown to be derived not from connective tissue, but from special primary fat cells. Adipose tissue as a whole is characterized by metabolic activity which is controlled by neurohumoral regulatory mechanisms [5]. Besides supplying energy, adipose tissue performs the role of mechanical buffer and heat insulator in the body, so that its contribution to the vital functions is even more important. However, at least so far as white adipose tissue is concerned and, in particular, when it is compared with the other tissues of the body, this opinion is not universally shared. In my own opinion this is partly due to the inadequate sensitivity of traditional methods used to study adipose tissue.

The author has made an ultrasonic study of adipose tissue under normal conditions and in various pathological processes. The aim of the investigation was to obtain acoustic parameters of pathologically changed adipose tissue, which can be used to develop technical systems for ultrasonic diagnosis. Data on acoustic parameters only of normal adipose tissue have been published [6]. They are used for intravital ultrasonic measurement of the thickness of the subcutaneous fat layer in animals [4] and man [1]. This defect limits the differential diagnostic potential of ultrasonic systems for visualization of the internal organs and, in particular, of acoustic computer-assisted tomographs.

EXPERIMENTAL METHODS

The main group of experiments was carried out on 113 segments of adipose tissue of the omentum, mesentery, breast, lipoma, intermuscular fat, and subcutaneous fatty areolar tissue, freshly removed during operations on adult men and women. The method of ultrasonic reflectometry was used, by which the acoustic resistance (AR) of areas of tissue at the point of contact with a standard medium, was used. Full details of the acoustic part of the technique were described by the writer previously [3]. Contact was created between the tissue and the tip of an ultrasonic transducer, 5 mm in diameter. The material of the tip and the transducer as a whole can be cold-sterilized in disinfectant solutions. The error of measurement of AR did not exceed 0.8%. Values of AR of the tissue were averaged over the area of contact. The distance between the regions of tissue investigated was 1 cm. The surface param-

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