ACUTE EMOTIONAL STRESS AND CYCLIC NUCLEOTIDE LEVELS IN HEART AND BLOOD PLASMA

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In emotional stress because of excitation of adrenergic and cholinergic systems the functions of the endocrine glands are disturbed and this is accompanied by a marked increase in concentrations of catecholamines and other biologically active compounds in the heart tissues and blood [7, 8]. Elevation of the adrenalin level leads to activation of lipid peroxidation, which causes labilization of membranes of the cells and cellular organelles of the heart [4-6]. As a result of these processes arterial hypertension develops and leads to a disturbance of cardiac activity (disturbance of the cardiac rhythm, and so on), which may not infrequently cause death. Since hormonal regulation of myocardial function and metabolism is mediated through cyclic nucleotides, it was decided to study the character of metabolism of these vitally important compounds in order to determine the resistance of the body to emotional stress and to seek ways of controlling any pathological changes.

The object of this investigation was to study the concentrations of cyclic nucleotides in the heart and blood plasma of animals dying with acute emotional stress (AES).

EXPERIMENTAL METHOD

Experiments were carried out on 22 male Chinchilla rabbits weighing 1.8-2.5 kg. The experimental animals were divided into three groups: control animals (n = 10), immobilized (n = 6), and a group of animals exposed to AES (n = 6). AES was produced in immobilized rabbits by aperiodic stimulation of negative emotiogenic centers in the hypothalamus (ventromedial nuclei) and by electrodermal stimulation in accordance with a specially developed stochastic scheme. The ventromedial nuclei were stimulated by bipolar nichrome electrodes, and electrodermal stimulation was applied through steel needles, implanted subcutaneously into one of the animal's hind limbs. The current consisted of square pulses (50 Hz, duration 1 msec, strength 150-200 μA, each separate period of stimulation 1-2 min). Of the six animals of the last group, five rabbits died after AES. The arterial pressure (BP), ECG, and respiration of the rabbits were recorded continuously for 3 h on a Mingograf-34 apparatus (Siemens-Elema, Sweden).

Concentrations of cAMP and cGMP in the heart tissue were determined after extraction of the nucleotides with ethanol and appropriate purification [1]. To determine the concentrations of cyclic nucleotides blood was collected in cold test tubes containing 0.5 M EDTA (pH 7.5), in an amount equal to 1% of the volume of blood taken. Plasma was separated by centrifugation. After precipitation of the proteins with 2 volumes of ethanol, further treatment of the samples was as described in [1]. The cyclic nucleotides were assayed by means of the corresponding kits of the agents (for cAMP and cGMP) from Amersham Corporation (England).

EXPERIMENTAL RESULTS

Individual changes in BP, heart rate (HR), and respiration were observed in animals exposed to the action of AES in accordance with a single stochastic scheme. General rules governing changes in the BP level characteristic of the group of animals dying during a 3-h

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TABLE 1. Cyclic Nucleotide Levels in Heart (in pmoles/g tissue) and Blood Plasma (in pmoles/ml) during Exposure to Different Kinds of Stress

Experimental conditions	Heart tissue		Blood plasma	
	cAMP	cGMP	cAMP	cGMP
Control	294±38,6	5,4±0,75	9,2±5,5	14,4±1,7
Immobilization	513±49,4	5,1±0,85	79±20	14,2±4,8
AES	934±239	12,8±2,9	188±18	12,3±1,0

stress program were revealed. For instance, during the first hour BP of these animals increased by 21 ± 2 mm Hg, during the second hour it fell by 8 ± 1.6 mm Hg and, finally, during the third hour BP fell progressively until the animal died. In a resistant animal (which did not die after AES) during the first hour BP also rose by 20 mm Hg, during the second hour it fell by 12 mm Hg, and during the third hour it rose by 10 mm Hg, which was followed by a fall of 20 mm Hg (relative to the initial level).

The results of investigation of cyclic nucleotide concentrations in the heart tissues and blood of all the experimental animals are given in Table 1. They show that, both during immobilization and during AES, the cAMP concentration in the heart tissue and blood plasma rose considerably. The cAMP concentration in the heart rose by 1.7 and 3.1 times, and in the blood by 8.6 and 20 times, respectively. The cGMP concentration in the heart and blood plasma during immobilization did not differ from the control, whereas during AES its concentration in the heart rose by 2.4 times, but in the plasma it showed a tendency to decrease. According to data in the literature, the ratio cAMP/cGMP is an important indicator of the degree of resistance of the body to various experimental situations [2, 3]. The present experiments showed that AES leads to considerable changes in this ratio: Whereas in the heart of the control animals it was 54, in animals exposed to immobilization stress it rose to 100.6, on account of a sharp rise in the cAMP concentration, but during AES it fell to 73 on account of elevation of the level not only of cAMP, but also of cGMP (the increase in the cAMP concentration was greater than in that of cGMP).

Consequently, under conditions of stress more marked changes are observed in the cAMP level than in the cGMP level both in the heart tissues and in blood plasma. The degree of elevation of the cAMP level was determined by the intensity of stress: AES, by the stochastic scheme which we suggest, leads to a greater rise in the cAMP level than immobilization stress.

Elevation of the cAMP concentration in tissues of the body is known to reflect a strain of the adrenergic systems and it is the organism's first response to any kind of extremal influence. Meanwhile strengthening of such an influence lowers the resistance of the body. An increase in resistance of the body, on the other hand, is connected with activation of cholinergic systems mediated by cGMP, i.e., under extremal conditions adaptive reactions of the body arise in phases [2]. Because the change in the cGMP concentration was smaller than the change in cAMP, the results obtained under conditions of acute experimental stress in the present experiments indicate predominance of activation of adrenergic structures over activation of cholinergic structures, i.e., absence of adaptation to extremal conditions, and it may be this which led to death of the animals.

The results of these experiments thus show that a marked increase in the level of cyclic nucleotides in the heart and blood under conditions of AES is accompanied by elevation of BP and by increased work of the heart. In connection with the increased demand of the heart for sources of energy, which are not replenished because of vascular spasm, death of the experimental animals took place as a result of disturbance of myocardial function (acute heart failure or infarction occurred). These experimental data are evidence that the resistance of the organism to emotional stress can be increased by reducing the release of adrenalin, for the action of which cAMP is the mediator [7, 8].

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EFFECT OF NICOTINIC AND MUSCARINIC CHOLINOLYTICS ON EXPERIMENTAL EPILEPTOGENESIS

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Among the available antiepileptic agents used in clinical practice there are virtually none able to modify specifically the character of transmission of nervous impulses in brain synapses, although formation of a stable pathological state in epilepsy [3] evidently cannot take place without the participation of various mediator systems, including the cholinergic system.

In connection with the quest for new anticonvulsants, the writers have studied the effect of the nicotinic cholinolytic eterophen (IÉM-506, USSR origin) and the muscarinic cholinolytic metamizil (methyldiazine) [11, 12]. Eterophen, injected intravenously into rabbits, was shown to reduce excitability of the dorsal hippocampus, amygdala, caudate nucleus, and cerebral cortex but to have no effect or to increase only slightly the excitability of the mesencephalic reticular formation. Metamizil, on the other hand, has marked ability to block structures of the ascending reticular activating system (ARAS) and, at the same time, to increase the excitability of the hippocampus and amygdala.

Investigations on a penicillin model of epilepsy [7] have shown that nicotinic cholinolytics eterophen and gangleron,* when administered systemically against the background of epileptiform activity, completely suppressed or reduced the number of seizures in animals, whereas the muscarinic cholinolytic metamizil, on the contrary, provoked the appearance of seizures.

In the present investigation, by using a similar model of penicillin epilepsy, a more detailed study was made of the effect of the above-mentioned drugs and, in particular, of eterophen on epileptogenesis, both before and after the formation of the epileptogenic focus.

EXPERIMENTAL METHOD

Experiments were carried out on 16 male rabbits weighing 3-3.5 kg with chronically implanted electrodes in the dorsal region of the hippocampus, the mesencephalic reticular formation, and the sensomotor cortex. Epileptogenic foci were created by injection of 250 Units

*1,2-Dimethyl-3-diethylaminopropyl-p-isobutoxybenzoate hydrochloride.

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