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CHANGES IN ENERGY METABOLISM AND CONTRACTILITY OF THE HEART DURING THE DEVELOPMENT OF FOCAL MYOCARDIAL NECROSIS

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After the end of emotiogenic stimulation a quite long period of activation of the adrenergic and pituitary-adrenal system is observed, characterized by release of catecholamines and glucocorticoids and also by marked eosinopenia. At the culmination of the stress response, reflected in a fall in the corticosterone concentration and a peak of the eosinophil count taking place after eosinopenia, all these changes reach a maximum. Later processes of recovery begin to develop [2, 6, 7, 10]. If the blood eosinophil count is used as the criterion of functional activity of the pituitary-adrenal system, the temporal parameters of the phases of development of the lesion and of recovery of the changes taking place in the heart during during emotional stress can be determined [8]. One of the most important pathogenetic components of stress-induced heart damage is the action of high catecholamine concentrations [9], and there are accordingly good grounds for suggesting that in response to injection of cardiotoxic doses of adrenalin the same pattern of development of heart damage will be exhibited as during stress.

The aim of this investigation was to study changes in the energy metabolism and contractility of the heart at different times after injection of adrenalin, paying attention to the time course of changes in the biorhythm of the eosinophil count and corticosterone level in the blood and also the phases of development of injury to and restoration of the structure of the heart [5].

EXPERIMENTAL METHOD

Experiments were carried out in the fall and winter on 210 male albino rats weighing 180-220 g, with an initial blood eosinophil count of 220-340 cells/μl, at 9 a.m. Adrenalin, in a dose of 7.5 mg/kg, was injected subcutaneously into the animals once. The energy metabolism of the heart was assessed by determining the glycogen concentration in heart muscle by Khoreishi's method, and also by studying oxidative and phosphorylating functions of the mitochondria by the method described previously [7]. The state of the mitochondria was judged by the following parameters: RC_c — Chance's respiratory control; ADP/t — the velocity of oxidative phosphorylation (in μmoles ADP/mg protein/min). To assess the degree of cardiac damage on the basis of the level of accumulation of ^{99m}Tc pyrophosphate (^{99m}Tc-PP) the reagent Pirfotech-99M was used, and eluate from a technetium-99M generator from the "Medradiopreparat Factory was added to it. The resulting complex, in a volume of 0.3 ml and with activity of $11.1 \cdot 10^3$-$29.6 \cdot 10^3$ Mgq (dose monitored on a CRC^R-5 Radioisotope Calibrator, from Nuclear Chicago, USA), was injected into the caudal vein of the rats. The accuracy and completeness of injection of the preparation into the blood stream was verified visually on an LFOV gamma-camera with Scintiw computer (from Searle, The Netherlands). Radiometry of the heart was undertaken on an NK-150 well-type scintillation counter (Hungary). Accumulation of ^{99m}Tc-PP by the heart muscle was expressed as an index of radionuclide uptake,

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TABLE 1. Phosphorylating Function of Mitochondria, Glycogen Concentration, and ^{99m}Tc-PP Accumulation in Rat Heart at Various Times after Injection of Adrenalin in a Dose of 7.5 mgβkg(M ± m)

Variant of experiment	Parameter			
	RC_c (9)	ADP/t	glycogen, g/liter (12)	^{99m}Tc-PP uptake (9)
Control	3,1±0,25	496±38	5,13±0,5	0,08±0,007
After injection of adrenalin				
3 h	2,4±0,3	341±41*	2,12±0,2***	0,53±0,04***
24 h	2,0±0,2**	247±31**	1,29±0,15***	1,02±0,09***
51 h	1,75±0,3**	181±21***	1,59±0,12***	1;58±0,11***
96 h	2,4±0,2*	323±35*	3,12±0,2**	0,28±0,04**A

Note. Here and in Table 2, number of animals in each experiment given in parentheses(*P < 0.05, **P < 0.01, ***P < 0.001.

calculated as the quantity of ^{99m}Tc-PP taken up by the heart as a function of the injected dose, expressed relative to the weight of the heart, itself expressed as a percentage of the body weight of the rat [11]. Contractility of the heart under conditions of relative rest and isometric contraction (compression of the aorta for 25 sec) was evaluated *in vivo*, from the intraventricular pressure curve [6]. All the experiments were repeated 3, 24, 51, and 96 h after injection of adrenalin into the animals. The choice of these times of investigation was determined by the results of preliminary experiments [4, 5, 8], which showed that eosinopenia develops during the first 45 h after injection of adrenalin in a dose of 7.5 mg/kg and the blood corticosterone concentration increases three to fourfold. The eosinopenia is replaced by eosinophilia 45-51 h after the injection of adrenalin, but the blood corticosterone level falls sharply at this time. Later the eosinophil count and corticosterone concentration in the blood returned close to the control values. We know that the period of eosinopenia corresponds to the phase of development of structural lesions in the heart, whereas eosinophilia corresponds to the phase of maximal contractural and necrobiotic changes in the heart muscle. Later the myocardial structure is restored.

EXPERIMENTAL RESULTS

It will be clear from Table 1 that cardiotoxic doses of adrenalin give rise to gradually increasing inhibition of energy production and an increase in the ability of the heart muscle to accumulate ^{99m}Tc-PP. For instance, whereas 3 h after injection of adrenalin the intensity of oxidative phosphorylation was reduced by only 25-30%, after 51 h the parameters of phosphorylating function of the mitochondria were reduced by 1.8-2.7 times. Parameters of mitochondrial function were somewhat restored to normal 96 h after injection of adrenalin, but they still remained lower than initially. Changes of a similar character also were observed when the myocardial glycogen concentration was studied. A maximal fall of the glycogen concentration in the heart muscle was observed 24-51 h after injection of adrenalin. It will also be clear from Table 1 that uptake of ^{99m}Tc-PP by the myocardium was sharply increased under the influence of adrenalin. Under these circumstances technetium accumulation after injection of adrenalin increased gradually, and by 51 h after the injection it was 20 times higher than the level of accumulation of the radionuclide in intact animals. The degree of technetium uptake was reduced 96 h after injection of adrenalin, without, however, reaching the control values. It must be recalled that one possible mechanism of accumulation of ^{99m}Tc-PP is through a change in permeability of the cardiomyocyte cell membrane for it, due to disturbance of ATP production [1]. This is in agreement with the data showing agreement between the times of maximal accumulation of ^{m}Tc-PP and of inhibition of the phosphorylating function of the cardiac mitochondria under the influence of adrenalin.

It will be clear from Table 2 that three principal periods also can be distinguished in the changes in parameters of cardiac contractility. In the initial period (3-24 h after injection of adrenalin) only a small decrease was observed in the parameters studied, whereas after 51 h cardiac contractility was considerably depressed. After 96 h only latent disturbances of cardiac contractility were observed, when the heart was working under isometric conditions.

TABLE 2. Contractile Function of Heart in Rat at Different Times after Injection of Adrenalin in a Dose of 7.5 mg/kg (M ± m)

Parameter	Variant of experiment (12)	Relative rest	Duration of clamping of aorta, sec	
			5	25
Developed pressure, mm Hg	Control	98,0±3,5	184,8±18	170,4±12
	After injection of adrenalin			
	3 h	112±6,4	186,3±14,2	161,1±8,9
	24 h	79,1±5,8*	167,5±14	115±11**
	51 h	74,2±5,1*	119±11,3**	78±8,1***
	96 h	89,8±6,2	154±10,9	138,1±7,9*
Intensity of functioning of structures, mm Hg/min/mg	Control	83,2±5,3	169,4±13,1	151,4±10,8
	After injection of adrenalin			
	3h	85,6±7,8	161,1±9,1	124,9±11,2
	24h	67,5±8,1	128,4±11,6*	81,1±9,2**
	51h	59,1±7,2**	96,8±10,2**	48±6,9***
	96 h	80,1±6,3	128,1±14,1*	101,6±10,3**

It can be concluded from a general assessment of these results, and also of data published previously [4, 5, 8], that the time course of changes in the biorhythm of the blood eosinophil count, of metabolism, structure, and function of the heart, and also of ^{99m}Tc-PP accumulation, after injection of adrenalin, is phasic in character and follows the same pattern as after exposure to emotional stress. It must be emphasized that the timing of the phases of formation of the cardiac lesions depends on the type of influence, its intensity, and the duration of exposure to it [4], as well as on the level of resistance of the animal to stress [3].

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