BIOPHYSICS AND BIOCHEMISTRY

Effects of Energostim on the Sympathoadrenal System and Contents of Pyridine Nucleotides during Acute Myocardial Infarction

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The contents of myofibrillar creatine phosphokinase and cytochrome *c*, the key enzyme of the mitochondrial respiratory chain, increased, while the content of nicotinamide coenzymes and redox potential (NAD/NADH ratio) sharply decreased over the first 6 h of acute myocardial infarction. The contents of norepinephrine and epinephrine increased by 51 and 49%, respectively, 6 h after onset of acute myocardial infarction. By contrast, dopamine concentration decreased by 116% during this period. The increase in the content of cytochrome *c* directly correlated with the concentration of myofibrillar creatine phosphokinase and Peel index. No correlations were found between norepinephrine/epinephrine and dopamine/(norepinephrine+epinephrine) ratios. The antihypoxant with direct action energostim normalized the content of cytochrome *c*, increased NAD and dopamine concentrations and NAD/NADH ratio, and decreased the content of norepinephrine and epinephrine to the baseline level in patients with acute myocardial infarction. These results indicate that energostim possesses not only antihypoxic and antioxidant activities, but also pronounced antisympathomimetic properties.

Key Words: *acute myocardial infarction; energetic; sympathoadrenal system; energostim*

The development of acute myocardial ischemia and pronounced deficiency of energy in ischemic and intact tissues trigger cascade metabolic disturbances, which is accompanied by the release of norepinephrine and epinephrine from the ischemic myocardial zone and extracardiac regions (nervous system and adrenals) [3,8,9,11]. These processes reflect the stress reaction. β-Adrenoceptor blockers are widely used for the therapy of acute myocardial infarction (AMI) [5,7,14].

Here we evaluated the relationship between changes in the sympathoadrenal system (SAS) and energy supply to the myocardium during the acute period of AMI. We studied whether the antihypoxant with direct action energostim possessing pronounced antioxidant and antianginal properties can normalize these disturbances [2,4].

MATERIALS AND METHODS

We examined 39 patients (26 men and 13 women, average age 53.1±2.6 years) with AMI. This diagnosis was made by the symptoms of anginal attack, changes in ECG, and increase in plasma level of myofibrillar

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protein creatine phosphokinase (MP-CPK). The patients with clinical signs of pronounced cardiac insufficiency, oncological and acute inflammatory diseases, chronic diseases of the kidneys, lungs, and blood, endocrine disturbances, and arterial hypertonia, as well as patients receiving cardiac glycosides, diuretics, and pressor amines, were excluded from observations. The patients were randomly divided into 2 groups. Control patients (n=20) were treated with nitrates, β-blockers, heparin and aspirin, angiotensin-converting enzyme inhibitors, and antiarrhythmic drugs (if necessary). Other patients (n=19) received not only these preparations, but also energostim in a daily dose of 220 mg in 100 ml 5% glucose for 7 days (intravenous transfusions). The clinical course of AMI, incidence of complications, and prognostic mortality rate (Peel index [1]) were evaluated. The activity of MP-CPK and contents of lactate and pyruvate were estimated using Boehringer Mannheim diagnostic kits. The concentrations of cytochrome *c* and pyridine nucleotides were measured as described previously [2]. Plasma levels of epinephrine, norepinephrine, and dopamine were measured fluorometrically on a MPF-4 spectrofluorometer (Hitachi).

The results were analyzed by Excel 7.0 software (Student's t test and correlation analysis).

RESULTS

Plasma contents of MP-CPK and key enzyme of the mitochondrial respiratory chain cytochrome *c* increased 4.6±1.2 h after anginal attack. The concentration of cytochrome *c* peaked by the 6th hour, remained high over 1 day (standard therapy), and decreased by the end of day 7 (Table 1). These variations in cytochrome *c* content directly correlated with changes in MP-CPK concentrations (r=0.82, p<0.001) and decrease in NAD level (r=0.71, p<0.005) and NAD/NADH ratio (r=0.76, p<0.001). Although energostim contains 10 mg cytochrome *c*, this preparation normalized enzyme content by the end of the 3rd day (Table 1). These results indicate that energostim blocks degenerative processes in the myocardium and intensifies consumption of exogenous and endogenous cytochrome *c* by myocardial tissues, which involves NADH.

In control and energostim-receiving patients the content of norepinephrine increased by 46 and 55%, respectively, 6 h after the incidence of AMI. In these patients epinephrine concentration was 41 and 57% above the baseline level, respectively. However, dopamine content decreased by 81 and 153%, respectively, 6 h after anginal attack. Changes in the state of SAS were similar in patients of both groups 6 h after the incidence of AMI (Table 1).

A permanent increase in the content of cytochrome *c* directly correlated with variations in the prognostic index of Peel. No correlations were found between norepinephrine/epinephrine and dopamine/(norepinephrine+epinephrine) ratios (r=0.23 and r=0.34, respectively, insignificantly).

Energostim significantly improved or normalized the state of SAS in patients with AMI. The content and ratio between cardiotonic neurotransmitters returned to normal after 3-day therapy with energostim, but remained high by the end of day 7 in control patients. These changes correlated with the energostim-induced increase in NAD content and decrease in the NAD/NADH ratio (Table 1). In control patients NAD concentration and NAD/NADH ratio were low, while the lactate/pyruvate ratio remained high over 7 days (Table 1).

The activity of SAS remained high not only over the first 72 h, but also 7 days after the incidence of AMI (Table 1). During this period all compensatory reactions are involved in adaptation to ischemic myocardial damages and low blood supply to peripheral tissues. However, these changes cannot be used as independent prognostic criteria of AMI not complicated by pronounced disturbances in pump functions of the heart.

High plasma level of catecholamines in patients with AMI is most likely to be associated with the intensive release of catecholamines from damaged myocardial regions [3,8,9,11], disturbed norepinephrine uptake in the synaptic gap [6], NAD and flavin adenine dinucleotide deficiency. These compounds serve as coenzymes of monoamine oxidase, which degrades norepinephrine (sympathetic nerve endings in the brain, heart, and other organs) and epinephrine (various organs and tissues) by deamination. The decrease in dopamine concentration is probably related to its intensive degradation into norepinephrine [10]. Moreover, the impairment of dopamine synthesis can be associated with reduced activity of NADPH-dependent tyrosine hydroxylase [13], which results from a sharp decrease in NADPH level during AMI [2].

The increase in NAD content that normalizes degradation of norepinephrine [6], ratio between oxidized and reduced pyridine nucleotides (Table 1), and concentration of NADPH regulating dopamine level [2] contributes to energostim-induced improvement of the neurohormonal state. A 6-fold increase in the dopamine/(norepinephrine+epinephrine) ratio reflecting the relationship between vasoconstrictor and vasodilator components of SAS indicates normalization of catecholamine synthesis and degradation. Thus, energostim containing NAD, cytochrome *c*, and inosine [2] produces not only the antihypoxic, antiischemic, and antioxidant effects, but also possesses pronounced antisympathomimetic properties.

TABLE 1. Contents of Pyridine Nucleotides, Cytochrome *c*, Lactate, Pyruvate, Epinephrine, Norepinephrine, and Dopamine in the Acute Period of AMI after Standard Therapy (Numerator) and Treatment with Energostim (Denominator, *M*±*m*)

Parameter	Normal	AMI, h				
		6	24	48	72	168
Cytochrome *c*, nmol/ml	0.62±0.06	0.88±0.08**	0.98±0.07*	0.86±0.02***	0.73±0.02***+++	
		0.92±0.08*	0.75±0.03***+++ooo 0.83±0.07**	0.76±0.03***	0.68±0.02+++	0.65±0.03+++
NAD, nmol/ml	17.8±0.3	13.4±0.7***	11.4±0.4*	11.8±0.3*	8.8±0.3*+++	8.6±0.3*+++
		12.8±0.6**	10.4±0.3*	11.9±0.3*	12.5±0.4**	13.7±0.3***
NADH, nmol/ml	21.6±2.3	24.3±2.7	23.6±10	21.4±2.9	19.8±1.6++	19.2±1.2++
		26.3±1.9	21.2±10	18.9±2.3***	17.8±1.8++	18.6±1.3++
NAD+NADH, nmol/ml	45.5±2.4	37.8±1.8***	34.5±1.9	33.7±2.4	28.0±1.4**	27.8±1.2**
		38.9±2.7***	31.6±1.0	31.4±2.9***	30.8±1.8**	32.5±1.5**
NAD/NADH NAD/NADH	1.0±0.2	0.55±0.12*	0.48±0.07*	0.54±0.06*	0.45±0.05+++	0.45±0.03*
		0.49±0.08*	0.49±0.05*	0.63±0.05*++oo	0.70±0.06*++o	0.74±0.03*++o
Pyruvate, mmol/ml	34.5±4.1	30.3±2.7	24.3±1.4***	20.6±3.3***	18.7±2.9**	15.7±2.0*
		23.3±2.9***	24.3±1.4***	30.0±3.0	28.7±2.8	31.7±2.1
Lactate, mmol/ml	1.6±0.1	1.2±0.3	2.1±0.2***	2.6±0.8**	2.2±0.3**	2.1±0.3***
		1.7±0.2	1.9±0.3	1.85±0.25	1.7±0.3	1.7±0.2
Lactate/pyruvate	61±10	46.3±10.3	86.4±8.3	126.2±13.5**	117.6±5.5**	124.5±6.5*
		73.3±9.1	79.4±6.2	62.2±3.5	59.5±4.6	54.5±4.5
Norepinephrine, pg/ml	120±40	223±21*	273±35*	269±25*	245±24*	219±21*
		265±23*	202±19*+++	189±19***+++	161±13++oo	151±13++ooo
Epinephrine, pg/ml	45±12	67.5±10.7	95.6±7.5*	88.2±8.3*	86.7±2.7*	84.8±2.3*
		80.7±12.6***	72.8±8.5*	62.5±2.3*	55.2±2.9	51.2±2.3+++ooo
Norepinephrine/ epinephrine	3.5±0.8	3.3±0.4	2.84±0.24***	3.0±0.2	3.15±0.13	2.65±0.10***
		3.3±0.3	3.0±0.3	3.1±0.2	3.0±0.3	3.0±0.2
Dopamine, pg/ml	3.8±0.4	2.1±0.2*	1.5±0.7*	1.1±0.4*	0.68±0.13*+	0.84±0.12*+
		1.5±0.2*	2.0±0.5*	2.1±0.4*	2.7±0.3	2.85±0.15***+++
Dopamine/ (norepinephrine+ epinephrine), 10^{-2}	2.45±0.24	0.72±0.08*	0.41±0.03*+	0.31±0.02*+	0.21±0.03*+xx	0.28±0.04*+#
		0.23±0.08*	0.73±0.03*+	0.85±0.02*+	1.39±0.03*+xx	1.43±0.10x#

Note. *p<0.001, **p<0.01, and ***p<0.05 compared to normal; +p<0.001, ++p<0.01, and +++p<0.05 compared to 6 h; op<0.001, oo$p$<0.01, and ooo$p$<0.05 compared to 24 h; xp<0.001 and xx$p$<0.01 compared to 48 h; #p<0.05 compared to 72 h.

This contributes to an energostim-induced decrease in the content and ratio between norepinephrine and epinephrine and increase in dopamine concentration in patients with AMI. It should be emphasized that energostim produces the antiischemic, antihypoxic, and antioxidant effects not only in the myocardium, but also in other tissues during histotoxic hypoxia. The influence of energostim on the brain is of particular importance [7]. These processes underlie the antisympathomimetic effect of energostim and play a key role in the recovery of SAS activity and regulatory mechanisms.

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