CORRELATION BETWEEN ANTIOXIDANT AND ANTI-ISCHEMIC EFFECTS OF SOME ENERGY-YIELDING COMPOUNDS

P. V. Sergeev, G. V. Snegireva, V. M. Gukasov, and V. V. Gatsura

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Reduction of the enzyme pool for antioxidant protection and activation of lipid peroxidation (LPO) of the membranous structures of cardiomyocytes are important steps in ischemic degeneration of the myocardium [4, 8]. From this point of view the study of correlation between the effect of energy-yielding substances on LPO and their cardioprotective action, as shown by the test of limitation of the zone of myocardial necrosis and their effect on metabolic acidosis is of definite interest as a means of understanding the formation of their anti-ischemic action.

This paper gives data on correlation of these effects following administration in experiments on of fructose-1,6-diphosphate, succinate, malate, and cytochrome a model of acute myocardial infarction.

EXPERIMENTAL METHOD

Shifts of LPO potential of the myocardial tissue were assessed by measuring the kinetics of chemiluminescence (ChL) of products of iron-induced LPO in homogenates of intact and ischemic rat myocardium [1]. The parameters recorded are linked with particular reactions of LPO. The intensity of the quick flash (the amplitude of the quick flash, in mM) is proportional to the content of lipid hydroperoxides in heart tissue homogenate, the latent period characterizes the potential of the endogenous antioxidant system, and the velocity of the initial region of the slow flash (tangent of the angle α) denotes the LPO process at the stage of branched chain reactions. The light sum of the slow flash, determined as the area beneath the curve of ChL of the slow flash (in mm^2), characterizes the total yield of peroxide radicals in branched chain reactions. Experiments were carried out on noninbred male rats weighing 180-200 g. Acute myocardial ischemia was induced by ligating the anterior descending branch of the left coronary artery. The effect of the test substances on changes in pH of the outflowing perfusion fluid and the duration of myocardial contractile activity were studied on a model of metabolic acidosis, on the isolated rat heart [5]. The integral anti-ischemic action of the test substances was assessed by studying the results of determination of the size of the zone of necrosis and the zone of myocardial ischemia by means of an indicator-differential method [6] 4 h after ligation of the coronary artery. Substances for testing were injected intravenously into the femoral vein in the course of 60 min after ligation of the coronary artery (the doses and number of experiments in the series are given in Table 1).

The study of the dynamics of LPO development depending on the duration of ischemia showed that initial changes in LPO were observed after 60 min of ischemia caused by ligation of the coronary artery, and the changes reached a peak 2-3 h after occlusion [3].

It is important to note the increase taking place in acute myocardial ischemia both of LPO products, namely hydroperoxides of malonic dialdehyde, and of the LPO potential, reflected in the rate of rise and the light sum of the flash of iron-induced ChL from 285 ± 38 mm^2 in the intact myocardium to 487 ± 84 mm^2 in the ischemic myocardium.

A similar picture also was observed in thermal ischemia of the heart, but unlike in acute coronary ischemia, in these experiments the period of induction of the slow flash of ChL was shortened.

N. I. Pirogov Second Moscow Medical Institute. All-Union Scientific Center for Biologically Active Substances.
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TABLE 1. Antioxidant and Anti-Ischemic Effects of some Energy-Yielding Substances

Experimental conditions	n	Intensity of quick flash of ChL, I, relative units	Latent period, τ, min	Concentration of malonic dialdehyde, nm/mg protein		Zone of necrosis/ zone of ischemia, %
				initially	Fe^{2+}-induced	
Control	10	64,2±5,6(100)	0,89±0,07	9,7±0,8	45,8±11,5*(472)	68±4,2 (n=9)
Fructose-1,6-diphosphate, 300 mg/kg	9	47,4±3,5*(73,4)	2,3±0,07*(258)	15,8±2,3	20,9±2,9(132)	28±5,5* (n=9)
Cytochrome c, 20 mg/kg	10	40,7±4,4*(63,4)	2,86±0,31(321)	6,0±1,2	9,1±2,9*(152)	32±3,4* (n=7)
Sodium succinate, 100 mg/kg	10	52,9±5,4(82,4)	0,74±0,07(83)	6,8±0,2	36,9±2,9(543)	38±5,9* (n=6)
Sodium malate, 200 mg/kg	10	58,0±3,2(90,6)	0,78±0,08(88)	7,7±0,5	36,8±3,8(478)	30±6,0* (n=11)

Legend. *$p < 0.05$ — Differences from control are significant. Figures between parentheses are percentages.

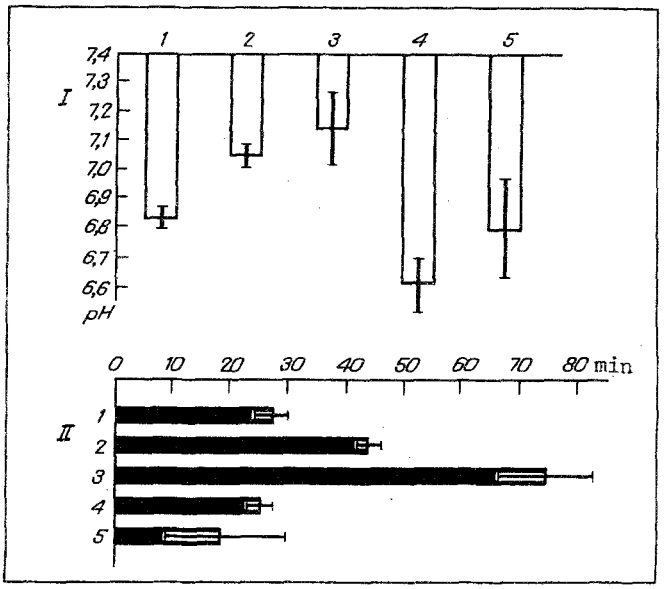

Fig. 1. Effect of energy-yielding substances on pH of outflowing perfusion fluid (I) and duration of contractility (II) of myocardium of isolated rat heart during metabolic acidosis. 1) Control, 2) fructose-1,6-diphosphate, 10^{-4} M; 3) cytochrome c, 10^{-5} M; 4) sodium succinate, 10^{-3} M; 5) sodium malate, 10^{-3} M.

The time course of LPO in acute ischemia suggests that attempts to inhibit it 1.5-2 h after the beginning of ischemic changes may be therapeutically valid, for by this time the compensatory powers of the first phase of LPO are already exhausted, at least so far as maintenance of homeostasis of the main mass of ischemic cardiomyocytes is concerned.

The data in Table 1 indicate that strong correlation exists between the effect of fructose-1,6-diphosphate and of cytochrome c on LPO, and their cardioprotective effect, whereas intermediates of the Krebs' cycle do not possess this correlation. The experimental results point to the possibility of limiting the size of the zone of necrosis 4 h after ligation of the carotid artery without any significant lowering of the LPO potential, as revealed by the addition of bivalent iron to the myocardial homogenates.

Incidentally, the cardioprotective effect of malate and succinate were not exhibited even during total hypoxia of the isolated heart, secondary to the development of metabolic acidosis (Fig. 1).

The existence of an integral antioxidant action of these substrates can also be correlated with the marked antiacidotic action of fructose-1,6-diphosphate and cytochrome c, for inhibition of acidification of the cytoplasm in the zone of ischemia blocks one of the trigger mechanisms of LPO in acute myocardial ischemia [8], and it also weakens the degree of exhaustion of the acidosis-linked exhaustion of the pool of endogenous antioxidants.

The beneficial effect of the preparations studied on the lactate excess, the collateral coronary circulation, permeability of the membranes, and other functional parameters of the heart with regional myocardial ischemia [2, 7] is thus accompanied by inhibition of LPO, but only when activators of glycolytic energy production are inhibited.

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