corresponding decrease of stab neutrophils and segment-nuclear leukocytes in the blood.

It should be noted that combined addition of 5-FU and sympathetic antagonists *in vitro* resulted in a decrease of the bone marrow cell count 1.5 times compared to the control 24 h after incubation (Table 2). There was a significant increase (174-210% of the control level) in the number of immature (with some nuclear material) erythrocytes in the blood on the first day of the experiment *in vivo*, which can be probably related to disturbances of the cellular adaptive mechanisms.

Thus, the joint injection of 5-FU and sympathetic antagonists has a depressive effect on hemopoiesis in mice. It should be emphasized that we obtained similar data under immobilization stress, when sympathetic blocking agents were used according to the same scheme. In this case the phenomenon of hemopoietic hyperplasia was absent, and hypoplasia of erythropoietic tissue developed [2,3]. The sympatheticoadrenal system may control the adaptive response of hemopoietic tissue by affecting the aplastic and repair processes. The negative regulative effects of sympathetic neurotransmitters on hemopoietic tissue repair after 5-FU treatment seem to be beyond question. Sympathetic antagonists used 2-4 days after 5-FU injection accelerate the bone marrow reparative processes and increase the mature cell output to the blood. The findings provide a basis for the correction of hemopoiesis disturbances induced by antitumor therapy.

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Effect of Nifedipine and Ruthenium Red on the Contractile Function and Oxidative Metabolism of the Myocardium

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The myocardial adrenoreceptors have been shown to participate in metabolism, being involved not only in glycolysis but in the processes of oxidative phosphorylation as well [2]. These effects are mediated by the adenylate cyclase system, this attesting to a specific role of Ca^{2+} in this mechanism. The available data on the protective role of Ca^{2+} blockers on the cardiac function during hypoxia argue in favor of this assumption [1,4,5]. It is known that the Ca^{2+} sup-

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TABLE 1. Effect of NF on Functional and Metabolic Parameters of the NE–Activated Myocardium, % of initial level ($M \pm m$)

Parameter	Experimental conditions	NF				NE			
		LR rats		HR rats		LR rats		HR rats	
		1 min	5 min	1 min	5 min	1 min	5 min	1 min	5 min
HR	C	–	–	–	–	112±2.4	131±4.8	126±6.8	144±8.2
	E	95±1.8	84±3.4	96±1.8	94±2.3	94±3	112±2.5	110±4.7	117±4
HBF	C	–	–	–	–	84±1.9	61±4.3	85±2.2	76±7.4
	E	92±1.9	86±2.9	99±0.8	89±2.7	100±6.2	103±9.7*	101±8.6	82±11
Vf	C	–	–	–	–	121±8.7	121±8.3*	148±11	161±8.6
	E	115±2.9	133±5.3	128±6.7	149±6.6	104±5.4*	116±8.8*	137±9.2	152±12.3
Vr	C	–	–	–	–	123±9.6	169±16.5*	120±7.3	192±10.4
	E	126±13.5	91±11.3	124±8.6	109±17.6	122±10.8	155±16.1	164±14	223±13.6
Lactate	C	–	–	–	–	161±29.5*	194±32.9	415±141	596±124
	E	58±5.6*	34±10.5*	181±33.4	71±27.5	203±33.8*	250±38.5	597±225	401±164
Pyruvate	C	–	–	–	–	193±64.8	209±61.2	–	–
	E	46±9.9*	86±17.8*	76±8.3	39±6.6	–	52±13.4*	–	98±28
CPK	C	–	–	–	–	33±12.2	419±211	47±9.7	141±60.6
	E	46±10.2	314±167*	47±9.7	47±10.2	–	129±46.5	–	301±175

Note: here and in Tables 2 and 3: * – reliable differences of parameters in HR and LR rats ($p<0.05$). C: control; E: experiment.

plied through the slow channels and the Ca^{2+} of the intracellular pool (mitochondria and sarcoplasmatic reticulum) are involved in the activation of the contractile system of the myocardium. Ca^{2+} may influence the rate of oxidative phosphorylation maintaining the function of the slow channels through pyruvate dehydrogenase, a mitochondrial enzyme. Thus, the cellular oxidative metabolism is probably controlled by the adrenoreceptors, their influence being realized via Ca^{2+} metabolism.

The aim of the present study was to investigate the effects of intracellular and extracellular Ca^{2+} on the functional and metabolic parameters of the myocardium.

MATERIALS AND METHODS

Experiments were carried out on the contracting isolated rat heart perfused after Langendorff (method modified by the authors) [2]. The animals (male albino rats weighing 250-300 g) were previously divided by their sensitivity to hypoxia into low-resistance (LR) and high-resistance (HR) rats [2]. Nifedipine (NF) in a concentration of 4×10^{-7} M was used as a blocker of the slow Ca channels; changes of the intracellular Ca^{2+} were blocked by ruthenium red (RR) in a concentration of 2×10^{-6} M. Their effects were studied in the myocardium against the background of myocardial β-adrenoreceptor stimulation by norepinephrine (NE) in a concentration of 2×10^{-7} M.

RESULTS

NF depressed the heart rate (HR) and heartbeat force (HBF), this being more pronounced in the LR rats. At the same time, NF, which is characterized by vasodilator properties [3], intensified the flow of

TABLE 2. Effect of RR on Functional and Metabolic Parameters of the NE–Activated Myocardium, % of initial level ($M \pm m$)

Parameter	Experimental conditions	NF				NE			
		LR rats		HR rats		LR rats		HR rats	
		1 min	5 min	1 min	5 min	1 min	5 min	1 min	5 min
HR	C	–	–	–	–	112±2.4	131±4.8	126±6.8	144±8.2
	E	98±1.2	45±2*	96±1.4	94±3.7	105±6.2	114±11.6	109±4.8	113±6.3
HBF	C	–	–	–	–	84±1.9	61±4.3	85±2.2	76±7.4
	E	94±0.6	92±1.6	96±1.0	93±2	103±4.9	90±8.5	101±2.2	96±2.9
Vf	C	–	–	–	–	121±8.7	149±11	121±8.3	161±8.6
	E	91±2.3	92±1.7	90±2	82±3.5	88±3.7	113±6	89±4.4	114±3.4
Vr	C	–	–	–	–	123±9.6	169±16.5	120±9.7	192±10.4
	E	88±5.2	93±3.7	86±3.2	79±4.9	104±4.5	150±8.9	90±8.5	154±4.4
Lactate	C	–	–	–	–	161±29.5*	194±32.9*	415±141	546±124
	E	67±11.5	124±27.2*	54±13	39±15.4	–	110±25.5*	–	401±101
Pyruvate	C	–	–	–	–	193±64.8	209±61.2	–	–
	E	77±4.6	85±9.5	–	64±16.7	72±6.3	122±7.2*	88±26	80±22.3
CPK	C	–	–	–	–	33±12.2	419±211*	47±9.7	141±60.6
	E	–	56±19.3*	–	168±112	26±9.5*	49±20.5	251±207	34±10.2

TABLE 3. Effect of NF and RR on Functional and Metabolic Parameters of the NE–Activated Myocardium, % of initial level ($M \pm m$)

Parameter	Experimental conditions	NF	NF				NE			
			LR rats		HR rats		LR rats		HR rats	
			1 min	5 min	1 min	5 min	1 min	5 min	1 min	5 min
HR	C	see Table 1	–	–	–	–	112±2.4	131±4.8	131±4.8	144±8.2
	E		87±4.1	77±10.3	95±2	93±1.7	109±5.2	108±4.5	106±1.4	111±1.2
HBF	C		–	–	–	–	84±1.9	61±4.3	85±2.2	76±7.4
	E		87±7.3	66.13	90±6.8	81±7.3	–	66±12.9	–	50±7.8
Vf	C		–	–	–	–	121±8.7	148±11	121±8.3*	161±8.6
	E		137±5.6	126±5.2	132±9.6	134±10.8	123±10.7	133±11.9	113±8.4	119±8.7
Vr	C		–	–	–	–	123±9.6	169±16.5	119±7.3	192±10.4
	E		–	106±7*	92±7.6	88±7.9	86±7*	150±15.2	121±17.3	152±14.7
Lactate	C		–	–	–	–	161±29.5*	199±32.9	415±141	596±124
	E		10±3.2*	35±5	21±13.1	–	93±36.6	172±25.8	111±43.2	183±52.7
Pyruvate	C		–	–	–	–	193±64.8	209±61.2	–	–
	E		71±10.3	66±23.4	79±33.3	50±26.6	72±6.4	77±11	–	88±20.6
CPK	C		–	–	–	–	33±12.2	419±211*	47±9.7	141±60.6
	E		413±149*	285±110*	19±8.9	206±12.8	384±182*	154±81	78±9.5	–

perfusion fluid through the myocardium (V_f), especially in HR rats. NF also influenced the respiration rate (V_r). A biphasic reaction was characteristic of the LR rat myocardium: an initial short-term stimulation followed by normalization after 5 min (Table 1). Such a phasic pattern was less marked in the HR rat myocardium, although a slight intensification of respiration was observed in this case too. Thus, NF produced a weak stimulating effect on the aerobic processes of oxidation.

Suppressed lactate and pyruvate production was noted in the myocardium of LR rats, this being indicative of glycolysis inhibition. In 30% of cases this was preceded by a short-term intensification of glycolisis, followed by its suppression just 5 min later. In the myocardium of HR rats the initial brief activation of glycolysis gave way to its suppression in 65% of cases; it was absent in 35% of cases, where the process was immediately suppressed (Table 1).

Thus, a positive linkage between the slow Ca^{2+} channels and both myocardial contractility and oxidative metabolism is not open to question. Ca^{2+} supplied through these channels promotes respiration suppression, glycolysis intensification, and a V_f decrease. Even under conditions of partial suppression of these channels, transformation of both aerobic and anaerobic metabolism occurs, this being one of the causes of decreased cardiac mechanical function. At the same time, judging by the decreased release of creatine phosphokinase (CPK) into the perfusion fluid from HR rat myocardium, suppression of the slow Ca^{2+} channels leads to condensation of the plasma membranes (Table 1). In LR rats, on the contrary, labilization of the membranes occurs.

RR also depressed, though negligibly, the HR and HBF in HR and LR rats. V_f and the levels of lactate and pyruvate dropped simultaneously, the drop being more pronounced in HR than in LR rats (Table 2). Thus, RR inhibits aerobic oxidation as well as glycolysis. Consequently, intracellular Ca^{2+} also participate in the regulation of myocardial contractility and oxidative metabolism. However, the effects produced by intracellular and extracellular Ca^{2+} differ in principle. Being necessary for the realization of the myocardial motor activity, intracellular Ca^{2+} in contrast to extracellular Ca^{2+} stimulates aerobic and anaerobic processes. At least two different pools of Ca^{2+} exist in the myocardial cells. Both of them are necessary for implementing and activating the mechanical function of the heart, but their effects on oxidative metabolism are not only diverse, but reciprocal. The ratio of these pools and their role in the myocardium are different in HR and LR rats.

This conclusion is supported by experiments on the combined effect of RR and NF. A summed response is the result both in the case where the effects of NF and RR are uniform (HR and HBF suppression) and nonuniform (V_f) (Table 3).

Thus, the intracellular and extracellular Ca^{2+} pools control oxidative metabolism in the cardiomyocytes independently, regulating the intensity of respiration and glycolysis. On the basis of these data and taking into account the role of intracellular Ca^{2+} in the realization of the adrenergic response, the question naturally arises: what is the role of the two calcium pools in this response?

It is known that NE stimulates HR, V_r, and the rate of glycolysis, acting via the cAMP system and via intracellular Ca^{2+}. The response of the majority of the parameters studied is unchanged under the influence of NF which reduces myocardial contractility. The values of HR, HBF, V_r, and glycolysis are unchanged, although the rate of glycolysis is lower in the myocardium of LR rats. Thus, the suppression of

the slow Ca^{2+} channels is not reflected in the ability of NE to activate the contractile function of the myocardium and to produce an effect on the oxidative metabolism. V_p, markedly reduced under such circumstances, is the exception. Consequently, either the extracellular Ca^{2+} pool is not actively functioning in the chain of successive reactions of adrenoreceptor activation or it can be replaced by intracellular Ca^{2+} from other sources.

In contrast, NE stimulation of HR and HBF in the presence of RR blocking decreased reliably in the myocardium of LR rats, and marked decrease of its effects on V_r and glycolysis was observed. In the myocardium of HR rats the stimulating effect of the agonist decreased and the intensity of glycolysis increased. One may note, first, the regulatory role of intracellular Ca^{2+} in the formation of the specific response of the myocardial adrenoreceptors and, second, its different role in these processes in the HR and LR animals (it is much greater in the latter). Furthermore, simultaneous application of the inhibitors of both pools of Ca^{2+} (NF and RR) markedly alters the effect of NE on the functional and metabolic parameters of the myocardium; these changes are more pronounced in LR than in HR rats. The stimulating effect on HR and HBF is reduced and manifests itself just for a short period. As the result, an inhibition phase follows a brief activation phase. The stimulating effect of NE on respiration and glycolysis is manyfold reduced. Consequently, both Ca^{2+} pools contribute to the realization of the NE-induced adrenoreceptor stimulation. Summation of the effects in the case of the inhibition of both Ca^{2+} pools or even the potentiation of these effects suggests that the regulatory effect of both Ca^{2+} pools is mediated by different mechanisms. At the same time, the absence of any significant influence of NF on the effect of NE together with its undoubtable impact for its simultaneous application with RR provide evidence of a possible compensatory consumption of extracellular Ca^{2+} for the realization of a number of reactions controlled by the extracellular Ca^{2+} pool.

Thus, oxidative metabolism in the cardiomyocytes is controlled by two different intracellular Ca^{2+} pools; their relationships, which determine aerobic and anaerobic homeostasis, are reciprocal. Their contribution, ratio and significance in the myocardium of LR and HR rats vary. Intracellular and extracellular Ca_{2+} independently participate in the formation of the adrenergic response to NE.

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