ACTION OF STROPHANTHIN K AND β-ACETYLDIGOXIN IN VITRO ON ENERGY TRANSFORMATION BY THE MYOCARDIAL CONTRACTILE PROTEIN SYSTEM IN TOXICO-ALLERGIC CARDIOMYOPATHY

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One of the main causes of heart failure in inflammatory diseases of the myocardium is a sharp decrease in the ability of the myocardial contractile protein system (MCPS) to generate force and perform work [5]. It has also been shown on a model of toxico-allergic myocarditis (TAM) that in inflammatory lesions of the heart muscle what happens is not simply a quantitative reduction of the contractile activity of MCPS, but also a qualitative change: the already reduced amount of internal energy (enthalpy) released from ATP, as in heart failure in man, is transformed wastefully, and the mechanical efficiency of the contractile process declines sharply [3]. Meanwhile, it has been shown on bundles of normal cardiomyocytes with differentially destroyed or functionally inactivated noncontractile subcellular structures, that strophanthin K and β-acetyldigoxin exert their inotropic action through direct action on MCPS: they sharply increase the force generated by the system [2]. Under these circumstances strophanthin K was found to increase significantly the economy of energy utilization (efficiency of the contractile process), whereas β-acetyldigoxin acts quantitatively ("extensively") by stimulating MCPS [4].

This paper describes a study of the action of these cardiac glycosides (CG) in a concentration of 10^{-6} M on transformation of energy of the isolated MCPS by bundles of glycerinized myocardial fibers (BGMF) of a rabbit with TAM, kept in a 50% aqueous solution of glycerin at −18°C for 1 month.

EXPERIMENTAL METHOD

Experiments were conducted on 15 chinchilla rabbits weighing 2.5-4 kg with TAM, produced by the method in [1]. The BGMF of 7 of these rabbits were used to study the action of strophanthin K, and of 8 to study the action of β-acetyldigoxin. Normalized mechanical and thermodynamic parameters of contraction of BGMF under the influence of CG were compared with normalized control values (TAM) and with normal values taken from studies undertaken at the same time but published previously (having an importance of their own) [3, 4]. These publications included references to the methods used, descriptions of the experimental techniques, and details of the statistical analysis of the data.

EXPERIMENTAL RESULTS

BGMF of rabbits with TAM used in this study showed reduction of the generated voltage (P) by more than half, reduction of work done (A) by more than 3.5 times, reduction of the integral enthalpy (ΔH) of ATP hydrolysis by half, reduction of the usefully utilized energy ($\Delta H - \Delta Q$) of MCPS by 2.5 times, absence of a corresponding reduction of the amount of energy dissipated in the form of heat (ΔQ) and, as a result, a significant reduction of the economy of energy utilization $(\Delta H - \Delta Q)\cdot(\Delta H)^{-1}$ and of the mechanical efficiency of the contractile process $(A\cdot(A + \Delta Q)^{-1})$ (Table 1).

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TABLE 1. Mechanical and Thermodynamic Parameters of Contraction of BGMF in TAM under the Influence of 10^{-6} M Strophanthin K and β-acetyldigoxin

Period	Complete		Normal (n = 16)	Control (n = 15)	TAM, strophantin K (n = 7)	β-acetyldigoxin (n = 8)
Complete	P, mN/mm^2		4,1±0,4	1,8±0,4***	3,1±0,2*	3,1±0,1*
	$A \cdot 10^{-3}$	mJ/mg	1,4±0,4	0,4±0,1**	1,5±0,2+++	1,0±0,1+++,§
	δH	mJ/mg	216,0±10,7	107,3±8,7***	141,8±6,8++,**	135,7±9,6+,***
	δQ	mJ/mg	68,3±6,2	44,1±5,0**	55,1±3,2	69,6±10,8++
	$\delta H - \delta Q$	mJ/mg	154,7±12,8	61,3±8,7***	86,9±8,13+,***	67,7±14,4***
	$\frac{\delta H - \delta Q}{\delta H} \cdot 100$	%	68,0±3,0	53,0±5,0*	64,0±3,3	45,0±7,4**
	$\frac{A \cdot 10^{-3}}{A + \delta Q} \cdot 100$	%	4,3±0,9	1,0±0,2**	2,6±0,4+++	1,7±0,4
Generation of force and work performance	δH	mJ/mg	177,3±8,6	65,1±5,0***	87,1±8,2+,***	106,7±7,1+++,***
	δQ	mJ/mg	42,5±3,9	28,5±2,9**	27,5±2,5*	39,5±4,6+,§
	$\delta H - \delta Q$	mJ/mg	126,5±9,6	37,9±4,3***	59,7±6,6***	67,3±9,1++,***
	$\frac{P}{\delta t'}$	$\frac{mN}{mm^2 \cdot min}$	0,66±0,07	0,39±0,06***	0,65±0,09+	0,57±0,05
	$A/\delta t \cdot 10^{-3}$	mJ/mg·min	0,20±0,05	0,087±0,016**	0,36±0,10+++	0,18±0,024++,§
	$\delta H/\delta t$	mJ/mg·min	31,2±2,9	13,2±1,2***	20,0±1,3++,**	19,6±2,2++,**
	$\delta Q/\delta t$	mJ/mg·min	7,0±0,6	6,1±0,5	5,7±0,3	7,5±1,1
	$\frac{\delta H - \delta Q}{\delta t}$	mJ/mg·min	23,6±0,6	7,9±0,6***	13,6±0,5+++,***	12,0±1,1++,***
	$\frac{\delta H - \delta Q}{\delta H} \cdot 100$	%	76,0±1,5	56,0±4,0***	71,0±2,4+	62,0±5,3**
	$\frac{A \cdot 10^{-3}}{A + \delta Q} \cdot 100$	%	3,0±0,6	1,3±0,2**	4,4±0,4+++,*	2,8±0,6+,§
Maintenance of tension	$\delta H/\delta t$	mJ/mN·min	8,8±1,2	4,8±1,6*	7,1±0,5	7,4±0,1
	$\delta Q/\delta t$	mJ/mN·min	3,2±0,3	2,5±0,4	3,7±0,5+	4,1±0,7+
	$\frac{\delta H - \delta Q}{\delta t}$	mJ/mN·min	4,1±0,4	3,6±0,3	5,6±1,2+	3,9±1,5
	$\delta H/F \cdot \delta t$	mJ/mN·min	2,3±0,2	3,6±0,7*	2,5±0,3	1,7±0,5+
	$\delta Q/F \cdot \delta t$	mJ/mN·min	0,8±0,1	1,4±0,1**	1,3±0,2**	1,2±0,2**

Legend. +) Significance of differences when comparing action of CG with control, *) with normal, §) of strophanthin X with β-acetyldigoxin. One symbol — $p < 0.05$, two symbols — $p < 0.01$, three symbols — $p < 0.001$.

The phase of maintenance of the contracted state of BGMF in TAM is characterized by a rather less than normal reduction of the rate of release of enthalpy compared with the phase of force generation (a reduction of 2.7 rather than 3.5 times) and by a small but not significant reduction of the rate of heat loss, due to higher than normal rates of loss of enthalpy ($H/\Delta t \cdot F^{-1}$) and heat ($\Delta Q/\Delta t \cdot F^{-1}$) per unit of maintained force (Table 1).

Thus the reduction of all integral parameters of contraction of BGMF in TAM is due mainly to processes taking place in BGMF in the phase of generation of force and performable work. Under the influence of both strophantin K and β-acetyldigoxin the maximal force developed by BGMF of a rabbit with TAM rose sharply (equally with both CG), and the performable work was restored to normal. Strophanthin K, however, had a much stronger action. The integral value of enthalpy of ATP hydrolysis also increased significantly, but under the influence of strophanthin K so also did the amount of usefully utilized energy of MCPS. It is striking that ΔH and a $\Delta H - \Delta Q$ increased by a lesser degree than tension and, in particular, work. The integral amount of energy dissipated as heat, in the case of β-acetyldigoxin rose back to normal, whereas in the case of strophanthin K it rose only by an amount such that, while returning close to the normal value until differences in the mean values were no longer significant, there was likewise no significant deviation from the control value, namely the value observed in TAM. As a result, the economy of utilization of the energy of MCPS rose to normal under the influence of strophanthin K, whereas in the case of β-acetyldigoxin it remained unchanged; however, the mechanical efficiency of contraction increased significantly under the influence of both CG.

Analysis of the mechanical and thermodynamic parameters of contraction of BGMF of rabbits with TAM during the phases of contraction shows that the strongest action of both CG [3] is directed toward processes taking place in the contractile apparatus of the cardiomyocyte in the dynamic phase of force generation and work performance — processes selectively disturbed in TAM. Accordingly, all effects of CG revealed by analysis of the integral values, during a phase-by-phase assessment of parameters of contraction of BGMF, and in particular during assessment of the velocities of the processes taking place, stand out more clearly in relief, and differences in the actions of β-acetyldigoxin and strophanthin K are seen more distinctly. For instance, the rate of work performance not only was restored to normal by strophanthin K, unlike by β-acetyldigoxin, but it actually exceeded the normal mean value by some degree (although, admittedly, not significantly). The rate of useful utilization of energy $(\Delta H - \Delta Q) \cdot (\Delta t)^{-1}$ of MCPS rose significantly under the influence not only of strophanthin K, as normally [4], but also of β-acetyldigoxin. The quantity of heat lost (with no significant change in the rate of loss) in the case of strophanthin K remained at the level observed in TAM (significantly lower than normally), but in the case of β-acetyldigoxin it rose to normal. The mechanical efficiency of the contractile process was normalized with greater reliability by β-acetyldigoxin, but exceeded normal under the influence of strophanthin K.

Thus, β-acetyldigoxin exerts its positive inotropic action in TAM through quantitative stimulation of the contractile activity of MCPS without any significant action on economy of useful utilization of energy, whereas strophanthin K acts through both qualitative and quantitative changes (toward greater economy), as under normal conditions, in the functioning of the unique "economizer" of MCPS [4].

Our findings do not conflict with results obtained by Gibbs and Gibson [6], who showed on myocardial strips that ouabain does not act on the economy of energy transformation, for ouabain, like rhodesid , according to data published previously, has no direct action on MCPS [2].

Differences in the actions of strophanthin K and β-acetyldigoxin on economy in emergy transformation and also on the quantity and rate of work done may be connected with differences in the effect of strophanthin K and β-acetyldigoxin on the conformational state and dynamics of conformational conversions of the actomyosin junction (N. V. Karsanov et al., unpublished data).

The results of the present investigation also indicate that in inflammatory lesions of the myocardium MCPS is not responsible for refractoriness of the heart failure to CG (such responsibility must be sought in other systems) and that in the case of administration of CG in inflammatory lesions of the heart muscle preference should be awarded to strophanthin K, for in inflammatory conditions of the myocardium one of the main factors (besides disturbance of function of MCPS and of Ca^{2+} transport through membranes) leading to the development of heart failure is the rapid onset of deficiency of ATP, the immediate source of readily available energy (its concentration in the myocardium falls by over 40% [5]).

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