CHANGES IN ATP, AMP, AND CERTAIN OXIDATIVE ENZYME LEVELS IN THE MYOCARDIUM DURING PHARMACOLOGICAL ACTION ON ADRENERGIC RECEPTORS

I. S. Chekman

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Experiments on rabbits showed that the α-adrenomimetic noradrenalin reduces the concentration of the ATP and AMP in the myocardium. The β-adrenomimetic isoprenaline causes no change in the ATP level but stimulates cytochrome-c oxidase activity. Blocking the α-adrenergic receptors by phentolamine leads to an increase in the ATP concentration whereas blocking the β-adrenergic receptors by anapriline does not change the level of this high-energy compound.

Most aspects of the pharmacodynamics of the adrenolytics have been studied in detail [3-6, 10-12]. However, their effect on biological oxidation has received little investigation [1, 12]. Different workers have expressed conflicting opinions regarding the effect of catecholamines on metabolism in the myocardium [7-9].

For this reason it was decided to study the effects of activation and blocking of the α- and β-adrenergic receptors on certain stages of biological oxidation of the heart.

EXPERIMENTAL METHOD

Experiments were carried out on 72 rabbits weighing 1.8-2.3 kg. The content of ATP, ADP, and AMP in the myocardium was determined by electrophoresis on paper [16], inorganic phosphorus (as in [2]), glycogen (by the anthrone method), and protein also were determined. Activity of cytochrome-c oxidase (1.93.1) was determined colorimetrically and expressed in indophenol units (i.u.) per milligram protein per minute [17], and succinate dehydrogenase (13.77.1) activity was estimated from reduction of the neotetrazolium chloride salt to the colored formazan, and the results expressed in μg formazan/mg protein [14].

Noradrenalin (40 μg/kg) and isoprenaline (10 μg/kg) were injected intravenously and the myocardium was taken for investigation 3 min later. Under these conditions noradrenalin, which excites α-adrenergic receptors, led to a marked pressor effect, while isoprenaline, which excites β-adrenergic receptors, induced a depressor effect. Phentolamine (5 mg/kg) and anapriline (1 mg/kg) also were injected intravenously. The animals were sacrificed 1 h and 30 min later, i.e., at times of almost total blocking of the α- or β-adrenergic receptors. For prolonged pharmacological blocking of the α- or β-receptors phentolamine (2 mg/kg) and anapriline (1 mg/kg) were injected subcutaneously daily for 10 days.

EXPERIMENTAL RESULTS

It will be clear from the results in Table 1 that noradrenalin reduced the ATP level by 18.2% and AMP by 30.3%, whereas the other parameters investigated were unchanged. A tendency for the glycogen level to fall and the inorganic phosphorus level to rise could be detected in the myocardium.

Department of Pharmacology and Biophysical Division, Central Research Laboratory, Kiev Medical Institute. (Presented by Academician of the Academy of Medical Sciences of the USSR A. I. Cherkes.)
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TABLE 1. Effect of Noradrenalin, Isoprenaline, Phentolamine, and Anapriline on Some Parameters of Metabolism in the Rabbit Myocardium (M ± m)

Treatment	ATP	ADP	AMP	ATP + ADP + AMP	Inorganic phosphorus (in mg%)	Glycogen (in mg%)	Cytochrome-c oxidase (i.u./mg prot.)	Succinate dehydrogen. (μg formazan/mg prot. in 30 min)
	(in μg/g tissue)							
Control (9)	2,3±0,2	1,36±0,1	0,89±0,1	4,55±0,5	41,8±2,2	603±27	0,49±0,03	1028±92,8
Noradrenalin (40 μg/kg) (8)	1,78±0,12	1,22±0,06	0,62±0,03	3,62±0,11	48±2,1	521±37	0,42±0,03	973±70
	$P=0,05$		$P<0,05$	$P=0,05$	$P=0,1$	$P=0,1$		
Isoprenaline (10 μg/kg)	2,46±0,3	1,21±0,06	0,74±0,07	4,41±0,2	48±2,6	507±38	0,66±0,04	1166±53
						$P<0,05$	$P<0,05$	
Phentolamine for 10 days (7) (2 mg/kg)	2,17±0,2	1,15±0,11	1,08±0,12	4,44±0,4	46,2±3,8	419±37	0,42±0,02	677,9±37
Anapriline for 10 days (7) (1 mg/kg)	3,13±0,4	2,1±0,13	1,17±0,1			$P<0,01$	$P<0,1$	$P<0,05$
	$P<0,05$	$P<0,05$	$P<0,05$	6,4±0,3	46,6±1,7	716±36	0,41±0,02	946±91
Control (16)	2,29±0,1	1,67±0,31	1,02±0,08	$P<0,05$		$P=0,05$	$P<0,1$	$P<0,1$
Phentolamine (9) (5 mg/kg)	3,04±0,19	1,87±0,1	1,26±0,11	4,98±0,2	57,2±2,1	523±30	0,27±0,02	840±60
	$P<0,01$		$P<0,05$	6,17±0,3	49,8±3,4	561±40	0,27±0,037	728±69
Anapriline (8) (1 mg/kg)	2,74±0,14	1,74±0,22	0,87±0,12	$P<0,01$	$P<0,1$			
	$P=0,1$			5,35±0,12	67,2±2,3	607±42	0,24±0,02	763±86
						$P<0,1$		

Note. Number of experiments indicated in parentheses; values of P given only if $P \leq 0.1$.

A decrease in the ATP concentration in the rabbit myocardium after intravenous injection of noradrenalin has been described by other workers [13]. Unlike noradrenalin, isoprenaline does not affect the concentration of adenosine phosphates but it increased the cytochrome-c oxidase activity by 30.6%. The glycogen concentration fell by 15.9%.

Blocking of the α-adrenergic receptors by phentolamine was accompanied by an increase in the ATP level by 32.6% and the AMP by 23.5%. The ATP/ADP ratio was increased by 34%. Activity of the enzymes of the respiratory chain was unchanged by a single injection of the adrenergic blocking agent. Administration of phentolamine for 10 days led to a decrease in the glycogen concentration in the myocardium and to inhibition of succinate dehydrogenase activity. A single dose of anapriline caused no significant changes in the level of the adenosine phosphates or inorganic phosphate or in the activity of cytochrome-c oxidase and succinate dehydrogenase. During administration of anapriline for 10 days the ATP concentration rose by 28.9%, ADP by 54.0%, and AMP by 31.4%. The increase in the concentration of the adenosine phosphate during prolonged administration of anapriline was evidently due to the ability of this drug to block not only β-, but also α-adrenergic receptors [15, 18]. Unlike phentolamine, anapriline increases the glycogen concentration in the myocardium.

These investigations show that excitation or blocking of α- and β-adrenergic receptors leads to various changes in the concentrations of adenosine phosphates and activity of the oxidative enzymes in the rabbit myocardium.

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