EFFECT OF STROPHANTHIN ON METABOLISM OF HIGH-ENERGY PHOSPHORUS COMPOUNDS IN THE MYOCARDIUM OF RATS IN THE EARLY STAGES OF INDIVIDUAL DEVELOPMENT

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Wistar albino rats aged 7, 14, 30, and 60 days and 3-5 months received a single subcutaneous injection of strophanthin K in small (0.1 mg/100 g) and large (1 mg/100 g) doses. Injection of the small dose of strophanthin increased ATP synthesis in the 7-day animals but did not affect this process in the older age groups. A large dose of strophanthin reduced ATP synthesis in the myocardium of the animals of all age groups studied. However, the younger animals were more resistant as regards the degree of the decrease in their ATP content in response to injection of large doses of strophanthin.

Young animals of various species are more sensitive to digitalis than fully grown animals [5, 15]. However, many workers consider that sensitivity to the glycosides digitalis and strophanthin is lower at an early age [6, 7, 10, 11, 19]. Haag and Corbell [14] could find no age differences in responses to preparations containing cardiac glycosides. Therapeutic doses of digitalis and strophanthin are known to improve the production and utilization of energy of ATP, whereas large doses stimulate degradation of ATP.

It was accordingly decided to study the effect of strophanthin on metabolism of high-energy compounds in the heart muscle in the early stages of ontogenesis.

EXPERIMENTAL METHOD

Experiments were carried out on Wistar albino rats aged 7, 40, and 30 days (of both sexes) and on females aged 60 days and fully grown. Strophanthin K was injected subcutaneously as single small (0.1 mg/100 g) and large (1 mg/100 g) doses. The animals were decapitated 40-45 min after injection of the drug. The heart was quickly removed, frozen in liquid nitrogen, the heart tissue was ground, and its content of ATP, ADP, and AMP was determined by electrophoresis on paper followed by spectrophotometry [16], and its content of inorganic phosphorus (IP) and creatine phosphate (CP) was determined by a colorimetric method [1, 12, 13]. Statistical analysis of the results was carried out in the usual way [3].

EXPERIMENTAL RESULTS

During development of cardiac activity in the growing animal the ATP and ADP contents of the heart increase, as also do the ATP/ADP molar ratio (reflecting the energy level of the adenosine system of the myocardium) and the content of CP and IP (Table 1). Meanwhile, the content of AMP in the heart muscle of young rats is considerably higher than in the adult animal. According to the literature [8] a relatively low content of ATP and CP in the myocardium of young animals is observed despite the high rate of their renewal. The reason is evidently because ultilization of high-energy phosphates for the various needs of the cell, especially structural, takes place at a higher rate in early ontogenesis than their synthesis.

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TABLE 1. Effect of a Single Injection of Strophanthin K in Small (A) and Large (B) Doses on Content of Adenosine Phosphates (in μmoles/g) and of CP and IP (in mg%) in Myocardium of Rats at Various Ages (M ± m)

Age of rats (in days)	ATP			ADP			AMP		
	dose of strophanthin								
	control	A	B	control	A	B	control	A	B
7	0,58±0,02	0,82±0,02	0,35±0,04	0,70±0,05	0,63±0,03	0,69±0,02	0,42±0,03	0,26±0,02	0,45±0,04
P	<0,001	>0,02	<0,001	<0,01	>0,25	>0,5	<0,001	<0,001	>0,5
14	0,63±0,04	0,65±0,02	0,34±0,02	0,63±0,03	0,69±0,09	0,70±0,06	0,47±0,01	0,30±0,02	0,32±0,02
P	<0,001	>0,05	<0,001	<0,002	>0,05	>0,05	<0,001	0,001	<0,001
30	0,68±0,02	0,74±0,03	0,12±0,01	0,73±0,06	0,88±0,03	0,74±0,03	0,39±0,03	0,33±0,02	0,43±0,03
P	<0,001	>0,05	<0,001	<0,001	>0,05	>0,05	>0,05	<0,002	>0,25
60	1,48±0,09	1,35±0,06	0,43±0,03	0,91±0,04	0,81±0,07	0,67±0,06	0,31±0,04	0,28±0,07	0,42±0,03
P	>0,1	>0,05	<0,001	>0,05	>0,05	<0,02	>0,05	>0,25	>0,05
Adult	1,65±0,04	1,44±0,04	0,87±0,02	1,15±0,07	1,12±0,07	1,02±0,03	0,25±0,02	0,24±0,01	0,42±0,03
P		>0,05	<0,001		>0,05	>0,1		>0,1	>0,25

TABLE 1 (continued)

Age of rats (in days)	ATP/ADP			CP			IP		
	dose of strophanthin								
	control	A	B	control	A	B	control	A	B
7	0,84±0,06	1,30±0,06	0,50±0,05	3,86±0,05	4,85±0,16	0,53±0,08	15,3±0,08	13,3±0,33	12,7±1,33
P	<0,001	<0,001	<0,002	<0,01	<0,01	<0,001	<0,001	<0,05	>0,1
14	0,96±0,07	0,96±0,05	0,49±0,05	5,00±0,03	5,47±0,023	1,2±0,17	14,0±1,0	12,1±0,6	24,4±0,49
P	<0,001	>0,5	<0,01	>0,05	>0,5	<0,001	<0,001	>0,1	<0,001
30	0,93±0,04	0,79±0,06	0,16±0,01	3,1±0,13	3,5±0,16	0,46±0,08	18,4±1,4	15,5±0,85	50,1±2,74
P	<0,001	>0,05	<0,001	<0,001	>0,01	<0,001	<0,05	>0,1	<0,001
60	1,65±0,17	1,73±0,2	0,64±0,08	4,85±0,2	4,66±0,2	1,0±0,22	19,6±1,4	13,1±0,89	42,2±1,99
P	>0,05	>0,5	<0,01	<0,05	>0,25	<0,001	>0,05	<0,05	<0,001
Adult	1,43±0,06	1,32±0,06	0,85±0,01	6,1±0,4	5,96±0,23	2,2±0,22	25,0±1,75	18,5±0,96	58,5±1,35
P	—	>0,25	<0,01		>0,5	<0,001		<0,02	<0,001

Note: P calculated relative to control.

After injection of a small dose of strophanthin (Table 1) an increase in the content of ATP and CP and in the ATP/ADP ratio and a decrease in the AMP and IP content were found in the myocardium of the 7-day rats. These changes were probably due to a shift in the metabolism of high-energy phosphates toward synthesis. In the older animals no difference compared with the control was found in the the reactions of the adenosine system or of its reserves (CP and IP), in agreement with data in the literature [2, 4].

A high dose of strophanthin led to a decrease in the content of ATP and CP and in the ATP/ADP molar ratio in the myocardium of the rats of all age groups (Table 1); meanwhile the IP content was sharply increased (except in the 7-day animals, in which it was unchanged). The content of ADP and AMP did not generally go beyond the control limits. Administration of the large dose of strophanthin thus stimulates ATP degradation. It is noteworthy that 7-day rats were less sensitive to the large dose of glycoside. The most sensitive animals were those aged 1 month (their ATP content was reduced by 82%). In toxic doses cardiac glycosides induce myocardial hypoxia [9]. The lower sensitivity of the young animals to large doses of strophanthin was evidently connected with the high level of the carbohydrate content and the high intensity of glycolysis (glycogenolysis) in the myocardium [17]. Glycolysis (glycogenolysis) is the reserve mechanism of formation of ATP energy in the heart (which is characterized by an aerobic type of metabolism) if, for various reasons, the ATP content is reduced and the oxidative mechanism alone is evidently insufficient to provide for ATP synthesis.

The reaction of the high-energy phosphates of the myocardium to strophanthin thus shows certain special features in the early stages of individual development. On the one hand, these experiments confirm the existing view that a single injection of therapeutic doses of cardiac glycosides does not change the balance of high-energy compounds in the myocardium of intact animals; second, in the presence of a relative ATP deficiency (which is evidently the case in 7-day rats) a small dose of glycoside stimulates and increases the production of ATP energy in the myocardium. At the same time, it should be noted that young animals are more resistant (in the degree of decrease in their ATP content) to large doses of strophanthin than adults.

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