EFFECT OF METHYLXANTHINES ON THE CONTENT OF CATECHOLAMINES AND ADENOSINE PHOSPHATES IN THE RAT MYOCARDIUM

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Experiments on rats showed that theophylline, theobromine, and caffeine in a dose equimolar to 50 mg/kg of theophylline base, increase the catecholamine concentration in the rat myocardium 1 h after intraperitoneal injection. These compounds, except caffeine, had a similar effect in a dose of 125 mg/kg. Theophylline reduced the degree of lowering of the catecholamine level in the myocardium after administration of tyramine and strophanthin. Elevation of the catecholamine level after administration of caffeine was accompanied by an increase in the ATP and ADP content and a decrease in the AMP content, as well as by the formation of inosine monophosphate, adenosine, and inosine.

KEY WORDS: myocardium; methylxanthines; catecholamines; adenosine phosphates.

The hemodynamic effects of theophylline and the closely similar compounds are analogous with the action of β-adrenomimetics [12, 13]: by blocking phosphodiesterase and inhibiting the breakdown of cyclic 3',5'-AMP in the cells [11], methylxanthines potentiate the effect of catecholamines [14]. Data on their effect on the metabolism of biogenic amines have also been published [4, 8, 10].

TABLE 1. Effect of Methylxanthines on CA Content in Myocardium of Rats (in μg noradrenalin base/g wet weight of tissue)

Group of experiments	Experimental conditions	Dose (in mg/kg)	No. of experiments	Total content of catecholamines in myocardium (M ±m)	
1	Control	—	19	1,41±0,08	—
2	Theophylline	25	10	1,86±0,2	$P_{1-2} > 0{,}05$
3	"	50	10	1,85±0,067	$P_{1-3} < 0{,}001$
4	"	125	10	1,88±0,052	$P_{1-4} < 0{,}001$
5	Tyramine	10	10	0,87±0,05	$P_{1-5} < 0{,}001$
6	Theophylline + Tyramine	50 10	10	1,24±0,14	$P_{5-6} < 0{,}05$
7	Strophanthin	1	6	0,96±0,1	$P_{1-7} < 0{,}02$
8	Theophylline + Strophanthin	50 1	8	1,25±0,14	$P_{7-8} > 0{,}05$
9	Control	—	9	1,37±0,057	—
10	Theobromine	25	8	1,66±0,082	$P_{9-10} < 0{,}02$
11	"	50	9	1,95±0,08	$P_{9-11} < 0{,}001$
12	"	125	9	2,04±0,097	$P_{9-12} < 0{,}001$
13	Control	—	11	1,62±0,13	—
14	Caffeine	53,7	8	2,3±0,067	$P_{13-14} < 0{,}001$
15	"	134,2	12	1,67±0,14	$P_{13-15} > 0{,}05$

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TABLE 2. Effect of Methylxanthines on Content of Adenosine Phosphates and Inorganic Phosphorus in the Rat Myocardium (M ± m)

Experimental conditions	No. of experiments	ATP	ADP	AMP	total adenosine phosphates	inosine monophosphate	Inosine	Adenosine	Inorganic phosphorus
		in μmoles/g tissue						in mg %	
Control	10	2,4±0,16	2,18±0,115	1,47±0,08	6,06±0,27	—	—	—	26,8±2
Theophylline P_{1-2}	8	2,67±0,26 >0,05	2,75±0,2 <0,05	1,74±0,15 >0,05	7,17±0,31 <0,02	0,56±0,12 <0,05	Appears in individual experiments		30,81±2,48 >0,05
Theobromine P_{1-3}	9	2,68±0,18 >0,05	2,67±0,25 >0,05	1,89±0,19 >0,05	7,25±0,52 >0,05	Absent	0,43±0,11 <0,05	Absent	28,7±1,2 >0,05
Caffeine P_{1-4}	8	3,54±0,26 <0,002	2,75±0,23 <0,05	0,65±0,11 <0,001	6,95±0,4 >0,05	1,01±0,06 <0,05	0,96±0,21 <0,05	0,76±0,083 <0,05	28,8±2,47 >0,05

The object of this investigation was to study the effect of methylxanthines on the catecholamine (CA) content in the rat heart. Considering that the liberation and storage of CA are brought about through the energy of ATP, the concentration of adenosine phosphate in the myocardium also was studied.

EXPERIMENTAL METHOD

Experiments were carried out on 180 rats weighing 180-240 g. The total CA content in the myocardium was determined by fluorescence analysis [5, 7] and expressed in μg noradranelin base/g wet weight of tissue. The content of adenosine phosphates (ATP, ADP, and AMP) was determined by electrophoresis on paper [15] followed by spectrophotometry at wavelengths of 260 and 290 nm. Inorganic phosphorus also was determined [2].

During investigation of the CA level, theophylline, theobromine, and caffeine were injected intraperitoneally in doses equimolar with 25, 50, and 125 mg/kg respectively of theophylline base, equivalent to 5, 10, and 25% of 1 LD_{50} theophylline for albino mice when administered in this way [6]. Before determination of the adenosine phosphates, the drugs were injected intraperitoneally in a dose equimolar with 50 mg/kg theophylline. This dose effectively influences the various aspects of myocardial metabolism [10, 16, 17]. The animals were decapitated 1 h after injection of the preparations.

EXPERIMENTAL RESULTS AND DISCUSSION

In doses of 50 and 125 mg/kg theophylline increased the catecholamine content in the heart by 31.2 and 33.3% respectively. Theobromine had a similar action, but it significantly increased the CA level when given in a dose of 25 mg/kg also. As regards caffeine, in a dose equimolar with 50 mg/kg theophylline it raised the myocardial CA level by 41.9% above its initial value; increase in the dose, however, abolished this effect (Table 1).

The effect of theophylline on the myocardial CA depots was studied with the aid of tyramine, a sympathomimetic with an indirect type of action, and the cardiac glycoside strophanthin, which facilitates the liberation of CA from the depots [9]. Injection of theophylline 1 h before tyramine (10 mg/kg) or strophanthin (1 mg/kg) reduced the liberation of CA under the influence of these compounds. These results suggest that methylxanthines inhibit the release of CA from the labile depot.

The study of the level of adenosine phosphates (Table 2) showed that whereas theophylline and theobromine increased the content of ATP, AMP, and ADP in the heart only very slightly, caffeine modified their metabolism very definitely: the ATP and ADP levels rose by 47.5 and 26% respectively, but the AMP level fell to 44.2% of its initial value. Such a sharp decrease in the AMP content under the influence of caffeine can hardly be connected with inhibition of phosphodiesterase, an enzyme hydrolyzing cyclic 3',5'-AMP with the formation of 5-AMP, for all methylxanthines have the ability to block phosphodiesterase and theophylline is more effective in this respect than caffeine [11]. The fall in the AMP level, together with the rise in the ADP and ATP levels are more likely to indicate the more rapid renewal of the phosphorus compounds. For example, caffeine has been shown to increase the intensity of uptake and subsequent elimination of radioactive phosphorus by heart muscle [3]. The decrease

in the AMP level under the influence of caffeine was accompanied by the appearance of its dephosphorylation product, adenosine. The level of inorganic phosphorus was substantially unchanged in all series of experiments.

The combination of elevation of the CA level in the heart with a tendency for the level of adenosine phosphates to rise accords with the view that the methylxanthines not only inhibit the liberation of CA from the labile depot, but also stimulate their accumulation in the stable depot. This latter process is known to be due to the formation of a complex of CA with adenosine phosphates in the ratio of 1:4 or 1:5 [1].

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