Effect of Beta-Adrenergic Stimulation on Myocardial Adenine Nucleotide Metabolism

By Heinz-Gerd Zimmer and Eckehart Gerlach

ABSTRACT

The effects of isoproterenol, propranolol, and compound D600 (α-isopropyl-α-[N-methyl-N-homoveratryl]-γ-aminopropyl]-3,4,5-trimethoxyphenylacetanilide) on myocardial adenine nucleotide metabolism were studied in rat hearts in situ. Isoproterenol in doses between 0.1 and 25 mg/kg induced an increase in heart rate concomitant with a significant acceleration in the de novo synthesis of adenine nucleotides (ATP, ADP, and AMP) and a diminution in their concentration. The effects of isoproterenol were antagonized by propranolol (1 and 50 mg/kg), which alone caused a reduction in the de novo synthesis of adenine nucleotides without inducing a change in their concentration. Compound D600 (10 mg/kg) brought about a slight elevation in the concentration of adenine nucleotides but did not influence the rate of de novo synthesis. The isoproterenol-induced diminution in adenine nucleotide concentration was prevented by D600; under these conditions, the acceleration of de novo synthesis was attenuated. These findings indicate that de novo synthesis of myocardial adenine nucleotides in the normal and the isoproterenol-stimulated heart is regulated not only by a feedback mechanism dependent on the concentration of adenine nucleotides but also by β-receptor-mediated alterations in carbohydrate metabolism which can cause changes in the size of the available pool of 5-phosphoribosyl-1-pyrophosphate.

KEY WORDS

compound D600

isoproterenol

propranolol

de novo synthesis of adenine nucleotides

rats

1-14C-glycine

cardiac hypertrophy

Oxygen deficiency causes a breakdown of myocardial adenine nucleotides that results in the formation of purine nucleosides and bases (1-6). Since the dephosphorylated nucleotide breakdown products can readily penetrate the myocardial cell membrane (7-10), oxygen deficiency leads to a remarkable diminution in the intracellular levels of adenine nucleotides which can still be detected during subsequent periods of postanoxic recovery (11). Recently, we have demonstrated that de novo synthesis of adenine nucleotides is enhanced in the rat heart during recovery from oxygen deficiency (12). Furthermore, we have observed an acceleration of the de novo formation of myocardial adenine nucleotides in rats during the development of cardiac hypertrophy following aortic constriction. Under this condition, a decline in myocardial adenine nucleotide levels (13) has been shown to precede the enhancement of de novo synthesis of adenine nucleotides (14, 15).

Since isoproterenol causes a reduction in myocardial high-energy phosphate stores (16, 17) and induces cardiac hypertrophy (18, 19), we decided to study its influence on the rate of de novo synthesis of adenine nucleotides in the heart. We used the β-adrenergic blocking agent propranolol (20) and the "calcium-antagonistic" compound D600 (21, 22), which both inhibit the isoproterenol-induced diminution of adenine nucleotide levels, as tools for establishing different cardiac adenine nucleotide levels and elucidating the relationship between the rate of de novo synthesis and the concentration of adenine nucleotides in the myocardium. Thus, we performed in vivo experiments utilizing these three substances to determine whether de novo synthesis of cardiac adenine nucleotides is controlled by a nucleotide concentration-dependent feedback mechanism (23, 24) alone or in combination with some other mode of regulation of purine nucleotide biosynthesis.

Methods

Female Sprague-Dawley rats (200-220 g) fed a diet of Altromin were used in all experiments. 1-14C-Glycine (specific activity 56 mCi/mmol) was purchased from the

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Radiochemical Centre, Amersham, England. Isoproterenol was obtained from C. H. Boehringer Sohn, Ingelheim, propranolol was a gift from Rhein-Pharma, Heidelberg, and compound D600 (α-isopropyl-α-[N-methyl-N-homoveratryl]-γ-aminopropyl)-3,4,5-trimethoxyphenylacetonitrile) was generously supplied by Knoll AG, Ludwigshafen. All other chemicals were obtained from Merck AG, Darmstadt, and were of analytical grade.

EXPERIMENTAL PROCEDURES

Isoproterenol dissolved in saline (0.9%, w/v) was injected subcutaneously in doses of 0.1, 5, and 23 mg/kg. Propranolol (1 or 50 mg/kg) and compound D600 (10 or 15 mg/kg), also dissolved in saline, were administered subcutaneously either alone or simultaneously with isoproterenol. Control rats were injected with 1 ml of saline. Measurements of heart rate were performed using a telemetric device consisting of a biotransmitter (S.N.R. 102 G, Sandev) in combination with a receiver (frequency 102.2-102.4 MHz). The signals were transmitted to an oscilloscope (Tektronix Inc.) for visual control and recorded on an electrocardiogram on a Clevite Brush Mark 220 recorder. The frequency of the R spikes served as a measure of heart rate.

At various times after administration of the drugs, measurements of de novo synthesis of myocardial adenine nucleotides were performed. The rats, which had been fasted for 12 hours, were intravenously injected with 1-14C-glycine (0.25 me/kg in 1 ml of saline). At the end of a 60-minute exposure to 1-14C-glycine, the rats were anesthetized with diethyl ether and their hearts were rapidly excised. The ventricles were freed of adhering blood and quickly frozen in liquid nitrogen. Blood samples taken from each rat at the time of excision of the heart were heparinized and immediately centrifuged for separation of the plasma.

ANALYTICAL PROCEDURES

Extraction.—Ventricular myocardium was ground to a fine powder under liquid nitrogen and extracted with 0.3N HClO4 (5 minutes at 0°C). After centrifugation, the extracts were neutralized with 3N KOH, kept in an ice bath for 60 minutes, and separated from the KClO4 precipitate.

Concentration of Adenine Nucleotides.—Adenosine triphosphate (ATP), adenosine diphosphate (ADP), and adenosine monophosphate (AMP) levels (nmoles/g wet weight) were determined in samples of the extracts according to methods described previously (25). To exclude the consequences of experimentally induced changes in tissue wet weight, appropriate corrections for a constant dry weight of 20% were made in all experiments.

De Novo Synthesis of Adenine Nucleotides.—Rates of de novo synthesis of myocardial adenine nucleotides (nmole/g wet weight hour−1) were calculated from the total radioactivity of the adenine nucleotides (dpm/g wet weight) and the mean specific activity of the intracellular glycine (dpm/nmole). Wet weights were corrected as indicated in the preceding section. Details of the methods and calculations have been published previously (12).

Determination of Radioactivity.—14C-Activities were measured in a Packard Tricarb liquid scintillation spectrometer (model 3380). Each sample was made up to 10 ml with scintillation fluid prepared by dissolving 5.5 g of 2,5-diphenyloxazole and 0.15 g of 1,4-bis-2(5-phenyloxazoyl)benzene in 666 ml of toluene and 334 ml of Triton X-100. Counting efficiencies ranged between 87% and 90% under these conditions.

Results

Kinetic studies on rat hearts in vivo under control conditions and 5 hours after administration of a single high dose of isoproterenol (25 mg/kg) revealed that the specific activity of intracellular glycine (Fig. 1A) and the total radioactivity of myocardial adenine nucleotides (Fig. 1B) were consistently higher in isoproterenol-stimulated hearts. The total radioactivity of adenine nucleotides, however, was elevated to a much greater extent than was the specific activity of the precursor glycine. Thus, the rate of de novo synthesis, which rose linearly between 15 and 60 minutes of exposure to 1-14C-glycine under both conditions, was considerably enhanced after application of isoproterenol (Fig. 1C).

Time course studies of the changes in the concentration and radioactivity of the precursor glycine and the adenine nucleotides (Table 1) showed that the concentration of glycine was significantly elevated 5, 12, and 24 hours after the administration of isoproterenol, whereas the mean specific activity of glycine was increased only after 5 hours. In contrast, the concentration of ATP and of the sum of adenine nucleotides decreased progressively during the 24-hour period following application of isoproterenol, whereas the total radioactivity of adenine nucleotides was considerably elevated over the whole period with the highest value occurring after 5 hours.

The alterations in the rate of adenine nucleotide synthesis and heart rate which occurred during the first 3 days subsequent to a single high dose of isoproterenol exhibited a rather similar pattern (Fig. 2). After a steep increase within the first 5 hours, both parameters remained elevated at a high level up to 12 hours and declined gradually thereafter.

Isoproterenol proved to be effective not only in high doses but also in low doses: 5 mg/kg and even 0.1 mg/kg of isoproterenol caused an increase in the total radioactivity of adenine nucleotides without significantly affecting the mean specific activity of precursor glycine (Table 2). The increase in de novo synthesis of adenine nucleotides amounted to 630% and 270%, respectively.

Table 2 also includes data from experiments with propranolol. It is evident that propranolol in high...
and also in low doses caused a strong diminution in the total radioactivity of adenine nucleotides. The mean specific activity of glycine, however, was not changed. Consequently, the rate of de novo synthesis of adenine nucleotides was considerably diminished. According to separate kinetic experiments, the time course of changes in the specific activity of myocardial glycine during a 60-minute exposure to $^{14}$C-glycine was very similar in propranolol-treated rats and control rats (Fig. 1).

Table 3 summarizes studies comparing the effects of isoproterenol, propranolol, and isoproterenol plus propranolol on de novo synthesis, ATP concentration, and heart rate. It is particularly interesting that propranolol applied alone caused a diminution in the synthesis of adenine nucleotides without any apparent changes in the concentration of ATP. Furthermore, propranolol antagonized the isoproterenol-induced alterations in de novo synthesis, ATP concentration, and heart rate.

The main results of our studies on the effects of compound D600 are given in Table 4. D600 did not appreciably affect the rate of de novo synthesis.

### Table 1

**Time Course of Changes in the Concentration and Mean Specific Activity (MSA) of Intracellular Glycine and in the Concentration and Total Radioactivity of Myocardial Adenine Nucleotides during the First 24 Hours after Administration of Isoproterenol (25 mg/kg)**

<table>
<thead>
<tr>
<th>Time after isoproterenol (hours)</th>
<th>Concentration Glycine</th>
<th>MSA Glycine</th>
<th>Concentration Adenine nucleotides</th>
<th>ATP</th>
<th>ADP, AMP</th>
<th>ΣATP, ADP, AMP</th>
<th>Total radioactivity (dpm/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>N=32</td>
<td>425 ± 10</td>
<td>180 ± 5</td>
<td>4340 ± 50</td>
<td>5700 ± 120</td>
<td>992 ± 60</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>N=7</td>
<td>434 ± 40</td>
<td>192 ± 16</td>
<td>3800 ± 90*</td>
<td>5360 ± 111t</td>
<td>3294 ± 249t</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>N=9</td>
<td>496 ± 13t</td>
<td>255 ± 11*</td>
<td>3370 ± 120*</td>
<td>4710 ± 100*</td>
<td>9885 ± 366*</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>N=10</td>
<td>480 ± 28t</td>
<td>186 ± 6</td>
<td>3250 ± 120*</td>
<td>4300 ± 160*</td>
<td>6340 ± 569*</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>N=4</td>
<td>561 ± 28t</td>
<td>151 ± 4</td>
<td>3170 ± 50*</td>
<td>4200 ± 130*</td>
<td>2396 ± 103*</td>
<td></td>
</tr>
</tbody>
</table>

The rats were exposed to $^{14}$C-glycine (0.25 mCi/kg) for the last 60 minutes of the indicated time after application of isoproterenol. The concentrations of adenine nucleotides were determined in separate experiments which were identical except for the omission of $^{14}$C-glycine and for the method for excising the heart (13). Values are means ± se. N = number of experiments.

* P < 0.005.
† P < 0.05.
‡ P < 0.01.
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FIGURE 2
Time course of changes in the rate of de novo synthesis of myocardial adenine nucleotides and in heart rate after administration of a single dose (25 mg/kg) of isoproterenol. The control range is indicated by the hatched areas. The number of experiments is given in parentheses. Values are means ± SE. When it was applied alone, although it caused a slight elevation in the concentration of ATP, when isoproterenol was administered simultaneously with D600, the isoproterenol-induced decrease in adenine nucleotide concentration was completely prevented, but the increase in de novo synthesis was only attenuated.

Discussion

The studies reported in this paper demonstrate that isoproterenol is a powerful stimulator of de novo synthesis of adenine nucleotides in the rat heart. Since isoproterenol is known to cause cardiac hypertrophy in rats (18, 19), it is interesting to compare the time course of isoproterenol-induced changes in adenine nucleotide synthesis with those occurring in the hypertrophying rat heart after aortic constriction (13-15). In this latter condition, myocardial adenine nucleotide synthesis transiently decreases within 5 hours after banding of the aorta, gradually increases after 24 hours, and reaches a maximum on the third day. In contrast, a single high dose of isoproterenol causes an almost immediate steep rise in the rate of adenine nucleotide biosynthesis; maximal values are observed after 5 and 12 hours (Fig. 2).

Irrespective of the qualitative and the quantitative differences concerning onset and extent of the increase in adenine nucleotide synthesis, there is one common feature in both models of cardiac hypertrophy—the initial reduction in the concentration of myocardial high-energy phosphate compounds (13, 16, 17, Table 1). It is thus not surprising that a diminution in myocardial levels of ATP has been suggested as a causal factor for the stimulation of nucleic acid and protein synthesis during the development of cardiac hypertrophy.

TABLE 2
Influence of Different Doses of Isoproterenol and Propranolol on the Mean Specific Activity of Intracellular Glycine and the Total Radioactivity and De Novo Synthesis of Myocardial Adenine Nucleotides

<table>
<thead>
<tr>
<th>Dose admin. (mg/kg)</th>
<th>Time after drug administration (hours)</th>
<th>Mean activity of glycine (dpm/nmole)</th>
<th>Total radioactivity (dpm/g)</th>
<th>De novo synthesis (nmoles/g hour⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>32</td>
<td>180 ± 5</td>
<td>992 ± 60</td>
<td>5.3 ± 0.34</td>
</tr>
<tr>
<td>Isoproterenol</td>
<td>5</td>
<td>8</td>
<td>201 ± 9</td>
<td>7600 ± 370*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>38.6 ± 2.97*</td>
</tr>
<tr>
<td></td>
<td>0.1</td>
<td>3</td>
<td>177 ± 8</td>
<td>3390 ± 310*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>19.5 ± 2.23†</td>
</tr>
<tr>
<td>Propranolol</td>
<td>50</td>
<td>5</td>
<td>166 ± 19</td>
<td>147 ± 55*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.8 ± 0.25†</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>3</td>
<td>152 ± 4</td>
<td>264 ± 79†</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.8 ± 0.57†</td>
</tr>
</tbody>
</table>

The rats were exposed to 1-¹⁴C-glycine (0.25 mc/kg) for the last 60 minutes of the indicated time after administration of the drugs. Values are means ± SE. N = number of experiments.

* P < 0.0005.
† P < 0.005.
‡ P < 0.01.

TABLE 3
Influence of Isoproterenol (25 mg/kg) and Propranolol (50 mg/kg) on De Novo Synthesis of Adenine Nucleotides, Concentration of ATP in the Myocardium, and Heart Rate in Rats

<table>
<thead>
<tr>
<th>De novo synthesis (nmoles/g hour⁻¹)</th>
<th>ATP (nmoles/g)</th>
<th>Heart rate (beats/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>5.3 ± 0.34</td>
<td>4340 ± 50</td>
</tr>
<tr>
<td></td>
<td>(N = 32)</td>
<td>(N = 32)</td>
</tr>
<tr>
<td>Isoproterenol</td>
<td>39.3 ± 2.31†</td>
<td>3370 ± 120*</td>
</tr>
<tr>
<td></td>
<td>(N = 9)</td>
<td>(N = 9)</td>
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<tr>
<td>Propranolol</td>
<td>0.8 ± 0.25*</td>
<td>4390 ± 150</td>
</tr>
<tr>
<td></td>
<td>(N = 9)</td>
<td>(N = 9)</td>
</tr>
<tr>
<td>Isoproterenol + Propranolol</td>
<td>5.3 ± 1.20</td>
<td>4370 ± 50</td>
</tr>
<tr>
<td></td>
<td>(N = 5)</td>
<td>(N = 6)</td>
</tr>
</tbody>
</table>

Measurements were taken 5 hours after drug administration. Values are means ± SE. N = number of experiments.

* P < 0.0005.
† P < 0.005.
‡ P < 0.01.
(26, 27). Our experiments indicate that the acceleration of de novo synthesis of adenine nucleotides which occurs concomitantly with or subsequently to the initial diminution in myocardial adenine nucleotide levels (13-15, Fig. 2) is a further obligatory event among those metabolic processes which finally lead to an enhanced synthesis of nucleic acids and proteins. In this connection some observations deserve attention. (1) After banding of the aorta, the enhancement of the de novo synthesis of myocardial adenine nucleotides precedes the increase in the synthesis of deoxyribonucleic acid (DNA) (28) and proteins (13) and occurs at about the same time that nuclear ribonucleic acid (RNA) polymerase activity (29) and RNA labeling become enhanced (30). (2) In the isoproterenol-stimulated heart, de novo synthesis of adenine nucleotides increases prior to the acceleration of the synthesis of DNA, RNA and proteins (31, 32). (3) Enhanced incorporation of low molecular weight precursors of de novo synthesis into DNA (14C-formate, 2-14C-glycine, 4-14C-aspartate) has been shown to occur as early as 6 hours after administration of isoproterenol (31), i.e., at the same time that the de novo synthesis of myocardial adenine nucleotides reaches its maximum.

The results of our studies concerning the influence of isoproterenol, propranolol, and compound D600 on cardiac adenine nucleotide metabolism provide some particular information with respect to the mechanisms by which the pathway of de novo adenine nucleotide synthesis may be regulated in the myocardium. Two mechanisms are known to be involved in the control of purine biosynthesis: (1) feedback control of 5-phosphoribosyl-1-pyrophosphate amidotransferase (EC 2.4.2.14), the activity of which depends on the concentration of adenine nucleotides (23, 24), and (2) changes in the available pool of 5-phosphoribosyl-1-pyrophosphate (PRPP) (33). In trying to explain the acceleration of de novo synthesis elicited by isoproterenol, one has to take into account the interactions between the effects of this beta-receptor-stimulating compound on heart function, myocardial carbohydrate metabolism, and adenine nucleotide concentrations. Some of the pertinent interrelationships are summarized in Figure 3. It is well documented that isoproterenol increases myocardial contractility due to its calcium-dependent, positive inotropic effect (Fig. 3, route b); this change is paralleled by a moderate diminution in the concentrations of adenine nucleotides (16, 17, 21, Table 1). Such a diminution of adenine nucleotide concentration (Fig. 3, route c) can cause an acceleration of the de novo synthesis of adenine nucleotides, since it can result in a release of feedback inhibition of PRPP amidotransferase (Fig. 3, route d). In addition, isoproterenol, like other catecholamines, is known to stimulate adenylyl cyclase (Fig. 3, route a) to produce greater amounts of 3',5'-cyclic AMP (cAMP) (34, 35). cAMP is intimately involved in the enhancement of glycogenesis which results in an increased formation of glucose-6-phosphate (36, 37). Glucose-6-phosphate, however, is one of the substrates of the pentose phosphate pathway, which has been shown to be activated under the influence of isoproterenol (38). Thus, it seems conceivable that isoproterenol may lead via an enhancement of glycogenolysis to an increase in the formation of ribose-5-phosphate and consequently of PRPP, although another mode of action cannot be excluded. Due to the greater availability of PRPP, the de novo formation of adenine nucleotides should be accelerated. Unfortunately, the assumed series of metabolic reactions can hardly be proved directly, since it is not possible as yet to determine in cardiac tissue the concentration of PRPP because of its high instability during the extraction procedure.

The results of our experiments with isoproterenol and propranolol do not permit an estimate of the respective contributions of the two possible mechanisms to the observed enhancement of de novo synthesis, because propranolol antagonizes the effects of isoproterenol on both heart function and cardiac contractility due to its calcium-binding properties (24). It is most likely that the isoproterenol-induced changes in the concentrations of adenine nucleotides and in the activity of the enzymes involved in the adenine nucleotide metabolism are the result of the complex interactions between the effects of isoproterenol on heart function and on myocardial carbohydrate metabolism.
Schematic illustration of the effects of isoproterenol, propranolol, and compound D600 on the de novo synthesis of myocardial adenine nucleotides. Solid arrows = metabolic reactions, and broken arrows = primary and secondary effects of isoproterenol. Route a = primary effect on the activity of myocardial adenyl cyclase. Route b = primary effect on heart function. Route c = secondary effect on the concentration of cardiac adenine nucleotides, which results in changes in the activity of PRPP amidotransferase (route d). The inhibitory actions of propranolol and compound D600 on the primary effects of isoproterenol are symbolized at the top of the figure. For further details see text. G-1-P = glucose-1-phosphate, G-6-P = glucose-6-phosphate, R-5-P = ribose-5-phosphate, PRPP = 5-phosphoribosyl-1-pyrophosphate, GLU = glutamine, PRA = 5-phosphoribosylamine, GLY = glycine, GAR = glycineamide ribonucleotide, and ASP = aspartate.

carbohydrate metabolism (Fig. 3, routes a and b). In contrast, the studies with compound D600 and isoproterenol make it possible to indirectly distinguish between the two kinds of regulation of de novo synthesis. Compound D600 inhibits predominantly the calcium-dependent positive inotropic effect of isoproterenol (Fig. 3, route b) and thus abolishes the reduction in adenine nucleotide concentration by preventing an additional utilization of ATP (Table 4). Therefore, it probably attenuates the isoproterenol-mediated acceleration of de novo synthesis that is dependent on feedback regulation (Fig. 3, route d). Thus, the attenuated elevation of de novo synthesis under the influence of D600 and isoproterenol (Table 4) may reflect the pure action of isoproterenol on carbohydrate metabolism (Fig. 3, route a), which is supposed to finally result in a greater availability of PRPP. It appears that the effects of isoproterenol on cardiac performance and carbohydrate metabolism can actually be dissociated by use of compound D600, which inhibits transmembrane calcium movements (22). Similar to our experimental approach with compound D600, lanthanum has recently been shown to be a suitable tool for dissociating the inotropic and glycogenolytic responses (activation of myocardial phosphorylase) to isoproterenol (39).

All our findings favor the concept that the greater availability of PRPP can be regarded as an important factor in the isoproterenol-induced acceleration of de novo synthesis of myocardial adenine nucleotides. It is of particular interest that in normal hearts, too, de novo synthesis seems to be greatly dependent on the available pool of PRPP. As is evident from our observations, propranolol does not cause changes in the concentration of adenine nucleotides but does suppress de novo synthesis of adenine nucleotides considerably, whereas compound D600, which induces a slight elevation in ATP and adenine nucleotide concentrations, does not appreciably affect de novo synthesis. Hence, propranolol influences de novo synthesis not through an adenine nucleotide concentration-dependent feedback inhibition of PRPP amidotransferase but rather through an inhibition of the effects of endogenous catecholamines on carbohydrate metabolism at the β-receptor. Provided this interpretation is valid, it seems reasona-
ble to assume that endogenous catecholamines can play an important role in the regulation of the biosynthesis and in the maintenance of the levels of cardiac adenine nucleotides.

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