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Regulation of and intervention into the oxidative pentose phosphate pathway and adenine nucleotide metabolism in the heart

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Abstract

The capacity of the oxidative pentose phosphate pathway (PPP) in the heart is limited, since the activity of glucose-6-phosphate dehydrogenase (G-6-PD), the first and regulating enzyme of this pathway, is very low. Two mechanisms are involved in the regulation of this pathway. Under normal conditions, G-6-PD is inhibited by NADPH. This can be overcome in the isolated perfused rat heart by increasing the oxidized glutathione and by elevating the $NADP^+$/NADPH ratio. Besides this rapid control mechanism, there is a long-term regulation which involves the synthesis of G-6-PD. The activity of G-6-PD was elevated in the rat heart during the development of cardiac hypertrophy due to constriction of the abdominal aorta and in the non-ischemic part of the rat heart subsequent to myocardial infarction. The catecholamines isoproterenol and norepinephrine stimulated the activity of myocardial G-6-PD in a time- and dose-dependent manner. The isoproterenol-induced stimulation was cAMP-dependent and due to increased new synthesis of enzyme protein. The G-6-PD mRNA was elevated by norepinephrine. As a consequence of the stimulation of the oxidative PPP, the available pool of 5-phosphoribosyl-l-pyrophosphate (PRPP) was expanded. PRPP is an important precursor substrate for purine and pyrimidine nucleotide synthesis. The limiting step in the oxidative PPP, the G-6-PD reaction, can be bypassed with ribose. This leads to an elevation of the cardiac PRPP pool. The decline in ATP that is induced in many pathophysiological conditions was attenuated or even entirely prevented by i.v. infusion of ribose. In two *in vivo* rat models, the overloaded and catecholamine-stimulated heart and the infarcted heart, the normalization of the cardiac adenine nucleotide pool by ribose was accompanied by an improvement of global heart function. Combination of ribose with adenine or inosine in isoproterenol-treated rats was more effective to restore completely the cardiac ATP level within a short period of time than either intervention alone. (Mol Cell Biochem **160/161**: 101–109, 1996)

Key words: adenine nucleotide synthesis, catecholamines, cardiac hypertrophy, ischemic heart disease, 5-phosphoribosyl-1-pyrophosphate, ribose

Introduction

It is typical for the heart that it restores its adenine nucleotide pool only very slowly once it has been depleted by a brief period of ischemia. Upon reperfusion it takes several days both in the dog and rat heart until normal ATP levels are regained [1, 2]. This phenomenon is related to the fact that the degradation products of ATP such as adenosine, inosine, and hypoxanthine that are produced during ischemia can permeate the cell membrane. They are washed out and lost from the heart [3, 4] and thus are not available for reutilization via the 'salvage pathways'. The repletion of the ATP pool can therefore be attained only via the de novo synthesis (biosynthesis) of adenine nucleotides (Fig. 1). This process, however, is very slow [5], since the available pool of 5-phosphoribosyl-pyrophosphate (PRPP), an important precursor substrate for the synthesis of purine and pyrimidine nucleotides, is limited in the heart [6]. PRPP originates from ribose-5-phosphate (Fig. 2) which is generated in the oxidative pentose phosphate pathway (PPP).

The oxidative PPP [7] is the link between carbohydrate and fatty acid as well as purine and pyrimidine nucleotide metabolism (Fig. 2). Glucose-6-phosphate (G-6-P) originating from glycogenolysis or from glucose taken up by the myo-

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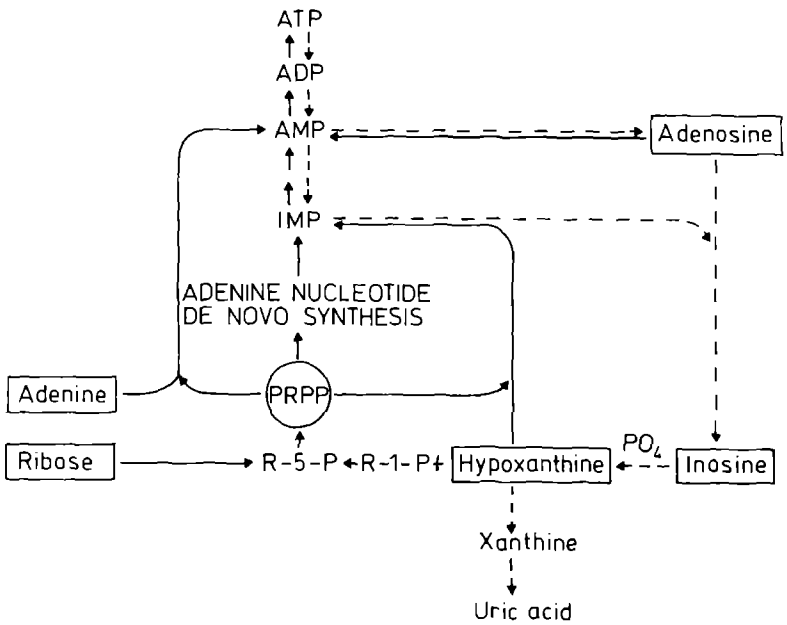

Fig. 1. Schematic representation of the central role of 5-phosphoribosyl-1-pyrophosphate (PRPP) for purine nucleotide metabolism. PRPP is the starting point for adenine nucleotide *de novo* synthesis and can be used up by adenine and hypoxanthine for AMP and IMP formation, respectively. The degradation pathways are indicated by the broken arrows. The routes of synthesis are symbolized by the continuous arrows. The precursor substances that can be used in the various synthetic processes are in boxes. IMP: Inosine monophosphate; AMP: Adenosine monophosphate; ADP: Adenosine diphosphate; ATP: Adenosine triphosphate.

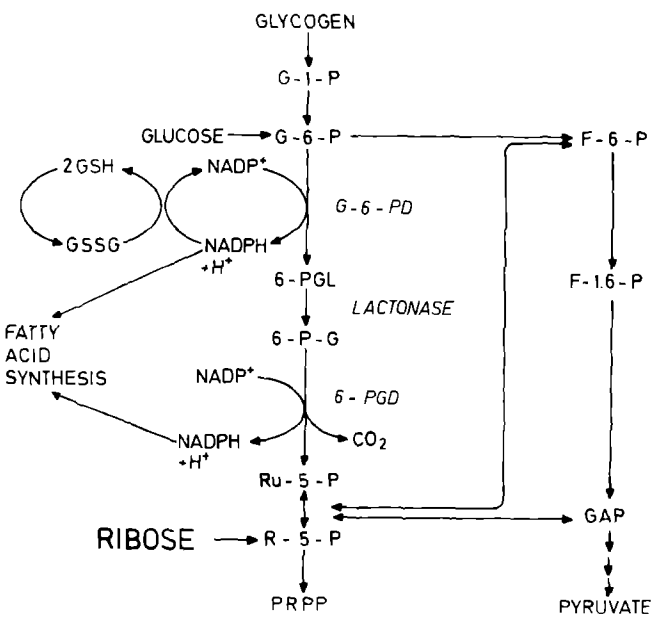

Fig. 2. The oxidative pentose phosphate pathway (center), and its connections to glycolysis (right hand side) via the transaldolase and transketolase reactions. G-1-P: Glucose-1-phospate; G-6-P: Glucose-6-phosphate; F-6-P: Fructose-6-phosphate; F-1,6-P: Fructose-1,6-biphosphate; GAP: Glyceraldehyde-3-phosphate; 6-PGL: 6-Phosphogluconolactone; 6-PG: 6-Phosphogluconate; Ru-5-P: Ribulose-5-phosphate; R-5-P: Ribose-5-phosphate; PRPP: 5-Phosphoribosyl-1-pyrophosphate; $NADP^+$: Nicotinamide Adenine Dinucleotide Phosphate; GSH: Reduced glutathione; GSSG: Oxidized glutathione; G-6-PD: Glucose-6-phosphate dehydrogenase; 6-PGD: 6-Phosphogluconate dehydrogease.

cardial cell is metabolized predominantly via glycolysis. A small portion of G-6-P, however, enters the oxidative PPP of which G-6-PD is the first and rate-limiting enzyme. This pathway serves mainly two functions: (1) It provides reducing equivalents in the form of NADPH [7] which can be used for the synthesis of free fatty acids and for the conversion of oxidized (GSSG) to reduced glutathione (GSH). This is important for the detoxification of reactive oxygen species. (2) Ribose-5-phosphate is generated which is transformed to 5-phosphoribosyl-1-pyrophosphate (PRPP), and this is an essential precursor substance for the de novo synthesis of purine nucleotides, for the utilization of orotic acid for UTP synthesis as well as for the salvage of the purine bases adenine and hypoxanthine to form AMP and IMP, respectively (Fig. 1).

In comparative studies the capacity of the oxidative PPP has been assessed in several rat organs. To do this, the activity of G-6-PD [8, 9], the available pool of PRPP [10], and the rate of purine nucleotide biosynthesis [5] were measured. There was a parallel behaviour of these three parameters in the organs examined. They were all highest in kidney, followed by liver, heart and skeletal muscle [6]. Thus, the capacity of the oxidative PPP is very low in muscular organs. In the heart, this becomes of critical importance when there is a need for restoration of the ATP pool as during the reperfusion following severe ischemia. In this situation, the PRPP pool is limiting for the biosynthesis of adenine nucleotides as well as for the conversion of adenine to AMP and of hypoxanthine to IMP.

The low capacity of the oxidative PPP is not confined to the rat heart. Comparative studies on a variety of animal species including man have shown that the activity of G-6-PD is always lower than the activity of 6-PGD, another enzyme in the pathway, and that G-6-PD activity in the human heart is on the same order of magnitude as in the rat heart on which most of the studies were done [1 l]. Thus, the cardiac PPP is poorly developed in all animal species.

There are two possibilities to elevate the available pool of PRPP in the heart: (1) Stimulation of the activity of cardiac G-6-PD, the first and regulating enzyme of the oxidative PPP. (2) Bypass of this rate-limiting step with ribose. Both approaches have been utilized in experimental studies. As to the regulation directed at the G-6-PD, there is a short-term and long-term control.

Short-term control of the oxidative pentose phosphate pathway

Studies on rat liver have shown that G-6-PD is always inhibited by NADPH [7, 12]. This inhibition was competitive with $NADP^+$. Since the enzyme was almost completely inhibited at physiological concentrations of free $NADP^+$ and free NADPH, it followed that the regulation of G-6-PD is a matter of de-inhibition. It turned out that among over hundred cell constituents tested, only two of these counteracted the inhibition by NADPH. These were AMP and GSSG. Only GSSG was highly effective at concentrations that may occur physiologically [7].

On the basis of these results, studies were carried out on the isolated perfused Langendorff rat heart. A 40-fold elevation of the GSSG concentration was induced by perfusion with an oxidizing agent, tert-butyl hydroperoxide. In addition, the $NADP^+$/NADPH ratio was increased 2-fold under these conditions. So if GSSG is able to overcome the inhibition of G-6-PD exerted by NADPH, then the flow through the oxidative PPP should be stimulated. This should result in an elevation of the available pool of PRPP. In fact, the incorporation of ^{14}C-adenine into myocardial adenine nucleotides which was used as a relative measure of the PRPP pool was increased 3-fold within the first 15 min after tert-butyl hydroperoxide administration [13].

Since both an increased GSSG and $NADP^+$ concentration can overcome the NADPH-mediated inhibition of G-6-PD, it was difficult to decide which of these two factors may be more relevant. Since GSSG was elevated to a greater extent than the $NADP^+$/NADPH ratio and since the latter may still be inhibitory, it was concluded that GSSG is more important for the regulation of G-6-PD [13]. This appears to be a rapid control mechanism that becomes effective within minutes. Such a mechanism may be activated when oxygen free radicals are produced in the myocardium. In the neutrophils, the activation of the oxidative PPP has been shown to be associated with the respiratory burst and with the process of phagocytosis [14].

Long-term effects on the oxidative pentose phosphate pathway

Apart from the 'fine' control mechanism exerted by NADPH that is involved in the short-term regulation of G-6-PD, there is a long-term mechanism operating in the heart. This is also directed at G-6-PD. It involves the increase in enzyme protein synthesis and has been shown to be activated in the rat heart during the development of cardiac hypertrophy and by catecholamines which stimulate α- and β-adrenergic receptors.

Cardiac hypertrophy

Figure 3 shows the changes in the activity of G-6-P D, in the rate of adenine nucleotide *de novo* synthesis, and in protein synthesis in the rat heart subsequent to constriction of the abdominal aorta. This time-course study revealed that the first increase in cardiac G-6-PD activity occurred after 48 h and reached its maximum after 3 and 4 days. The synthesis of both cardiac adenine nucleotide and protein synthesis decreased within the first few hours after aortic banding and then started to increase. Thus, the stimulation of the oxidative pentose phosphate pathway correlated very well with the elevation of adenine nucleotide and protein synthesis [15].

A similar picture evolved in another model of compensatory cardiac hypertrophy. After ligation of the descending branch of the left coronary artery in rats, the non-ischemic part of the heart develops hypertrophy. Enzymehistochemical studies have revealed that G-6-PD activity started to increase in the non-ischemic area of the infarcted heart after 10 h, and this increase was maintained until the fifth day following coronary artery ligation [16]. Interestingly, the rates of adenine nucleotide and protein synthesis were also found to be elevated in the non-infarcted rat heart after 48 h [17].

Catecholamines

Pure stimulation of cardiac β-adrenergic receptors with isoproterenol also resulted in the development of cardiac hypertrophy. This was characterized by an elevation of G-6-PD activity, adenine nucleotide and protein synthesis (Fig. 4). However, the sequential increase was different. Cardiac adenine nucleotide *de novo* synthesis was maximally stimulated already after 5 h, at a time when there was no change in G-6-PD activity. Protein synthesis reached its peak after 12 h, at a time when G-6-PD activity had just started to be elevated.

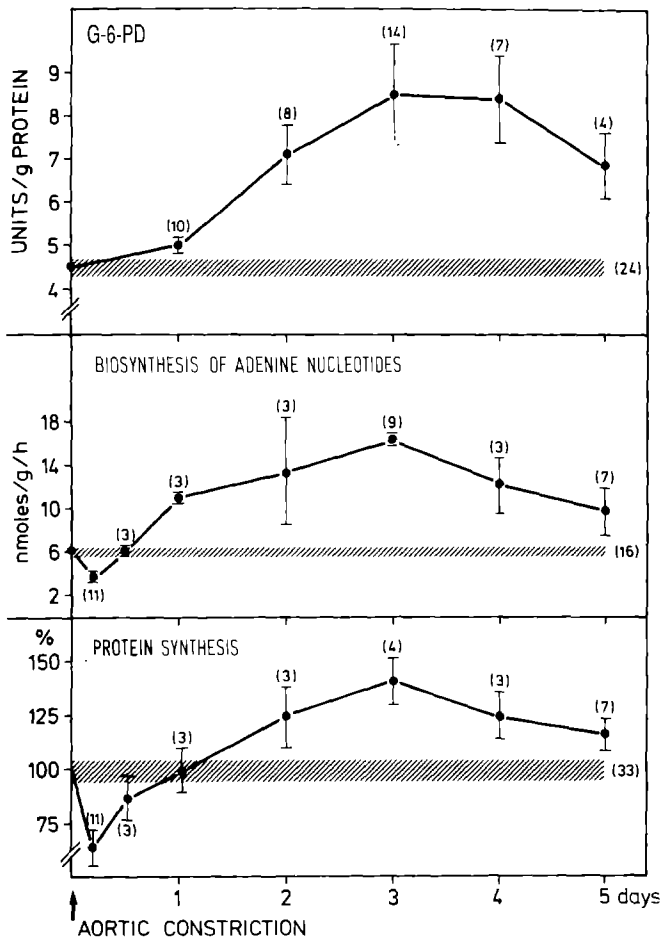

Fig. 3. Changes in the activity of glucose-6-phosphate dehydrogenase (G-6-PD), in the rate of adenine nucleotide *de novo* synthesis, and in protein synthesis in rat hearts subsequent to constriction of the abdominal aorta. This was induced by placing a metal rod of 0.65 mm diameter alongside the abdominal aorta beneath the diaphragm. A thread was placed around the aorta and the metal rod and tightly fixed with a nod. The metal rod was then pulled out leaving the aorta constricted to a diameter corresponding to the diameter of the rod. Mean values ± S.E.M.; number of experiments in parentheses.

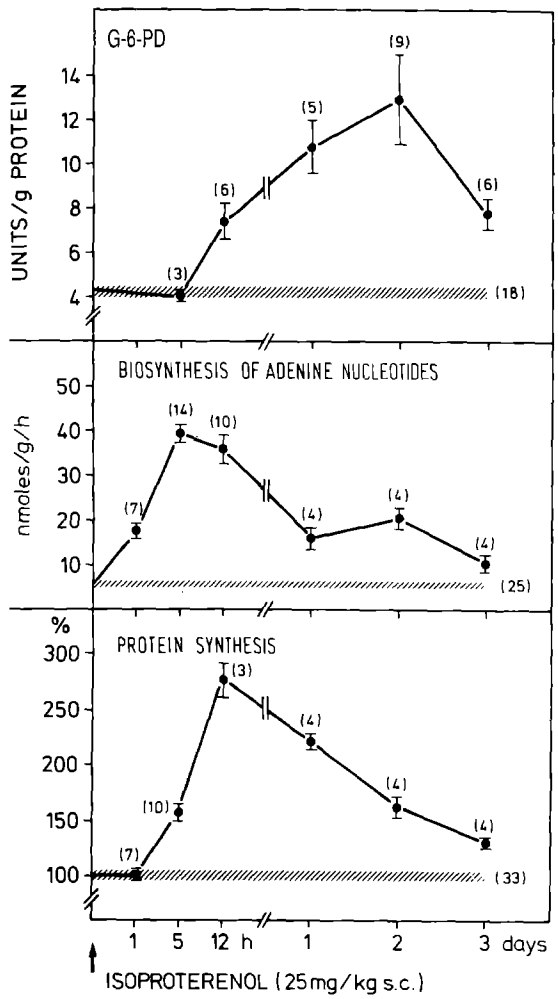

Fig. 4. Effect of isoproterenol (25 mg/kg, s.c.) on the activity of glucose-6-phosphate dehydrogenase (G-6-PD), adenine nucleotide and protein synthesis in rat hearts. Mean values ± S.E.M.; number of experiments in parentheses.

It thus appears that there are two phases that can be distinguished subsequent to isoproterenol application: The first phase was characterized by an immediate increase in the cAMP and G-6-P contents. Parallel to these metabolic changes, heart rate and contractility were also elevated [6]. After 12 and 24 h, these parameters had returned to the respective control levels. However, myocardial adenine nucleotide biosynthesis which was also enhanced very early remained elevated, though at a somewhat lower level (Fig. 4). In the second phase which started at about 12 h subsequent to isoproterenol injection, protein synthesis began to increase and when this had achieved the maximum, G-6-PD activity became stimulated.

From this time course it was inferred (1) that cAMP may be the trigger for the stimulation of cardiac G-6-PD activity and (2) that G-6-PD activation is dependent on protein synthesis and thus may reflect an increased enzyme protein synthesis. Studies were therefore performed to eliminate the isoproterenol-induced increase in the cAMP signal and to prevent the increase in protein synthesis. It was then examined which effect these interventions have on cardiac G-6-PD activity. In fact, β-receptor blockade with atenolol completely prevented the stimulation of enzyme activity [6]. Likewise, cycloheximide which inhibits translation, and actinomycin D which interferes with transcription blunted the stimulating isoproterenol effect on G-6-PD activity [6]. These results strongly indicated that cardiac β-adrenergic receptors and enzyme protein synthesis are involved in the isoproterenol-mediated increase in G-6-PD activity.

In this context, recent molecular biological studies are of interest. Continuous i.v. infusion of norepinephrine for three days which induced cardiac hypertrophy [18] increased both the mRNA level and the activity of cardiac G-6-PD in a time-

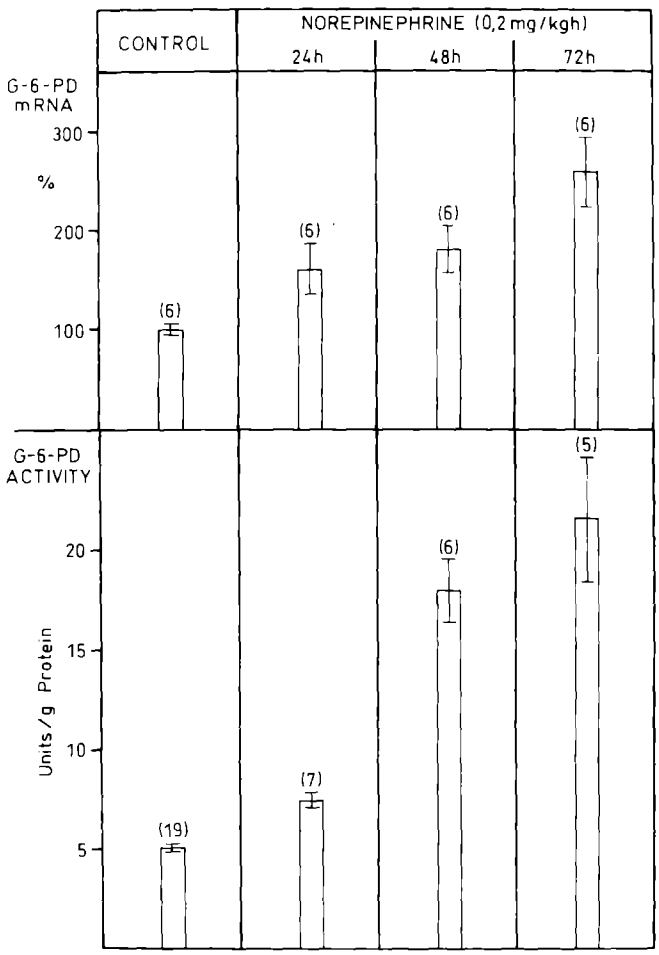

Fig. 5. Changes in the mRNA and activity of myocardial glucose-6-phosphate dehydrogenase (G-6-PD) within the first three days during continuous i.v. infusion of norepinephrine (0.2 mg/kg/h). Data are mean values ± S.E.M.; number of experiments in parentheses.

dependent fashion (Fig. 5). This increase was antagonized by simultaneous administration of carvedilol, a β-adrenergic blocker and vasodilator with α_1-blocking activity [19]. The mRNA and activity of 6-phosphogluconate dehydrogenase (6-PGD), one of the following enzymes of the oxidative PPP, was only slightly and unspecifically enhanced. It thus appears that both α- and β-adrenergic agonists promote specifically gene expression of cardiac G-6-PD.

Since the effects of α- and β-adrenergic stimulation on the oxidative PPP are similar, it is interesting to explore the mechanisms whereby different second messengers trigger the same metabolic process. In regard to isoproterenol it is known that cAMP is the second messenger for a number of metabolic and mechanical processes such as stimulation of glycogenolysis, lipolysis, and the inotropic effect. β-Adrenergic blockade prevented the isoproterenol- [6] and attenuated the norepinephrine-induced increase in cardiac G-6-PD activity [19]. It has been speculated that cAMP may induce transcription of the respective genes by activating a cAMP-dependent protein kinase and by phosphorylation of protein factor(s) that may act as transcriptional activators of a cAMP-sensitive promoter [20, 21]. It is not quite clear how the second messengers of α-adrenergic stimulation, i.e. inositol-1,4,5-trisphosphate (IP_3) and diacylglycerol [22] are related to the stimulation of the oxidative PPP. However, it is known that diacylglycerol activates protein kinase C which in turn phosphorylates a range of cellular proteins [23]. Moreover, protein kinase C may be involved in the increase of c-*myc* mRNA levels as well as of c-*fos*, c-*jun*, and egr-1 mRNAs [24] that has been shown to occur as a result of α_1-adrenergic stimulation in neonatal rat cardiac myocytes in culture. Also in the isolated perfused working rat heart it has been demonstrated recently that norepinephrine increased the mRNA of c-*fos* and c-*myc* [25]. These members of the immediate early gene program, alone or together with other transcription factors, may potentially regulate gene expression such as that of G-6-PD.

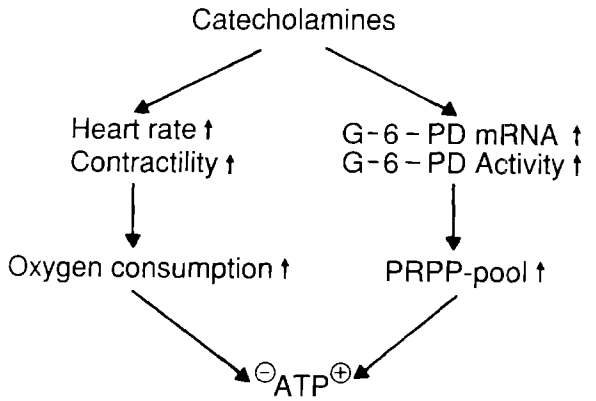

Fig. 6. Proposed homeostatic mechanism regarding the cardiac effects of catecholamines.

The stimulation of the oxidative PPP by catecholamines may represent part of a long-term homeostatic mechanism (Fig. 6). This concept is based on the fact that catecholamines increase heart rate, contractility, and oxygen consumption of the heart. Thus, there is a tendency for the decline in the ATP level in the catecholamine-stimulated heart. In the long run, this can be counteracted by the α- and β-receptor-mediated increase in the capacity of the oxidative PPP which leads to the elevation of the available PRPP pool. This can then be used up for the *de novo* synthesis and for the salvage pathways that are involved in ATP resynthesis (Fig. 1).

Thyroid hormones

Triiodothyronine (T_3) also induces cardiac hypertrophy [15]. However, the effect on the oxidative PPP is quite different depending on the rat model. Fig. 7 shows that daily injections of T_3 for 5 days have no effect whatsoever on the activity of

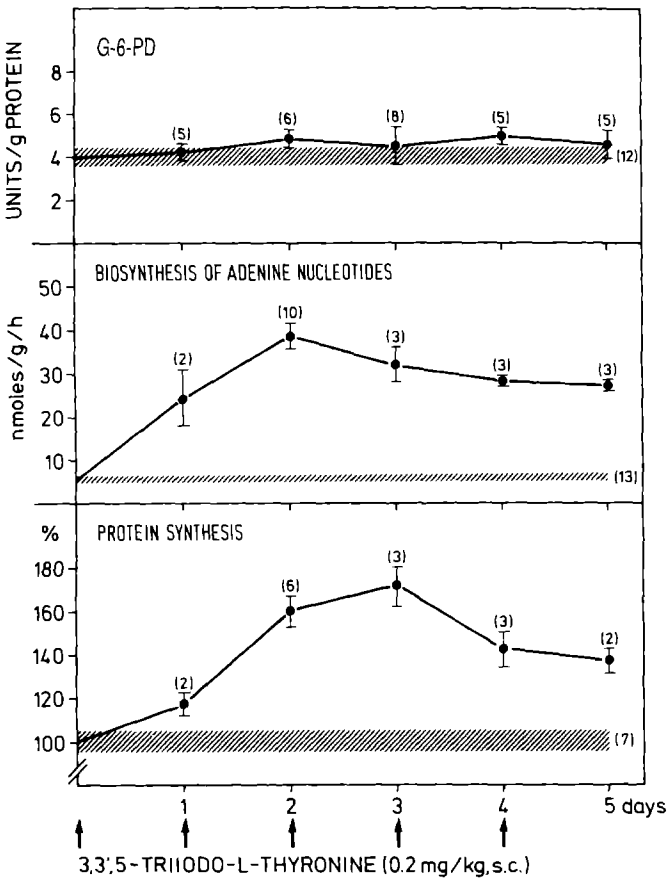

Fig. 7. Effect of daily s.c. injection of 3,3',5-triiodo-L-thyronine (T_3) on the activity of glucose-6-phosphate dehydrogenase (G-6-PD), and on adenine nucleotide and protein synthesis in rat hearts. Data are mean values ± S.E.M.; number of experiments in parentheses.

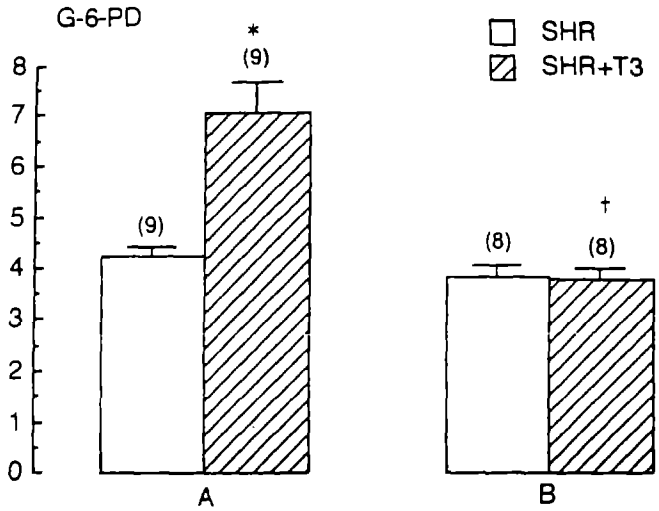

Fig. 8. Activity of cardiac glucose-6-phosphate dehydrogenase (G-6PD) in spontaneously hypertensive rats (SHR) with daily injections of 0.9% NaCl (blank bars) and with injections of triiodothyronine (T_3) at the end of the treatment period (hatched bars) of 14 days' duration (A) and at the end of 14 days after discontinuation of treatment (B). Mean values ± S.E.M.; number of experiments in parentheses. * $p < 0.05$ vs. control; $^+ p < 0.01$ vs. T_3 in A.

cardiac G-6-PD, although there is a substantial stimulation of both adenine nucleotide and protein synthesis. In spontaneously hypertensive rats, however, daily applications of T_3 for 14 days do increase cardiac G-6-PD activity. When T_3-treatment is discontinued for 14 days, cardiac G-6-PD activity is normal again (Fig. 8).

From the results obtained in the studies with catecholamines and T_3 one can deduce a particular time course of metabolic events that is of general interest. After administration of both catecholamines and T_3, there is an immediate stimulation of glycogenolysis and glycolysis [26] and a positive chronotropic and inotropic effect as well as a concomitant elevation in the PRPP pool, in adenine nucleotide and protein synthesis. During this immediate phase, there was no change in G-6-PD activity [6]. It was only in the subsequent second phase that cardiac G-6-PD activity was enhanced. Since G-6-PD activity was unchanged during the first phase, a mechanism other than an enhanced flow through the oxidative PPP may be responsible for the elevation of the PRPP pool and for the stimulation of adenine nucleotide biosynthesis. The alternative is that the PRPP may be elevated via the non-oxidative PPP through the transaldolase and transketolase reactions. This is a very likely mechanism, since the activities of the enzymes of the non-oxidative PPP were shown to be much higher than those of G-6-PD and 6-PGD in muscle [27]. Furthermore, the large amounts of NAD^+ present in the heart [28] may favor glycolysis, whereas the small quantity of $NADP^+$ may be limiting rather than stimulating the oxidative PPP.

Ribose

Apart from affecting the activity or the mRNA of cardiac G-6-PD, there is another intervention into the oxidative PPP that ultimately results in an elevation of the myocardial PRPP pool and consequently of adenine nucleotide *de novo* synthesis. This is the administration of ribose. Ribose bypasses the critical and rate-limiting step in the oxidative PPP, the G-6-PD reaction (Fig. 2), and leads via ribose-5-phosphate to the formation of PRPP and to the enhancement of adenine nucleotide biosynthesis [10].

This metabolic approach has been utilized in many experimental models, e.g. in isolated cardiac myocytes [29], after isoproterenol stimulation of the intact rat heart [10, 30], during development of cardiac hypertrophy [31], during recovery from temporary oxygen deficiency in the isolated rat [32, 33] and guinea pig heart [34], in the *in vivo* rat [2] and dog heart [35–38], after permanent coronary artery ligation [39], in chronic alcoholic cardiomyopathy as assessed in the isolated working rat heart [40], and in primary rat muscle cultures [41].

In all these studies, ribose proved to be an intervention that either attenuated or prevented entirely the decline of the myocardial ATP pool. For instance, after 15 min of reversible regional ischemia the ATP fell by about 40%. During the reperfusion period, the ATP pool recovered to some extent, most probably due to the rephosphorylation of ADP and AMP. However, even after three days ATP was still lower than the respective control value of sham-operated rats [2]. This corresponded well with the results obtained in dogs [1]. However, when ribose had been administered as continuous i.v. infusion, ATP had been normalized already after 12 h. So the metabolic recovery period was speeded up by at least 60 h [2].

In two pathophysiological situations in the intact rat there was a good correlation between the restoration of the cardiac ATP pool achieved by ribose and heart function. To evaluate heart function *in vivo*, a sensitive method that is applicable in small laboratory animals was developed. Ultraminiature catheter pressure transducers (Millar Instruments, Inc., Houston, Texas) were inserted into the left ventricle via the right carotid artery to measure heart rate, left ventricular pressure, and contractility as the maximal rate of rise in pressure, LV dp/dt_{max} [42]. Using this method it was examined whether a depressed heart function may be improved by normalizing the cardiac ATP pool with ribose.

In the first model, depression of all hemodynamic parameters was induced in rats by severe constriction of the abdominal aorta in combination with a single s.c. dose of isoproterenol. 24 h after this combined intervention, both the ATP level and heart function had deteriorated in animals that had received continuous i.v. infusion of 0.9% NaCl. When ribose had been administered for 24 h, the biosynthesis of cardiac adenine nucleotides was stimulated to such an extent that the depression of ATP and of the total adenine nucleotide pool was prevented. This metabolic normalization was accompanied by an elevation of the depressed left ventricular pressure and LV dp/dt_{max}. The pressure-rate-product had also returned to a near normal value [43]. Thus, ribose was able to normalize an impaired global heart function concomitantly with the restoration of the cardiac adenine nucleotide pool.

A marked impairment of heart function was also obtained by experimental myocardial infarction which was induced by ligation of the descending branch of the left coronary artery in rats. There was a progressive decline in left ventricular systolic pressure, in LV dp/dt_{max}, and in the pressure-rate-product [39]. Left ventricular enddiastolic pressure was elevated markedly. Cardiac output and stroke volume were depressed. The ATP content in the nonischemic region was lower than control after 24 h and recovered spontaneously toward the control within the following three days. Continuous i.v. infusion of ribose attenuated the fall and promoted the restoration of the ATP level in the nonischemic myocardium within 4 days after coronary artery ligation. The elevation of left ventricular enddiastolic pressure was attenuated with ribose after 2 and 4 days [39]

Combination of ribose with verapamil, metoprolol, adenine, and inosine

Ribose has the advantage that it has purely metabolic effects and is entirely neutral in functional terms as far as the heart and circulatory system is concerned [36, 44]. This is in contrast to the purine nucleosides adenosine [45] and inosine [46]. Another characteristic feature of ribose is that is can be combined with drugs that are used in conventional therapy of heart diseases. Ribose did not alter the hemodynamic effects of the calcium antagonist verapamil and of the β-adrenergic receptor blocker metoprolol in the intact rat. The negative chronotropic and inotropic effects of metoprolol and verapamil were not affected by ribose. Neither the verapamil-induced decrease in total peripheral resistance nor the metoprolol-induced reduction of cardiac output were influenced by ribose. On the other hand, ribose retained its typical metabolic effect, i.e. the stimulation of cardiac adenine nucleotide biosynthesis, despite the pronounced hemodynamic changes brought about by these drugs [44]. Thus ribose appears to be a suitable and appropriate adjunct in the medical therapy of certain heart diseases.

In another study, the cardiac ATP pool in intact rats was reduced by isoproterenol. Continuous i.v. infusion of ribose for 5 h did not affect the isoproterenol-induced ATP decline. Likewise, adenine administration for the same period of time had no effect, while inosine attenuated the ATP fall to some extent. Thus, the exposure time was too short to affect substantially the cardiac ATP pool. However, when ribose was given in combination with adenine (Fig. 9) or inosine (Fig. 10) for the same period of time, 5 h, the cardiac ATP level was entirely normal. These results indicate that neither the biosynthesis of adenine nucleotides (ribose application) nor the salvage pathways (adenine, inosine administration) by themselves are capable to replenish the cardiac ATP within 5 h. Only when the available PRPP pool is elevated by ribose (Fig. 1) can the ATP be normalized within this period of time [47]. This is an important aspect, when one considers ribose for clinical application.

The combination of ribose with adenine also proved to be beneficial in liver and kidney. Assessment of ATP by means of nuclear magnetic resonance spectroscopy in a mouse liver perfusion model detected a faster and more complete recovery within the first minutes of reperfusion after a period of exhaustive ischemia [48]. ATP levels and total adenine nucleotide contents were also higher in slices of dog kidneys that were obtained after 5 days of hypothermic preservation with adenine in combination with ribose compared to control values and with values obtained after adenosine treatment [49].

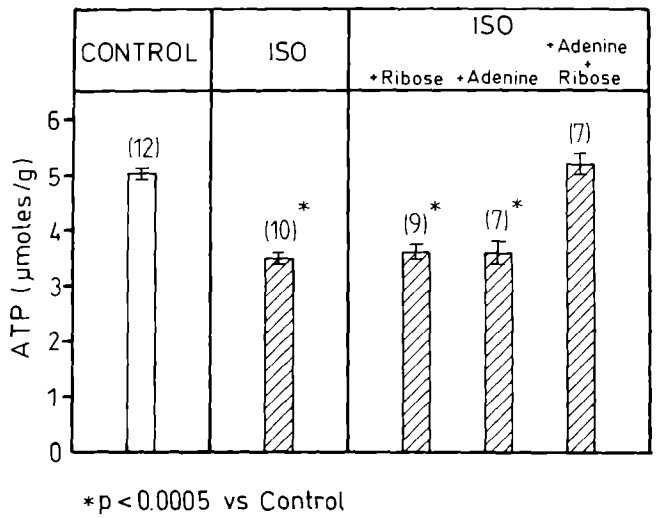

Fig. 9. Myocardial ATP values in rat hearts under control conditions, 5 h after s.c. application of isoproterenol (ISO, 25 mg/kg) alone or together with continuous i.v. infusion of ribose (200 mg/kg/h), or adenine (50 mg/kg/h) alone and in combination. Mean values ± S.E.M.; number of experiments in parentheses.

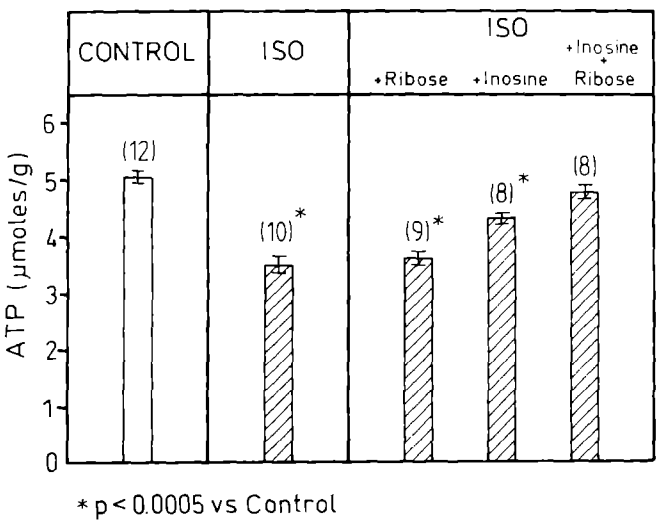

Fig. 10. Myocardial ATP values in rat hearts under control conditions, 5 h after s.c. application of isoproterenol (ISO, 25 mg/kg) alone or together with continuous i.v. infusion of ribose (200 mg/kg/h), or inosine (200 mg/kg/h) alone or in combination. Mean values ± S.E.M.; number of experiments in parentheses.

Conclusion

It is a characteristic feature of cardiac carbohydrate metabolism that the capacity of the oxidative PPP is very limited. This metabolic deficiency has two consequences. (1) The heart cannot replenish immediately and completely its ATP pool once it has been depleted. This creates many problems in the setting of myocardial ischemia and reperfusion. (2) The heart has no efficient system to detoxify oxygen free radicals. There are several possibilities for intervention into the oxidative PPP in the heart. (1) Immediated 'fine' control of G-6-PD activity by GSSG and the $NADP^+$/NADPH ratio, (2) long-term increase in G-6-PD synthesis by catecholamines, (3) administration of ribose to bypass the reaction catalyzed by G-6-PD. From these possibilities the last two are of physiological and therapeutic interest.

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