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Editorial: Metabolic Supplementation with Orotic Acid and Magnesium Orotate

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Summary. **Orotic acid (OA), a naturally occurring substance, is a key intermediate in the biosynthetic pathway of pyrimidines. Previous investigations in the heart suggest that orotate can protect recently infarcted hearts against a further ischemic stress and may be beneficial in certain types of experimental cardiomyopathy. At the Hamburg symposium on magnesium orotate, a number of studies of this form of metabolic supplementation were presented that indicate orotic acid and its magnesium salt have a modest beneficial effect on the myocardium under conditions of stress ranging from myocardial infarction to severe physical exercise. The following conclusions can be drawn: (1) Orotic acid can improve the energy status of the recently infarcted myocardium (rat hearts). (2) Orotic acid may improve myocardial purine and pyrimidine levels by stimulating hepatic release of uridine into the bloodstream, which in turn augments depleted myocardial pyrimidines and purines (rat heart). (3) Orotic acid improves the tolerance of the recently infarcted heart to global ischemia (rats). (4) Magnesium orotate may reduce the severity of chronic myocardial dysfunction and structural damage in cardiomyopathy (cardiomyopathic hamsters). (5) Magnesium orotate may improve exercise tolerance in patients with coronary artery disease and in trained athletes (humans). (6) Magnesium orotate has only a weak inotropic effect, if any, on normal hearts (rats). (7) Further clinical testing is indicated to determine if the effects described could be of significant clinical benefit in the treatment of heart disease.**

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This supplement to *Cardiovascular Drugs and Therapy* reports the proceedings of an international symposium on orotic acid and magnesium orotate held in Hamburg, Germany in June 1995. This was the third such symposium sponsored by Worwag Pharma. The first was held in Magdeburg in March 1990 and the second in Rudesheim, Germany in November 1991. The purpose of these symposia was to bring together people from around the world who were investigating the actions of orotic acid and magnesium orotate in the areas of basic science and medical therapy.

What is orotic acid and what is its importance in medicine? Orotic acid (OA) is a naturally occurring substance, found in high concentration in cow's milk. OA is a key intermediate in the biosynthetic pathway of pyrimidines (Figure 1). Pyrimidine nucleotides are important constituents of RNA and of the phospholipids in cell membranes. Uridine is also essential for the synthesis of glycogen. In times of high metabolic demand, orotic acid can enter the de novo synthetic pathway for pyrimidines beyond the rate-limiting step and thus improve throughput. This process is particularly evident in the liver.

Orotic acid has been widely used in clinical practice for a variety of conditions, including pernicious anaemia [1], neonatal jaundice [2] and hyperuricemia [3]. No adverse effects arising from OA administration in humans have been reported, although in the rat feeding orotic acid may lead to disturbances in lipid metabolism, resulting in fatty liver [4].

Previous Research on Cardiac Actions of Orotic Acid

Felix Meerson was the first to propose that orotic acid administration might be beneficial to the heart [5]. Meerson believed that during the development of cardiac hypertrophy or heart failure there was enhanced demand for RNA and that the relevant biosynthetic pathway might be unable to provide RNA rapidly enough, and thus the rate of hypertrophy could be limited. If this were true, then supplying an excess of orotic acid could accelerate the rate of muscle hypertrophy. In swimming mice (skeletal muscle hypertrophy) [6] and in rabbits after myocardial infarction (cardiac hypertrophy) [5], Meerson demonstrated that administration of orotic acid could improve performance. Meerson then encouraged his colleagues in clinical cardiology in the USSR to study orotic acid and its calcium and potassium salts in cardiac patients. Most of the trials in patients with heart failure, chronic coronary artery disease, and acute myocardial infarction reported clinically important benefits from therapy with orotic acid or its salts, as summarized by Simon-

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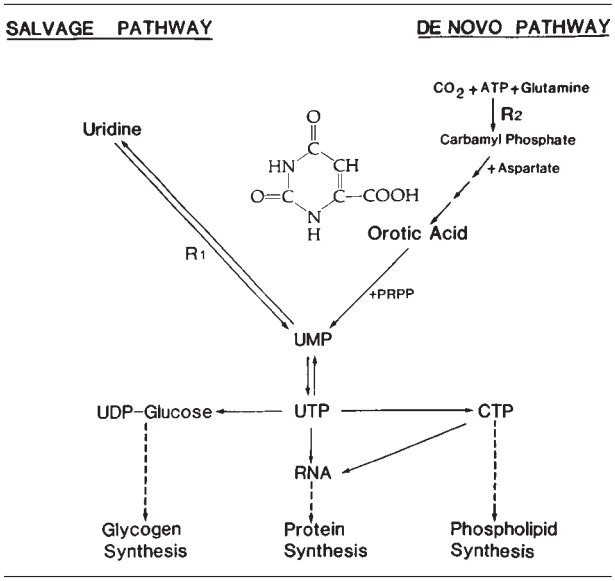

Fig. 1. *Metabolic pathways for pyrimidine nucleotide synthesis, degradation, and utilization. In the heart, the salvage pathway is more active than the de novo pathway. Uridine is probably supplied to the heart via de novo synthesis in the liver. R1 - the proposed rate-limiting enzyme of the salvage pathway (uridine kinase); R2 - the proposed rate-limiting enzyme of the de novo pathway (carbamyl phosphate synthetase II); UMP - uridine monophosphate; UDP - uridine diphosphate; UTP - uridine triphosphate; CTP - cytidine triphosphate; PRPP - phosphoribosylpyrophosphate; RNA - ribonucleic acid.*

son in 1973 [7]. However, the results of these trials are difficult to interpret because they were not blinded and some were not placebo controlled. It appears that the use of orotic acid in cardiology in the former Soviet Union has declined in recent years [8].

In the early 1970s, Williams and his colleagues in Canberra, Australia showed that orotic acid administration to rats with hypertrophying hearts could improve contractile function, increase myocardial glycogen levels, and augment the rate of protein synthesis (as evidenced by increased myocardial incorporation of tritiated leucine) [9–12].

In our laboratory at the Baker Institute, we studied the effect of orotic acid administration in the dog [13] and rat [14,15] in various preparations, including a model of emergency cardiac surgery soon after acute myocardial infarction. We found that orotic acid had no detectable effect on cardiac function, either when infused into isolated normal rat hearts [16] or when given for 1–4 days after myocardial infarction in dogs [17]. However, when infarcted hearts were subjected to global ischemia and reperfusion, there was profound depression of function. This depression of function could be markedly improved [13] or completely eliminated [14,15] by orotic acid therapy given for 2–4 days after infarction. Although this orotic acid effect would be expected to be enhanced by the addition of ribose, we could not demonstrate this [16].

All these experimental studies were concerned with the acute cardioprotective effect of orotic acid over 2–4 days. There is evidence in an animal model of chronic heart disease (the dystrophic Syrian hamster) that orotate can also have a prolonged beneficial effect. Orotate feeding for 60 days resulted in increased contractile activity in atrial strips from myopathic hearts [18]. Also, potassium orotate for 80 days prolonged survival and prevented heart failure in cardiomyopathic hamsters [19].

The large body of research on the effect of orotate on the heart can be summarized as follows:

1. Orotate does not improve baseline function in normal hearts or recently infarcted hearts.
2. Orotate can protect recently infarcted hearts against further ischemic stress.
3. Chronic orotate therapy is beneficial in certain types of experimental cardiomyopathy.

The presentations at the Hamburg Symposium of recent investigations on orotate have added to this knowledge. The presentations can be divided into: (1) animal studies mainly concerned with actions and mechanisms of action of orotic acid and magnesium orotate in normal animals and in animal models of cardiac disease, and (2) clinical studies in normal individuals and in patients with coronary artery disease. The main findings are summarized.

Recent Investigations of Cardiac Actions of Orotate

Animal studies

Pyrimidine metabolism (Rossi et al.). Over the past 20 years Rossi and coworkers have conducted systematic investigations that have greatly contributed to our understanding of pyrimidine metabolism. The importance of the pyrimidines, uridine and cytidine, in myocardial energy metabolism is usually overshadowed by their more well-known purine counterparts, especially adenosine. However, despite the low concentrations of pyrrimidine nucleotides in the myocardium (one quarter to one fifth of purine nucliotides), their turnover rate is four to sevenfold higher than that of the purines. Thus any alterations in the utilization, supply, or synthesis rate of pyrimidines in the heart could have profound metabolic consequences. Ischemia can reduce myocardial UTP (uridine triphosphate) and CTP (cytidine triphosphate) much more than ATP. Beta-adrenergic receptor stimulation can lower UTP and CTP pools, and hypertrophy can expand these pools.

Pyrimidines can be synthesized via de novo or salvage pathways. In the heart de novo synthesis is inefficient; hence, UTP and CTP losses from the myocardium are best replenished by salvage of cytidine

and uridine from the bloodstream following release by the liver. Administration of uridine and ribose to rats can restore depleted myocardial glycogen stores. Orotic acid has a similar effect. Administration of uridine or cytidine can increase postischemic recovery of pyrimidine nucleotides and, surprisingly, can also increase postischemic ATP levels.

The conclusion from this work is that depletion of pyrimidines may be an underappreciated feature of stress-induced changes in the myocardium. Administration of uridine, and probably orotic acid, has the potential to correct myocardial pyrimidine deficiency, to restore depleted ATP and glycogen stores, and thus to enhance the recovery of the heart. Further basic science and clinical studies in this area are indicated to improve our understanding of these processes.

Significance of PRPP for action of ribose and orotic acid (H.G. Zimmer). Phosphoribosylpyrophosphate (PRPP) is a key energy-supplying compound in the de novo and salvage synthetic pathways of both purines and pyrimidines. The supply of PRPP is limited in the heart due to the low capacity of the pentose phosphate pathway to generate ribose-5-phosphate, the immediate precursor of PRPP. The supply of ribose-5-phosphate in the myocardium can be enhanced by the supply of additional ribose. Thus an extensive series of studies in rats in Zimmer's laboratory has shown that the administration of ribose can reduce the myocardial ATP depletion induced by inotropic stimulation or infarction, with consequent improvements in functional recovery.

A recent study from the same laboratory suggested that orotic acid had a weak inotropic effect in normal rat hearts [20]. It is suggested that the combination of PRPP elevation by ribose and the provision of purine and pyrimidine precursors, including adenine, hypoxanthine, and orotic acid, could have additive if not synergistic effects. However, it should be noted that one study that did examine the effect of adding ribose (500 mg/kg) to orotic acid administration in infarcted rat hearts failed to detect any effect of ribose in augmenting the effect of OA on cardiac functional recovery [16].

Mechanisms of cardioprotective effect of orotic acid (F.L. Rosenfeldt et al.). Three studies from the Baker Institute were designed to investigate the mechanism of action of orotic acid (OA) on the heart. In the first study it was found that the administration of a single large dose of orotic acid to normal rats caused the following sequence of events: an increase in uridine and cytidine nucleotides in the liver, a rise in plasma levels of uridine and cytidine, and a delayed increase in uridine nucleotides in the heart.

The second study in infarcted and normal (sham-operated) rat hearts showed (1) infarction induces a depletion of ATP in the remote noninfarcted myocardium and (2) orotic acid administration after infarction prevents ATP depletion in the remote myocardium and improves overall contractile function. In the third study, myocardial ATP depletion was induced acutely in isolated rat hearts by hypoxic perfusion. The addition of uridine to the perfusate prevented ATP depletion and increased glycogen levels, probably by stimulating anerobic glycolysis.

These three studies strongly suggest that orotic acid acts to maintain the cardiac pool of high-energy phosphate rather than to stimulate RNA production and protein synthesis, as was previously believed. This view is in accord with the findings of Yeh in rat hearts (see later).

Effect of orotic acid and magnesium orotate in cardiomyopathic hamsters (G. Jasmin and L. Proschek). Compared with normal hamsters, cardiomyopathic hamsters die prematurely from cardiac failure. They appear to exhibit defective transmembrane ion movement in the myocardium. Necrotic and calcific lesions are seen in the myocardium and in skeletal muscle such as the tongue. Previous studies have shown that orotate can reduce cardiomegaly and prolong survival in these animals [19,21]. The current study in cardiomyopathic hamsters examined the short-term (< 30 days) and long-term (> 180 days) effect of treatment with OA or magnesium orotate (MgO) on electrocardiographic (ECG) abnormalities, histological damage, and survival. The results showed that MgO, rather than OA, reduced the severity of microscopic damage in the myocardium and skeletal muscle. MgO also reduced ECG abnormalities. Both MgO and OA tended to reduce mortality (44%) compared with untreated hamsters (62%). The findings are consistent with the hypothesis that MgO can correct abnormal calcium flux. The indication is that the effect is mainly due to magnesium rather than orotate. However, previous studies of orotate salts in cardiomyopathic hamsters suggested that the beneficial effect was due to orotate itself rather than to metallic cations such as potassium, sodium, or calcium [18,19,21].

Effect of magnesium orotate on exercise tolerance in patients with coronary artery disease (K.-R. Geiss et al.). This was a well-designed, double-blind, prospective, placebo-controlled study, but with only a small number of patients (six per group). The patients had angiographically proven coronary artery disease and documented left ventricular dysfunction. Four weeks of therapy with magnesium orotate improved exercise duration, reduced ventricular volume, and increased ejection fraction. It was not possible to determine whether the beneficial effect in these patients was caused by OA, magnesium, or both. The effect was surprisingly clearcut in such a small group of patients but is in keeping with previous (not so carefully designed) studies in the USSR in the 1970s. These results are sufficiently encouraging to justify further similar trials on a larger scale.

Effective magnesium orotate with exhaustive exercise in athletes (S.W. Golf et al.). In a double-blind, randomized trial, 23 competitive triathletes were given MgO or placebo for 4 weeks and then exercised maximally, performing swimming, cycling, and running. The MgO group had slightly faster times for all activities, but this reached statistical significance only for swimming. Improved metabolic performance in the orotate group was shown by a smaller increase in blood glucose and a higher venous pO_2. There was also a less elevated leukocyte count in the treated group, suggesting reduced stress levels. Improved performance resulted from the improved energy supply associated with orotate treatment. The authors suggest that the MgO may improve athletic performance by correcting the magnesium deficiency they have previously described in athletes [22].

Orotic acid improves ventricular function 4 days after heterotopic transplantation (T.H. Yeh et al.). This study, previously published [23], is presented here only in abstract form. This is an important study because it indicates for the first time that OA given after ischemia, rather than before, can improve postischemic recovery of myocardial contractile function over a period of several days. This suggests that OA therapy could have a place in improving the recovery of the stunned myocardium, for example, following cardiac surgery or medical thrombolysis. This study also tested the hypothesis that the mechanism of OA-induced improvement in systolic function might be preservation or augmentation of beta-myosin heavy chain expression. This was not found to be altered by the action of OA. Thus, no evidence of a stimulatory action of OA on protein synthesis was found. However, evidence of enhanced contractility in the absence of any demonstrable effect on protein synthesis would be consistent with an alternative mechanism of action, that is, via enhanced energy production.

Summary and Conclusions

Metabolic supplementation

The studies described here center around the concept of metabolic supplementation. This is illustrated in Figure 2 and is explained as follows: for normal function of an organ or tissue, flux through metabolic pathways is regulated by feedback controls to provide sufficient but not excessive end products. Supply of additional amounts of various intermediates produces little difference in the rate of flux through the pathway.

When an acute stress, such as ischemia-reperfusion, or acute hypertrophy is applied to an organ or tissue, demands that are greater than normal are made on the metabolic pathways, feedback inhibition is removed, and flux through the pathway increases. However, there are usually rate-limiting steps that place a ceiling on increased flux. The levels of intermediates beyond these rate-limiting steps tend to fall, as does the end product, which is being utilized at a greater rate than it can be produced. However, if additional supplies of an intermediate(s) beyond the rate-limiting step are supplied, then increased throughput may occur, thus satisfying the increased demand. This effect has been demonstrated in the case of orotic acid and recent infarction.

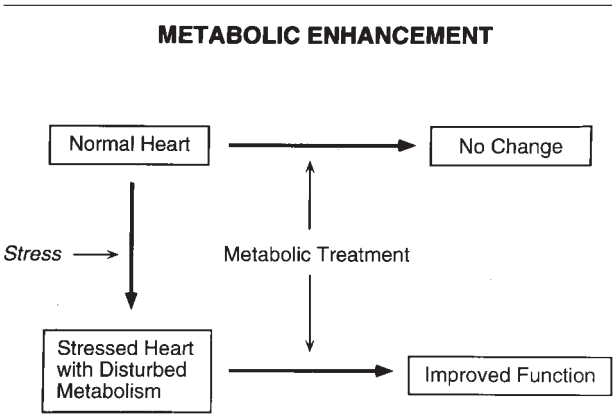

Fig. 2. *A model for the role of orotic acid and other substances in metabolic supplementation.*

A large acute infarct places an increased load on the remaining noninfarcted myocardium because a reduced mass of ventricular myocardium has to take over the full cardiac workload. This increased demand by the contractile fibers uses up ATP at a greater rate than it is supplied. This produces a fall in the myocardial level of ATP. Administration of orotic acid stimulates the release of uridine from the liver, which over time normalizes myocardial ATP levels. By contrast, in normal hearts orotic acid has no effect on contractility or ATP levels. Thus, a modest depletion of ATP levels may not be associated with a readily detectable change in baseline contractility. However, if the energy-depleted heart is subjected to a further ATP-consuming stress, such as cardioplegic arrest, there is marked depression of function. This depression of function may be prevented by systemic administration of orotic acid, beginning immediately after the infarct.

This scenario represents a classical metabolic supplementation response: a beneficial effect in stressed tissues but no effect in normal tissues (Figure 2). Other examples are the effect of the nucleotide precursors—adenine, inosine, and ribose—in normalizing ATP levels depleted by isoprenaline stimulation [24], or glucose-insulin-potassium in restoring myocardial glycogen stores depleted by valvular heart disease [25]. There may be other cardiac diseases associated with metabolic abnormalities that may respond to metabolic therapy. However, to demonstrate a clinical benefit generally requires large clinical trials. To

mount such trials with outcome measures such as non-invasive measurements of ventricular function using impedance cardiography or radionuclide angiography is a major undertaking, requiring hundreds of patients. Because metabolic supplements are not patentable medications, funding from drug companies is infrequent and few trials are performed. This is undoubtedly one reason why the benefits of metabolic supplementation remain largely unproven in the clinical arena despite encouraging results from animal experiments.

The Hamburg symposium on magnesium orotate brought together a number of studies that had a consistent message. Orotic acid and its magnesium salt have a modest beneficial effect on the myocardium under certain conditions of stress, ranging from myocardial infarction to severe physical exercise. The following conclusions could be drawn from these studies.

Conclusions

1. Orotic acid can improve the energy status of the recently infarcted myocardium (rat hearts).
2. Orotic acid may improve myocardial purine and pyrimidine levels by stimulating hepatic release of uridine into the bloodstream, which in turn can augment depleted myocardial pyrimidines and purines (rat heart).
3. Orotic acid administration improves the tolerance of the recently infarcted heart to global ischemia (rat).
4. Magnesium orotate may reduce the severity of chronic myocardial dysfunction and structural damage (cardiomyopathic hamster).
5. Magnesium orotate may improve exercise tolerance in trained athletes and in patients with coronary artery disease (humans).
6. Magnesium orotate has only a weak inotropic effect, if any, on normal hearts (rat).
7. Further clinical testing is indicated to determine if the benefits described are of clinical significance in the treatment of heart disease.

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