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The role of ribose in human skeletal muscle metabolism

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Summary Bioenergetic pathways in muscle provide high-energy compounds that are required for cellular integrity and function. Increased cellular demand for adenosine triphosphate (ATP) or limitations in the rephosphorylation rate of adenosine diphosphate (ADP) can decrease the total adenine nucleotide (TAN) pool, which may take several days to recover or may not recover at all in cases of chronic ischemia. Total adenine nucleotide levels may be significantly decreased as a result of myocardial or skeletal muscle ischemia, certain metabolic diseases, repeated intense skeletal muscle contractions or in repetitive high-intensity exercise. Ribose, a naturally occurring pentose sugar, has been shown to enhance the recovery of myocardial or skeletal muscle ATP and TAN levels following ischemia or high-intensity exercise. Furthermore, ribose has been demonstrated to modulate the production of oxygen free radicals during and following exercise. The following paper reviews skeletal muscle energetics and the potential role of ribose during and following exercise.

Background

The importance of bioenergetic pathways in contracting skeletal muscle has long been appreciated. Archibald Vivian Hill and Otto Fritz Meyerhof won the Nobel Prize in Physiology in 1922 for their works in skeletal muscle bioenergetics. A.V. Hill's studies centered on heat production in skeletal muscle and O. F. Meyerhof's interests focused on the relationship between the consumption of oxygen and the metabolism of lactic acid in skeletal muscle. Energy metabolism, centering on biochemical pathways in skeletal muscle, continues to be researched.

Intense, repetitive muscular contractions, ischemia and certain metabolic diseases create a hypoxic state in skeletal muscle. During these hypoxic conditions high-energy phosphate compounds are utilized with production rates unable to meet demand. Subsequently, reductions in these molecules can result in metabolic fatigue [1–3]. Partial recovery takes place within hours, however, complete recovery can take days [4]. In addition to lower adenosine triphosphate (ATP) levels, total adenine nucleotides (TAN) are similarly affected. The adenine nucleotide pool is essential for basic

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metabolic reactions, including protein, glycogen and nucleic acid synthesis, cyclic nucleotide metabolism, energy transfer reactions, fueling ionic pumps and providing allosteric regulation. Little is known about the resultant consequences when a significant reduction in the TAN pool occurs during and following exercise. The mechanisms involved in the recovery of energy compounds have not been defined, although many agree that an alteration in established bioenergetic pathways play an important role in ATP resynthesis.

Cellular metabolism

Cells require ATP and a balance in the adenine nucleotide pool to maintain their integrity and function. Intracellular concentrations of total adenine nucleotides become depressed during periods of hypoxic or anaerobic metabolism and must be replaced to maintain homeostasis. With the utilization and depletion of adenine nucleotide molecules, resynthesis occurs through either the salvage or de novo pathways of purine nucleotide metabolism. Glucose, through the pentose phosphate pathway (PPP), is key to this regenerative process. Glucose-6-phosphate, an intermediate in the PPP is converted through several intermediate steps to ribose-5-phosphate (R-5-P) and then to 5-phosphoribosyl-1-pyrophosphate (PRPP). Once formed, PRPP is indirectly converted to inosine monophosphate (IMP) that, in turn, is converted to adenylosuccinate by adenylosuccinate synthetase and then to adenosine monophosphate (AMP) through adenylosuccinase. AMP is then available for rephosphorylation to replenish lowered ATP pools. In addition, PRPP plays a role in the salvage pathway by combining with products of adenine nucleotide catabolism (adenine, hypoxanthine or inosine) to form AMP (see Fig. 1).

Glucose-6-phosphate dehydrogenase (G-6-PDH) and 6-phosphogluconate dehydrogenase (6-PGDH) are two enzymes in the PPP with low-level activity in heart and skeletal muscle tissues. Exogenous ribose enters the PPP and is converted to R-5-P by ribokinase, bypassing the rate-limiting steps of G-6-PDH and 6-PGDH in the formation of PRPP, thereby enhancing adenine nucleotide synthesis and salvage [5–7]. The effect of ribose in enhancing adenine nucleotide synthesis is not species specific. Glucose-6-phosphate dehydrogenase activity is on the same order of magnitude in the human heart and skeletal muscle as in other animal species. The effectiveness of exogenous ribose administration in forming PRPP, independent of G-6-PDH, is similar in such species as rats, guinea pigs, dogs, and humans [8,9].

Pharmacokinetics of ribose

An effective dose of ribose depends on factors such as intestinal absorption, renal clearance, and muscular uptake. Intestinal absorption of ribose is 87.9% to 99.8% at doses up to 200 mg/kg/h. Steady states of ribose in serum vary according to the administered dose. A steady state has been observed at 45–120 min when 83 mg/kg/h is given

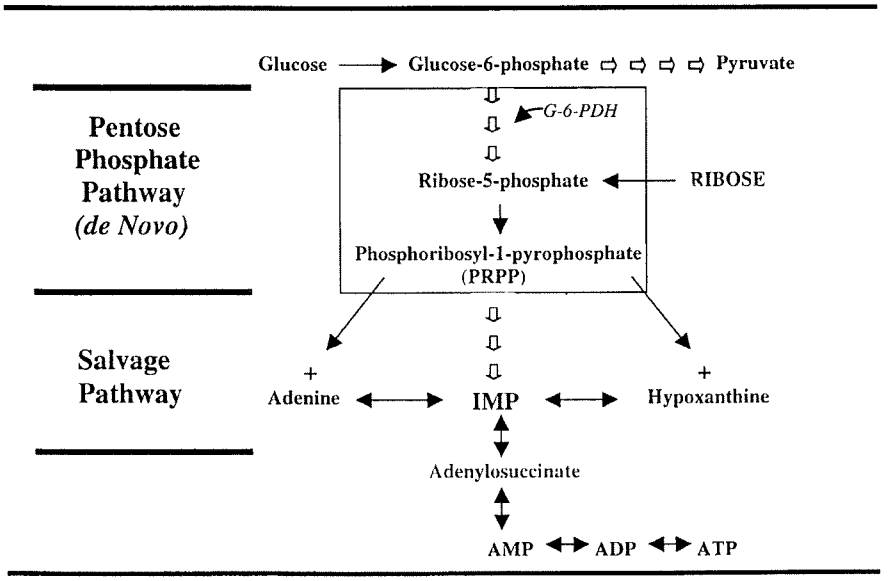

Figure 1 The role of ribose in adenine nucleotide synthesis.

and after 120–150 min at higher does of 166.7 mg/kg/h [10]. The utilization of ribose, i.e., the difference between absorption and excretion in a steady state, has been evaluated. Following an administration of 83 mg/kg/h, 92% linear disappearance has been reported in serum (averaging 1.25 mg/dl/min after achieving a steady state). Further, oral supplementation of ribose is almost totally absorbed within 2 h; however, both absorption and utilization seem to be dose dependent [10].

The effects of ribose on substrates and products of energy metabolism were investigated in nine healthy men, exercising on a cycle ergometer (30 min, 1125 W). Subjects received either no ribose or 2 g of ribose every 5 min during the exercise session. After 30 min of exercise without ribose, an increase in plasma lactate ($p < 0.05$), ammonia (NH_3) ($p < 0.01$) and hypoxanthine ($p < 0.05$) occurred with a decrease in serum glucose levels ($p < 0.05$). When ribose was administered, the noted increase in hypoxanthine was no longer significant and these investigators postulated that the decrease in serum hypoxanthine could have resulted from an enhanced salvage of hypoxanthine [11].

The effect of oral ribose on blood levels of glucose and lactate, as well as the estimated rate of carbohydrate oxidation has also been investigated. Six non-diabetic subjects ingested either 0, 2, 5, or 10 g of ribose in 300 ml of water following a 12 h fast. Blood samples were obtained over a 2-h period after consumption. There was a slight, non-significant increase in lactate levels with increasing doses of ribose. Blood glucose levels fell with increasing doses of ribose, with a significance noted between 0–2 g and 2–10 g. Serum glucose levels returned to baseline by 2 h. There was no significant difference in the rate of carbohydrate oxidation at any dose, although there was an increase in oxidation rates with increasing doses of ribose [12].

Animal studies

Effects of ribose on exercised isolated skeletal muscle tissue

The ability of ribose to increase the recovery of the skeletal muscle TAN levels has also been investigated in isolated muscle fibers [5]. The fibers perfused with a ribose solution revealed a 3.4 to 4.3-fold increase in de novo adenine nucleotide synthesis rates, depending on the type of muscle fiber tested. The addition of ribose to muscle perfusate also showed that de novo synthesis during exercise exceeded that observed at rest, supporting the hypothesis that R-5-P limits de novo synthesis of adenine nucleotides.

Another study employed isolated rat hindlimbs to investigate whether or not muscle ATP production via the salvage pathway could be sustained during 1 h recovery following intense contractions [13]. Salvage of adenine to ATP was compared with and without the addition of ribose to the muscle perfusate. ATP recovery was incomplete and low adenine salvage rates were observed in both resting and recovering muscle when no ribose was supplied; however, the addition of ribose produced an approximate 5-fold increase in adenine salvage in both resting and recovering muscle. These findings indicated that enhancing nucleotide salvage with ribose administration could be important in the recovery of ATP following intense contractions. This observation was borne out in a follow-up study showing that availability of ribose in muscle perfusate led to a 6-fold increase in adenine salvage in fast-white muscle fibers and a 3 to 4-fold increase in slow- and fast-red fibers, respectively [14]. Similar results were found for hypoxanthine salvage rates.

Human studies

Metabolic effects of ribose during exercise in human skeletal muscle

Bouts of strenuous skeletal muscle exercise result in a decrease in ATP levels [2,3,15] that could affect both cellular processes and muscular performance. The ability of ribose to enhance high-energy compound recovery has been investigated both in animal and human clinical studies. Additionally, there has been increased interest in the potential role of ribose in not only enhancing energy compounds but also in improving performance during exercise. The possibility of an ergogenic effect with ribose is based on the observation that there is a reduced TAN pool during intense exercise and adequate adenine nucleotides are necessary to maintain work performance.

Skeletal muscle is composed of various fiber types. The fast-white muscle fibers have the fastest turnover rate for ATP and are probably responsible for much of the noted reduction in TAN levels during contractions. Approximately 4 min of intense exercise in humans causes an approximate 3-fold increase in inosine during exercise and an approximate 2-fold additional increase during

recovery. Further, the total purine content also declines and becomes significantly lower during the acute recovery phase, reflecting a possible loss of purines into the circulation [16].

Muscle biopsy data has demonstrated that ATP levels decreased approximately 19% ($p < 0.05$), IMP levels increased 28-fold ($p < 0.05$), NH_3 levels elevated approximately 5-fold, and inosine and hypoxanthine levels were unchanged in males performing knee extensor exercises to exhaustion [17]. During the first 30 s of exercise there was no change in muscle ATP, IMP, or NH_3 levels, although estimated free ADP and AMP increased. Ten minutes following exercise, IMP levels decreased 58% ($p < 0.05$) from peak exercise concentrations with inosine and hypoxanthine products accounting for 30%. The release of inosine and hypoxanthine during exercise and recovery corresponded to a decrease in net ATP during exercise or at rest following exercise. The researchers involved in this study concluded that an inhibition in AMP deaminase activity may have occurred in the initial period of intense exercise with the production and release of purines from the muscle, leading to a resultant loss of adenine nucleotides.

Studies investigating metabolic activity during and following a single bout of high intensity exercise have also revealed lower muscular ATP levels and increased plasma urate and hypoxanthine levels. Ninety minutes following a single exercise bout, muscle ATP levels were reduced 18%, while plasma levels of hypoxanthine and urate increased 83% and 65% above baseline, respectively. These investigators concluded that a single, high intensity exercise session caused a significant release of purines from the muscle cell into the blood, thereby affecting ATP resynthesis [3]. Similar findings were reported in 10 subjects undergoing prolonged cycling to fatigue. At fatigue, plasma hypoxanthine levels increased 8-fold and NH_3 and lactate levels were also increased significantly when compared to rest [18]. Concurrently, muscle TAN levels decreased with a noted increase in IMP. These data led to the conclusion that plasma hypoxanthine is an indicator of adenine nucleotide degradation and energetic stress during exercise.

In another study, repeated bouts of intense, cyclic ergometric exercise (two sessions/day for one week) reflected a 24% and 23% reduction in ATP and TAN levels, respectively (each demonstrating $p < 0.001$), of which neither recovered entirely by 72 h. Adenosine triphosphate and TAN levels recovered to only 80% of baseline, 72 h post exercise [4]. A similar study also reported the effect of intense exercise on ATP and TAN levels. In this study, ATP and TAN levels decreased by 19% and 18%, respectively ($p < 0.05$), following high intensity exercise, which could be attributed to an inability of the muscle to restore adenine nucleotides due to the lost precursors necessary for resynthesis of ATP [15].

The effect of supplemental ribose on skeletal muscle adenine nucleotide concentration following high intensity exercise has been investigated [19]. Sixteen male subjects were randomized into one of two supplemental groups with each subject consuming either 20 g of ribose/day or 20 g of glucose/day. After an initial 72 h of supplementation, each subject performed five days of high intensity cycle sprints. Each session was 15 min and consisted of 15—10 s sprints at 7% body weight (kg resistance). A 65 h recovery period followed the five days of exercise. Skeletal muscle biopsies were measured for TAN content. Immediately following the exercise period, TAN levels were significantly lower (38%) in the glucose group compared to the ribose subjects (26%). Further, following the 65-h post-exercise recovery period the measured TAN levels in the ribose group returned to pre-exercise levels, those in the glucose supplemented group were still 23% below pre-exercise values ($p < 0.05$). Measured power output and fatigue indices were also assessed during the exercise sessions. The ribose subjects demonstrated a larger change in mean power output (4.2% vs. 0.6%) than the glucose group over the five-day training period. The ribose group also had a significantly greater peak power output at the last sprint session compared to the first, with no difference noted in the glucose group. These data suggest that ribose may provide an ergogenic benefit over time in high intensity cycling exercise [20].

Free radicals are produced through reductive and hypoxic environments, nucleotide metabolism, or ischemia and reperfusion. In a recent double-blind, cross over design study, the effect of oral ribose administration on free radical production, malondialdehyde (MDA) and reduced glutathione levels were investigated [21]. Seven subjects cycled twice at their respective lactate threshold for 25 min. The subjects breathed 16% O_2 during the entire ride. Seven grams of ribose (dissolved in 250 ml of water) or placebo (water itself) were consumed immediately before and after the ride. Exercise significantly increased urinary MDA levels in the placebo arm, but levels in the ribose arm actually dropped below pre-exercise levels. Plasma glutathione levels also dropped in the ribose arm, but increased in the control arm following exercise. Ribose administration also led to a significantly lower heart rate than placebo following the 25-min exercise (175 ± 1.3 bpm vs. 181 ± 1.3 bpm, respectively). There were no differences between groups for SpO_2, uric acid or blood glucose [21].

Effects of ribose on performance in humans during exercise

In a four-week study involving recreational male bodybuilders, ribose was given to determine its effects on exercise performance and body composition. Although there was no significant difference in pre-/post-exercise body composition between the ribose and placebo groups, the ribose group did experience significant gains in strength and muscle endurance [22]. The ribose group posted a significant increase in 1-repetition maximum strength ($p = 0.008$), whereas the placebo group did not. The ribose group also had a significant increase in total work performed (as measured by total repetitions for 10 sets of bench press before muscular failure; 1-min rest interval between sets; $p = 0.028$).

While some studies have shown a performance benefit associated with ribose administration, there have also been some that found there to be no effect. The effect of ribose on repeated maximal exercise performance and ATP recovery was evaluated in 19 subjects performing multiple bouts of dynamic knee extensions [23]. ATP and TAN content were decreased by approximately 25% and 20% immediately after and 24 h after exercise in both the ribose and placebo groups. The power-outputs were approximately 10% higher in the post-test than in the pre-test but were similar between ribose and placebo. It was concluded that oral supplementation of ribose, 4 g four times a day, did not show a positive impact on post-exercise muscle ATP recovery and exercise performance.

Potential role of ribose in skeletal muscle diseases

Ribose may also offer an important benefit in clinical diseases affecting skeletal muscle metabolism. Vascular and metabolic diseases frequently reflect an alteration in adenine nucleotide synthesis. Extrapolating from the results following myocardial ischemia, it is reasonable to postulate that ribose may offer a similar benefit in skeletal muscle ischemia. For example, ischemic peripheral vascular disease is a state in which energy demands outstrip supplies. Supplemental ribose may help regenerate energy compounds and enable patients to sustain a prolonged state of exercise.

Myoadenylate deaminase (MAD), also known as AMP deaminase, is a rate-limiting enzyme that catabolizes AMP to form IMP in the purine nucleotide cycle. Deficient MAD activity has been associated with several types of muscular dystrophy and other neuromuscular diseases, which present clinically with severe muscle soreness and cramping following even mild exercise [24]. Investigators have pondered what role ribose might play in muscular enzymatic diseases. Some studies in which ribose was administered to MAD deficient patients have shown improved exercise tolerance coupled with decreased cramping and soreness. Four grams of ribose per dose provided relief from muscle discomfort following exercise, but lower doses (450 mg) were not effective. Further, when ribose was given in very high doses (i.e., greater than 25 g/dose), some patients experienced gastrointestinal distress [2,10,25].

In McArdle's disease, there is a deficiency in glycogen phosphorylase, and ribose supplementation allowed patients to increase exercise power output from 60 to 100 W with the elimination of post-exertional cramps [26]. Another study also investigated the potential benefit of ribose in patients with McArdle's disease. Five patients with McArdle's disease consumed either ribose or a placebo (60 g/day) for one week and thereafter were subjected to exercise testing. The amount of leg fatigue at peak exercise and 3 min after exercise was similar to baseline for both treatments. Further, there were no changes in the metabolic substrate levels in the blood between the treatments. These results failed to show any significant improvement in exercise potential, however, some normalization of the ventilatory responses to exercise was observed [27].

Ribose has also been investigated for its potential effect in Duchenne's muscular dystrophy [28]. Ribose had no influence on either muscular ATP concentrations or the clinical state of the patients with Duchenne's. However, the authors hypothesized that the ATP content in the muscle fibers in these patients was probably normal and the reduced PCr/ATP and PCr/Pi ratios could be due to poor oxidative coupling in some of the fibers, a low creatine content, or to a general immaturity of the muscle fibers [28].

Conclusion

When oxidative phosphorylation is limited in skeletal muscle due to disease state or exercise, turnover rates of ATP are jeopardized and TAN pools are decreased. Metabolic pathways, such as the purine nucleotide pathway and the pentose phosphate pathway, needed to replenish these pools are active but rate limited. The reduced levels of adenine nucleotides may not recover for days, oxygen free radical products may be elevated for a considerable time period and performance may potentially be reduced. The combination of

these metabolic effects may affect cell integrity and function. Exogenous ribose increases cellular levels of R-5-P, bypasses the rate-limiting enzymatic steps in the PPP to form PRPP and ultimately improves adenine nucleotide synthesis and salvage. Supplementation of ribose offers a potential benefit in energy metabolism by attenuating the loss and/or enhancing the recovery of TANs and modifying oxygen free radical production. This protective and enhancing benefit may have significant implications in maintaining cellular integrity, modulating function of key cellular mechanisms and positively altering exercise performance.

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