Mitochondrial Restoration, Part III

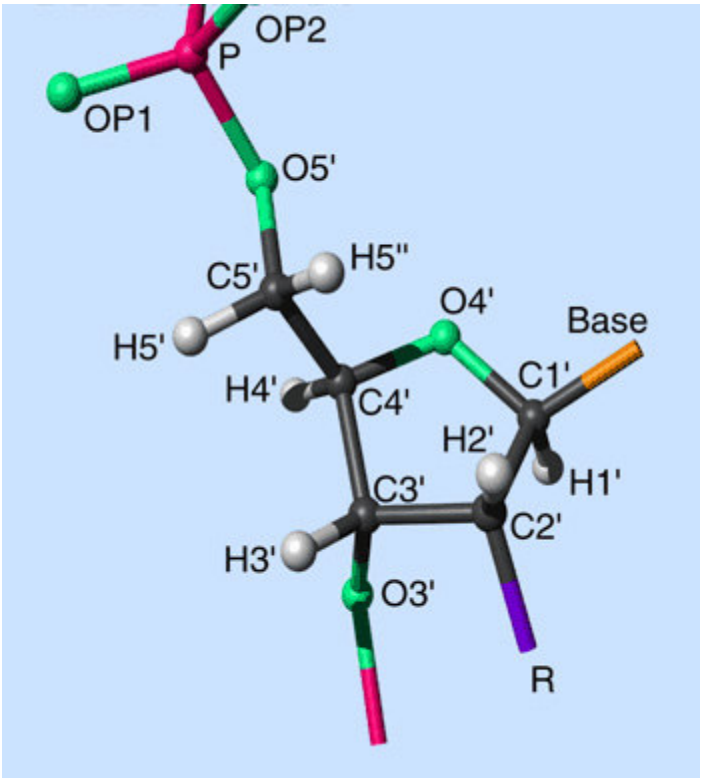
D-Ribose and Creatine Increase Mitochondrial Energy Production

Ward Dean, MD

A series of recent articles in Vitamin Research News have examined aspects of the Mitochondrial-Free Radical Theory of Aging, describing how the declining function of mitochondria— the tiny organelles responsible for producing ATP— contribute to aging and the diseases of aging. Additionally, the articles outlined a number of nutritional approaches aimed at restoring functional performance to aging mitochondria to increase their ability to produce ATP at more youthful levels.
Here we present additional substances that are also proven to enhance mitochondrial oxidative phosphorylation and energy production. These include:

D-Ribose

D-Ribose—Energy-Producing ATP Substrate

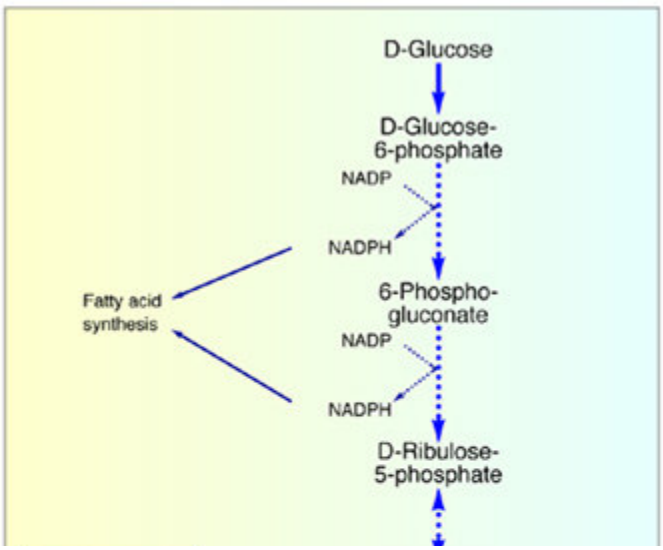


Ribose is a naturally occurring 5-carbon sugar produced in the body from glucose (Fig. 1). In addition to serving as the carbohydrate backbone for ribonucleic acid (RNA) and deoxyribonucleic acid (DNA), ribose is also an essential ingredient in the manufacture of ATP. The mitochondria found in high-energy output organs—such as the heart, liver, adrenals, GI tract, brain, muscles and endocrine glands—utilize two methods for building or conserving cyclic nucleotides like ATP, ADP, and AMP.

The first process by which these nucleotides are synthesized is the de novo pathway, in which nucleotides are made “from scratch,” starting with ribose. This is the slower of the two pathways.

The second, faster pathway, is the salvage pathway, in which the mitochondria “pick up the pieces” of ATP metabolites to form new ATP. In this manner ribose enables the cells to quickly and efficiently recycle (i.e., salvage) the end products formed by the breakdown of ATP to form new ATP molecules. Thus, this is known as the salvage pathway of ATP formation.

Ribose is essential for both the salvage and de novo reactions to work. Ribose is formed in the body from glucose, through a process known as the pentose phosphate pathway (Fig. 2). Aside from this relatively time-consuming pathway, there are no foods able to provide enough ribose to rapidly restore ribose levels, should the need arise, as when exercising or working, and especially during a heart attack or stroke.



Restoring Ribose Levels

Scientists have found that oral or intravenous ribose can rapidly restore ribose levels in nerves and muscles. Ribose supplementation can dramatically improve recovery of failing ATP levels during and following acute or chronic anoxia or ischemia. Research has shown that taking ribose has a positive effect on ATP production in all muscle fiber types, especially the heart. Ribose supplementation increases the de novo production of ATP through oxidative phosphorylation by 340 to 430 percent. Ribose also activates the salvage pathway, causing nucleotides to be revitalized into the manufacture of ATP by over 700 percent.

Ribose and Cardiovascular Diseases

Dr. Wolfgang Pliml and colleagues in Germany, demonstrated that oral administration of ribose is effective in increasing the heart’s tolerance to ischemia (reduced blood flow). Twenty

patients diagnosed with coronary artery disease completed two treadmill tests on consecutive days to establish pain thresholds for each patient. The researchers then gave each patient 60 grams of ribose per day for three days, and administered another treadmill test. Patients supplemented with ribose were able to walk further before pain symptoms occurred than those given the placebo. (1)

In a second recent study, 12 patients diagnosed with unstable coronary artery disease and congestive heart failure were administered five grams of ribose, three times daily, for three weeks. Evaluation by pre- and post-ribose echocardiogram revealed improvement in many parameters, including stroke volume index, ejection fraction, and left ventricular systolic volume. (2)

Ribose and Athletic Performance

Ribose has also been shown to increase athletic performance. Supplementation (ten grams per day) in young male recreational bodybuilders resulted in significant increases in muscular strength and total work performance after four weeks, compared with pre-treatment levels. No changes were noted in those using a placebo. (3)

Another study of seven healthy men who performed two sessions of bicycle ergometry to exhaustion at a one-week interval indicated that ribose improved efficiency of energy production, as evidenced by reduction of oxidative stress during vigorous exercise. Prior to the second trial, the subjects ingested seven grams of ribose. Ribose ingestion resulted in a reduction of urinary MDA (an indicator of oxidative stress), and lower heart rates at the same intensity of exercise as compared to the unsupplemented group. (4)

Creatine

Energy Enhancing Supplement

Creatine is an essential, natural substance that is synthesized in the body from three amino acids: glycine, arginine, and methionine. Creatine plays a very powerful role in energy metabolism as a muscle fuel in its role in regenerating ATP.

Operating through the ATP/ADP cycle (Fig. 3), creatine phosphate maintains ATP levels by serving as a reservoir of high-energy phosphate bonds in muscle and nerve tissues. The energy required to rephosphorylate ADP into ATP depends on the amount of phosphocreatine (PCr) stored in muscle tissues. As phosphocreatine is depleted during exercise, energy availability declines due to a loss of ability to resynthesize ATP at the rate required.

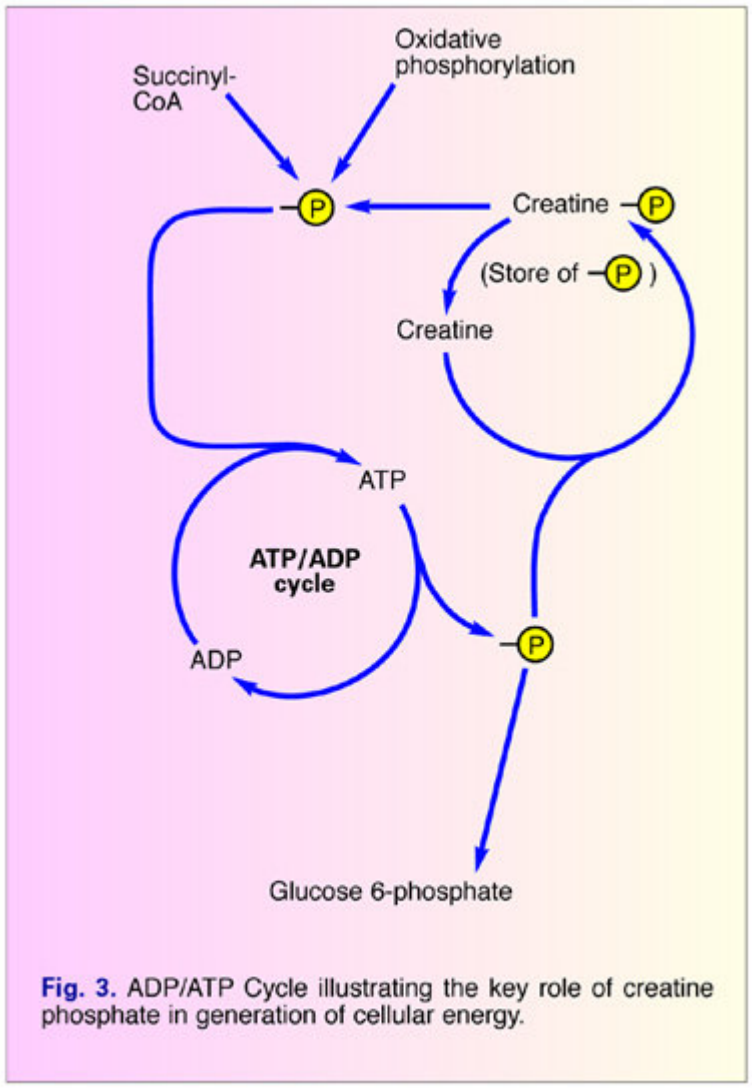


Fig. 3. ADP/ATP Cycle illustrating the key role of creatine phosphate in generation of cellular energy.

While scientists have been aware of creatine since 1832, it was not tested as a performance-enhancing nutrient until 1943, when researchers learned that creatine supplementation extended the cycling times of athletes. (5) This nearly-forgotten, single, isolated report languished in the medical literature for over 50 years. Recently, however, a number of studies have corroborated this early study, showing that creatine enhances both strength and endurance in athletes. In one study, creatine was given to 25 football players who had reached a plateau while undergoing a weight-training program. After 28 days of supplementation with creatine, researchers measured a 41 percent increase in “lifting volume” (sum of all lifts). (6)

Another five-week study of 42 football players also showed gains in strength and mass. (7) as did a study of 29 women who took supplemental creatine for ten weeks. (8) Some researchers have shown strength gains with as little as five to seven days of supplementation. (9,10)

Creatine Increases Strength and Energy in Older Adults

Because older people have lower levels of energy-producing muscle phosphocreatine, (11) researchers examined creatine to see if supplementation could help seniors overcome this deficit. Subsequent studies have demonstrated that supplemental intake of creatine can effectively increase the available "pool" of creatine stored in muscles and enhance the capacity of older subjects to produce phosphocreatine. In 1998 Smith and colleagues administered creatine to younger (average age, 30) and older (average age, 58) men and women, and then tested their ability to perform a leg exercise. Both older and younger subjects experienced increased muscular endurance. In addition, the phosphocreatine resynthesis rate (PCr) of the older subjects was restored to that of youthful adults (Fig. 4) . (12)

Also in 1998, Rawson and colleagues at the University of Massachusetts demonstrated that five days of creatine administration to a group of older men resulted in a small increase in lean body mass, and a slight improvement in exercise performance. (13) This short study was followed up by a larger (20 male subjects, ranging in age from 60-82) and longer (30 days) study in which the subjects were first given a loading dose (20 grams per day) for ten days, followed by four grams of creatine per day for 20 days. (14) At the end of the study, six of the ten creatine users reported an increased feeling of muscle strength or less difficulty performing daily activities. Five subjects demonstrated an increase in body mass, three showed an increase in arm strength, and four demonstrated reduced leg fatigue. One subject increased in all three measures. The authors concluded modestly that creatine might have a beneficial effect on reducing muscle fatigue.

Scientists at the University of Saskatchewan conducted a double blind study of the effects of creatine and a weight training program in men over 70. They demonstrated a significant advantage of creatine over placebo in terms of increased lean body mass, reduction in body fat, and increased muscular strength, and endurance. (15)

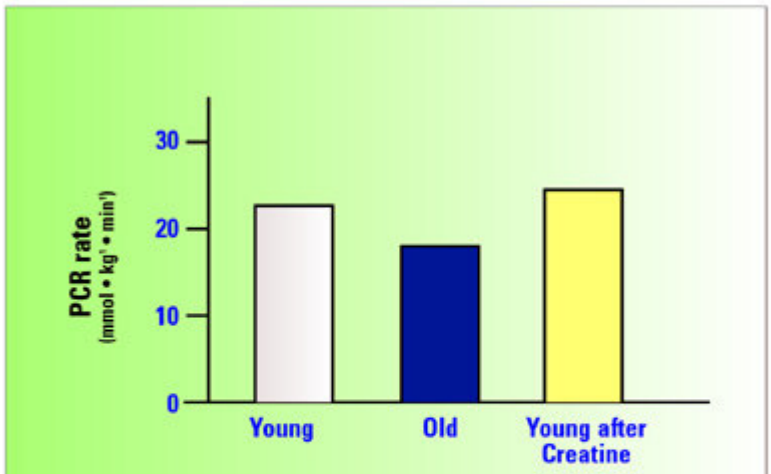


Fig. 4. Restoration of Phosphocreatine (PCr) resynthesis rate with oral creatine. The PCr resynthesis rate on young (avg. age 30) and older adults (avg. age 58) was determined using 31Phosphorous Magnetic Resonance Spectra (31P-MRS). Creatine in a dose of 20 gm daily completely restored the PCr level of older adults to that of young adults (Smith, et al, 1998).

Cardiovascular Benefits of Creatine

Creatine is not just of benefit to athletes. In a study of older men (ranging from 43 to 70 years) suffering from chronic heart failure, researchers noted improvements in exercise performance and increased muscle creatine and phosphocreatine levels after ten days' ingestion of 20 grams of creatine each day. (16)

In Italy, physicians administered six grams of creatine each day to 13 patients hospitalized with congestive heart failure. After four days, they noted a reduction in heart size, reduced vascular resistance, and increased ejection fraction—all indicators of improved heart function. (17)

Neuroprotective Effects of Creatine

In a review article, Tarnopolsky concluded that creatine monohydrate supplementation results in an increase in skeletal muscle total and phosphocreatine concentrations, increased fat-free mass, and enhanced high-intensity exercise performance in young healthy men and women. (18) He also noted "neuroprotective effects, which have been proposed to be of benefit in Parkinson's disease, Alzheimer's disease, ALS, and after ischemia." He concluded that creatine appeared to have potential to attenuate age-related muscle atrophy and strength loss, as well as to protect against neurodegenerative disorders.

Shortly after Tarnopolsky's review, FDA granted "orphan drug status" to creatine as a treatment for patients with amyotrophic lateral sclerosis (Lou Gehrig's disease), based on creatine's demonstrated ability to enhance cellular energy production. In addition, a European patent has also recently been issued for the use of creatine compounds to prevent aging effects and to treat muscle atrophy. (19)

Conclusion

Creatine and ribose, acting at the mitochondrial level, enhance muscular, cardiovascular, and neurological function. Although very high doses of creatine and ribose were used in many of the studies cited in this article, other researchers have shown that regular, long term use of lower doses may be equally effective. For greatest effect these substances should be consumed on a continuous basis (around the clock), and especially prior to high energy requirements. Also, it is likely that combinations of various mitochondrial enhancers/ "resuscitators," acting on various portions of the mitochondrial energy production process (reviewed in previous articles in this series, and summarized in Table 1, in Part I), will have complementary/additive effects, even though slightly lower doses may be used than when the substances are taken alone.

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