

BIOENERGY RIB#SE®

Yesterday you did a week's worth of yard work and finished up with gardening in the afternoon. Today, you're paying the price with sore muscles and fatigue. And who would have thought that an impromptu game of touch football with your friends would have you heading for the medicine cabinet in search of relief for the days of leg pain and stiffness? On the other end of the spectrum, the marathon is next month and your long training runs leave you drained and dragging with sore and spongy legs and mind-numbing exertional fatigue. Or perhaps your situation is much simpler. You struggle to muster up the energy to take your daily walk.

How can people in all these walks of life rebuild and restore energy in tired tissue? The answer is simple – Bioenergy RIBOSE. This patented, all-natural product supplements the body with the most fundamental energy source the body can have. Ribose is what the body uses to build energy stores naturally, and taking Bioenergy RIBOSE helps the body quickly restore energy levels that have been depleted by hard work, exercise, or age.



Molecular Bioenergetics The Science of Energy and Health

ATP plays a central role in the function of every cell. While the medical community has designed some strategies to improve the efficiency of cellular ATP utilization, we are in our infancy applying what is known about the biology and chemistry of ATP toward developing effective methods for preserving cell viability and function. To achieve this goal, an understanding of the metabolic machinery for ATP supply and demand is required. Because the amount of ATP in muscle cells is extraordinarily small in relation to its ongoing demand, the cell must continually re-synthesize and recycle its energy supply to maintain normal function. This distinction between the concentration of ATP and the efficiency of ATP turnover rate is central to our understanding of molecular bioenergetics.¹

The Volume of Energy Substrates Provides the Chemical Driving Force for Cellular Reactions

The concentration of energy substrates in the cell defines its energetic status and establishes whether there is sufficient chemical driving force to allow cellular reactions to occur. Cellular activities, such as moving ions against their concentration gradients and energizing muscle contraction, rely on the volume of energy substrates to provide this chemical driving force. The free energy of hydrolysis of ATP (ΔG_{-ATP}), also referred to as the cellular energy charge, calculates the chemical driving force for cellular reactions. This calculation defines the cell's ability to supply energy in sufficient quantity to fuel the enzymes, called ATPases, that catalyze the reactions of cellular function. The concentration, or volume, of substrates in the cellular energy pool determines the cell's energy charge, defines its energy status, and determines whether or not cellular reactions can proceed normally. Ribose is required for the cell to synthesize energy substrates needed to sustain a high cellular energy charge.

The difference between the cell's energy charge and the energy charge required to fuel a particular cellular reaction determines the likelihood that such a reaction can actually take place. As the cell's energy pool shrinks and reaches the threshold needed to drive a specific reaction, the cellular function driven by the reaction slows. Once the energy charge falls below the required threshold, the cellular function driven by the reaction ceases altogether.

Compare this relationship between energy charge and cellular function to that of the batteries in a flashlight. As the energy drains from the batteries, nearing the threshold required to keep the light illuminated, the light dims. When the battery's energy drains below that threshold, the light will not shine at all. Similarly, as cellular energy is depleted the functions fueled by that energy dim. Additional pressure on cellular energy reserves increases the probability that the chemical driving force will fall below the threshold needed to fuel a reaction, and the cellular function will be severely limited or will fail altogether. In and skeletal muscle tissue the chemical driving force required to fuel the reactions associated with cellular calcium management and ion movement significantly exceed that needed to energize muscle contraction. This explains why energy depletion is first felt in terms of muscle stiffness, soreness, and fatigue, followed by cellular edema. In skeletal muscle, delayed onset muscle soreness (DOMS), exertional fatigue, and weak, spongy muscles result.

Free Energy of Hydrolysis of ATP to Fuel Specific Cell Functions

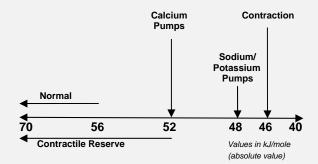


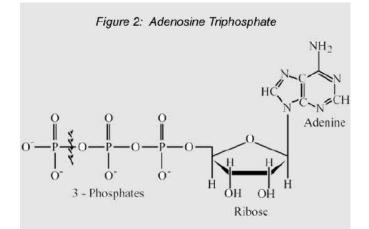
Figure 1: The free energy of hydrolysis of ATP defines the chemical driving force available for cellular reactions to occur. The cellular concentration of energy substrates – ATP, ADP, and AMP – establishes the cellular energy charge. Ribose is required for the cell to synthesize energy substrates needed to sustain a high cellular energy charge. (Source: Inwall¹)

ATP Preserves Cell and Tissue Health

The human body relies on adenosine triphosphate, or ATP, as its "energy currency." Part of a class of compounds known as adenine nucleotides, ATP keeps muscles contracting, and cells functioning. Cells need fully charged energy pools to synthesize important compounds, such as proteins, to maintain cell wall integrity, and to preserve ion balance. Without ATP, tissues would cease to function and life would end. ATP is critically important to the life and health of every cell, and ribose is the fundamental building block of ATP.

A good example of the importance of a fully charged ATP pool is shown in the operation of cellular calcium pumps. Calcium pumps use ATP to both energize and "lubricate" the pumps that discharge calcium from muscle cells following contraction. This lubrication function, called an allosteric effect, exerts control over pump function, determining whether or not the biochemical reaction associated with pump function can occur. The calcium pumps rely on high levels of ATP in their microenvironment to provide this allosteric effect, even though little ATP may actually be used to energize the pumps themselves.¹⁻⁴ A high concentration of ATP, and its associated energy substrates, must be available in close proximity to the calcium pump ATPase or the ability to manage the cellular calcium load will be lost. The result is stiff, sore muscles or loss of cardiac diastolic function.

It is the *volume* of energy substrates, not the efficiency of ATP turnover, that regulates the activity of cellular calcium pumps and sustains normal tissue function. In turn, cells rely on ribose to maintain healthy levels of energy substrates needed to preserve their energy charge.



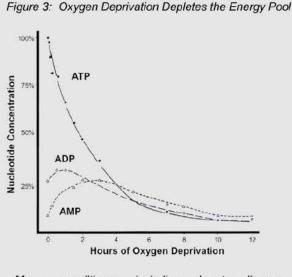
Ribose is the fundamental building block of ATP, the energy currency of the cell. Energy is released to the cell when the bond holding the final phosphate group to the ATP molecule is broken. Adenosine diphosphate (ADP) and inorganic phosphate (Pi) are the byproducts of this reaction.

Metabolic Stress Depletes the Cellular Energy Pool

Food (fuel) and oxygen are required to sustain the cellular mechanisms of energy turnover. As long as these ingredients are present in sufficient quantity, energy levels are maintained allowing cells and tissues to function normally. As we age, or if we suffer from various diseases or metabolic deficiencies, the cellular mechanics of ATP turnover can be disrupted. In these situations, supplements that promote oxidative processes of ATP turnover can help improve energy turnover efficiency. L-Carnitine, Coenzyme Q10, and many other common energy supplements are used in this capacity. However, while these supplements may be useful to enhance energy turnover efficiency, none address the critically important consideration of cellular energy concentration. Only ribose performs this vital metabolic function.

The rigors of daily living frequently present situations in which oxygen or metabolic fuels are not adequately available. Muscle enzyme deficiencies are associated with low tissue oxygen tension, poor energy utilization, or dysfunctional energy metabolism. In addition, strenuous labor or high-intensity exercise increase the demand for oxygen, reduce its availability to tissue, and disrupt the balance of energy supply and demand.

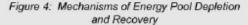
When we use oxygen faster than it can be supplied through respiration and vascular distribution, the body cannot generate energy fast enough to keep pace with demand. This metabolic stress forces the breakdown of ATP substrates, driving the catabolic products out of the cell and depleting the cellular energy pool. This loss of energy substrates reduces the chemical driving force of the cell and contributes to physiological stress resulting in tissue fatigue, free radical formation, disruption in ion balance, pain, and tissue dysfunction. Oxygen deprivation that is severe enough, goes on long enough, or happens often enough can deplete cellular energy reserves sufficiently to result in tissue failure.⁵⁻⁸

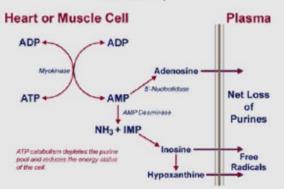


Many conditions, including heart disease, neuromuscular disease, strenuous work, highintensity exercise, and metabolic disorders deprive tissues of oxygen. This oxygen deprivation drains cellular energy reserves and depletes the energy pool. Ribose regulates energy synthesis and recovery. (Adapted from Ingwall¹)

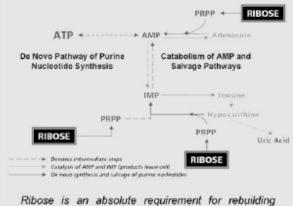
Even with rest and the restoration of normal tissue oxygenation it may take several days for energy pools to recover. Studies have shown that it can take more than three days for depleted skeletal muscle energy levels to return to normal following strenuous exercise.

The body rebuilds depleted energy supplies through a metabolic mechanism called de novo (meaning "new") synthesis. During periods of metabolic stress the body also attempts to conserve energy substrates before they can be lost from the cell. These salvage pathways help to preserve the cellular energy pool, keeping it from being used up too quickly. Both de novo and salvage pathways of energy metabolism are regulated by ribose and rate limited by ribose availiability.¹²⁻¹⁵ Only ribose performs this critical metabolic function. If cells don't have ribose available when energy pools are under attack, the metabolic pathways driving energy synthesis and salvage simply will not function. Ribose is the most fundamental of all energy compounds and forms the basic building block of ATP synthesis.





When ATP is consumed faster than it can be supplied ADP concentrations increase. To preserve the cellular ratio of ATP to ADP, and to increase ATP availability, the cell combines two molecules of ADP forming one molecule of ATP and one of adenosine monophosphate (AMP). AMP then is broken down and the byproducts are washed out of the cell, lowering the concentration of energy substrates and producing powerful free radicals.



energy pools. Ribose regulates the activity of both the de novo and salvage pathways of adenine nucleotide metabolism.

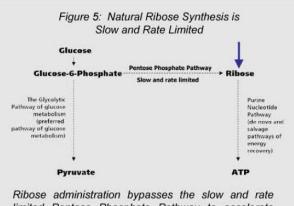
Ribose in the Body Naturally

The role of ribose in regulating energy synthesis and salvage gives it a special significance among sugars. The cell understands the unique nature of ribose and treats it quite differently than other sugars. Simple sugars, or in their more complex chain form, carbohydrates, are one of the three main fuel sources for the cell. The others are fats and proteins. As fuels, the fates of fats, carbohydrates, and proteins are very similar. All are burned to provide fuel for cellular energy turnover, much like gasoline in a car. To accommodate this tremendous difference between ribose and other simple sugars cells have set up enzymatic pathways that keep ribose from being squandered as a fuel like the more readily available glucose. As a result, ribose makes a poor fuel, but instead is essential in actually forming the ATP molecule, making it available so it can be recycled in the normal cellular processes of energy turnover.

Ribose is made naturally when the body converts the simple sugar, glucose, into ribose. Once formed, ribose

can then be used to drive the de novo and salvage pathways of energy metabolism. However, most body tissues cannot make enough ribose to quickly restore energy levels once they have been depleted. This delay retards cell and tissue energy recovery.

The body forms ribose through a metabolic pathway known as the pentose phosphate pathway or the hexose monophosphate shunt. In muscles, the pentose phosphate pathway is slow and inefficient because these tissues lack certain enzymes that are needed to shunt glucose metabolism in the direction of ribose synthesis. Instead, these tissues prefer to use glucose to fuel ATP turnover via the glycolytic pathway, an energy recycling pathway of vital importance during metabolic stress. glucose-6-phosphate gatekeeper enzymes, These dehydrogenase (G-6-Pdh) and 6-phosphogluconate dehydrogenase (6-PGdh), preserve glucose metabolism at the expense of ribose synthesis. As a result, when ribose is needed to re-supply ATP pools, the process is sluggish. Providing exogenous ribose to muscle tissue significantly accelerates the normalization of depleted ATP pools and promotes functional recovery of affected tissue.12,16,1



limited Pentose Phosphate Pathway to accelerate energy recovery.

A large body of scientific evidence proves that ribose administration significantly improves ATP synthesis and tissue recovery when energy levels have been stressed by strenuous work, high-intensity exercise, or disease.^{5,18-27}

Ribose is easily absorbed into the bloodstream and is readily assimilated by tissues working to restore energy pools.^{28,29}

Athletes and Exercise

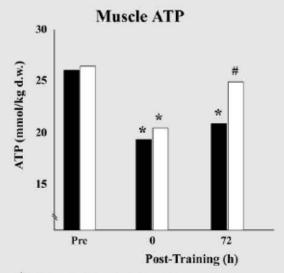
The definition of "high-intensity" exercise varies from person to person. To the highly trained athlete it may mean rigorous daily workouts required in preparation for an upcoming marathon, or it could describe two-a-day football practices under a blazing August sun. For a more sedentary person, strenuous work may include raking leaves, home maintenance, or going for a daily walk. Older individuals, those suffering with chronic disease, or those in recovery may narrow the definition even further.

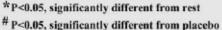
Similarly, the physiological ramifications of depleted tissue energy reserves vary. Buildup of harmful free

radicals, mind-numbing fatigue, muscle soreness, stiffness, and cramping, delayed muscle recovery, and tissue dysfunction are all possible results of prolonged depletion of cellular energy stores. In broad segments of the population these conditions may significantly affect physical performance, exercise tolerance and quality of life.

For serious athletes, recovery time is paramount. High-intensity exercise drains muscle energy pools, contributing to delayed onset muscle soreness (DOMS), exertional fatigue, weak and spongy muscles, and loss of peak performance. The fundamental role of ribose in energy synthesis and salvage is to accelerate tissue energy recovery, helping to restore the physiological condition of muscle, reduce cell damage and limit free radical formation. Athletes incorporating ribose into their nutritional regimen recover more quickly, allowing them to train longer and harder, raise their level of conditioning, and optimize performance.^{8,44-49}

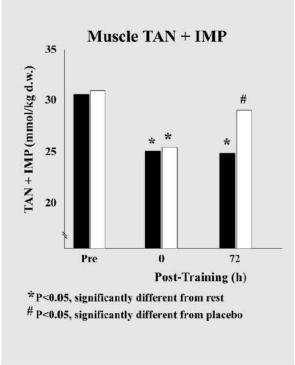
For those who exercise more sporadically muscle soreness and fatigue can be debilitating. Recovery from a weekend run, a long cycle ride, or even hard work in the yard can take days, limiting a desire for the frequent exercise needed to promote cardiovascular health and weight control. Ribose shortens recovery time, reduces muscle soreness, and limits the onset and severity of fatigue. Faster recovery, less fatigue, and reduced muscle pain promotes exercise, benefiting overall health. Figure 7: Skeletal Muscle ATP and Total Adenine Nucleotide Recovery Following High-Intensity Exercise





High-intensity exercise depletes the cellular ATP pool. Ribose administration in association with exercise promotes ATP synthesis, enhancing recover, delaying exertional fatigue, reducing delayed onset muscle soreness, and placing muscle in better physiological condition.

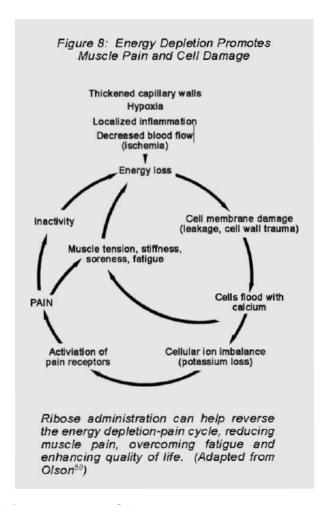
Similarly, the total energy pool is depressed by chronic hypoxia associated with frequent bouts of exercise. Providing ribose to stressed skeletal muscle allows the tissue to refill the energy pool. In this double blind, placebo controlled, crossover trial ribose treatment provided full recovery within 72hours post-exercise, while placebo-treated muscle remained energy starved. (Source: Hellsten, et al.**)



Muscle Health

Countless people suffer from chronic myalgia, or muscle pain. For many these symptoms can be overwhelming. Myalgia can result from simple exercise or muscle overwork. Energy depletion unleashes a cascade of cellular reactions that contributes to muscle pain.50,51 Energy depletion impacts the cell's ability to manage its calcium load, sustaining muscle tension and putting even more pressure on cellular energy reserves. Cellular calcium retention forces potassium efflux that activates membrane associated pain receptors, called nociceptors, causing muscle pain and reducing exercise tolerance. Pain further exacerbates muscle stiffness. using even more ATP and continuing this vicious cycle. By fueling ATP synthesis and restoring the cellular energy charge ribose helps reverse this energy depletion-pain cycle, reducing muscle pain, overcoming fatigue, and enhancing quality of life.⁵²

Myalgia can also be associated with the poor expression of muscle enzymes associated with energy metabolism. A deficiency in myoadenylate deaminase or the enzymes associated with glycogen storage and utilization depletes cellular energy pools. Ribose administration restores cellular energy, helping to overcome the pain, soreness, stiffness, and fatigue associated with poor energy metabolism, helping sufferers lead more normal, active lives.^{33,53-58}



Bioenergy RIBOSE Safe, Effective and Patent Protected

Following almost three years of laboratory, animal, and human studies an independent expert panel of highly qualified food scientists and toxicologists evaluated the safety of Bioenergy RIBOSE. The panel concluded that Bioenergy RIBOSE is Generally Regarded as Safe (GRAS) for use in specific foods when manufactured according to the stringent process and quality specifications defined by Bioenergy Life Science, Inc.

The panel's findings make it safe for manufacturers to use Bioenergy RIBOSE in a variety of food and beverage products, such as sports/energy/health beverages, fruit juices or flavored drinks, drink mixes, nutrition/energy/breakfast bars, meal replacements, soft drinks, dairy products, or cereal products.

Additionally, Bioenergy RIBOSE is safe for use in dietary supplements in doses up to 20-grams per day. A pre-market safety notification has been submitted to the U.S. Food and Drug Administration according to guidelines established by the Dietary Supplement Health Education Act (DSHEA). In 2008, Bioenergy Life Science, Inc. received its No Questions letter from the FDA and became FDA GRAS affirmed.

Bioenergy RIBOSE is all natural and completely safe. Does of up to 60-grams per day have been taken without significant side effects.³² There are reports of mild diarrhea and lightheadedness when fasting subjects consumed ribose in individual doses greater than 10grams. These side effects of Bioenergy RIBOSE are not unique. Large doses of many hydroscopic carbohydrates will cause diarrhea because they change the osmotic pressure of the intestines. Significantly, there are no known interactions between Bioenergy RIBOSE and any food, dietary supplement, over-the-counter, or prescription drug.

Bioenergy Life Science, Inc. has more than 15 issued and pending patents protecting the use of ribose in a broad array of medical and nutritional applications. Bioenergy Life Science, Inc. has been an active sponsor of laboratory and clinical research and believes that wellfounded, basic scientific research is a key contributor to the success of any nutritional or medical product. The patent protection afforded Bioenergy RIBOSE is fundamental to the sound use of this ingredient now and well into the future. This patent protection presents a considerable advantage to our customers. A full summary of issued and pending patents is available upon request.

Few ingredients in the nutritional market are available with the proven effectiveness, safety profile, and patent protection of Bioenergy RIBOSE.

The Ideal Energy Supplement

All that has been described suggests several reasons why ribose is an ideal energy supplement:

- Ribose is an indispensable component of the most important molecules within the cell, including ATP, RNA, DNA, cAMP, riboflavin, and more.

– Deficiency states of ribose can be easily demonstrated. We have found that ATP levels, for example, are severely depressed in skeletal muscle following periods of extreme activity, ischemia, hypoxia, or metabolic stress. Similar deficiency states have been shown in cells of virtually every tissue in the body.

 Ribose is the rate-limiting compound to correct these deficiency states. The tightly regulated synthesis of ribose means energy recovery will be slow, and research has borne out this observation.

Giving ribose promptly corrects the deficiency.
Ribose shortens recovery time to one day. Similar results are evidenced in skeletal muscle and other tissues.

There is no way to get more basic than ribose or gain greater benefit by giving another compound. Ribose is the most elemental molecule for energy synthesis and salvage. Any other molecule would first have to be slowly converted to ribose to be effective.

- There are virtually no negative effects of ribose administration. It is completely safe, natural and will not interact with foods or pharmaceutical drugs.

All in all, ribose is ideal. And its scope is just unfolding.

To Learn More

Energy is the top reason consumers buy nutritional supplements or functional foods and beverages. Bioenergy RIBOSE stands alone in its ability to deliver a real, natural, demonstrable, safe, and patent protected

benefit to health conscious consumers. To learn more about the science behind Bioenergy RIBOSE call Bioenergy Life Science, Inc. (877) 4-RIBOSE or (763) 757-0032, or contact us on-line at www.bioenergyribose.com

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