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Improved energy for improved exercise

The balance between energy and fatigue is key to powering exercise and can be managed via intake of nutrients and related natural compounds.

Steve Myers | Apr 15, 2019

For sports nutrition consumers, managing energy is about balancing fuel and fatigue. The heart of energy production is in the mitochondria, the inner part of body cells. Here, enzymatic and oxidative reactions create the “energy molecule” adenosine triphosphate (ATP), which releases energy as its bonds are broken. Increasing ATP production is one part of the energy balance; the other is limiting fatigue. Various molecules can trigger fatigue signals, which are processed in the

brain, and blocking these signals or situations that trigger them is a very popular approach to promoting continued energy for workouts and competition.

Mitochondrial Energy Production

Nutrition drives ATP production. In the earliest stages of intense activity—up to about 10 or so seconds—the body draws quick energy from stored ATP and quick re-synthesis. In this phosphagen system, phosphate can be added to spent ATP—breaking the bonds cleaves off phosphate(s) and leaves either adenosine diphosphate (ADP) or adenosine monophosphate (AMP)—to quickly restore this energy molecule. To do this, the body taps into muscle stores of phosphocreatine.

A popular method of maximizing phosphocreatine stores is to supplement with **creatine**. Creatine monohydrate and hydrochloride were the main forms for many years, but recent innovations include buffered creatine and creatine nitrate, which are marketed for various improvements such as safety, stability, absorption and bioavailability.

Another way to boost ATP stores is to supplement with ATP itself. TSI Inc. offers an **ATP disodium** ingredient called PEAK ATP®. ATP supplementation increases energy production within the cell and promotes increased blood flow outside of the cell.1

In the ATP molecule, adenosine and the three phosphates are joined in the middle to a sugar compound called **ribose**. Supplemental ribose is marketed to improve ATP production.

Ribose is a rate-limiting compound in the synthesis of purines and pyrimidines, which are crucial to synthesis of important body components like DNA and RNA, as well as certain vitamins, according to Bioenergy Ribose. The company noted ribose is made in the body from glucose, but the process is slow, making supplementation a touted complement.

Glucose is the primary nutrient feeding the process of ATP production for higher-intensity activities as the phosphagen system depletes. Mainly sourced and stored from carbohydrates, glucose undergoes a breakdown process called glycolysis to drive ATP production.

Early or “fast” glycolysis starts to increase as the phosphagen system wanes and works in anaerobic conditions until the oxygen from increased breathing makes its way to the cells. This only produces a small number of ATP molecules (per glucose molecule), so the system only sustains for about 30 seconds, give or take.

Everything in anaerobic glycolysis happens quickly. The process creates ATP and the byproducts NADH+ (nicotinamide adenine dinucleotide plus hydrogen ions) and pyruvate. When oxygen presence is lacking, the pyruvate quickly turns into lactate, which further breaks down enzymatically into lactic acid and hydrogen ions.

Contrary to long-held theories, lactic acid does not promote fatigue but instead can either remain in the cell for energy or be shuttled to the muscles for use as fuel.2 The fatiguing culprit is the hydrogen ion. As these ions accumulate in the muscles, they increase acidity and contribute to muscle fatigue—the research community is still searching for the exact mechanisms of muscle fatigue from unsustainable workloads, including the buildup of other metabolites such as chloride and potassium.

Carnosine is a dipeptide in the muscles that helps buffer metabolites including hydrogen ions. Carnosine is comprised of the amino acids L-histidine and **beta-alanine**. Supplementing with beta-alanine has become a popular method of addressing muscle fatigue for improved workout and performance.

Once oxygen hits the cells, aerobic slow glycolysis kicks in; it takes longer to produce ATP, but more is produced than in fast glycolysis. Slow glycolysis can sustain for up to the two-minute mark of moderate to intense activity.

With oxygen now present, the byproduct pyruvate oxidizes into acetyl coenzyme A (CoA) that can combine with oxaloacetate to form citric acid and feed the krebs

cycle; also known as the citric acid cycle, this process features a series of reduction and oxidation reactions to produce ATP and various byproducts such as carbon monoxide.

Pyruvate from glycolysis, or glucose, is just one way to feed the krebs cycle. Fat and protein can also contribute to the krebs cycle and ATP production.

When carb and fat supplies are insufficient, amino acids can be oxidized into pyruvate, CoA or oxaloacetate to enter the kreb cycle. This is not the primary method of energy production, so supplemental proteins and amino acids tend to be marketed for their other sports nutrition benefits, including building muscle.

Fats are a preferred source of nutrition for energy production, especially in lower intensity and endurance activities. Fatty acids stored as triglycerides can be oxidized into CoA for use it the krebs cycle.

“Fatty acid oxidation [FAox] occurs during submaximal exercise intensities but is also complimentary to carbohydrate oxidation (CHOox),” reported researchers from Longwood University, Virginia.3 “Due to limitations within FA transport across the cell and mitochondrial membranes, FAox is limited at higher exercise intensities.”

They noted fatty acid oxidation is at its max during moderate-intensity exercise, about 45 to 60 percent VO2max, and reaches it limit at greater intensities—exercise above 65 percent VO2max prefers carb-driven energy.

To be oxidized into CoA, fatty acids must get into the mitochondria. This job falls to **carnitine**, found mostly in skeletal muscle; carnitine can be ingested from meat, but supplemental carnitine is a popular way to boost muscle stores and promote increased energy from fatty acid oxidation.

Medium chain fatty acids are more easily digested and transported throughout by the body than are long chain fatty acids. **Medium chain triglycerides** (MCTs)

more quickly reach the muscles, where they are oxidized for energy, and the liver, where they are converted into ketone bodies.

There are a few dietary sources of MCTs, but supplemental MCTs, mostly synthesized from coconut oil, are a popular way to get an energy boost for exercise, especially among keto dieters.

When carbohydrate consumption plummets and blood glucose levels are very low, low insulin levels trigger liver mitochondria to convert CoA to **ketone bodies**, including acetoacetate and **beta-hydroxybutyrate (BHB)**. The liver lacks the enzymes needed to use these ketones to produce energy, but other tissues in the body can do so—the brain struggles with fatty acid metabolism and so favors glucose for energy production, but ketones can be a fuel source for the brain under very low glucose conditions, such as fasting or a very low-carb/keto diet.

The use of ketones to make energy spares the glucose system and inhibits gluconeogenesis, the process of making glucose, which spares the use of protein to make glucose. Some researchers have reported the use of ketones generates more ATP than does the same amount of glucose.4

For all its stages, the krebs cycle doesn't produce many ATPs, but it produces byproducts that carry many electrons that go through a process called oxidative phosphorylation to make ATP. Central to this process is the electron transport chain (ETC).

Electrons from the krebs byproducts reach the ETC and are then repeatedly transferred down the chain, which is comprised of proteins and other organic molecules. These reactions create energy that forms a proton gradient and releases hydrogen ions. The flow of these ions across the gradient is harnessed by enzymes to turn ADP and phosphate into ATP.

Of all the ways to make energy molecules, oxidative phosphorylation produces the most amount of ATP per glucose molecule. **Coenzyme Q10** (CoQ10) helps carry

electrons down this chain, making it an essential nutrient for ATP production. CoQ10 is popular for increasing energy in heart patients, particularly those with chronic heart failure (CHF), but it also has been highlighted for its energy benefits in sports nutrition.

The mineral **magnesium** is a cofactor of many enzymes crucial to ATP production,5 including creatine kinase in the phosphagen system, pyruvate kinase and others in the glycolytic system and dehydrogenases in the kreb cycle. This mineral, which may also help protect ATP, has been added to many sports nutrition formulas, including pre-workouts containing creatine.

Magnesium is critical for everyday and athletic performance, assured Samantha Cassetty R.D., chief nutrition officer for OMG! Nutrition, which uses magnesium glycinate (magnesium bisglycinate chelate) in its products.

“While it’s involved in over 300 processes in your body, a few specific to sports performance are its role in oxygen uptake (which allows your body to utilize more oxygen during intense workouts); transporting energy to your muscle cells; muscle contraction and relaxation; and it’s function as an electrolyte that gets depleted during sweaty workouts,” she explained, adding athletes and active consumers should pay attention to the form of magnesium used. “Common forms, like magnesium citrate, can cause cramping and a laxative-like effect, which may interfere with performance goals. I always recommend magnesium glycinate because it’s more available to your body than other forms, and it’s not associated with any GI distress.”

Several other minerals such as iron, copper and manganese also are required to make the necessary enzymes. Mineral or multivitamin-mineral supplements are widely available, but a few specialty mineral sources have reached the market to offer natural and multi-faceted supplements for energy and sports nutrition.

Shilajit is a mineral-rich resin from Himalayan rocks used in India’s Ayurveda traditional medicine for improved energy. Natreon, which make Primavie® shilajit,

noted the ingredient helped preserve muscle strength in fatiguing exercise,6 and also offers antioxidant benefits due to its fluvic acid content.

Ancient peat is another earthy source of minerals important to energy production. FutureCeuticals's elevATP™ combines ancient peat with antioxidant apple polyphenols to both increase energy and protect the mitochondria from harmful reactive oxygen species (ROS).

Protecting the mitochondria from oxidative stress is an increasingly popular complement to ingredients that directly impact ATP production. Apples are one of several fruits and vegetables containing the flavonoid quercetin, which can protect the mitochondria from oxidative damage and improve both mitochondria count and function.7

The carotenoid astaxanthin, found in red plant foods and seafood, is another antioxidant protector of the mitochondria that can help manage the energy-fatigue balance.8

Tannins from **French oak wood** (*Quercus robur*) may offer antioxidant protection as well as impact signaling for increased energy production. Horphag Research, which developed the Q. robur extract Robuvit®, reported the extract can improve recovery time and reduce muscle fatigue.9

Ellagitannins in the Robuvit can convert into ellagic acid. According to U.S. researchers, ellagic acid may increase fatty acid oxidation and activate AMP-activated protein kinase (AMPk), a type of switch that turns on ATP production when rising ADP and AMP levels indicate low cellular energy.10

The botanical ***Gynostemma pentaphyllum*** may stimulate AMPk via the plant's saponins, including damulins A and B, which may also increase glucose uptake and fat oxidation into CoA. A heat-processed extract (as ActivAMP®, from Gencor) was shown to stimulate AMPk in muscle.11

Glutathione is a potent antioxidant found in plants, animals and fungi; the human body also produces glutathione. In addition to its antioxidant properties, glutathione may help improve blood flow via vasodilation.

Scientists studying a combination of glutathione and **L-citrulline** (as Setria®, from Kyowa Hakko) in resistance-trained men noted glutathione can support production of the vasodilator nitric oxide (NO) and protect NO from oxidative damage.12 The men taking Setria had increased lean mass and strength, compared to those taking placebo.

NO relaxes blood vessel walls and increases blood flow. The improved circulation delivers more nutrients and oxygen to the muscles and other cells. NO levels in the body increase in response to exercise. It is synthesized from the amino acid L-arginine.

Citrulline can be converted to arginine and NO, and is often combine with **malate**, a participant in the krebs cycle. This combination can help increase oxidative ATP production and phosphocreatine restoration.13

Citrulline may better increase blood arginine levels than arginine supplementation, as a good deal of ingested arginine may be lost, degraded or used for other processes than NO production.14

However, an **inositol-stabilized arginine silicate** (as Nitrosigine®, from Nutrition 21) may be an exception, as research shows the ingredient increased blood levels of arginine and NO in healthy male adults.15 Blood flow increased to the brain and muscles, resulting in muscle function benefits.

NO can also be made from nitrites and nitrates, which are found in the soil and, thus, in many plants.

Beets and **beetroot juice** contain high amounts of nitrate and are one of the earliest forms of blood flow supplementation for athletes. A review of existing

studies indicated beetroot juice consumption may improve performance, especially during intermittent high-intensity exercise.16 The research reviewers noted the benefits were attributed to faster phosphocreatine re-synthesis. “The findings of some studies also suggested improved indicators of muscular fatigue, though the mechanism involved in this effect remains unclear,” they added.

Another nitrate-rich plant is **amaranth** (*Amaranthus dubius*), also known as **red spinach**. A study of a proprietary red spinach extract (as Oxystorm®, from PLT) found increased plasma nitrate and nitrite levels, resulting in improved NO production.17

Delaying fatigue

There are different types of fatigue. Muscular fatigue can result from the accumulation of glycolysis metabolites, a process still being explored and determined by scientific research, but cellular fatigue can result from an inability of the mitochondria to provide sufficient energy, including from impairment, lack of nutrition and oxidative damage.

The abundance or deficiency of certain metabolites in the muscles—including potassium, hydrogen ions, magnesium, ROS and others—could affect the muscles’ ability to contract. Inflammation may also play a role in muscle fatigue.18 Further, the breakdown of AMP and amino acids, particularly the branched chain amino acids (BCAAs), in muscle elevates levels of ammonia, which can cross the blood brain barrier and impact central fatigue, cognitive function and brain energy metabolism.19

A combination of the amino acids **L-alanine** and **L-glutamine** (as Sustamine®, from Kyowa Hakko) may help delay fatigue by removing ammonia from the muscles; this may result in improved time-to-exhaustion.20 A bonus with this combo is that glutamine can be converted to α-ketoglutarate, which helps drive the krebs cycle.

Accumulating ammonia in muscle and plasma from amino acid breakdown, which may result from increased use of protein for energy in the muscle due to carbohydrate depletion, may be attenuated by carbohydrate ingestion.21

Israeli company Matok V'Kal, Ltd. has developed a carbohydrate spray, Fit4style Energy Spray, designed and marketed to extend a workout. The idea is that the mere presence of carbs in the mouth can fool the brain into thinking the body has ingested carbs for energy.

Some research has shown this theory of a carb mouth rinse triggering taste receptors to promote continued energy and exercise has merit,22 while other studies have not found such mouth rinses perform any better than traditional fluid intake during exercise, including water.23

At least in the United States, dietary supplements must be designed for ingestion, not simply coating the mouth. "Our product is a regular beverage," said Noam Kaplan, CEO of Matok V'Kal. "It is under food and beverage regulations, not dietary supplement."

Signaling the brain to wake or rest is a big part of the energy-fatigue equation in exercise. While some ADP and AMP can be restored into ATP, they can also further lose remaining phosphates to become just adenosine and the ribose backbone. This adenosine molecule can settle into adenosine receptors in the brain and signal fatigue. This is only one part of the body's orchestra of sleep-wake signaling, but these adenosine receptors are central to the most common fatigue-inhibitor in sports nutrition and the entire world: caffeine.

Caffeine is a purine alkaloid that can antagonize or compete for the adenosine receptors. As the receptors take up caffeine, the fatigue signaling of adenosine is thwarted or delayed. Instead, caffeine speeds up neuronal activity, causing the pituitary gland to release adrenaline. This stimulant effect can help prolong exercise and improve performance, but it can also overamp the cardiovascular system and tax the heart.

Caffeine can constrict blood flow in some parts of the body. It constricts vessels in the skin to slow bleeding from cuts—caffeine is an ingredient in some aftershaves. Yet, it can increase blood flow to the muscles. In the brain, caffeine has reportedly decreased24 and increased25 cerebral blood flow.

The other issue with caffeine is a building up of tolerance, which then requires more caffeine to maintain the prior effect. Chronic and increased doses of caffeine have been linked to addiction/dependence, which can lead to cardiovascular and perinatal problems.27

The key to caffeine may be timing and dosage.

The U.S. Army used alertness testing to develop an algorithm—available online as 2B-Alert—to personalize the timing of caffeine consumption to maximize the benefits while reducing the overall consumption amount.30

“We assessed the algorithm by comparing the caffeine-dosing strategies (timing and amount) it identified with the dosing strategies used in four experimental studies, involving total and partial sleep loss,” the researchers explained. “The algorithm identified strategies that resulted in equivalent performance to that in the experimental studies while reducing caffeine consumption by up to 65 percent.”

In addition to timing and dosing strategies, ingredient suppliers have introduced innovative caffeine versions to help brands formulate effective but responsible energy and pre-workout products.

For example, ingredient manufacturer zümaXR developed targeted release caffeine ingredients (co-commercialized by PLT Health Solutions) to avoid the typical crash as caffeine depletes. Delayed release delivers a shorter, but more pronounced, caffeine effect, while extended release provides a longer, but steady, caffeine effect.

Many energy and pre-workout formulas contain caffeine anhydrous, a dehydrated source that is very concentrated and pure, but some consumers use this form of

caffeine on its own. However, FDA has warned against the use of pure caffeine powders in bulk form, which can result in accidental overdosing and lead to dangerous health problems, including death.

Caffeine anhydrous can be made synthetically or naturally. Synthetic caffeine tends to be less expensive and is often used in sports nutrition formulas.

Despite the popularity of synthetic caffeine among formulators, many consumers demand more natural sources of caffeine, and ingredient suppliers have responded with many options.

Applied Food Science offers organic caffeine from **coffee** (as PurCaf® and JAVA.g™), **tea** (PurTea™) and **guayusa** (as AMATEA™).

Guayusa (*Ilex guayusa*) is super leaf from a holly species found in the Amazon region, and it has similar benefits to synthetic caffeine without the associated safety concerns, such as increased epinephrine and adrenaline.28

Another plant-based option is **theacrine**, a component of coffee and certain tea varieties (*Camellia sinensis*) with a similar structure to caffeine. Unlike caffeine, theacrine (as Teacrine®, from Compound Solutions) appears to avoid cardiovascular issues and habituation in healthy adults.29

Bodybuilding.com has just launched a new brand of sports nutrition products, called Revel, formulated for female athletes and active consumers. Instead of caffeine, the revel energy formula features TeaCrine, Nitrosigine and PeakO2™, a **mushroom** blend from Compound Solutions designed to, among other benefits, increase endurance, oxygen uptake and utilization, and exercise capacity. It also contains coconut water powder to promote hydration.

Charina Lumley, vice president of product and brand development at Bodybulding.com, noted two of these ingredients have been validated on women, not just their male counterparts. “The first is TeaCrine—the patented version of

theacrine—which has been studied in women30 to be a potent cognitive enhancer that delivers focus, concentration, and energy without the use of stimulants," she explained. "The second is Peak02, a non-GMO, vegan and gluten-free blend of six mushroom adaptogens. This includes **cordyceps**, which has been shown to improve athletes' oxygen utilization to allow them to perform longer and at their highest levels."31

Adaptogens are increasingly popping up in sports nutrition partly for their ability to help the body adapt to stress. One of the most popular adaptogens is ashwaghanda, a staple of India's Ayurveda traditional system of medicine often prescribed for increased energy and as a general tonic.

Ashwagandha has been shown to improve endurance and oxygen capacity in both sedentary adults and athletes.32 Specifically, ashwagandha supplementation increased VO2max and time to exhaustion; researchers attributed these benefits to the ability of the herb's constituents to improve the capacity of the blood to transport oxygen to muscles during exercise.

Pre-workout and energy formulas

While there are formulas designed and marketed to boost energy or blood flow, sports nutrition consumers increasingly turn to pre-workout formulas for these and other workout goals. These products typically contain some combination of either caffeine, beta-alanine, creatine, carnitine, nitrates, amino acids and other energy- and performance-related ingredients.

As there are so many ways to approach the energy-fatigue balance, the idea that a multi-ingredient pre-workout supplement (MIPS)—most often a ready-to-mix powder—could contain a range of ingredients that can address many such methods appeals to many consumers.

Research reviewers from the Mayo Clinic, Wisconsin, and Lindenwood University, Missouri, said most MIPS studied in published literature do not list ingredients

and/or amounts beyond a proprietary blend, making it hard to perform direct comparisons between the MIPS and the individual ingredients.

However, their review of MIPS studies showed some limited research has found MIPS, compared to placebo, can increase exercise endurance (time to exhaustion) and muscle endurance (reps to fatigue), but other studies found no such benefits.33

Researchers from Coastal Carolina University, South Carolina, noted caffeine is included in most MIPS and is likely responsible for much of the performance benefits.34 To fill a gap in research on MIPS compared not to placebo, but to caffeine alone, they performed a pilot study on a pre-workout formula (as Perform Kinetics, from ATP Nutrition) compared to caffeine in trained men (at least one year of resistance training).

After the subjects underwent various exercise protocols, the researchers found no significant differences on vertical jumps, bench and squat repetitions or chest pass velocity between those taking the MIPS and those taking just caffeine. The only difference between the groups was the MIPS group had more quality squat repetitions than those taking just caffeine.

While their study found very little evidence MIPS ingredients work synergistically better than caffeine alone, they cautioned the sample size was small. “Our preliminary results do not discount the possibility that a [pre-workout supplement] may be more ergogenic than a matched dose of caffeine, but rather support the need for ongoing data collection,” they concluded.

Another gap in determining the synergistic value of MIPS is on female subjects. Another team from Lindenwood University and Mayo Clinic Wisconsin set out to change this.

“Although there have been multiple studies supporting the use of MIPS, the majority of the available research to this point has focused primarily on males,” they said, in

their research publication.35 “There are limited data regarding the effectiveness of pre-workout supplementation in female populations.

They found recreationally active females who consumed a female-specific MIPS formula (as FitMiss Ignite™, from Musclepharm) experienced acutely increased resting metabolism, a benefit they theorized was likely due to the caffeine content. However, they reported no adverse effect on heart rate and systolic blood pressure, but there was increased diastolic blood pressure. They speculated caffeine’s vasoconstricting effect from its impact on adenosine was a leading culprit, but the exact amounts of caffeine and other ingredients are not labeled—the product features a proprietary FitMiss Ignite Blend.

The study also showed improved upper body muscular endurance and anaerobic capacity following high intensity exercise in those taking the FitMiss supplement; focus was also subjectively improved in the treatment group.

The body’s regulation of energy production and fatigue signaling is complex, and formulating effective products to help athletes and active consumers not only fuel their exercise and daily activities, but also to enhance performance and gains is quite a challenge. While studies on ingredients and formulas is a great guide, there are many gaps in the research and answers yet to be found, not to mention new approaches yet to be discovered.

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