dotFIT NO7Rage[3] ™

Goal

Supply a pre-workout/activity NSF Certified for Sport product to allow users acute performance benefits such as individual training session or competition outcomes, and long-term benefits by helping to maximize training induced adaptation potential via continuous stronger workout sessions building on each other helping to avoid training plateaus. The formula ingredients individually and collectively have well known positive effects on muscular endurance and size, strength and performance through multiple unique mechanisms of actions offering the potential for additive effects. The combination includes ingredients that demonstrate the ability to increase nitric oxide (NO) production to enhance blood and nutrient flow in and out of exercising muscles through inducing hyperemia (excess blood in the vessels causing vasodilation) to amplify the training session and response. These novel NO booster ingredients (Nitrosigine, citrulline malate, glycerol) are supplied together with other compounds (e. g. caffeine, taurine, creatine, beta-alanine) known to improve strength, force production, time to exhaustion and training endurance while also delivering positive cognitive benefits such as improving training desire, reaction time and focus. In totality, including the raw materials' superior patented forms and accurate clinical dosing, this product has the ability, through multiple pathways, to significantly enhance the desire to exercise and improve strength, performance, size, and training induced outcomes in the short and long-term when compared to similar mass market commercial products or a non-supplemented state.

Note: *When formulating multi-ingredient pre-workout supplements (MIPS) and especially when stimulants are included, the combined ingredients at the recommended dosage must exhibit a strong and acceptable safety and efficacy profile for each ingredient. Often the efficacy of a MIPS is limited by the safety level of the stimulant per serving. Meaning when all ingredients are in one matrix such as a powder, an effective dose of stimulants (e.g., caffeine, yerba mate, etc.), ergogenic components (e.g., creatine, beta-alanine, etc.), and vasodilators (e.g., citrulline, arginine, etc.) may not line up to accomplish the efficacy side of the equation without surpassing the safety boundaries, making a single product delivery form problematic. In other words, adjusting the dosage for efficacy by individual (e.g., body weight, ingredient sensitivity, activity, etc.) may surpass a safety/comfort level of the stimulant or cause an adverse reaction because of individual differences in reaction to stimulants or any other ingredient contained in the fixed formula since they all increase together as the serving size increases. As an example: getting a creatine dose necessary to be helpful may push the caffeine and/or beta-alanine to an uncomfortable level in susceptible persons. The dotFIT formulation solves this dilemma for almost all qualified users through dosing by weight so that all increments can be efficiently managed to deliver effective and safe amounts. Additionally, dotFIT makes a non-stimulant variation and a separate creatine monohydrate product that can be added as needed so that other ingredients remain safe and effective as necessary such as during creatine or beta-alanine loading.*

Rationale

Background

Dietary supplements in the athletic world are designed and incorporated as low and no calorie controllable delivery of desired compounds in effective accurate amounts that can be timed throughout the day including around meals and training to improve performance, thus eliminating the problems with food only delivery such as diet preferences, ingredient and amount availability, delayed absorption, and unwanted foods or accompanying/inseparable components and/or calories.[1,2]

Dietary supplements for improving performance and muscle gain have two primary goals:[3]

1. Supply energy enhancing compounds to maximize each training session and/or competition, thus consistently increasing acute performance and muscle adaptation potential.[4,5]
2. Speed and enhance recovery through minimizing protein breakdown while maximizing synthesis to produce better continuing muscle and performance gains (maximize adaptation).[6]

The desired outcome of using supplements properly is to accomplish a greater, faster and prolonged accrual of gains as opposed to a non-supplemented state. Therefore, dietary supplements in general, especially those targeting muscle size, strength and performance should be considered in two categories: 1) acute performance enhancers that also would maximize muscle adaptation potential; and 2) recovery enhancers leading to measurable size or performance benefits over the long-term because of continuous improved and full recovery, thus maximizing muscle adaptations and staving off the inevitable age and training experience performance decline.

Introduction

Competitive athletes and exercisers constantly seek physical improvement to remain competitive in their respective sport by attempting to make continuous progress in strength and performance gains, or as with avid exercisers, simply enhanced exercise sessions over time. In the presence of amino acids (protein), exercise stimulates natural human skeletal muscle protein synthesis and muscle performance throughout life when compared to a non-exercise state.[6,7,8,9] Various forms of mechanical loading (exercise design) initiate muscle protein's related anabolic signaling and the mode, intensity and volume of exercise differentially affect signaling, thus long-term outcomes.[10,11,12,13,14,15] The general goal of most athletes is to maximize the body's natural muscle protein synthesis (MPS) processes, which include applying peak strength during exercise and recovering adequately from each training bout to constantly increase performance and if desired, increase skeletal muscle (SM) size. Thus, athletes/exercisers attempt to progressively improve physically by making each training session build on the previous, leading to continuous athletic and physical progress since unaccustomed exercise regularly sets the stage for the desired muscle remodeling (anabolism) that would potentially improve performance or size.[1,16,17,18,19] However, despite exercise's constant MPS initiation or stimulus, positive training progress slows dramatically with age and experience (the younger and/or less experienced, the more gains),[20] and training plateaus become common occurrences,[17,21,22,23] leading researchers and athletes to believe that something is missing (nutritionally) in the pre or post exercise period that would otherwise continue progression from proper unaccustomed training.[3,24,25,26] In other words, although at some point aging clearly blunts the human response to exercise and nutrition, unaccustomed exercise is a successful continual trigger event for the desired result, leaving nutritional/bio-ingredient modulations to deliver the progressive outcome including maintaining health.[1,8,22,27,28] These conditions set the stage for dietary supplementation when all else is equal and training and diet protocols are optimized for the desired progression, including attempts to stave off the eventual age-related inevitable final size and/or performance plateau.

Primary Pre-Workout Multiple Ingredient Rationale

The primary ingredients contained in NO7Rage[3] are individually well documented in accomplishing size, performance and nitric oxide increases under equal circumstances and compared to placebo. The ergogenic potential of: 1) creatine for size and strength;[29,30] 2) beta-alanine for force production and anaerobic endurance;[31,32] 3) caffeine,[33,34] glucuronolactone and taurine[35,36] for endurance and mental focus, are combined with the effects of Nitrosigine,[37,38] and L-citrulline[39,40,41] for their nitric oxide (NO) production potential to increase vasodilation, thus enhancing the inward and outward flow of these ergogenic ingredients and their metabolites and training-induced waste products. These ingredients combined, thus simultaneously ingested, may have additive effects setting the stage to maximize each training session's contribution to various adaptations including MPS by creating a post exercise musculoskeletal environment prepared for continuous positive change where further nutrition modulations related to improved recovery can now complete the desired adaptation result, helping to avoid common training plateaus and stave off the inevitable age/experience end to performance or size gains.

Nitric Oxide Boosters/Vasodilators

It is well established that regulation of cell volume is imperative to the functioning of a variety of different human cells, including swelling leading to a cellular increase in anabolism and shrinkage causing a decrease in protein synthesis.[42,43] Cellular swelling from increased blood flow initiated by exercise, related metabolites and subsequent

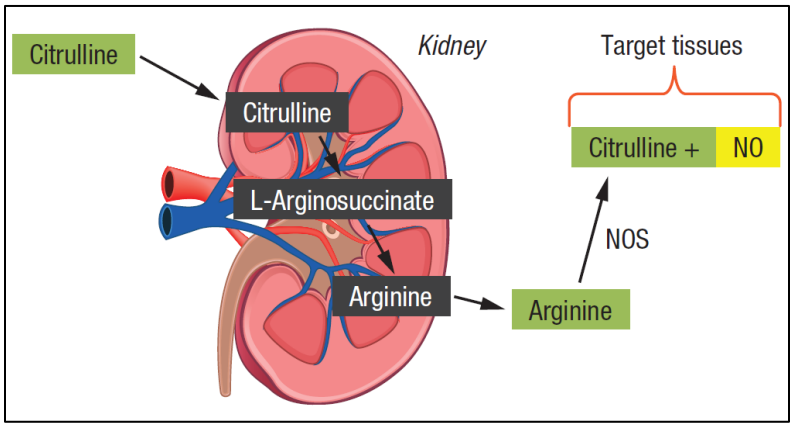
obligatory vasodilation are all considered part of the hypertrophy process, which has led researchers to develop supplements that may promote exercise hyperemia and resulting muscle fluid storage to enhance hypertrophy through the enhanced and prolonged swelling of muscle cells and nitric oxide production.[44] Often termed "cell volumizing or swelling," is suggested to contribute to muscle hypertrophy through an increase in muscle fluid retention from the exercise induced (repeated loaded muscle contractions) venous pooling and vasodilation of arteries.[45,46] This subsequent enhanced reperfusion of effected muscles is commonly explained as the "pump" (exercise-induced hyperemia).[47] Although mechanisms have not been completely elucidated, there is evidence that the action of cell swelling has a unique contribution (beyond its exercise-induced causes) to muscle hypertrophy,[48] possibly via the cell stretching being sensed by integrins in the cell membrane altering the protein synthesis signaling through gene transcription, mitogen-activated protein kinase (MAPK)[43] and amino acid uptake.[49] Collectively, the evidence continues to favor the use of isolated compounds that contribute to vasodilation and cell volume to produce a synergistic and potentially additive unique contribution to skeletal muscle hypertrophy.[44] Nitric oxide is known as a vasodilator that helps regulate blood flow and mitochondrial respiration, especially during exercise.[41,50] Increasing nitric oxide in muscle demonstrates effects before and after exercise such as increased muscle blood flow and contractility, glucose uptake, and recovery through satellite cell activation.[41,44,51] The combination of these effects from enhancing nitric oxide production and cell volume sets the stage for the use of NO precursor substances and other muscle cell swelling agents to improve athletic performance and skeletal muscle hypertrophy.

L-Citrulline as Citrulline Malate

L-Citrulline is converted to L-Arginine in the body, leading to increases in both L-Arginine and nitric oxide.

L-Citrulline is a naturally occurring alpha-amino acid. It is a non-essential amino acid and is not used in protein synthesis.[52,53] L-citrulline can be obtained from the diet and is also synthesized in the intestinal mucosa and liver from glutamine and ornithine.[54,55] L-citrulline passes through the liver unchanged, taken up by the kidneys where it is converted to L-arginine and released into circulation.[56] L-arginine is converted to nitric oxide by NO synthase in the endothelium of blood vessels and other tissues, with L-citrulline reformed in the process (see Figure 1).[53,54,57] An elevation in plasma L-arginine has been shown to improve endothelial function because the vascular endothelium uses NO to signal the surrounding smooth muscle to relax, thus resulting in vasodilation and increasing blood flow.[56,58]

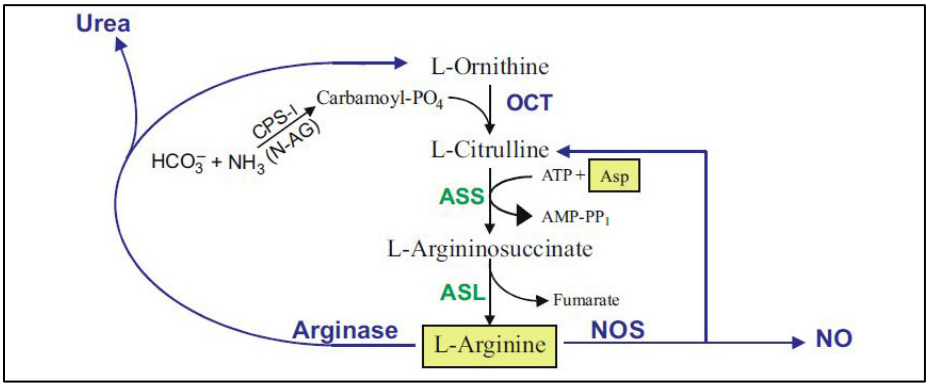
Figure 1 - Citrulline Conversion to Arginine and NO



The discovery of L-citrulline (LC) metabolic pathways described here (conversion to L-arginine) led researchers to believe LC is better than arginine as a supplement for NO production.[39,53,59] In fact, doses of 0.75 to 3.0 g of L-citrulline

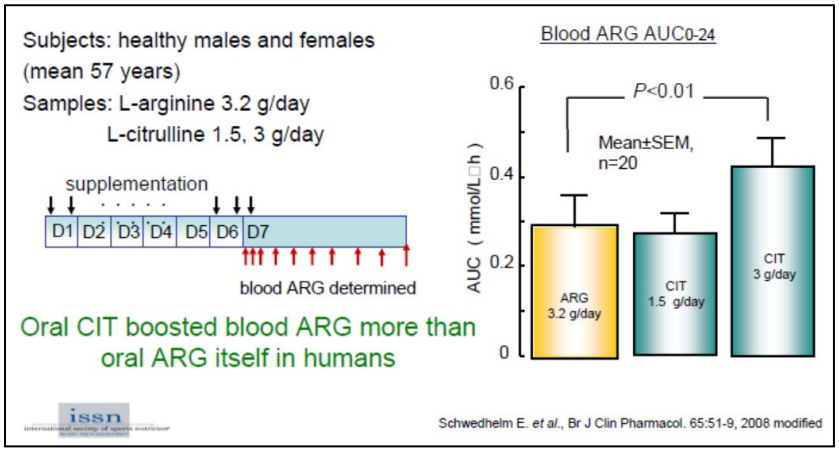
increase plasma L-arginine levels dose-dependently, and to a greater extent than L-arginine supplementation.[53,54] While LC escapes the liver unchanged, consumed L-arginine is metabolized by liver and intestinal arginase before it can reach the systemic circulation, significantly reducing its availability and leads to excessive production of urea.[52,53,54,60] Early research led to L-arginine becoming the primary amino acid found in nitric oxide producing supplements,[61] since it was shown to be involved in the production of NO[62,63,64,65,66] and creatine biosynthesis.[67] However, as described above, oral L-arginine's rapid metabolism by arginase activity makes it less effective at increasing NO production.[39,53,59,68,69,70,71] These actions gave rise to LC as the preferred or additional substrate for NO production since it is not metabolized in the intestines or liver and does not promote arginase activity, thus allowing the body to readily convert LC-to L-arginine and concurrently raising plasma and tissue levels of L-arginine, leading to enhanced NO production (see Figure 2).[69,70,72,73]

Figure 2 - Metabolic Pathway for NO Production



Schwedhelm et al. demonstrated LC supplementation's superiority to L-arginine in humans as shown in Figure 3[53] as well as El-Hattiab et al.[74] Abbreviations: CPS-I, carbamoyl PO_4 synthase I; N-AG, *N*-acetylglutamate

Figure 3 - Effect of Oral L-citrulline on Blood L-arginine in Humans



It has been shown that approximately 75% of LC taken up by the kidneys is converted to L-arginine and released into the circulation.[73,75] LC is contained in this product for its influences on blood vessels via its actions in NO production, vasodilation, blood flow acceleration and potential unique or synergistic performance contribution.[53,73,76,77,78,79,80] In other related studies using L-citrulline including citrulline malate (CM), Bailey et al. used 6 g/d of LC versus 6 g/d of

arginine and placebo and showed that LC supplementation, but not arginine or placebo, can improve blood pressure, $V0_2$ kinetics and exercise performance in healthy adults.[81] Because of the ability of LC to increase NO, and increases of NO have been associated with enhancing performance, supplementation with LC combined with a salt/anion of malic acid known as citrulline-malate (CM), has been studied alone (no supporting ingredients) in exercise generally using 2.4-6.0 g/d of LC or 8.0 g/d of CM. Some resistance training studies have shown improvements in completed repetitions and total work performed compared to placebo.[82,83,84,85,86] Suzuki et al. found that 2.4 g/d for seven days significantly improved cycling time trail performance compared to placebo and suggested the enhancement was due to the measured NO availability.[87] Other studies using LC or CM alone showed little to no performance enhancement.[88,89,90] Nevertheless, LC as CM is contained in this product to increase NO availability, which it does, and therefore may work in synergy with other cell volume and performance enhancing compound contributors, as described above, to support the hypertrophy process through enhanced training sessions.

The compound form of L-citrulline, citrulline malate (CM), is used in this formula as the L-citrulline component because both and LC and clinical doses of CM can evenly increase NO,[91] but CM may have an added ergogenic effect[82,83,84,85] based on the potential malate moiety's contribution in energy production via its metabolic role in the Krebs Cycle, specifically production of ATP.[92] Finally, LC and arginine combined may have additive effects on raising NO production.[93]

Nitrosigine - Better Forms of Arginine to Enhance Plasma Arginine for NO Production

L-arginine is an amino acid necessary for protein synthesis. As noted above, arginine is best known for its effects on the vascular system.[94] L-arginine is a substrate for the nitric oxide synthase (NOS) enzyme. NOS in vascular endothelial cells converts L-arginine to nitric oxide (NO), also known as endothelium-derived relaxation factor (EDRF), which causes vasodilation.[95,96] As previously noted, orally ingested L-arginine is relatively inefficient in raising NO production, especially compared to LC,[53] leading to continuous research into creating a form of oral arginine that may more efficiently raise plasma arginine to increase NO production thus avoiding injections or use of large oral doses that may cause gastric distress.[97,98] Nitrosigine (trade name for an inositol stabilized arginine silicate compound) is a tested and potentially effective oral related form of arginine that may accomplish an additive NO production effect when combined with CM.[98,99,100]

Nitrosigine

Nitrosigine* is an inositol stabilized arginine silicate compound that has been shown to enhance plasma arginine and markers of nitric oxide.[37,101] Kalman et al. used 1,500 mg/d in healthy subjects and measured significantly increased plasma arginine levels in 30 minutes that remained elevated for three hours. From the author's study, Figure 4 shows enhanced markers for NO levels which were superior to arginine HCl and found significantly enhanced blood proteins related to vasodilation and heart health.[37]

Figure 4 - Effect of Nitrosigine Supplementation on Plasma Arginine Levels[37]

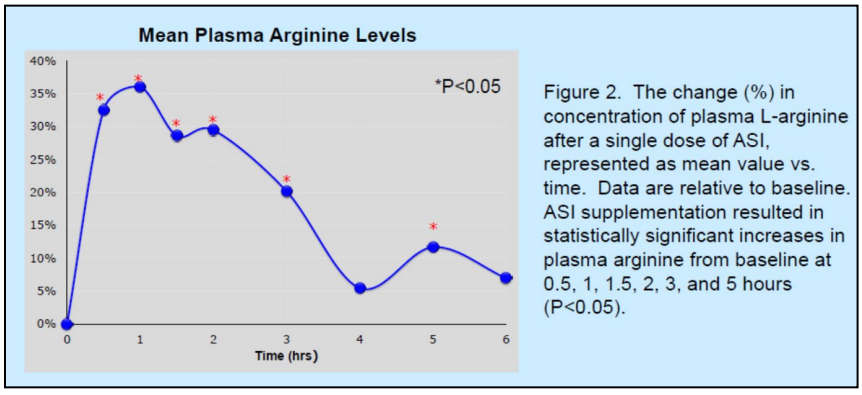
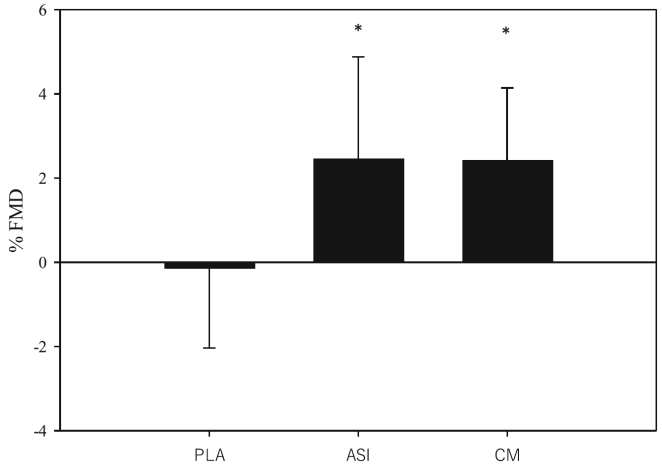


Figure 2. The change (%) in concentration of plasma L-arginine after a single dose of ASI, represented as mean value vs. time. Data are relative to baseline. ASI supplementation resulted in statistically significant increases in plasma arginine from baseline at 0.5, 1, 1.5, 2, 3, and 5 hours ($P<0.05$).

Komorowski et al. evaluated differences in arginine pharmacokinetics between inositol-stabilized arginine silicate (ASI;Nitrosigine®) and arginine hydrochloride (AHCl) in raising plasma arginine. [102] Ten males per group were randomly assigned to take a single oral dose of ASI or AHCl (each containing a total of 500 mg of arginine) for 14 days. ASI supplementation significantly increased plasma arginine levels at multiple time-points up to six hours post-dose whereas AHCl was elevated for only one hour. Additionally, results showed that ASI supplementation delivered a greater than 70% increase in plasma arginine area under the curve (AUC) compared to AHCl, suggesting that ASI is a more bioavailable and predictable source of arginine. [102]

A recent randomized double blind trial tested the effectiveness of 1.5 g of Nitrosigine, 8.0 g of citrulline malate (CM) and 8.0 g of placebo (dextrose) on vasodilation using ultrasound and flow mediated dilation (widening of an artery when blood flow increases in that artery), in healthy men and women.[100] The authors demonstrated that both 1.5 g of Nitrosigine and 8.0 g of CM significantly and equally increase endothelium response to shear stress – i.e. endothelial-dependent vasodilation (Figure 5 below). Their conclusion supported previous work that Nitrosigine can be part of an effective pre-workout supplement in producing NO and partially acts through a different mechanism than CM. The study showed that a 1.5 g dose of Nitrosigine may be equally as effective at increasing endothelial response as a larger 8.0 g dose of CM.[100] Because of these results including acting through different mechanisms to enhance arginine levels and subsequent NO production, both citrulline malate and Nitrosigine are included in this formula in established doses.

Figure 5 – Percentage Flow Mediated Dilation (FMD) Increase for Each Supplement Group.[100] (Results are presented as the mean change in percentage from pre supplement to post supplement. CM: 7.15-9.60; ASI (Nitrosigine) 8.0-10.48; Placebo: 8.01-7.87).



Ergogenic Aids

Creatine Monohydrate

See CreatineMonohydrate *PDSRG 3rd Edition* for complete details on goal, rationale, mechanisms of actions, clinical trial exercise results, dosing protocols, safety, effective use, myths, precautions, contraindications, etc. The safety and efficacy of creatine monohydrate in specific sport/exercise activities are well documented.[5,24,29,30,103]

Goal

The goal of supplementing creatine monohydrate (CM) is to increase intramuscular levels of creatine and speed the regeneration of creatine phosphate (PCr) beyond what can practically be accomplished by diet alone. Creatine loading is much like the goal of carbohydrate loading by endurance athletes but instead of increasing glycogen storage and

thus delaying glycogen depletion, loading creatine would enhance PCr levels and delay its depletion and speed repletion.[29,30] This practice would benefit strength and power activities that are dependent on PCr as an energy source, including sprinting and weightlifting and their crossover activities which also require repetitive bursts of speed and power, such as specific intermittent activity (team sports – i.e. combined intermittent aerobic and anaerobic activity such as football, baseball, rugby, hockey, etc.).[24,29,30,104, 105]

Rationale

Creatine (Cr) is an amino compound found in skeletal, cardiac, and smooth muscle that plays an indispensable role in energy metabolism in these tissues.[106] The phosphorylated form, creatine phosphate, provides an immediate energy source for the brain and muscles and therefore, the primary rationales for supplementation are to increase, replete and prolong this energy source and assist in recovery.[4,28,29,30,104,106]

Mechanisms of Action Summary

Creatine supplementation has been shown to:

- Increase the body's creatine pool to enhance PCr levels and delay its depletion while accelerating repletion, making more available ATP[105,107,108,109,110,111,112,113]
- Increase the total creatine pool resulting in more rapid ATP regeneration between exercise sets, allowing athletes to maintain a greater training intensity and improve the quality of the workouts throughout the entire training period. In other words, the result is improved training sessions that can build on each other.[114,115]
- Cause a reduction in plasma concentrations of hypoxanthine and lactate following exercise, suggesting lower levels of anaerobic glycolysis, another possible contribution to delaying muscular fatigue by attenuating the exercise induced decrease in muscle pH[116,117]
- Initiate changes in gene expression and cell swelling[44,118,119,120,121]
- Increase satellite cell proliferation and insulin-like growth factor signaling[112,122]
- Increase growth hormone[122,123]
- Cause alterations in myogenic transcription factors leading to a reduction in serum myostatin (muscle growth inhibitor)[122,124]
- Improve neuromuscular function (facilitating the reuptake of Ca^{2+} into sarcoplasmic reticulum)[125,126,127]
- Reduce exercise induced blood lactate[116,128,129]
- Participate in reducing muscle damage from high intensity resistance training and endurance exercise[130,131,132]

Creatine Effective Dose in NO7Rage³

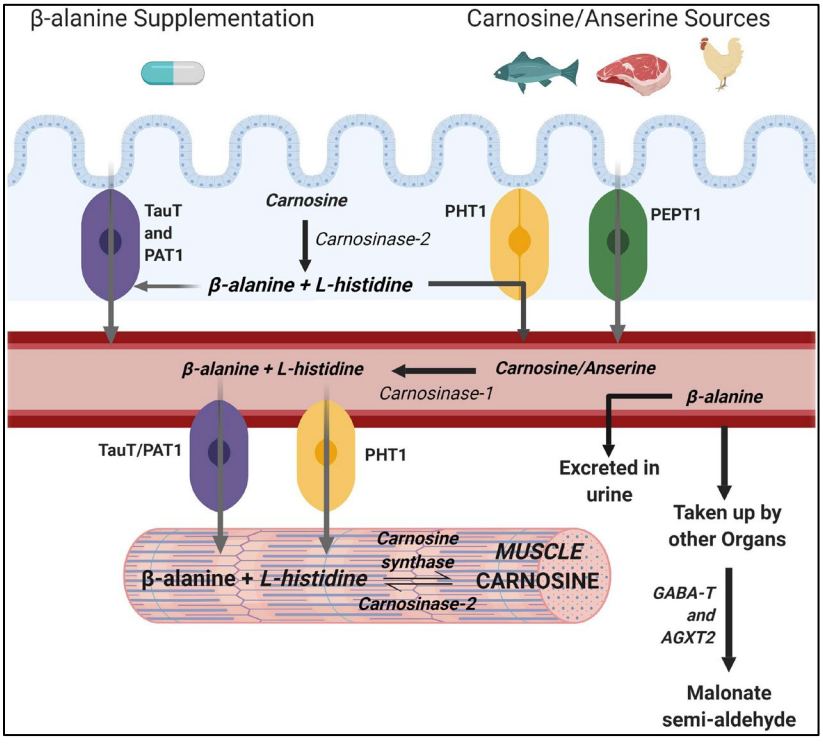
The most common way to maximize muscle creatine stores is to start with a loading phase of 20 g of creatine monohydrate (CM) per day split into four daily intakes of 5.0 g each; or ideally 0.14 g of CM/lb/d (ex: 200 lbs =28 g) split in four 7.0 g servings),[30,133] followed by a maintenance phase of 3.0 to 5.0 g CM/d or 0.014 g CM/lb/d (dotFIT prefers 0.03 g CM/lb/d based on experience and other experts[30,134]) for the duration of the supplementation period. A single daily dose of 3.0-5.0 g (as contained in NO7Rage³) has been shown to achieve maximum muscle creatine stores after approximately 30 days and therefore is considered an effective dose, albeit the ***initial*** performance effects may be less than if loading took place, but saturation should be accomplished by end of week four.[29,111,134] Therefore, if creatine benefits are desired and no other creatine products are being used daily, NO7Rage³ should be consumed daily because to maintain muscle creatine saturation, it requires ***daily*** ingestion of a minimum of 3.0-5.0 g beyond general food intake. See Muscle Stacks for combining creatine products.

β-alanine

Beta-alanine (BA) is a non-proteogenic amino acid (not used by the body to synthesize proteins) formed in the liver from the degradation of uracil and thymine and obtained by humans from the consumption of primarily animal

meats.[135] Harris et al. showed that β-alanine availability is the rate-limiting factor for carnosine synthesis in skeletal muscle and BA supplementation can increase intramuscular levels of carnosine.[135,136] Carnosine is a naturally occurring dipeptide, formed by combining L-histidine and BA using the enzyme carnosine synthetase.[137] Carnosine (β-Alanyl-L-histidine) has many physiological functions including acting as an intramuscular pH buffer, (sequestering protons [H+])[137,138,139,140,141] and therefore increasing carnosine levels can reduce exercise-induced acidosis and potentially prolong time to exhaustion.[31,142,143,144] Evidence has also pointed to carnosine being more effective at sequestering protons than bicarbonate and inorganic phosphate.[140,145,146,147,148] Carnosinase, the enzyme that catalyzes the breakdown of carnosine, is located in serum and other tissues but not in skeletal muscle (SM), rendering oral carnosine supplementation inefficient in raising human muscle carnosine levels.[140,149,150] The ingested carnosine would be metabolized to its constituent amino acids before reaching skeletal muscle (see Figure 6 Carnosine Metabolism by Perim et al. [151]).[149,152] To be sure, very little carnosine is located in human blood.[153] This fact gives rise to BA supplementation since it can enter SM and be converted to carnosine where its molecular structure of nitrogen atoms on the imidazole ring can attract protons at physiological pH.[146] The contribution of carnosine to the buffering capacity of muscle is significant but not totally quantified.[139,154,155] What is clear is beta-alanine supplementation's (BAS) ability to increase muscle carnosine concentrations[135,140,156] and attenuate exercise induced reductions in pH,[157] highlighting that carnosine plays an important role in buffering exercise-induced acidosis, thus potentially delaying fatigue and/or improving performance.[31,140,142,143,144,158]

Figure 6 - Beta-Alanine Transport And Subsequent And Conversion To Carnosine In Skeletal Muscle.[151]



Carnosine has also been shown to act as an antioxidant by scavenging free radicals and singlet oxygen,[159] thereby reducing oxidative stress.[160,161,162] Reactive oxygen species (ROS) are produced at an accelerated rate during exercise[163] and thought to contribute to muscle fatigue and exercise-induced muscle damage.[164] Perim et al. found that carnosine functions as an acrolein (highly reactive toxin) scavenger in skeletal muscle, which is important to the detoxification of this aldehyde produced during exercise.[151] The authors found that β-alanine supplementation

enhanced carnosine's aldehyde-detoxification function, offering support for the role of carnosine in the detoxification of lipid peroxidation by-products formed during exercise, which may benefit athletes participating in regular bouts of intense exercise and possibly contribute in the longer term to BA's ergogenic effects.[151,161]

In summary, since BA has been shown to be the rate-limiting precursor to carnosine synthesis, BAS has been shown to consistently increase skeletal muscle carnosine levels regardless of baseline values[165] and may subsequently, through its skeletal muscle buffering and antioxidant capacities, improve performance during high-intensity exercise and/or enhance the quality/capacity of training in strength and power athletes especially in activities when lactic acid buildup is a factor in fatigue.[31,32,142,143,144,149,158,166,167] Further, some evidence in specialized activities suggests that co-ingestion of BAS and sodium bicarbonate (SB), also used as a pH buffering agent, may deliver an increase in exercise benefits over BA alone through an additive increase in intracellular and extracellular buffering capacity.[148,158,168,169] If SB were to be used in addition to BA, it would require separate supplementation to control the loading and proper daily dosing because a MIPS containing stimulants and other ingredients, would not allow for effective dosing without compromising one of the other ingredient's safety or efficacy profile.

Beta-alanine and Exercise Studies

Early studies, where BAS compared to a placebo were shown to improve exercise induced lean body mass,[170,171] endurance performance,[171] training volume while reducing feelings of fatigue,[172] sprint performance in endurance cycling,[173] and muscle endurance in the elderly,[174] helped establish current effective doses. These studies also demonstrated safety.[178,175,176]

Beta-alanine supplementation compared to placebo has been shown to be effective in improving performance in certain activities (primarily repeated high intensity movements) using dosages ranging from 4-6 grams per day for a minimum of four weeks.[31] Results in exercise measures to a certain extent have been averaged to ~2.85% improvement, which is significant in all aspects of competitive performance.[31]

In a systematic review by Zanella et al. of BAS in a wide range of athletes, sports and non-athletes, less evidence was found for improving performance, but BAS showed improvement in perceived exertion and biochemical parameters related to muscle fatigue. Average intervention period was five weeks with a mean dosage of 4.8 grams per day.[32] The mixed results may be partially related to dosage variances and certain activities that are generally not affected by BAS, both conditions, which might water-down an overall analysis. In other words certain exercise-type sub-groups may have prospered more and especially at higher dosages.[32,158] Additionally, human muscle carnosine levels generally range from 4.5-18.0 mmol per pound of dry weight with 9.0-13.6 mmol/lb. being the average.[177,178,179] Therefore, differences in individual outcomes using proper BAS dosing are also likely due to a user's baseline carnosine levels, which may be higher in males, persons with higher percentages of type II fibers, high meat diets and trained athletes.[142,177,178,179,180,181] Further, Perim et al. describes various modifiable factors including dose, duration, meal co-ingestion, co-supplementation with other compounds, and type of exercise, which may affect or maximize beta-alanine muscle carnosine response to BA supplementation.[151] The review by Brisola et al.[144] on the effects of BAS on different sports modalities uncovered inconsistent results in aerobic parameters,[182] strength exercises and intermittent high-intensity work,[158] but found strong evidence of BAS for improving work capacity at the neuromuscular threshold,[182] and supramaximal continuous mode intermittent exercise.[31,32,144,158] The authors named sports such as 4 km cycling racing, swimming 100 and 200 meters,[183] combat modalities[184] and water polo,[183,185] as sports modalities where participants may benefit from BAS.[144] Further, the Saunders et al. systematic review and meta-analysis of BAS in exercise (40 studies using 65 different exercise protocols and totaling 70 measures in 1,461 participants) found a significant overall effect size of 0.18 (0.8 to .28). Duration and type of exercise were the major moderators of effect sizes showing a greater effect size for exercise capacity compared to performance.[158] Larger effect sizes were found in exercises 0.5 to 10 minutes in duration (such as 4 km cycling; 100, 200 and 400 meter swimming; 400, 800 and 1500 meter running, etc.) coinciding with previous and subsequent reviews.[144,186] But in contrast to the Trexler et al. position and summary,[31] Saunders et al. found exercise duration of longer than four

minutes yielded slightly higher effect sizes than exercise less than four minutes (0.233 vs 0.210)[158] commenting that activities of six to seven minutes may benefit more than shorter intense continual movements since BAS's primary mechanism is increasing carnosine, which in turn increases pH buffering. Regardless of positive effect sizes related to the activities studied, any major or minor benefit compared to placebo is of consequence to competitive athletes. Readers interested in individually studied exercise protocols and results are referred to Tables 1-3 in the Saunders et al. paper titled "β-alanine supplementation to improve exercise capacity and performance: a systematic review and meta-analysis."[158]

Related Studies That Help Determine Effective Dosages and Type of Activities That Benefit From BAS

- Painelli et al. demonstrated that 6.4 g/d for four weeks improved repeated high intensity cycling performance in both trained and untrained athletes.[142] This was an important study because of other similar studies showing modest or no performance improvement in highly trained athletes,[148,187,188,189,190] which was probably due to dosages, testing protocols (not sufficient in intensity or duration to be influenced by increased carnosine-induced buffering [decreased pH]) or high percentage of non-responders based on carnosine baseline conditions described earlier.[142,177,178,179,180,181]
- Using 4.8 g/d of BAS, Gross et al. showed improvements in explosive and repeated jump performance in elite alpine skiers. The authors surmised that BAS enhancement of muscle contractility could explain the improved explosiveness and repeated jump performance.[191]
- Ducker et al. used 36 mg/lb/day for 28 days which resulted in improved 800-meter track performance in club runners when compared to the same subjects under the same conditions with no supplementation.[192]
- Using 6 g/d of BAS, Hoffman et al. found 30-days of BA ingestion increased muscle carnosine content and improved aspects of military specific performance including cognitive skills (although brain carnosine was not increased).[193]
- Hoffman et al. used an assessment on military performance supplementation and found that over 50% of military personnel use dietary supplements for this purpose. They also determined that mounting evidence supporting the use of BAS in competitive and recreational athletes would suggest similar benefits for tactical athletes and recent studies (as in the above) in military personnel provide direct support for the use of BAS for enhancing combat-specific performance. In this case, BAS appears to be most beneficial for related high-intensity activities lasting 60-300 seconds. Additionally, though evidence is limited, BA supplementation may enhance cognitive function and promote resiliency during highly stressful situations.[194]
- In a 2014 systematic review on BAS, Quesnele et al. found moderate to high quality studies supporting that BA may increase power output and training capacity, decrease feelings of fatigue and exhaustion, and have positive effects on body composition and carnosine content. They also suggested that side effects may be under-reported (referring primarily to paresthesia or harmless tingling).[195]
- Of interest are the findings by Invernizzi et al. that acute (2 g of carnosine and 2 g BA taken 4 hours before test) supplementation produced positive effects on maximum voluntary contractions and jumps after a fatiguing (45 seconds of jumping) protocol and improved jumping performance during the 45 seconds of continuous jumping. Additionally, carnosine and BA reduced the rate of perceived exertion (RPE) and muscular pain 24 hours after the fatiguing protocol.[196]
- Notwithstanding the previous citation, in a review article on ergogenic effects of nutrition including supplementation, Sahlin summarized that there is clear evidence that prolonged periods with high doses of BAS can increase muscle carnosine concentration leading to an enhanced muscle pH buffering capacity with improvements in performance. The ergogenic effects are well documented in events lasting 1–4 minutes, during which lactic acidosis is most prominent.[197]
- Gross et al. found that BAS increased leg muscle carnosine (32 ± 13 %) but buffering capacity and incremental cycling were not affected. However, during 90 second severe cycling, BA supplementation increased aerobic

energy contribution concurrent with reduced O_2 deficit (-5.0 ± 5.0 %) and muscle lactate accumulation (-23 ± 30 %), while having no effect on pH. Beta-alanine also enhanced motivation and perceived state during the high intensity-training test. The authors concluded that although BAS did not affect buffering considerably, it had beneficial effects on severe exercise metabolism as well as psychological parameters during intense training phases.[198]

- Carpentier et al. found that using 4.0-5.6 g/d BAS in male and female trained athletes that supplementation resulted in a slight improvement of explosive force after 45 maximal consecutive jumps in these young athletes.[199]
- Glen et al., discerning those females may be more sensitive to the benefits of BAS (lower initial baseline carnosine levels) and that baseline intramuscular carnosine levels also naturally decrease with age, investigated trained master female cyclists using 800 mg four times daily for 28 days. The authors found no differences existed between groups at baseline or at the 7, 14, and 21-day time points for any variables. But at the last time point (28 days), when evaluating lower-body isokinetic strength (ISO), total work performed during the assessment (24.0% vs. 16.8% change) in flexion and average peak torque (5.4% vs. 2.9% change) in extension were significantly increased from baseline in BAS compared to placebo. No differences were displayed in handgrip strength or body composition. Therefore, 28-days of BAS increased peak torque and work completed, demonstrating that BAS improves lower body exercise performance in female master athletes.[200]
- In the same vein as the previous citation, Glenn et al. used the same dosing in master female cyclists and found 28 days of BAS increased cycling performance by enhanced time to exhaustion and total work completed, which were associated with lactate clearance during passive rest.[201]
- Furst et al. administered only 2.4 g/day of BA and found that 28-days of BAS in aging men and women increases endurance exercise performance and executive function. Their conclusion was that the study findings "reinforced that BAS correlates with improved exercise performance with potential secondary effects leading to improved muscle strength, decreased fall risk and improved cardiovascular health."[202]
- Santana et al. used 5.0 g of BA or placebo for 23 days in physically active adults to test performance in a 10 KM running time trial. Blood lactate concentration was measured after the 10 KM tests, before and after 23 days of supplementation. As in similar exercise protocols and dosage, compared to placebo, BAS improved the 10 KM running time trial and reduced lactate concentration.[203]
- In an interesting dosage breakout and description, Rosas et al. tested BAS on maximal-intensity exercise and endurance in female soccer players. The BAS group consumed 4.8 g/day (~38 mg/lb) divided into six doses of 0.8 g (0.7 mg/lb) that were ingested every two hours for six weeks (total of 201.6 g).[204] Because the BAS group had greater improvements in endurance and repeated jumping and sprinting performances, the authors concluded that "BAS during plyometric training may add further adaptive changes related to endurance, repeated sprinting and jumping ability." In other words, improved regular training results may translate to the field of play.[204] However, in the Smith et al. pilot study using BAS at 6.4 g/day for six weeks in rugby players, the authors found no improved performance effects in the BAS group compared to placebo, again suggesting BAS may not act in all related sports (i.e. specific intermittent athletes in team sports that combine intermittent aerobic and anaerobic activity) as a direct ergogenic aid.[205] Further, Bassinello, et al. found four weeks of BAS at 6.4 g/day to improve isometric (~17% compared to placebo), but not isokinetic or isotonic endurance performance.[206] Notwithstanding all the above as BAS relates to certain sports or specific activity benefits, improvements using BAS during training should not be ignored because consistently better training outcomes build on each other to help support a better, stronger athlete on "game days." Example: Maté-Muñoz et al. gave 30 subjects either BAS at 6.4 g/day (8 x 800 mg/dose at least 1.5 hours apart) or placebo during a 5-week strength training program. Compared to placebo the BAS group had greater increases in multiple performance tests: 1) pounds lifted a 1RM; 2) number of sets completed; 3) power output gains and maximum power; 4)power output for loads equivalent to 1RM; 5) pre-post gain in pounds lifted at 1RM in an incremental load test. Depending on the sports activity, these greater training adaptation results compared to placebo may translate to greater sports activity performance over time.[207]

B-alanine Dosing

From all data to date, it appears that 3.2-7.0 g daily, divided as necessary into 800-1,600 mg servings (serving size would help avoid potential paresthesia – i.e. generally harmless tingling[135,208]), for a minimum of four weeks (40-60% increase in carnosine levels[165]) and taken with food/carbohydrate including pre-workout snack/shake,[209,210] may all contribute in reaching maximum muscle levels of carnosine, thus optimizing its buffering effect during exercise.[1,31,32,144,158] Some evidence supports a lower dosage to maintain levels but that information is limited. Stegen et al. found that after 46 days of loading 3.2 g/day (4 X 800 mg), men and women were able to maintain muscle carnosine levels 30-50% above baseline using 1.2 g/d- for the remaining duration of the supplement period.[211] To maintain maximum carnosine levels, a maintenance dose of at least 3.2-6.4 g/day may be appropriate since little research says otherwise.

Safety

As mentioned, paresthesia (tingling) is a commonly known side effect of beta-alanine in individuals ingesting more than 800 mg of BA in one dose unless using a time-released formula.[135,208] If present, paresthesia generally disappears within 60 to 90 minutes following ingestion.[212] It's been hypothesized that BA activates Mas-related genes,[213] or sensory neuron specific G-protein coupled receptors that reach the skin.[214] If present, paresthesia generally affects the face, hands or neck and is dose dependent (the higher the dose, the greater chance of effect). Currently there is no data to support that this tingling is harmful in any way.[31,158,185] Further, Dolan et al. produced a systematic risk assessment and meta-analysis on the use of oral BAS and potential adverse effects in 101 human and 50 animal studies. Paresthesia was the only reported side effect with supplementation relative to placebo. The review concluded that BAS "within the doses used in the available research designs, does not adversely affect those consuming it."[215]

β-alanine Summary

Based on the current available peer reviewed data as shown above, beta-alanine supplementation appears safe and effective for improving performance in certain exercise/sport activities in healthy subjects at recommended doses. Four weeks of BAS at 3.2–7.0 g/d consumed in split dosages throughout the day (0.8-1.6 g every 3-4 hours to avoid potential acute effects of tingling or flushing) significantly raises muscle carnosine concentrations thus increasing intracellular pH buffering capacity. BAS can lead to increases in exercise performance especially in repeated high intensity activities lasting 30 seconds to 10 minutes. BAS may increase power output and training/exercise capacity (maximum amount of physical exertion a subject can sustain*), decrease feelings of fatigue and exhaustion with greater effects in untrained people and those with lower baseline levels of carnosine. Because of beta-alanine's unique mechanisms of action, combining it with other safe and proven ergogenic ingredients may deliver additive benefits important to competitive athletes.

** Exercise capacity tests are defined as those requiring exertion to the point of volitional fatigue (when muscle can no longer perform the action in perfect form – i.e., must alter/cheat to continue).*

Beta-alanine and Creatine in Combination

Note: *there are many multi-ingredient "pre-workout" supplements (MIPS) commercially available that contain both creatine and beta-alanine along with plentiful other ingredients (e.g. B-vitamins, amino acids, herbs, etc.) including stimulants (e.g. synephrine, caffeine, etc.) that will not be discussed here because of the complexity to establish an individual ingredient's contributions to a specified outcome.[216,217,218] However, many of the MIPS products that also include beta-alanine and creatine together, have been tested with good results.[219] Moreover, none to our knowledge have been shown to be harmful when formulated by the letter of the law (no illegal substances added) thus suggesting simultaneous ingestion of these types of ingredients appear to be generally safe in healthy individuals.[216,217,219,220,221]*

Beta-alanine and creatine monohydrate, both well-established ergogenic aids, are also commonly co-ingested by strength and power athletes with the goal of producing additive effects on performance or size as opposed to when used individually. Since both compounds have unique mechanisms of actions as described above, the rationale for

simultaneously ingesting them is to deliver a synergistic effect that would produce additive performance gains without one of these ingredients normal improvements simply overwhelming the other's contribution - i.e., are the gains from creatine supplementation at a point where BAS impact on pH buffering becomes fruitless or at least unnoticeable? Creatine supplementation increases the total muscle creatine pool allowing greater energy substrate availability and repletion while also improving the anabolic environment throughout the training and recovery periods, while BAS acts as an intramuscular pH buffer to reduce exercise-induced acidosis to extend time to fatigue. The studies below are examples of trials designed to determine if the co-ingestion of BAS and CS would deliver a superior performance contribution than either taken alone.

Relevant Studies

- Hoffman et al. tested placebo (P), creatine (C) and creatine plus beta-alanine (CA) on strength, power, body composition, and endocrine changes in 33 college football players during 10 weeks of training. During each testing session subjects were assessed for strength (maximum bench press and squat), power (Wingate anaerobic power test, 20-jump test), and body composition. Changes in lean body mass and percent body fat were greater in CA compared to C or P. Significantly greater strength improvements were seen in CA and C compared to P. Resting testosterone concentrations were elevated in C, but no other significant endocrine changes were found. Their conclusion was while the study validated the efficacy of creatine and creatine plus beta-alanine on strength performance, "creatine plus beta-alanine supplementation appeared to have the greatest effect on lean tissue accruement and body fat composition."[222]
- Zoeller et al. in a double-blind, placebo-controlled study, examined the effects of four weeks of placebo (P), beta-alanine alone (BA), creatine alone (C) and beta-alanine plus creatine (BAC) supplementation on indices of endurance performance in 55 male athletes performing a graded exercise test on a cycle ergometer to determine VO_2 peak, time to exhaustion (TTE), power output, VO_2, and percent VO_2 peak associated with ventilatory threshold and lactate threshold. They found no significant group effects, but within groups there was a significant time effect observed for BAC on five of the eight parameters measured, suggesting that BAC supplementation may potentially enhance endurance performance.[223]
- Stout et al. examined the effects of 28 days of beta-alanine (BA) and creatine (C) supplementation together (BAC) and alone versus placebo (P) on the onset of neuromuscular fatigue by using the physical working capacity at neuromuscular fatigue threshold (PWC(FT)) test in untrained men. PWC(FT) values for the BA and BAC groups were greater than those for the P. However, there were no differences between the C vs. P, BAC vs. BA, C vs. BA, or C vs. BAC groups. Results suggested that BA supplementation may delay the onset of neuromuscular fatigue and there appeared to be no additive or unique effects of C vs. BA alone on the onset of neuromuscular fatigue in this testing protocol.[224]
- Okudan et al., after 28 days of creatine (CR) at 5.0 g and beta-alanine supplementation (BAS) at 1.6 g twice daily found that separately each increased mean power and delayed fatigue but CR + BAS also increased peak power significantly in untrained exercisers.[225] Using relatively the same dosing, Kresta et al. found no consistent additive benefits of BAS combined with creatine over creatine alone in recreationally active women.[226]
- Durkalec-Michalski, Krzysztof et al. found that BAS combined with creatine supplementation (CS) in sprinters and endurance athletes in natural training conditions performed better than CS and with an extra-cellular alkaline buffering agent (ALK) and placebo.[227] At the end of eight weeks they found that the BAS and creatine group had greater increases in fat-free mass and exercise adaptation than CS with ALK. The purpose of highlighting this result is only to show that there had to be an incremental effect from the BAS since CS was in both groups.[227]

In totality and considering their individual and unique mechanisms of actions, most researchers and athletes alike believe that under certain athletic conditions/protocols and individual physiologic states, the combination of BAS and

CS may contribute in an additive effect size manner.[29,31,197,220,222,223.224,225,228,229] Furthermore, supplementing simultaneously with creatine and beta alanine has been shown to be safe as well as effective[31,220,222,223,224,225,227,230,231,232,233,234,235]

Mental Performance, Focus and Ergogenic Aid

Caffeine

Caffeine's brief discussion in this section, including summaries of basic mechanisms of action, is solely related to its rationale for inclusion in the NO7 product. Readers are referred to the "Caffeine" section in the WorkoutExtreme document for expanded details on caffeine and its metabolism including mechanisms of action related to specific sports activities, effects on health, cognitive and physical performance, myths, regulation in sports and more.

The use of caffeine supplementation (CAS) in many sports activities is widespread and proven to be a safe and effective ergogenic aid improving both physical and cognitive performance outcomes compared to placebo.[3,33,34,236,237] Further, caffeine (CA) may be the most commonly consumed pre-exercise ingredient, whether it's done deliberately as in purposeful calibrated pre-exercise use through supplementation,[3,33,34,216,217,218,219,236,238,239] or unintentionally as in routine daily consumption of caffeinated beverages such as coffee, tea or energy drinks, as caffeine is the most widely consumed drug (psychostimulant) in the world.[240,241] In the sports and fitness community there is little to no argument that caffeine supplemented properly can significantly improve performance in a variety of areas and activities, including but not limited to: muscle strength, speed, anaerobic power and jumping, as well as aerobic and muscular endurance, all of which can potentially transfer to most any strength and sport activities including specific actions within many team sports.[34,237,242,243,244,245]

Caffeine (1,3,7- trimethylxanthine) is a methylxanthine compound formed when three methyl groups are substituted on the parent compound xanthine and is structurally related to theophylline, theobromine, and uric acid.[246,247] It is 100% bioavailable after oral ingestion, and is metabolized primarily in the liver producing among others, the metabolites paraxanthine, theophylline and theobromine.[248,249,250] The half-life of caffeine in healthy adults is 5-6 hours.[247,251] Caffeine is rapidly absorbed from the gut and transported quickly and efficiently to tissues.[252,253,254,255] Peak tissue concentrations of caffeine and its constituents are reached generally one hour post ingestion,[252,255,256,257] including crossing the blood brain barrier.[254,258] Based on tissue uptake and urinary clearance, tissue levels are decreased by 50-75% within 3-6 hours of ingestion.[252,259] Therefore, removal time from the bloodstream is approximately the same as caffeine's rate of absorption and metabolism.[255,259]

Caffeine is a primary ingredient in this formula because of its positive effects on athletic performance[3,33,34,216,217,218,219,236,238,239,240,241,242,243,244,259,260,261] including focus/alertness,[237,259,262,263,264,265,266,267] which also plays a role in training protocol motivation and success.[237,257,260] Caffeine anhydrous (caffeine extract without water) elicits a greater and more predictable response than caffeine delivered in caffeinated coffee, and is therefore used in this formula.[238,268,269,270,271]

Mechanisms of Action (Depicted in Figure 7)

Caffeine's universal performance enhancing abilities are generally attributed to the fact that adenosine receptors are found throughout the body and caffeine can occupy these receptors thereby stimulating the CNS and setting off a cascade of events that lead to nervous system stimulation, enhanced neurotransmitter activities including neuromuscular recruitment, frequency of calcium channel opening in muscle tissue and release of calcium into the myoplasm to enhance muscle contraction. These actions coincide, or contribute to, caffeine's ability to reduce pain perception and rate of perceived exertion (RPE) while helping to initiate and maintain arousal. Therefore, the primary goal of caffeine supplementation is to enhance acute exercise/sport activities and delay fatigue when compared to no supplementation.

Caffeine has been suggested to have multiple mechanisms of actions related to its performance and cognitive enhancing effects. Caffeine's stimulation of the central nervous system (CNS) and its ability to compete with

adenosine for its receptor sites (A_1, A_{2a} and A_b) is generally regarded as its primary ergogenic properties.[254,237,247,248,257,259,260,272] Because caffeine is structurally similar to adenosine, its affinity and subsequent occupation of adenosine receptors causes a buildup of intracellular 3,5-cyclic-adenosine monophosphate (cAMP) leading to greater activity in cells.[247,248,273,274,275] Adenosine is found in every part of the body because of its role in fundamental ATP-related energy metabolism, but it has a unique brain function. Concentrations of brain adenosine are increased by various types of physical and mental metabolic stress.[248,272,276] Stress-related adenosine increases appear to be produced mainly by extracellular metabolism of ATP. Brain adenosine acts to protect the brain by suppressing neural activity and by increasing blood flow through A_{2A} and A_{2B} receptors located on vascular smooth muscle.[256,277] Caffeine, via occupying adenosine receptors, elicits dis-inhibitory effects on neural activity helping to maintain or increase arousal and alertness.[252,253,254,256,272,278] It is conceivable that caffeine's effects are more neural than muscular since the central nervous system is a primary site of caffeine's actions.[257,275,279] The enhanced sympathetic stimulation and/or the direct adenosine antagonism by caffeine have been shown to be responsible for caffeine's glycogen sparing effects through increasing lipolysis and fat oxidation as measured by a decrease in respiratory exchanged ratio (RER) during submaximal exercise.[280,281] Cruz et al. observed these results.[282] They found, using 2.75 mg/lb of caffeine, an improvement of 22% in time to exhaustion during maximum lactate steady state (MLSS) workload, and an accompanied decrease in respiratory exchange ratio (RER), demonstrating the favorable change in energy substrate use. The lower RER observed at MLSS suggests enhanced fat oxidation and depressed carbohydrate combustion after caffeine ingestion.[282] In these and other studies, the performance improvements were based upon an increased energy reliance on fat metabolism, as shown by increased free fatty acid concentrations and lower RER.[280,281,282,283] On the other hand, Glaister et al. had participants take caffeine one hour before activity at 2.3 mg/lb and measured its effects during submaximal exercise using multiple physiological tests including blood lactate concentrate (BLC), VO_2, RER, heart rate, ratings of perceived exertion (RPE) and minute ventilation.[284] The main finding, using a sophisticated testing protocol, was that caffeine compared to placebo stimulated glycolysis as shown by increases in BLC independent of exercise intensity but must have still been due to an increase in lactate efflux from the working muscles, therefore, supporting recent theories that caffeine's primary mechanisms are most likely related to its complex central and peripheral effects associated predominantly with the antagonism of the various adenosine receptors subtypes and leading to a corresponding increase in intracellular cyclic adenosine monophosphate.[259,260,285,286,287,288] In this case, a direct effect on skeletal muscle through the antagonism of A_1 adenosine receptors. Additionally, in this Glaister et al. study, they showed that the caffeine group suppressed RPE as in previous reports.[289] These main outcomes (glycogen stimulating/BLC and suppressed RPE) combined with significant multiple respiratory effects, give credence to caffeine's multifactorial whole body effects that primarily appear driven by changes in the central and peripheral nervous systems, especially when you consider its positive ergogenic effects across many ranges of intensities during both long and short-term activities, including when the compartmentalization of energy use appears unchanged compared to placebo during successful trials.[33,34,237,242,284,287,260,290,291]

The metabolites of caffeine mentioned above also contribute to caffeine's effects. Paraxanthine is responsible for an increase in the lipolysis process, releasing glycerol and fatty acids into the blood to be used as fuel by the muscles, thus potentially sparing glycogen.[250,254,292,293,294] Theobromine is a vasodilator that increases the amount of oxygen and nutrient flow to the brain and muscles.[275,293,294] Theophylline (vascular, bronchiole, muscular, and respiratory relaxant) acts as a smooth muscle relaxant that chiefly affects bronchioles and acts as a chronotrope and inotrope that increases heart rate and efficiency.[293,295,296]

Note on caffeine's vascular effects to control vascular tone: *CAs direct antagonism of vascular adenosine receptors promotes vasodilation and stimulation of endothelial cells to release nitric oxide further promoting relaxation of vascular smooth muscle cells. CA induced vasodilation becomes controlled by the increase in sympathetic tone from catecholamine release and positive cardiac inotropic and chronotropic effects, which promotes vasoconstriction. The total result of this complex interaction of constriction and dilation from caffeine and its metabolites is uniquely manifested by the individual user depending on dose, frequency of intake, genetics and possibly comorbidities such as diabetes or hypertension.*[247,293]

And finally, Cappelletti et al. supports the case that caffeine's effects on physical performance may also be related to the release of calcium from the sarcoplasmic reticulum and inhibition of its reuptake, reactions that would lead to an increase in nitric oxide through the activation of endothelial nitric oxide synthase (NOS).[297] The authors surmise that these actions may be associated with changes in neuromuscular function and increased contractile force in skeletal muscles[297,298] Figure 7 below from Sokemen et al.[299] depicts caffeine's proposed multiple mechanisms of action related to the molecule's known ergogenic effects.

Perceived Exertion and Muscle Pain

Reduced ratings of perceived exertion (RPE)[269,300,301] and/or sensations of muscle pain[257,302,303] during or following performance exercise trials using caffeine supplementation (CA) are often associated with enhanced performance outcomes.[257,260,284,289] These additional effects of caffeine supplementation can contribute to its ability to increase exercise intensity and total work, as well as increase time to exhaustion, and are probably tied to the CA adenosine blockade function.[254,257,259,260,272] Clearly adenosine levels increase during strenuous muscle activities[304] and when adenosine binds to the A_1 receptor site pain is induced.[305] Therefore, a significant portion of caffeine's ergogenic effects may be from its ability to mitigate the body's normal signals to slow down including CA antinociception properties (inhibition of A_1-, A_{2A}-and A_3Rs – i.e. receptor blockade leading to reduced pain[306]). In a meta-analysis by Doherty et al., it was surmised that caffeine's ability to reduce RPE might accomplish up to 30% of the measured improvement during constant load exercise trials.[289] Duncan et al. pointed out that along with reduced RPE, caffeine raised arousal and affective states, which may also contribute to its ergogenic effects.[302]

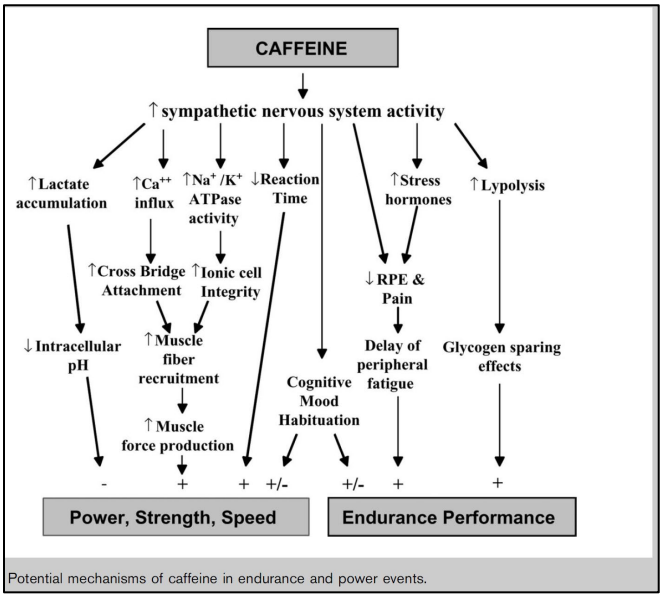


Figure 7
Caffeine's potential mechanisms of action through its stimulation of the CNS (adenosine receptor blockage) as depicted by Sokmen et al. with permission.

Responders and Non-responders

Like with all studies using supplements (or prescription drugs) there are caffeine investigations that showed little to no improvement in different performance measures in individuals and overall.[260] These results are generally attributed to dosing formulations (anhydrous or not), true non/less-responders (genetics [e.g. slow caffeine metabolism], lifestyle and habitual use[307]), type of activity, or study end-point measured. Some reports have discovered up to 30% of caffeine study participants derived little to no ergogenic benefits.[308,309] In fact, Womack et al. may have identified a genetic polymorphism as a primary reason for some people not deriving an ergogenic effect from caffeine supplementation.[310] Using 2.75 mg/lb in a 40-kilometer time trial, cyclists homozygous for the A variant (of the cytochrome P450 gene –faster caffeine metabolism) had a greater performance increase than those who possess the C variant (slower caffeine metabolism). Caffeine decreased 40-km time by an average of 3.8 minutes in the AA

homozygotes as compared to 1.3 minutes in the C allele carriers highlighting a specific polymorphism as a potential cause of variations in the performance effect of caffeine supplementation.[310] Polymorphisms of the ADORA2A gene (codes for A_2 receptors) may also influence individual responses to caffeine's stimulating effects.[311,312]

Data Summary

Caffeine exerts its effects by occupying adenosine receptors throughout the CNS and other body tissues leading to a cascade of events that collectively work to enhance cognitive and physical performance under both normal and energy/sleep deprived conditions. CA supplementation is dose dependent with significant variation in individual responses (e.g., responders, non-responders, fast and slow metabolizers). The ergogenic effects of caffeine have been demonstrated across a wide variety of cognitive and exercise activities including arousal, high intensity and anaerobic tests of power, agility, speed and muscular endurance that may transfer to related team sports; delay fatigue in endurance sports; and improvement in time trials. Caffeine does not upset fluid balance or induce diuresis during exercise.

Dosing

- Caffeine's effects on cognitive performance (alertness, vigilance, memory, etc.) are generally experienced at relatively lower doses such as .25-2.0 mg/lb of body weight.
- Dosages that induce improvements in exercise performance range from 1.4-3 mg/lb of body weight (not to exceed 600 mg) and taken approximately one-hour pre-activity.
- Except under unique circumstances, doses greater than 4.1 gm/lb of body weight appear to deliver no further benefit.
- For exercise performance, caffeine in the anhydrous form is preferred based on the ability to accurately assess and control the dosing.
- CA supplementation within recommended doses is considered safe for healthy individuals.
- Competitors should experiment with dosing described here during practice sessions in order to personalize their most effective protocol including testing abstention for two to four days.

NO7 Caffeine Dose

Based on weight, the anhydrous caffeine dose in NO7 at 1.5 to 2.5 scoops (225-375 mg) is within the range (1.4-2.75 mg/lb) that elicits both exercise and cognitive benefits for the average population.[34,237,242,243,260,268,287] We suggest not using other caffeine containing products within four hours of consuming NO7.

Glucuronolactone, Caffeine and Taurine

This combination of ingredients is common in energy drinks.[36,313,314] The reason they are included in this product with caffeine is for their potential additive effects to focus and performance/recovery. Based on solid evidence, it is easy to argue caffeine is the only ingredient of these three that delivers the desired effects described in the caffeine section above –i.e., mental/cognitive and/or physical performance improvements. However, studies using this combination have demonstrated similar success with a lower caffeine content, suggesting a possible additive (especially taurine) or at least a synergistic effect allowing lower caffeine doses, which may be important to certain caffeine sensitive individuals. Additionally, there appears to be little to no safety concerns with this combination.[36,313,313,314]

Taurine

Taurine (2-aminoethanesulfonic acid) is a semi-essential amino acid found in mammalian tissues that is not involved in protein synthesis.[315] The function of taurine is not completely understood but it is known that taurine modulates intracellular Ca^{2+} levels.[316,317] In skeletal muscle, its main roles are to facilitate Ca^{2+} dependent excitation contraction processes, contribute to the regulation of cellular volume, and aid in antioxidant defense from stress responses.[318,319,320] Its potent antioxidant role may contribute to its potential benefits in patients with heart failure.[321] Taurine also is involved in retinal photoreceptor activity, bile acid conjugation, white blood cell antioxidant activity,

central nervous system neuromodulation, platelet aggregation, cardiac contractility, sperm motility, growth, insulin activity,[322] and osmoregulation.[323,324]

Related Mechanism of Action

Dutka et al. studied taurine's (T) effects on sarcoplasmic reticulum Ca^2 (SR Ca^2) accumulation and contractility in human type I and II fibers in skeletal muscle, which is thought to be taurine's primary potential performance enhancing mechanism of action.[325] The study demonstrated that prolonged myoplasmic exposure to taurine (>10 minutes) significantly increases the rate of SR Ca^2 accumulation in both type I (which contains ~ 2 to 3 times more taurine than type II[326]) and II muscle fibers probably through taurine's actions in the sarcoplasmic reticulum lumen – i.e. most likely the result of taurine modifying sarcoplasmic reticulum $Ca2^+$-ATPase (SERCA) function from enhancing its maximum pumping rate and/or increasing its affinity for Ca^{2+} (See Figure 8[327]) Therefore, it is believed that taurine supplementation can enhance performance due to a greater ability to generate power through enhanced calcium regulation[328] by helping maintain maximum levels that would improve muscle contractile properties when taurine is otherwise at low physiological levels.[36,325] Finally, there have been reports that taurine interacts with certain neurotransmitter receptors in the CNS.[329,330]

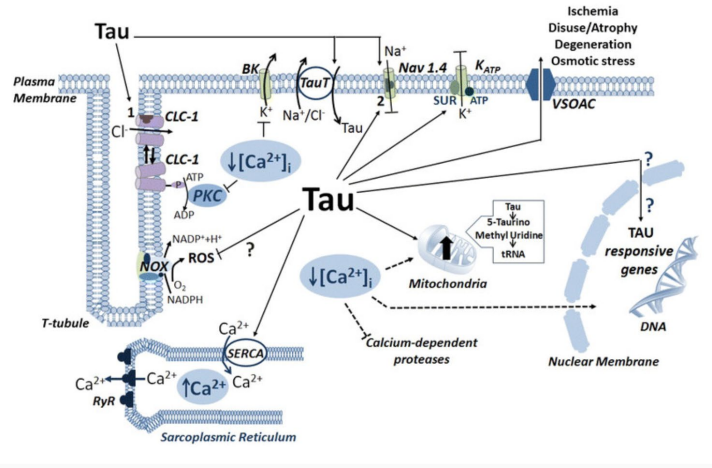


Figure 8 – Depiction of taurine's effects on modifying sarcoplasmic reticulum $Ca2^+$-ATPase (SERCA) function leading to enhanced calcium regulation, which under certain conditions, supplementation may lead to improved performance. Image adapted from De Luca et al.[327] and used per open access.

Generally, in purported energy products, taurine is used in combination with other ingredients such as caffeine, glucuronolactone, and carbohydrates. Studies are equivocal on the independent effect of taurine supplementation (TS) on muscle performance, but supplementation studies using one to six grams of taurine have yielded positive results related to muscle function, recovery[331,332] and endurance performance.[333,334]

Rutherford et al. found using 1.6 grams of taurine one hour before exercise did not increase time trial performance in well trained cyclists, but significantly increased fat oxidation (16% over 90 minutes).[335] In contrast, in a cycling time trial to exhaustion, Page et al. using 22.7mg/LB of body weight versus placebo found the supplement group to significantly increase time to exhaustion (10%) and decrease blood lactate (16.5%) and RPE.[336] Da Silva et al. showed taurine supplementation increased strength and decreased muscle soreness, lactate dehydrogenase levels, creatine kinase activity, and oxidative damage, but did not decrease the eccentric exercise inflammatory response following the activity.[337] The Song-Gyu Ra et al. study suggested using a combination of 3.2 g of branched chain amino acids (BCAA) and 2.0 g taurine, three times a day, for two weeks prior to and three days after exercise, to be useful for attenuating exercise-induced delayed onset muscle soreness (DOMS) and muscle damage.[338]

Milioni et al. found an acute dose of 6 g of TS before exercise did not substantially improve high intensity running performance and showed an unclear effect on alternative maximal accumulated oxygen deficit (MAODALT).[339]

Ward et al. found that a pre-exercise dose of 1,000 mg of taurine delivered no performance advantage during 4 km cycling time trials (TT) nor did it alter the blood buffering responses in trained cyclists.[340] Contrary to Ward, Balshaw et

al. found a 1.3 % improvement in 3 km TT running performance in well trained middle-distance athletes using an acute ingestion of 1,000 mg of taurine.[328]

In summary, TS in isolation has produced inconsistent performance enhancing effects at all ranges of doses but probably gives rise to its inclusion in many energy drink (ED) formulas. To this point, Souza et al. in a systematic review and meta-analysis (34 studies) on the effects of ED on physical performance found that the degree of improvement was associated with the taurine dosage. The author's conclusion: "The review and meta-analysis showed that ED intake improved performance in several physical and sport situations that included muscle strength protocols, jumping, endurance exercise tests and sport-specific action, and taurine dosage influenced the outcome.[36] The caffeine dosages ranged from 40 to 325 mg and taurine ranged from 71 to 3,105 mg. Compared to caffeine and taurine doses used in isolation for enhancing performance, the outcomes from this study appear to support a synergistic relationship between the two compounds in that the dosages found in these EDs were each generally lower but yielded similar benefits.[36,314]
And lastly, related to taurine in combination with caffeine, Warncok et al. studied caffeine (C), taurine (T), caffeine and taurine co-ingestion (C+T) or placebo (P) on repeated Wingate cycling performance and associated physiological responses.[341] Using C at 2.3 mg/lb of body weight, T at 22.25 mg/lb of body weight, C+T at 2.3 mg and 22.75 mg, P at 22.25 mg/lb of body weight, all supplements increased mean peak power (MPP), peak power (PP) and mean power (MP) compared to P, with greater MPP, PP and MP in T compared to C. Additionally C and C+T increased heart rate (HR), mean arterial pressure (MAP) and rate pressure product (RPP) compared to P and T at baseline but only remained higher in C compared to all conditions in the final sprint. Conclusion: "Taurine elicited greater improvements in performance compared to P, C or C+T, while reducing the typical chronotropic and pressor effects of caffeine (C)." While this latter study may not support an increase in performance through the synergy of caffeine and taurine compared to either in isolation, it does suggest that taurine at 3-4 grams one hour prior to exercise may be an effective performance dose and that the non-result from the addition of caffeine could be that dosage performance thresholds of each in the C+T trial were achieved and no further benefit attainable by combining the two. To this point, the difference between taurine and caffeine plus taurine was small to possible but certainly makes a case for taurine.[341]

Glucuronolactone

Glucuronolactone is a naturally occurring chemical that is an important structural component of nearly all connective tissues and found in many plant gums.[342] In the body, glucuronolactone is metabolized to glucaric acid, xylitol, and L-xylulose, and humans may also be able to use glucuronolactone as a precursor for ascorbic acid synthesis.[343] According to *The Merck Index*, it is also used as a detoxicant. The liver uses glucose to create glucuronolactone, which causes blood-glucuronide levels to rise. Glucuronides combine with toxic substances, by converting them to water-soluble conjugates, which are excreted in the urine.[344] Hypothetically, higher blood-glucuronides should help remove toxins from the body, leading to the claim that energy drinks are detoxifying.[345] We make no such claims. Its presence in this product (NO7Rage[3]), as mentioned above, is for any potential synergistic effect based on empirical data.[36,313] On this note, Miles-Chan et al. tested the non-caffeine bioactive ingredients in sugar free Red Bull (SFRB) against water and caffeine (WC). Their results were: SFRB and WC both increased REE to the same degree (+4%). But only SFRB briefly increased respiratory quotient (RQ) suggesting a temporary increase in carbohydrate oxidation that may have been due to the non-caffeine ingredient synergies (e.g., 240 mg/glucuronolactone and 800 mg/taurine).[346]
Although levels of glucuronolactone in energy drinks generally far exceed those found in standard diets, the European Food Safety Authority (EFSA) concluded that exposure to glucuronolactone from regular consumption of energy drinks is not a safety concern. The no-observed-adverse-effect level of glucuronolactone is 1,000 mg/kg/day.[347]

Energy Drinks Including Caffeine, Taurine and/or Glucuronolactone in Combination

Readers are directed to the WorkoutExtreme section for details on research related to the simultaneous ingestion of this combination of ingredients in energy drinks.

The bottom line is that caffeine dosing is effective for improving cognitive and physical performance and glucuronolactone and taurine do not appear to depress caffeine's well known effects and may produce a synergistic effect that would allow a lower dose of caffeine to produce higher dose effects.[36,314] Additionally, as Souza et al. found in the meta-analysis described above, taurine appears to be the primary ingredient, and possibly in a dose-dependent manner, that enhances the outcomes of energy drinks with formulas similar to the combination in NO7Rage[3] when compared to placebo.[36]

Glycerol

Glycerol (also called glycerine or glycerin) is a simple polyol (sugar alcohol) compound commonly used in food and pharmaceutical formulations. Supplemental glycerol increases serum osmolality.[348] Glycerol (GLY) has been shown to be an effective ingredient for expanding the water compartments in the body.[349,350,351] GLY seems to expand the intracellular water (ICW) like creatine supplementation,[352,353] but because water binds to the hydration shells around glycerol molecules, GLY also expands extracellular water (ECW).[354,355] Generally, doses of 0.45-0.7 gm/lb/d taken 2.5 to 4 hours before exercise increase total body water (TBW) compartments to reduce thermal and cardiovascular strain during exercise in the heat.[356] Supplementing with combined hydrating substances like GLY or creatine consistently produces moderate fluid retention of 400-800 mL.[357,358] Adding GLY to creatine demonstrates that the combination has an additive hyperhydration effect, as the inclusion of GLY to creatine significantly increased TBW more than Cr alone.[359] Therefore, glycerol is added to this formula for its modest fluid retention properties (not necessarily for its thermo-regulation properties since dosing with NO7 would be only before the workout and amounts in NO7 are far less than used in thermo-regulation studies), thereby potentially increasing volumization and the "pump" within the exercising muscles.[349,351,352,353,354,356,357,358,359,360,361,362]

Safety and Efficacy of Multi-Ingredient Pre-Workout Products Containing at Least Creatine, Beta-alanine, Caffeine and Purported Nitric Oxide Boosters

This section is to establish, at a minimum, the safety of Multi-ingredient pre-workout supplements (MIPS)

MIPS containing these ingredients and are now a commonly used supplement throughout the sports and fitness community and have shown safety and potential efficacy.[216,217,218,219,220,221] For an overview of MIPS studies, readers are referred the Harty et al. review "Multi-ingredient pre-workout supplements, safety implications, and performance outcomes: a brief review" and specifically Table 1 for ingredients and outcomes.[219] Other studies containing ingredients have also reported safety and efficacy. Schwartz et al. found ingestion of one serving of Bang Pre-Workout Master Blaster (BMB) prior to exercise increases lower-body power and muscular endurance (measured by vertical jump and leg extension exercises) without adversely affecting hemodynamics or clinical safety markers.[363] The authors using the same formula concluded that BMB supplementation combined with resistance training for 4 weeks resulted in superior adaptations in maximal strength and lean body mass (LBM) compared with a placebo and also reported no adverse resting hemodynamic or clinical blood safety markers.[364] Martinez et al. found the same combination of ingredients to safely improve both anaerobic peak power and mean power in recreationally trained male subjects.[365] However, in a cautionary note, while Cameron et al. found acute ingestion of MIPS to improve upper body muscular endurance and anaerobic capacity while improving feelings of focus following high-intensity exercise in recreationally active females, they also found it increased resting metabolism (albeit presumably desirable) following a single dose accompanied by an increase in diastolic blood pressure. Because an increase in diastolic blood pressure was demonstrated, the authors noted that individuals with risk factors for cardiovascular disease should proceed with caution before using such products.[366]

In summary, while MIPS containing these ingredients appear safe, and when formulated properly (in established effective doses per serving), demonstrate efficacy, sport and fitness practitioners should advise all clients not to purchase products with undisclosed purported individual active ingredient amounts, generally titled "Proprietary Blend."[218,219] To be sure, Jagim et al. identified the ingredient profile of the top selling commercially available MIPW supplements to compare ingredient dosages to known efficacious values.[218] They found that the average amount of beta-alanine per serving size fell far below the recommended effective dose. The average dose of caffeine is near the low end of an effective dose by body weight for a 70 kg individual at 1.7gm/LB. Almost half of the ingredients in the products were listed as part of a proprietary blend with undisclosed amounts of each ingredient and adding up the total grams and milligrams of these blends exposed the impossibility that many components such as creatine, taurine or citrulline could all be at an establish effective dose.[218,219]

Product Summary

As a pre-workout/activity NSF Certified for Sport formula, NO7Rage[3] contains a synergistic group of compounds (creatine, beta-alanine, caffeine, taurine, glucuronolactone, Nitrosigine, citrulline malate, glycerol), designed to work together via supplying clinically independently safe and effective doses to produce the following outcomes before and during exercise: 1) greater desire to exercise, 2) increased strength and power output and muscle endurance, 3) longer and enhanced alertness and focus, 4) enhanced nitric oxide production to induce hyperemia improving muscle vasodilation and blood volume leading to greater muscle swelling, energy substrate delivery and waste product removal, and 5) attenuation of muscle damage. These benefits, compared to a non-supplemented state or commercially available competitive products, would be the maximizing of an individual's adaption potential by offering the ability to execute greater overall quality workouts, subsequently setting up the post-exercise period with enhanced anabolic potential so that the result would be greater net protein synthesis and continuous performance gains overtime when post-exercise nutrition is also optimized by incorporating the proper post-workout formula and meal planning – i.e. maximizing adaption.

Typical Use

- A pre-workout/activity supplement for anyone, not adverse to effects of caffeine, wanting pre-and during training sustained stimulus, alertness and motivation while seeking an enhanced overall training session or competition outcome through greater and prolonged strength production during activities, delaying fatigue and decreasing feelings of exertion
- Experienced size, strength, and intermittent athletes (participants in team sports that combine intermittent aerobic and anaerobic activity such as in football, soccer, baseball, rugby, hockey, etc.) seeking to regularly enhance size, strength and overall activity performance gains in their chosen activity and avoid training plateaus
    - See NO7 inclusion in muscle performance stacking programs: Creatine Muscle & Performance Stacks
- Should not be taken within four (4) hours of other products containing stimulants (especially caffeine) such as coffee, energy drinks, etc. or mixed with other stimulants

Dosages Based on Product Purpose

*The total amount of ingredients contained in one scoop is designed so that a user may control administering the total recommended dose as desired, such as in ½ scoop increments in case they're uncomfortable to the harmless tingling effect (paresthesia) of higher single doses of beta alanine.[31,202] These users would split the dose in ½ scoop increments**

One scoop contains: 2.5 g creatine; 2.0 g beta-alanine; 150 mg caffeine; 3.0 g citrulline-malate; 1.6 g taurine; 400 mg glucuronolactone; 1.0 g Nitrosigine; 2.0 g glycerol

For Use as a Pre-Training Stimulus Product

Training Days

Take as listed by body weight

- Under 150 lbs – 1.5 scoops ~30 minutes before activity
- 150-200 lbs – 2 scoops ~30 minutes before activity
- Over 200 lbs – 2.5 scoops ~30 minutes before activity
- Do not exceed three (3) scoops (primarily due to caffeine content)
- * If tingling occurs and user is uncomfortable, split total dosage into ½ scoop increments ingesting each ½ scoop no less than ~1.5 hours apart so that total dosage is consumed before and during workout as necessary
    - Example: training at total dosage = 2 scoops. Divide dosage in ½ scoops and take at least 1.5 hours apart with final dose started before workout and may continue to drink during

Non-Training Days

- Not necessary

For Use as a Pre-workout Stimulus Product and Standalone Formula to Establish and Maintain Effective Creatine and Beat-alanine Levels

Training Days

Take as listed by body weight and split as directed

- Under 150 lbs – 1.5 scoops total: take 1 scoop ~30 minutes before activity and 1/2 scoop following
- 150-200 lbs – 2 scoops total: take 1 scoop ~30 minutes before activity and 1 scoop following
- Over 200 lbs – 2.5 scoops total: take 1.5 scoop ~30 minutes before activity and 1 scoop following
- Do not exceed three (3) scoops (primarily due to caffeine content)
- * If tingling occurs and user is uncomfortable, split total dosage into ½ scoop increments ingesting each ½ scoop no less than ~1.5 hours apart with at least 1 dose before the workout and 1 following
    - Example: training at total dosage = 2 scoops. Divide dosage in ½ scoops and take at least 1.5 hours apart with second to last dose (1/2 scoop) started before workout and may continue to drink during and last half scoop following training

Non-Training Days

- Take same total dose by weight as described above at any time during the day and at least 5 hours before sleep. May take all at once or split such as, half dose in morning and remaining half in afternoon, or split in ½ scoop doses as described above

Maintain this protocol for at least 28 days to fully saturate muscle stores.

For Use in Strength and Muscle Stacking Programs with Products also Containing Creatine and Beta-alanine

- Follow directions found here **Creatine Muscle & Performance Stacks**
- Not necessary on non-workout days because other products used daily in the stacks will supply the necessary creatine and beta-alanine to sustain desired levels

Sub-populations Precautions, Contraindications, Adverse Events, Upper Limits/Toxicity

The section below is a summary related to specific sub-populations. For expanded up to date information for sub-populations' potential contraindications, precautions, adverse events, including potential drug interactions, etc. of specific dietary supplement ingredients, qualified Practitioners are also referred to The Therapeutic Research Center (TRC) Natural Medicine Data Base and the ingredient's respective section:[367]

Precautions

NO7Rage[3] is a well-tolerated, ephedrine-free ergogenic aid. NO7Rage[3]™ contains central nervous system (CNS) stimulants and should be avoided by those sensitive to caffeine or who are contraindicated for caffeine-containing supplements or adverse to any other ingredient in NO7Rage[3]. Do not mix with other stimulants, especially bitter orange[368] or ephedra.[369] As noted, caffeine has no significant effect on hydration, fluid balance or electrolytes and therefore no contraindication related to hydration and exercise.[260,370,371,372] Creatine, as with any nitrogen containing acid (e.g. amino compounds), individuals with liver or kidney disease should avoid supplementation without supervision of a medical professional.[373]

Contraindications

NO7Rage[3]™ supplementation is contraindicated in pregnancy and lactation because of caffeine content at higher dosage[374] and because studies are not performed using this population with other ingredients. Taurine and caffeine can interfere with some medications such as lithium[375] and MAO inhibitors.[376] While caffeine consumption does not increase the risk of developing hypertension,[377] caffeine is contraindicated in hypertension, anxiety and thyroid disease.[272] Caffeine is also contraindicated in those with cardiac arrhythmias, other forms of heart disease and peptic ulcers.[378] Caffeine should not be mixed with beta-agonists since theoretically, concomitant use of large amounts of caffeine might increase cardiac inotropic effects of beta-agonists.[379] Do not mix with diuretic drugs. Theoretically, excessive amounts of caffeine in combination with diuretics may increase the risk of hypokalemia.[380] Although evidence that caffeine ingestion causes cardiac arrhythmias is inconclusive (in fact, recently it's been shown that levels of caffeinated coffee ingestion of 1–7 cups/week were associated with a reduction in atrial fibrillation risk),[381] individuals should consult with their physician first before using NO7Rage[3].[382] Creatine is a naturally occurring nitrogenous organic acid and therefore no precautions are known for healthy persons. However, as with any nitrogen containing acid (e.g., amino compounds), individuals with liver or kidney disease should avoid supplementation without supervision of a medical professional.[373] As noted above, CS often leads to weight gain from water retention and increases in fat free mass. Both these conditions are often desirable endpoints for many users.[1,2,3,30]
Because L-citrulline is converted to L-arginine, which can lead to vasodilation,[39,53,59,60,70,72,73,74] theoretically, concomitant use of Nitrates might cause additive vasodilation and increase the chance of hypotension.

Do not use if:

- Using other products containing high doses of caffeine or are caffeine sensitive. Alternatively, separate by at least four (4) hours
- Using erectile dysfunction drugs or any Nitrates
- Individual has a heart condition or is using related medications, liver or kidney disease
- Taking medication for hypothyroidism

Adverse Reactions

Creatine monohydrate: see CreatineMonohydrate pgs. 17-18. The safety of the proper use of creatine monohydrate is well established.[1,2,3,30,103,104]

Beta-alanine (BA): As mentioned, paresthesia (tingling) is a commonly known side effect of beta-alanine in individuals ingesting more than 800 mg in one dose unless using a time-released formula.[135,208] If present, paresthesia generally disappears within 60 to 90 minutes following ingestion.[212] It's been hypothesized that BA activates Mas-related genes,[213] or sensory neuron specific G-protein coupled receptors that reach to the skin.[214] If present, paresthesia generally affects the face, hands or neck and is dose dependent (the higher the dose the greater chance of effect). Currently there is no data to support that this tingling is harmful in any way.[31,158,185] Further, Dolan et al. produced a systematic risk assessment and meta-analysis on the use of oral BA supplementation and potential adverse effects. 101 human and 50 animal studies were included. Paresthesia was the only reported side effect with supplementation relative to placebo, (the harmless affect and can be attenuated by using divided lower doses [1.6gm] such as in NO7.[31,135,212]) . The review concluded that BA supplementation "within the doses used in the available research designs, does not adversely affect those consuming it."[215]

Caffeine: use may result in slight diuresis (increased water loss, usually in non-regular users) and insomnia when taken late in the day. Numerous studies on the safety of caffeine exist.[260, 383] Caffeine abuse can cause tension, anxiety, excitability and restlessness at doses over 400 mg at one time.[383] Doses over 1,000 mg at one time can elicit toxicity symptoms.[382,384] NO7Rage^3 has between 225-375mg per dose but adverse effects may occur in sensitive individuals. Taking NO7Rage^3 with other stimulants is not advised unless separated by at least four (4) hours. Adverse effects due to high amounts of caffeine are not likely to occur at the recommended dose of NO7Rage^3.[260,383] Individuals sensitive to caffeine may wish to start with a low dose and work up to the recommended dose.

Taurine: Taurine is an amino acid naturally present in many foods, especially meats and fish. It has been combined with caffeine in several beverage studies with no adverse events reported except in one study where a mild increase in mean arterial blood pressure (2.8 mm Hg average) and an eight-beat-per minute reduction in heart rate were shown.[385,386,387] Taurine is used for congestive heart failure at higher doses from two to six grams daily to help increase stroke volume with few side effects such as mild diarrhea.[388,389] It is also used for other disease states such as hepatitis and cardiac arrhythmias where doses from 12 to 20 grams daily were used.[388] Mild diarrhea was reported in a few subjects in the heart failure studies. People enrolled in research studies have not reported any significant side effects connected with the use of taurine.[36,172,321,332,390]

Glucuronolactone: Glucuronolactone is a substance found in many caffeine and taurine containing energy drinks at doses of 500 mg or more per drink. It is considered safe and well-tolerated in these beverages.[391,392] The European Food Safety Authority (EFSA) concluded that exposure to glucuronolactone from regular consumption of energy drinks is not a safety concern. The no-observed-adverse-effect level of glucuronolactone is 1,000 mg/kg/day.[347]

Citrulline: No adverse reactions have been reported in doses up to 8 grams of citrulline malate.[393] Citrulline has been used up to 9 g/d for 9 months with no reported side effects[57,82,89] and in single doses up to 15 g/d.[75] Because L-citrulline is converted to L-arginine, which can lead to vasodilation,[39,53,59,60,70,72,73,74] theoretically, concomitant use of Nitrates might cause additive vasodilation and increase the chance of hypotension. Further, although no interaction between citrulline and Phosphodiesterase-5 Inhibitors (PDE-5) have not been reported, until more is known, use with caution or avoid using in combination. PDE-5 inhibitors include sildenafil (Viagra), tadalafil (Cialis), and vardenafil (Levitra).

Nitrosigine: Nitrosigine* is a brand named inositol stabilized arginine silicate compound that has been shown to safely enhance plasma arginine and markers of nitric oxide in healthy subjects with no reported adverse effects.[37,98,99,100,101,102] However, based on Nitrosigine's ability to increase NO production leading to vasodilation, the same precaution as shown in the use of citrulline should be applied here (see **Citrulline** above).

Glycerol: At doses up to 1 gm/kg, glycerol is considered well tolerated, with a few incidences in clinical trials of gastrointestinal upset, nausea, vomiting, dizziness and bloating.[349,359,394] The dose of glycerol in NO7Rage[3] is far less, making such adverse events improbable and there are no known interactions with drugs or foods.[395]

Upper Limit/Toxicity

Caffeine: should not exceed 1,000 mg/day,[382,384] leaving the dose in NO7Rage[3] a safe level.[260,383]

Taurine: Taurine has an LD50 in rats of greater than 5 g/kg (5000 mg/kg) and >10 gm/kg (10,000 mg/kg) in other unspecified mammals, and therefore practically unattainable.[396]

Citrulline: The LD50 or known toxic level is not available at this time.

Glycerol: Acute Toxicity: Oral Glycerol LD50 Rat: 12.6 g/kg (12,600 mg/kg). No additional information[397]

Glucuronolactone: The no-observed-adverse-effect level is 1,000 mg/kg/day[347]

Creatine and β-alanine: there are no established limits for either[29,30,31,32] other than β-alanine potential to cause tingling at single doses above 800 mg[31,135,208]

Other ingredients: no upper limits have been established and shown to be safe at proper doses.

Summary

As a pre-workout/activity NSF Certified for Sport formula, NO7Rage[3] contains a synergistic group of compounds (creatine, beta-alanine, caffeine, taurine, glucuronolactone, Nitrosigine, citrulline malate, glycerol), designed to work together via supplying clinically independently safe and effective doses to produce the following outcomes before and during exercise: 1) greater desire to exercise, 2) increased strength and power output and muscle endurance, 3) longer and enhanced alertness and focus, 4) enhance nitric oxide production to induce hyperemia improving muscle vasodilation and blood volume leading to greater muscle swelling, energy substrate delivery and waste product removal, and 5) attenuation of muscle damage. These benefits, compared to a non-supplemented state or commercially available competitive products, would be the maximizing of an individual's adaption potential by offering the ability to execute greater overall quality workouts, subsequently setting up the post-exercise period with enhanced anabolic potential so that the result would be greater net protein synthesis and other muscular adaptations thus continuous performance gains overtime when post-exercise nutrition is also optimized by incorporating the proper post-workout formula and meal planning – i.e. maximizing adaption.

Purpose

- A pre-workout/activity NSF Certified for Sport formula (creatine, beta-alanine, caffeine, taurine, glucuronolactone, Nitrosigine, citrulline malate, glycerol) in clinically effective doses for anyone not adversely effected by caffeine, wanting pre-and during training sustained stimulus, alertness and motivation while seeking enhanced overall training sessions or competition outcomes through greater and prolonged strength/power production during activities, delaying fatigue, decreasing feelings of exertion and increased muscle "pumps"
- Experienced size, strength, and intermittent athletes (participants in team sports that combine intermittent aerobic and anaerobic activity such as in football, soccer, baseball, rugby, hockey, etc.) seeking to regularly enhance size, strength and overall activity performance gains in their chosen activity and avoid training plateaus
    - See NO7 inclusion in muscle performance stacking programs: Creatine Muscle & Performance Stacks
- As a pre (and during) workout formula, NO7Rage[3] contains a synergistic group of compounds designed to work together to produce before and during exercise:

  - greater desire to exercise
  - increased strength and power output
  - greater muscle endurance
  - longer and enhanced alertness and focus
  - enhance nitric oxide production to induce hyperemia improving muscle vasodilation and blood volume leading to greater muscle swelling, energy substrate delivery and waste product removal
  - attenuation of muscle damage
- These benefits, compared to a non-supplemented state or commercially available competitive products, would be the maximizing of an individual's muscular adaption potential by offering the ability to execute greater overall quality workouts, subsequently setting up the post-exercise period with enhanced anabolic potential so that the result would be greater net protein synthesis and other muscle adaptations thus continuous performance gains overtime when post-exercise nutrition is also optimized by incorporating the proper post-workout formula and meal planning – i.e. maximizing adaption

Unique Features

- Contains L-citrulline malate which has been shown to be a more effective substrate than arginine for inducing NO production
- Contains Nitrosigine (inositol stabilized arginine silicate) that can significantly increase plasma arginine and NO through partially different mechanisms than citrulline, offering a potential additive NO production effect
- Contains Hydromax™ a stable form of glycerol powder to contribute to the "muscle pump"
- A rare combination of clinically effective doses of both caffeine anhydrous and taurine where taurine may significantly amplify caffeine's well-known performance enhancement effects
- No "Proprietary Blends" listings, i.e., full individual ingredient amounts disclosure to prove clinically effective doses that are also validated by 3rd party testing
- Flavoring generally appeals to a greater portion of users than competitive products
- Can be used as a standalone product or part of a dotFIT™ muscle and performance stacking programs: Creatine Muscle & Performance Stacks
- Dosage instructions by weight will yield the product to be significantly more effective per individual compared to other competitive products

Supplement Facts Panel

Supplement Facts

Serving Size: 1 Scoop (14.5g)
Servings Per Container: 40

	Amount Per 1 Scoop	%DV*	Amount Per 2 Scoops	%DV*
L-Citrulline Malate (2:1)	3000 mg	**	6000 mg	**
Creatine Monohydrate	2500 mg	**	5000 mg	**
Beta Alanine	2000 mg	**	4000 mg	**
Hydromax® (Glycerol Powder 65%)	2000 mg	**	4000 mg	**
Taurine	1600 mg	**	3200 mg	**
Nitrosigine® (as Inositol Stabilized Arginine Silicate)	1000 mg	**	2000 mg	**
Glucuronolactone	400 mg	**	800 mg	**
Caffeine Anhydrous	150 mg	**	300 mg	**

* Percent Daily Values are based on a 2,000 calorie diet.
** Daily Value not established.

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