Efficacy and safety of ingredients found in preworkout supplements

ANNE E. EUDY, LINDSAY L. GORDON, BRANDON C. HOCKADAY, DANIEL A. LEE, VIVIANNE LEE, DANIEL LUU, CARLOS A. MARTINEZ, AND PETER J. AMBROSE

Purpose. Published evidence on common ingredients of "energy drinks" and other dietary supplements widely used by consumers in hopes of enhancing athletic performance is reviewed.

Summary. Preworkout products—unregulated dietary supplements—typically contain "proprietary blends" of multiple ingredients, including caffeine, dimethylamylamine, creatine, arginine, β-alanine, taurine, and phosphates. While some dietary supplement labels instruct consumers to seek the advice of a health care professional before using the products, the labels usually do not disclose all ingredients or their precise amounts, and evidence to support the purported performance-enhancing benefits is generally lacking. There is limited evidence to support the use of some preworkout supplement ingredients. For example, in one small placebo-controlled study (n = 12), the use of the energy drink Red Bull (containing caffeine and taurine) 40 minutes before a simulated cycling time trial appeared to provide a meaningful ergogenic benefit; in another small study (n = 12), the use of a similar caffeine-containing product (Redline) by strength-trained athletes was found to improve reaction time, energy, and mental focus relative to placebo use. However, published evidence on the use of the other ingredients listed above is scant, inconclusive, or conflicting. Adverse effects reported in association with preworkout supplements include gastrointestinal symptoms, cardiac arrhythmia, blood pressure increases, and potential effects on lipids and blood glucose.

Conclusion. Although evidence exists to support the performance-enhancement efficacy of some preworkout ingredients as standalone agents, published data on combination products are scant, inconclusive, or conflicting. The safety of these products may be compromised if users consume larger-than-recommended amounts or use more than one product.

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Consumers of all ages use a variety of products before exercise, such as caffeine-containing energy drinks, carbohydrate drinks, and supplement powders. A survey of 207 college athletes indicated that 89% were using these preworkout nutritional supplements; almost 75% reported using supplements in the form of energy drinks.[1] A study of 78 students in grades 7–11 found that the majority of 11- to 18-year-olds who reported taking dietary supplements did not recognize the risks of adverse events associated with their use.[2]

The use of some preworkout supplements has raised concern for consumer safety. A 2011 report by the Substance Abuse and Mental Health Services Administration revealed a rising trend in emergency room visits involving energy drinks by patients 18–39 years of age, with a 10-fold increase from 2005 to 2009.[3] While many of those emergency room visits involved the consumption of energy drinks in combination with drugs or alcohol, 56% were due to the consumption of energy drinks alone, and the reported adverse effects included arrhythmias, high blood pressure, anxiety, and nervousness.

Many preworkout products contain one or more central nervous system (CNS) stimulants that increase the risk of adverse events. Combining

ANNE E. EUDY is a student, Eshelman School of Pharmacy, University of North Carolina at Chapel Hill. LINDSAY L. GORDON is a student, School of Pharmacy, University of California, San Francisco (UCSF). BRANDON C. HOCKADAY is a student, School of Pharmacy, University of Southern California, Los Angeles. DANIEL A. LEE, VIVIANNE LEE, and DANIEL LUU are students, School of Pharmacy, UCSF. CARLOS A. MARTINEZ is a student, Thomas J. Long School of Pharmacy and Health Sciences, University of the Pacific, Stockton, CA. PETER J. AMBROSE, PHARM.D., FASHP, is Professor of Clinical Pharmacy and Vice Chair, Department of Clinical Pharmacy, School of Pharmacy, UCSF.

Address correspondence to Dr. Ambrose at the Department of Clinical Pharmacy, School of Pharmacy, University of California, C-152, Box 0622, San Francisco, CA 94143 (pambrose@memorialcare.org).

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Table 1.
Labeled Ingredients of Common Preworkout Products[a]

Product	Amount per Serving (mg)							
	Caffeine	Dimethylamylamine	Creatine	Arginine	β-Alanine	Taurine	Phosphate
N.O.-Xplode (Bio-Engineered Supplements and Nutrition, Inc.)	NS	NLI	NS	NS	NS	NS	NS
Jack3d (USPlabs, LLC)	NS	NS	N	N	N	NL	NLI
1.M.R (BPI Sports)	NS	NLI	NS	NS	NS	NS	NLI
M5 Extreme (Cellucor)[b]	150	NLI	5000	2000	2500	NLI	NLI
Assault (MusclePharm)[c]	NS	NLI	NS	NS	NS	NS	NS
Red Bull (Red Bull GmbH)	80	NLI	NLI	NLI	NLI	NS	NLI
Monster (Monster Energy Company)	NS	NLI	NLI	NLI	NLI	1000	NLI
Redline (Vital Pharmaceuticals, Inc.)	290	NLI	NLI	NLI	NLI	NLI	NLI

[a]Labeled ingredients per manufacturers' websites as of January 25, 2012. Exact ingredients may vary in different formulations of the same brand product. The listed products contain constituents in addition to those indicated here. NS = amount not specified on product label, NLI = not a labeled ingredient.

[b]Dual mixture; ingredients reflect one scoop of each.

[c]Manufacturer reports compliance with FDA Good Manufacturing Practices Program and asserts its products are by National Science Foundation and Informed-Choice as not containing banned substances per sports-governing bodies.[6]

exercise with the use of CNS stimulants can impose additional stress on the cardiovascular system, increasing the potential for and worsening the outcome of such events.[4]

The Dietary Supplement Health and Education Act of 1994 gave the Food and Drug Administration (FDA) expanded authority for the regulation of dietary supplement manufacturing, labeling, and marketing.[5] However, responsibility for determining the safety and efficacy of supplement ingredients and the accuracy of product labels remains under the control of manufacturers. Most preworkout products contain a mixture of ingredients—a "proprietary blend"—purported to increase energy, extend endurance, and boost muscle gains. An inherent problem with proprietary blends is that FDA does not monitor dietary supplement labels to ensure that specific amounts of all ingredients are listed on the labels. Manufacturers of dietary supplements have the opportunity to receive certification of product validity through organizations such as the United States Pharmacopeial Convention and ConsumerLab; however, the makers of most combination supplements do not seek such an "added seal of approval."

Table 1 lists the labeled content of some common ingredients in popular preworkout products. As a proprietary blend, the amount of each ingredient is often not disclosed. Suggested serving sizes do not take into account that these products are taken by consumers of all sizes and ages, including children. Ironically, some supplement labels suggest that the consumer seek the advice of a health care professional before using the product, yet the labels often contain insufficient information on the product's ingredients for the health care provider to use for consultation and recommendations. This article reviews the available published research on the efficacy and safety of supplement ingredients tested in

humans in association with athletic performance.

The products listed in Table 1 were selected based on our perceptions of the popularity of supplements sold in large-chain commercial stores and the extent of advertising (online and in stores). For those supplements chosen, the most commonly listed ingredients were identified for inclusion in this review. Sports medicine journals and articles in English obtained from MEDLINE and SportDiscus (through November 2011) were searched for relevant terms: *arginine, beta-alanine, caffeine, carnosine, creatine, dietary supplements, dimethylamylamine* (and its abbreviation *DMAA*), *energy drinks, human growth hormone, nitric oxide, performance enhancement, phosphates, phosphorus,* and *taurine.* Information was also obtained from dietary supplement product labels, manufacturer websites, and sports-governing agencies such as the National Collegiate Athletic Association and the World Anti-Doping Agency. Studies and reports evaluating the ergogenic and hemodynamic effects of preworkout product ingredients that were determined to be credible and scientifically sound were selected for inclusion in this review. Table 2 summarizes the available efficacy and safety results of published studies for the combination products listed in Table 1.

Caffeine

Also known as trimethylxanthine, caffeine is categorized as a stimulant and is available in a number of products, such as coffee, tea, soft drinks, energy drinks, chocolate, guarana, and over-the-counter medications. In the United States, an average of 280 mg of caffeine per person is consumed in the form of coffee on a daily basis.[12] Caffeine is frequently overlooked as an active product ingredient, and consumers may often be unaware of how much caffeine is in the products they ingest. It is one of the most common ingredients in preworkout supplements.

After oral ingestion, caffeine is 99% absorbed within 45 minutes by the gastrointestinal tract.[13] Caffeine increases levels of 3′- and 5′-cyclic adenosine monophosphate through the inhibition of phosphodiesterase, and it may alter skeletal muscle contraction.[14,15] Due to the lipophilic properties of caffeine, it readily passes through the blood-brain barrier.[14] Since caffeine can cross into nerve cells, its effects may be more neural than muscular.[16] Caffeine is believed to block adenosine receptors, inhibiting adenosine's actions, which include vasodilation and the inhibition of catecholamine release.[13,16] Caffeine may also have direct action on the CNS by stimulating the release of both β-endorphins and hormones, which alter sensitivity to pain from physical exertion.[17,18] Caffeine also acts to increase alertness, energy, and mental concentration.[16,17]

Proposed uses of caffeine to improve athletic performance are centered on CNS stimulation, enhanced endurance, and the ability to improve time-trial performance.[15,19,20] There are conflicting data on caffeine's effects on the performance of trained athletes. One study examined the performance of nine adult male runners who ingested caffeine (5 mg/kg) one hour before a running time trial and documented an average 31% increase in running time to exhaustion—a significant improvement over the runners' performance after receiving a placebo.[21] However, another study concluded that low and moderate quantities of caffeine did not improve the performance of nine male cyclists and triathletes.[22] In the latter study, which controlled for training level and the use of a high-carbohydrate diet, participants underwent three performance trials after ingesting capsules containing 1.5 or 3.0 mg/kg of caffeine; each athlete's maximal exercise capacity was ascertained during preliminary testing. Each of the three trials consisted of 120 minutes of steady-state cycling directly followed by a body weight-based cycling time trial. No significant improvement in time-trial performance was observed with caffeine use.

In 2008, the National Research Council of Canada published a paper that compiled the available literature regarding caffeine and its effects on endurance and exercise, listing studies that concluded that caffeine was effective in enhancing performance and other studies that stated it was ineffective.[23] While there are studies indicating that caffeine can be effective in increasing sprinting performance, other studies showed no effect, and there are no conclusive data on caffeine's efficacy in enhancing strength performance.[21-23]

The potential adverse effects of caffeine include arrhythmias, palpitations, restlessness, anxiety, insomnia, irritability, dizziness, and diuresis.[13,14,16,18] Slow metabolizers of caffeine who drink the caffeine equivalent of more than two cups of coffee per day may have a higher risk of experiencing coronary or arrhythmic events.[24] However, the purported performance-enhancing effects of caffeine may occur and peak at different levels of caffeine ingestion. While there is no specific range or defined limit for caffeine, it is generally believed that an amount of 100–500 mg provides beneficial effects (increased alertness, stimulation, and euphoric effects) while amounts above 500 mg have a higher potential to cause adverse effects such as restlessness, palpitations, and even decreased performance.[25-27]

Overall, the evidence on improved performance with caffeine use in trained athletes is inconclusive, and any such benefits may be dose dependent. In addition, many preworkout products do not precisely specify the caffeine content or list the amount of caffeine in a single serving. Moreover, the product container may include

Table 2.
Published Safety and Efficacy Evidence for Combination Preworkout Products[a]

Product	Reference	Trial Design	Subjects	Measured Outcomes	Results	Comments
Jack3d (USPlabs, LLC)	7	Open-label, pre–post	7 healthy males with no cardiovascular risk factors	Change in hemodynamic and hematologic parameters[b] after chronic supplementation (daily for 14 days)	Significant increase in fasting blood glucose ($p = 0.02$); no significant changes in other variables	Nonsignificant trend of increased SBP and resting HR
Red Bull (Red Bull GmbH)	8	Randomized, single-blind, placebo-controlled, crossover	15 female collegiate soccer players	Sprint performance, HR, RPE scale score	No significant changes versus placebo	The study considered the one serving of caffeine (80 mg) to be a low dose, which is not expected to provide ergogenic benefit
	9	Double-blind, crossover, repeated-measures	17 (9 male) healthy, regularly active adults	High-intensity run time-to-exhaustion test, RPE scale score, blood lactate	No significant change in any variable	Investigators speculated that lack of effect might have been due to absence of carbohydrates in sugar-free formulation or low dose of caffeine (2 mg/kg) used
	10	Double-blind, randomized, crossover	12 (6 male) healthy trained cyclists	Time to complete standardized endurance cycling test, respiratory exchange ratio, RPE scale score	Significant improvement in cycling-test performance (mean completion time 4.7% better versus placebo, $p < 0.010$); no difference in respiratory exchange ratio and RPE scale score	Lack of changes in RPE scale score and respiratory exchange ratio suggests energy drink allowed increased work output without increased feelings of exhaustion
Redline Extreme (Vital Pharmaceuticals, Inc.)	11	Randomized, double-blind	12 male strength- and power-trained athletes	Anaerobic power performance; quickness–reaction time test score; feelings of energy, focus, alertness, and fatigue	Significant increases versus placebo in quickness–reaction time test scores ($p < 0.05$) and feelings of energy and focus ($p < 0.05$); no significant change in anaerobic power performance or other variables	Despite lack of ergogenic effect on anaerobic power performance, improved reaction time and enhanced feelings of energy and focus may be beneficial

[a]SBP = systolic blood pressure, HR = heart rate, RPE = Rating of Perceived Exertion.
[b]Included resting HR, SBP, diastolic blood pressure, rate–pressure product, complete blood count, lipid panel, and comprehensive metabolic panel.

multiple servings, which may not be obvious to consumers due to some containers' relatively small size. Consumers may not realize that the effects of caffeine are additive when ingested from various sources such as energy drinks and preworkout supplements.[28]

DMAA

Also known as methylhexanamine, DMAA is another popular preworkout supplement ingredient.[29] It is a simple aliphatic amine with stimulant properties similar to those of ephedrine and amphetamine (it may cause a false-positive result for amphetamines on certain urine drug tests).[30,31] DMAA was trademarked by Eli Lilly and Company in 1944 and marketed as a nasal decongestant under the brand name Forthane (it is no longer marketed for any FDA-approved indication).[32] The agent was introduced as a synthetic dietary supplement in 2005 as Geranamine.[33] Although its mechanism of action is not fully understood, DMAA may act as a norepinephrine reuptake inhibitor or indirect norepinephrine-releasing agent.[34-37] Increased norepinephrine activity may lead to amplified lipolysis and elevated blood concentrations of available free fatty acids. Increased blood free-fatty-acid levels provide additional energy sources during exercise.[37] Anecdotal reports from athletes claim that DMAA can enhance mental concentration and reduce fatigue.[38] However, there are no studies to support these claims.

To date, one study regarding the use of DMAA before exercise has been published.[37] The study involved healthy and exercise-trained participants (six men and six women) 19–25 years of age. On each of four occasions, in random order, all participants received one of the following: a placebo, DMAA (1 mg/kg), caffeine (4 mg/kg), or a combination of DMAA and caffeine (1 mg/kg and 4 mg/kg, respectively). The study participants rested for 60 minutes after placebo or supplement ingestion and then completed a 10-km run. The performance measures evaluated included run time, perceived exertion (typically assessed using the Borg Rating of Perceived Exertion scale), "mood/vigor," and heart rate (HR). There were no significant intertrial differences in any of the performance variables in any of the participants. However, after ingesting the combination of DMAA and caffeine, many subjects reported feelings of intense euphoria, which they perceived to have hindered their performance during the 10-km run; on average, study participants finished the run 45 seconds slower than they did after receiving DMAA or caffeine alone. This study demonstrated that the combination product might have actually had a negative impact on running performance.

In addition to the potential for performance enhancement, the hemodynamic effects of DMAA have been examined.[38] In one study involving 10 exercise-trained males and females, diastolic blood pressure (DBP), systolic blood pressure (SBP), HR, and the rate–pressure product (RPP [calculated as SBP × HR], an indicator of myocardial oxygen consumption) were assessed after a one-time administration of 50 or 75 mg of DMAA alone, 250 mg of caffeine alone, or the combination of either 50 or 75 mg of DMAA plus 250 mg of caffeine. Sixty minutes after administration, in the groups that received the one-time administration of 75 mg of DMAA, there were significant increases in SBP (15 mm Hg, 12.7%), DBP (7 mm Hg, 10%), and RPP (7.7%). Also, in the group that received the combination of 75 mg DMAA and 250 mg caffeine, there were higher and significant increases in the same parameters: SBP (22 mm Hg, 18.4%), DBP (9 mm Hg, 12.6%), and RPP (8.7%). Across all treatment groups, there was no significant increase in HR. Several subjects reported adverse effects after a one-time ingestion of DMAA, such as feelings of coldness, fatigue, and lightheadedness.

Another recent study looked at the consumption of two common workout combination products containing DMAA: Jack3d (USPlabs, LLC, Dallas, TX) and OxyElite Pro (USPlabs).[7] In 11 males and females who were healthy and physically active, investigators noted that there were no significant changes in HR, SBP, DBP, and RPP after 14 days of administration. The use of OxyElite Pro was associated with a significant short-term change in SBP (+18 mm Hg, 14.5%). The study also evaluated the hematologic profiles of participants and found that there were no changes in lipid profile, cell blood count, and comprehensive metabolic panel results except for a significant increase in fasting blood glucose with Jack3d use. Chronic ingestion of DMAA alone has not been studied, and individuals with known hypertension should avoid DMAA until further studies are performed.

DMAA has been abused as a recreational drug. In December 2010, a 21-year-old man in New Zealand ingested two capsules of DMAA (approximately 278 mg each) with caffeine and alcohol and suffered a cerebral hemorrhage.[39]

Athletes continue to use DMAA despite the risks of adverse effects and the lack of evidence supporting its use as a performance enhancer.[40] Preworkout products add more concern because they often contain other CNS stimulants in undisclosed amounts. Another important consideration is that combination products of DMAA and caffeine, as noted by Bloomer et al.,[37] may alter mood and vigor perception and diminish performance ability.

Creatine

Creatine, a natural chemical derived from amino acids, is produced by the kidneys and the liver.[41] It is pri-

marily stored in skeletal muscle cells, where it serves as an energy source; once in cells, creatine is phosphorylated to produce phosphocreatine (PCr), a high-energy compound. PCr can donate a phosphate group to adenosine diphosphate to create adenosine triphosphate (ATP), the initial source of energy for muscle contraction.[42] Moreover, PCr can act to draw water into muscle cells, resulting in muscle hypertrophy. Though creatine is not an essential nutrient, it is one of the more popular supplements, with estimated U.S. sales of $14 million in 2011.[43] Creatine is available in four major forms as a dietary supplement: creatine monohydrate, creatine phosphate, creatine citrate, and creatine esters. The various forms are purported to differ in their rate of absorption by skeletal muscle cells; however, studies have yet to confirm these differences and the impact of most of these forms on performance enhancement.

Creatine monohydrate, which can be obtained as a standalone product or with other ingredients in a mixed proprietary blend, is the most extensively studied form of supplemental creatine. There are several established creatine regimens for performance enhancement. One commonly used creatine regimen entails a cycled schedule typically consisting of an initial "loading" amount of 20 g of creatine monohydrate per day (divided in four servings) for five to seven days, followed by a maintenance serving of 3–5 g per day for one to six weeks, with a break of about two weeks before the next cycle. The rationale is to saturate the body for a week before the start of a training regimen, followed by replenishing the PCr stores with daily maintenance supplementation immediately after training sessions.[44] Based on recent studies, the traditional regimen has been modified to a single 5-g serving 60 minutes before or immediately after exercise. There are no safety data on the use of amounts of >5 g/day.[45]

Supplementation of creatine monohydrate supplies an athlete with short bursts of energy through recycled ATP after the rapid depletion of energy stores during high-intensity exercise. In a study that tracked naturally occurring radioactive phosphorous molecules in PCr, subjects were loaded with creatine monohydrate or placebo before undergoing a 10-second maximal handgrip exercise.[46] Relative to placebo use, creatine supplementation resulted in 11.5% and 65% increases in resting and postexercise PCr levels, respectively; also, ATP synthesis significantly increased in the creatine-supplemented group. Studies of long-distance cyclists demonstrated that the rapid depletion of ATP, regardless of supplementation, renders creatine supplements ineffective in long-term endurance exercises.[47]

Studies support the positive ergogenic effects of creatine monohydrate as a training aid for high-resistance exercises and weightlifting, though the results are variable and possibly dependent on an athlete's natural creatine stores and diet. In a study that compared subjects on a typical creatine regimen versus placebo, subjects significantly increased their maximum deadlift volume after six days of supplementation.[48,49]

Serious adverse effects relating to the kidneys, gastrointestinal system, and liver are largely anecdotal, with scientific evidence lacking in healthy subjects taking creatine at the recommended amount for relatively short periods.[50-52] The safety of long-term use has not been established, though creatine use has been popular for over a decade. Additionally, there is insufficient information for creatine use in adolescents. There are reports of weight gain, likely due to water retention as a result of creatine uptake by cells, which may be the cause of an increase in compartment pressure of the lower leg, causing pain and tightness in study subjects before and after exercise.[46,53]

There is substantial evidence to support the claim that creatine monohydrate at the recommended amount improves exercise performance in adults performing high-intensity, short-duration exercises. However, there may be a significant variation in the magnitude of improvement in individuals.[54] In addition, studies are lacking on the benefits of creatine in marketed combination products and at the amounts contained in such products (which is often not disclosed on the product label).

Arginine

Arginine is a semiessential amino acid that is available in many nutritional supplement products and foods such as nuts, fish, chicken, pork, dairy products, and eggs.[55] Mammals synthesize arginine in the kidneys predominantly from citrulline, a byproduct of glutamine metabolism. However, the rate of synthesis does not compensate for inadequate dietary intake or depletion, leading to the rationale for the use of supplements by athletes and others seeking to replenish the body's arginine supply. Exogenous oral arginine is rapidly absorbed, though 50% is quickly converted in the body to ornithine by the enzyme arginase.[56] Arginine that is not converted into ornithine is broken down by one of four enzymes. Nitric oxide synthase converts arginine to nitric oxide, which is a potent vasodilator that can potentially increase blood flow and the delivery of nutrients to skeletal muscle. In addition, arginine has been shown to increase human growth hormone (hGH) secretion.[57,58] Arginine glycine amidinotransferase converts arginine to creatine, whose ergogenic potential has been previously discussed. Arginine decarboxylase converts arginine to agmatine, which may be a natural regulator of nitric oxide

activity. However, the physiological significance of this effect has yet to be elucidated.[59] Lastly, arginyl-tRNA synthetase converts arginine to arginyl-tRNA, a precursor of protein synthesis.[60]

There is conflicting evidence regarding the ergogenic potential of arginine supplementation. One study showed that the ingestion of arginine (5 g) 30 minutes before exercise did not increase hGH secretion and may have actually impaired hGH release in young adults.[61] However, another study of longer-term arginine and ornithine supplementation at lower amounts (1 g of each product taken five days per week for five weeks) reported higher gains in strength and enhancement of lean body mass among users of the two supplements relative to a control group.[62] In another study, 17 strength-trained athletes were randomly assigned to receive supplementation with L-arginine plus L-ornithine or a placebo to determine any effects on serum biomarkers, including hGH and insulinlike growth factor-1 (IGF-1).[63] The athletes were followed during a three-week regimen of heavy-resistance training. Resting levels of the hormones did not differ, but significant increases in hGH and IGF-1 were seen 2 minutes after the exercise protocol and after one hour of recovery, suggesting that the L-arginine–L-ornithine combination supplement had ergogenic potential. However, the findings of another study, by Tang et al.,[64] suggested that the increase in hGH may not translate into increased muscle blood flow or muscle protein synthesis. In that study, 8 healthy males ingested either an isonitrogenous control drink or a drink containing 10 g of essential amino acids and 10 g of L-arginine before performing a series of unilateral leg resistance exercises. A greater increase in hGH was observed after exercise with the arginine drink compared to the control. Although femoral artery blood flow and muscle protein synthesis increased in the exercised leg compared to the unexercised leg, there was no difference in either measure between the control and arginine groups. The results of the study by Tang et al. suggested that arginine may not have any effect on nitric oxide production, as there was no significant effect on femoral artery blood flow; evidence from other studies supports this conclusion.[65-69] Although athletes use arginine-containing supplements for their purported nitric oxide effects, much of the research that supports these benefits is based on i.v. administration of larger quantities (20–30 g).[65] Several studies investigating oral supplementation with 6–20 g of arginine have shown no effect on increasing nitric oxide concentrations, blood flow, or performance in intermittent anaerobic exercise.[66-69]

The reported adverse effects of arginine supplementation are mild and include bloating, diarrhea, and abdominal cramping.[70] Lowering of blood pressure may occur after oral arginine supplementation.[71] Further, there are two case reports of anaphylactoid reactions to i.v. arginine, but it is unknown if there is a similar risk associated with oral ingestion.[72] While some evidence suggests that arginine can increase hGH release, other studies have not correlated such hGH increases with ergogenic benefits. Furthermore, there is no evidence that oral arginine supplementation has any effect in producing greater nitric oxide release or enhanced blood flow, despite such claims by the manufacturers of many preworkout products that contain arginine.

β-Alanine

A nonessential amino acid produced in the liver, β-alanine is obtained in the diet from protein-rich foods such as chicken, beef, pork, and fish.[73] Its binding to histidine is the rate-limiting step in the formation of carnosine within muscle cells.[74] Carnosine is a cytoplasmic dipeptide located in skeletal muscle tissue that acts as an intramuscular buffer of hydrogen ions.[73] By virtue of a pKa of 6.83 and its high concentration in muscle, carnosine is more effective in sequestering protons than bicarbonate or inorganic phosphate, the other two major physicochemical buffers over the physiological pH range. Increasing an individual's ability to buffer protons prevents excessive acidosis and delays fatigue during severe muscle contractions. This may result in enhanced exercise performance, including increased power output and aerobic and anaerobic endurance.[74]

There is conflicting evidence about whether β-alanine supplementation can enhance athletic performance. One randomized study divided a group of 15 well-trained male sprinters to test the effects of β-alanine versus placebo in conjunction with a four-week training regimen in preparation for a 400-m run.[75] The β-alanine group received 2.4 g of β-alanine per day for four days followed by 3.6 g per day for the duration of the four-week trial. The results of the study indicated that supplementation with β-alanine did not improve performance times in the 400-m run. A study of college football players and wrestlers given β-alanine indicated improvements in sprinting time after supplementation, but the study did not have sufficient power to demonstrate significant benefits.[74] However, another study showed that supplementation with β-alanine increased muscle carnosine content, potentially enhancing muscle-buffering capacity, but the study did not test for effects on exercise performance.[76] Eight weeks of β-alanine supplementation has proven to significantly increase the ability to sustain power output during final sprints in high-intensity cycling tests.[77] Another randomized, double-blind, placebo-controlled study evaluated 46 male college students on a training regimen for six

weeks.[73] The test group was given 6 g of β-alanine per day for three weeks followed by 3 g per day for another three weeks. The results showed that β-alanine supplementation in combination with high-intensity exercise resulted in significant improvements in muscle oxygenation and an increased time to fatigue during exercise.

Synergistic effects of β-alanine and creatine on high-intensity performance have been reported by Zoeller et al.[78] A study they conducted examined the effects of β-alanine in combination with creatine monohydrate during a four-week period in 57 men with an average age of 24 years. The trial compared the effects of supplementation with creatine alone (5.25 g of creatine monohydrate), β-alanine alone (1.6 g), or β-alanine plus creatine (in the same quantities) relative to the use of a placebo (34 g of dextrose, also included in all three supplement regimens). Subjects who received the combination of creatine and β-alanine exhibited significant improvements on five of eight evaluated indexes of cardiorespiratory endurance. Subjects who received only creatine or β-alanine had significantly less improvements.

In two studies of β-alanine, the agent was administered in a loading phase (a total of 3–6 g daily, divided into two or three increments, for one to two weeks) followed by a maintenance phase (a total of 3 g daily taken in three increments for up to eight weeks).[73,77] Minimal to no adverse effects have been reported with β-alanine supplementation. The only known adverse effect is paresthesia, usually associated with the ingestion of large amounts, but this effect has been reported to dissipate within one hour of ingestion.[79] Further studies are necessary to evaluate the potential benefits of preworkout supplementation with β-alanine to reduce fatigue, particularly in the amounts contained in proprietary blends (i.e., amounts not specified on product labels).

Taurine

Taurine (2-aminoethanesulfonic acid) is abundant in the tissue of most animal species. It is readily available in foods such as dairy products, meat, poultry, eggs, and fish.[80] By definition, taurine is not an amino acid because it contains a sulfonic acid rather than a carboxylic acid, but it resembles an amino acid in structure. Taurine serves many functions, such as bile acid conjugation, antioxidation, cell membrane stabilization, osmoregulation, and regulation of calcium flux and neuronal excitability.

Taurine is a common component of commercially available energy drinks and has been used as a preworkout supplement alone and in combination products to improve athletic performance.[4] It acts similarly to creatine, in that it draws water into the muscles and increases cell volume, which result in muscle hypertrophy. In addition, it is claimed that taurine can help increase muscle strength, improve endurance, reduce exercise-induced DNA and muscle damage, and accelerate recovery after workouts.

Taurine concentrations in the skeletal muscle have been shown to deplete during exercise.[81] Studies in laboratory rats showed that taurine supplementation helped to maintain taurine concentrations in muscles and reduced the production of superoxide radicals.[81,82] It is thought that reactive oxygen species production can lead to skeletal muscle damage and acute-phase inflammatory responses.

In a study of taurine's effects on humans, 11 men 18–20 years of age performed identical bicycle ergometer exercises on two occasions, first without supplementation and then after receiving 6 g of taurine powder daily (2 g three times per day) for seven days.[83] Taurine supplementation was found to produce a significant lessening of exercise-associated DNA damage via the reduction of free-radical production. In addition, significant increases were observed in maximal oxygen consumption (VO_2 max), exercise time to exhaustion, and maximal workload after taurine supplementation. Another study of similar design evaluated the effects of seven days of taurine supplementation and found no significant improvements in skeletal muscle taurine content or carbohydrate-versus-fat oxidation during exercise.[84] However, a study of endurance-trained cyclists who received a single administration of 1.66 g of taurine found small but significant increases in fat oxidation during exercise, but no correlated benefit of taurine supplementation in improved time-trial performance was demonstrated.[85]

Taurine has also been studied as a component of combination products, including Red Bull (Red Bull GmbH, Fuschl am See, Austria).[8-10] One study of 15 collegiate women soccer players evaluated the effects of Red Bull (one serving containing 1 g of taurine, 80 mg of caffeine, and 27 g of carbohydrates) ingested one hour before timed "all-out" sprints, a high-intensity anaerobic activity. The combination product did not provide any significant improvement in repeated-sprint performance; stomachache and feelings of mild tremor were reported by 2 women after the consumption of Red Bull.[8]

In a double-blind crossover study by Candow et al.,[9] 17 physically active university students (9 men and 8 women) performed a high-intensity running test at 80% VO_2 max after the use of sugar-free Red Bull or a noncaffeinated placebo; the use of Red Bull was not correlated with benefits in terms of run time-to-exhaustion, perceived exertion, or blood lactate levels. However, another double-blind crossover study found that the ingestion of Red Bull can improve endurance performance.[10] In that study, 6 male and 6 female trained cyclists drank Red Bull (the evaluated serving contained 2 g of taurine, 1.2

g of glucoronolactone, 160 mg of caffeine, 54 g of carbohydrates, 40 mg of niacin, 10 mg of panthothenic acid, 10 mg of vitamin B_6, and 10 μg of vitamin B_{12}) or a flavored placebo 40 minutes before a simulated cycling time trial. The overall mean time to complete the time trial was significantly improved (by 4.7%) with the use of Red Bull, and 10 of the 12 participants finished the time trial faster after drinking Red Bull than they had after drinking the placebo.

Taurine alone has been taken orally in amounts of up to 3 g per day as a preworkout supplement without adverse effects.[86] Currently, insufficient research is available to justify supplementation with taurine alone or in combination products to improve performance.

Phosphorus

Phosphorus, in the form of phosphates, is the most abundant anion in the human body and plays a critical role in proper growth and development, buffering, excretion of hydrogen ions, and maintenance of calcium balance.[87] It is also associated with athletic performance through its effects on energy storage molecules, metabolic processes, and the protection of normal muscle and nerve function. Phosphorus is found in a normal diet and as phosphate salts in many vitamins and other dietary supplements, usually combined with sodium, calcium, or potassium.

There are multiple potential benefits of phosphate loading. One proposed mechanism for such benefits is the stimulation of the body's production and storage of ATP[87,88]; another is by increasing the buffering capacity of lactic acid within muscle cells to prevent soreness and fatigue.[89] Some researchers have studied the propensity of phosphate supplementation to increase levels of erythrocyte 2,3-diphosphoglycerate (2,3-DPG) and ATP, thereby shifting the oxygen dissociation curve to the right[89-96]; this increases the flow of oxygen from red blood cells into working muscle cells, improving the ability to complete endurance activities and prolonging the time to exhaustion.

Research on the potential performance-enhancing effects of phosphate loading has yielded conflicting results. To date, fewer than 10 randomized double-blind crossover studies on the use of phosphates to enhance exercise performance can be found in the literature.[90] Those studies were conducted over a period of more than 20 years and involved small samples of participants (6–11 subjects per study) performing exercise by running on treadmills or stationary cycling. Some of the studies found that phosphate loading (e.g., the use of 4 g per day for three to six days) can improve various biomarkers of exercise capacity by increasing 2,3-DPG and serum phosphate levels and raising the lactate threshold in muscles[89,91-93]; in addition, some research has indicated improved aerobic capacity (measured as VO_2 max), an increased anaerobic threshold, and a reduction in perceived feelings of exertion with phosphate supplementation.[89,91,92] However, other studies have shown no benefits.[94-96]

The effects of phosphate loading on the aforementioned biomarkers and oxygen-utilization measures and its possible beneficial effects on actual performance have not been consistently correlated. Some studies have indicated improved performance in conjunction with improvements in those measures, while other studies have indicated improved markers and measures without improved exercise performance.[91,93] One study demonstrated significant improvements in power output and timed-cycling performance with phosphate loading relative to placebo use; however, when the same researchers evaluated performance measures in a group of cyclists practicing phosphate loading using a non-placebo-controlled study design (i.e., the control group ingested nothing), only the measure of power output significantly increased with phosphate use, and finishing time was not significantly reduced.[90]

Other studies have shown no improvements in any measured variable with the use of phosphate supplementation.[94-96] Notably, the studies that found no significant exercise benefits with phosphate supplementation evaluated the effects of calcium phosphate, as opposed to phosphorus in the form of sodium phosphate salts, and did not involve a loading period of at least two days. In general, trisodium phosphate appears to confer beneficial effects on exercise markers and performance when there is a sufficient loading period.

The only reported adverse effect of phosphate in studies involving phosphate supplementation for periods of three to six days was in one subject who dropped out of a study due to gastrointestinal distress.[89-94] Dividing the desired daily amount and taking the incremental servings with adequate amounts of water may minimize gastrointestinal adverse effects. Long-term or consistent use of phosphates for endurance performance has not been studied. Continuous phosphate supplementation may lead to electrolyte imbalances and should be avoided in individuals with impaired kidney function and those prone to kidney stones.[87]

Considering all of the available evidence, one-time use of phosphates in any amount has not been shown to consistently enhance athletic performance. Phosphate loading with 4 g of trisodium phosphate daily (divided and ingested incrementally four times per day) for three days before a competition has the potential to improve work output and endurance exercise performance. However, the amount of phosphates contained in preworkout products is often unknown, making it difficult to advise consumers. Additionally, there are no studies available demonstrating

the safety or efficacy of phosphate supplementation in combination with other ingredients in preworkout products.

Discussion

There are numerous dietary supplements marketed to athletes as tools for achieving improved performance and increased energy. The preworkout products marketed today are problematic. First, the limited amount of data to support the claims made by manufacturers creates uncertainty for health care professionals with regard to advising consumers about the safe use of these products. There is positive evidence to support the efficacy of some ingredients as standalone agents for performance enhancement, but data on combination products are scant, inconclusive, or conflicting. Second, FDA does not regulate or test the purity, potency, and content of any dietary supplements. The lack of information regarding the active ingredients of proprietary blends can increase the potential for adverse effects and unintentional overdosing. Although some product labels instruct consumers to seek the advice of a health care professional before product use, full disclosure of ingredients is often lacking and difficult to obtain.

The information presented in this review may help health care professionals when advising consumers about the efficacy and safety of specific products and ingredients. However, this is not a comprehensive review of all ingredients or dietary supplements of this type currently available on the market, and the information provided here should only be used as a guide when analyzing preworkout product labels. Dietary supplement products are subject to significant turnover on commercial retail shelves, as new products are frequently released and gain popularity quickly. Moreover, manufacturers can reformulate their products, and neither the availability nor the content of new formulations may be apparent to the consumer or to health care professionals.

Conclusion

Although evidence exists to support the performance-enhancement efficacy of some preworkout ingredients as standalone agents, published data on combination products are scant, inconclusive, or conflicting. The safety of these products is unknown when users consume larger-than-recommended amounts or use more than one product.

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